World Glaucoma Association

Medical Treatment of Glaucoma

Robert N. Weinreb, Makoto Araie, Remo Susanna,
Ivan Goldberg, Clive Migdal, Jeffrey Liebmann

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MEDICAL TREATMENT OF GLAUCOMA

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The 7th Consensus Report of the

World Glaucoma Association

Editors

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and
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Medical Therapy of Glaucoma Consensus Meeting participants, Fort Lauderdale, May 1, 2010.

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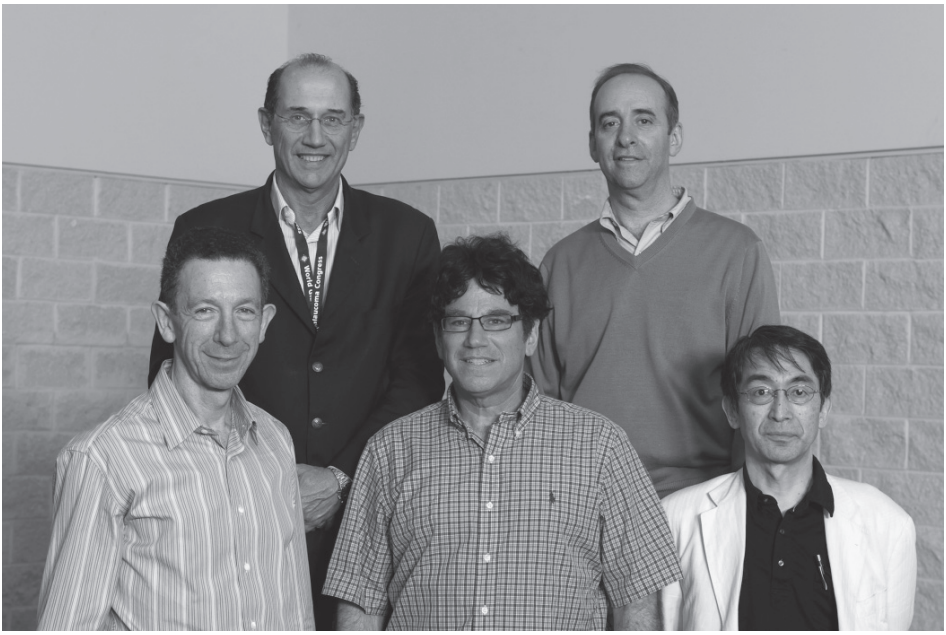

Consensus Chairs: Ivan Goldberg, Robert N. Weinreb, Makoto Araie (bottom row), Remo Susanna, Jeffrey Liebmann (top row).

Clive Migdal

CONTENTS

PREFACE

Medical Treatment of Glaucoma is the topic of the seventh World Glaucoma Association Consensus. Medical treatment of glaucoma continues to be at the core of glaucoma management. Hence, the results of this report will have broad and significant impact on glaucoma research and clinical practice. The global faculty, consisting of leading authorities on the clincial and scientific aspects of medical management, met in Fort Lauderdale on May 1, 2010 to discuss the reports and refine the consensus statements.

As with prior meetings, it was a daunting task to seek and obtain consensus on such a complicated and nuanced subject. It is unclear how each of us decides how we practice, and evidence to guide us often is sparse. Hence, this consensus, as with the others, is based not only on the published literature, but also on expert opinion. Although consensus does not replace and is not a surrogate for scientific investigation, it does provide considerable value, especially when the desired evidence is lacking. The goal of this consensus is to provide a foundation for medical treatment of glaucoma and how it can be best employed in clinical practice. Identification of those areas for which we have little evidence and, therefore, the need for additional research always is a high priority. We hope that this consensus report will serve as a benchmark of our understanding. However, this consensus report, as with each of the others, is intended to be fluid. It is expected that it will be revised and improved with the emergence of new evidence.

Robert N. Weinreb, Chair

Makoto Araie
Ivan Goldberg
Jeffrey Liebmann
Clive Migdal
Remo Susanna
Co-Chairs

Robert N. Weinreb, Consensus Chair.

Medical Treatment Chairs and Section Leaders.

INTRODUCTION

We mark the seventh consecutive year for the World Glaucoma Association Glaucoma Consensus with Consensus VII. Our topic is the Medical Treatment of Glaucoma.

Global experts were invited and assembled by our international co-Chairs beginning in November 2009, to participate in the Project Forum E-Room, a unique online opportunity to facilitate discussion of each of the consensus meetings. Participants then were engaged in the discussion of ten topical areas to reach consensus on key issues that surround and permeate all aspects of the medical treatment of glaucoma. The results of these thoughtful discussions then were summarized by each of the sections with preliminary consensus statements. The Draft of the Consensus Report, including the preliminary consensus statements, was distributed to the Societies and Partners for review and comments prior to the Consensus Meeting that took place in Fort Lauderdale on Saturday, May 1, 2010. Relevant stakeholders engaged on this day in a stimulating, educational, and thought-provoking session that highlighted the review and revision of the consensus statements. In reponse to comments during the discussion, sections on medical treatment of glaucoma during pregnancy and childhood glaucoma were added, along with Consensus Statments on these topics. The Consensus Report then was finalized by Consensus co-Chairs and Editors. Consensus statements were reviewed and finalized by the expert Consensus Panel.

Robert N. Weinreb and Jeff Liebmann, Editors

Stefano Miglior and Fotis Topouzis.

Bruce Prum, Augusto Paranhos, Tanuj Dada and others.

1. WHO SHOULD BE TREATED?

Felipe A. Medeiros, Remo Susanna Jr., Kuldev Singh

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Consensus statements

1. In general, treatment is indicated for patients with glaucoma or glaucoma suspects who are at risk for developing functional impairment or decrease in vision-related quality of life from the disease.
   Comment: Treatment is generally indicated when the risks of progressive disease outweigh the risks and potential side effects of treatment.
2. All treatment decisions should take into account the presence of coexisting ocular conditions, the patient's life expectancy and general health status, as well as his/her perceptions and expectations about treatment.
3. The rate of disease progression is of fundamental importance in considerations of treatment for glaucoma patients. Treatment is indicated for patients whose rates of progression will most likely result in loss in vision-related quality of life over the projected remaining years of life.
4. Treatment is generally indicated for patients with definitive glaucomatous visual field loss, particularly in circumstances when such loss has been determined to be progressive at a measurable rate.
5. Changes of the optic nerve and/or retinal nerve fiber layer (RNFL) characteristic of glaucoma predict functional vision loss in glaucoma and thus patients with such documented structural evidence of progressive damage should generally be treated with intraocular pressure lowering therapy.
6. The decision regarding whether or not to treat glaucoma suspects should involve a consideration of risk factors for disease development, including age, family history of glaucoma, intraocular pressure, central corneal thickness, presence of pseudoexfoliation, disc hemorrhages and measures of structural

Medical Treatment of Glaucoma, pp. 1-19
Edited by Robert N. Weinreb and Jeffrey Liebmann

and functional integrity of the optic nerve head and retinal nerve fiber layer.

Comment: While it is clear that progress has been made in establishing risk factors for glaucoma progression, much work remains to be done to better refine risk models. Nonetheless, the factors that affect the risk of progression help decide the expected prognosis of the individual's untreated disease and thereby the frequency of follow-up and aggressiveness of the therapy to be undertaken.

7. Imaging of the optic nerve head and retinal nerve fiber layer can provide useful predictive information about the risk of developing functional loss from glaucoma and thus can serve as a surrogate predictor of such vision loss.
8. Selective visual function tests may be predictive of functional loss in glaucoma patients and thus may be used as complementary tests to assist in treatment decisions.
9. Predictive models or risk calculators may assist clinicians in providing more objective estimates of the risk of glaucoma development for individual patients.

   Comment: Predictive models are based on restricted populations of patients that were selected based on strict inclusion and exclusion criteria and that may not be representative of all patients seen in everyday clinical settings. Use of these models should be restricted to those patients who are similar to the ones included in the studies used to develop and validate such models and calculators.

General concepts

Glaucoma is a progressive optic neuropathy that may result in significant visual impairment and a cascade of functional health status, quality of life and economic consequences to the patients.[1] With an ageing population, it is estimated that over 58 million people will have open-angle glaucoma by the year 2020 with approximately 10% being bilaterally blind, making it a leading cause of irreversible blindness in the world.[2] In the United States, the management of glaucoma costs about $2.5 billion per year and the disease is one of the most frequently reported reasons for a visit to the physician.[3] Furthermore, impaired physical and mental health status and decreased vision-related quality of life add significantly to the burden of the disease.

In the past decade, significant advance has been made towards our understanding of the role of intraocular pressure (IOP) in glaucoma. It is now clear that IOP lowering treatment may significantly delay or prevent glaucoma development and progression. However, although current ocular hypotensive therapy is generally considered safe, it may still be associated with significant local and systemic side effects. Additionally, treatment initiation may be associated with a decline in quality of life as a result of anxiety or depressive symptoms associated with the diagnosis, the burden of using medications daily, or the costs associated

with treatment. Therefore, the decision to initiate glaucoma treatment should be based on the assessment of the risks for development of functional impairment or decrease in vision-related quality of life, taking into account factors such as coexisting ocular conditions, the patient's life expectancy and general health status, as well as his/her perceptions and expectations about treatment.

Although there is little controversy about the need for treatment in patients with well-established visual function loss and at risk for visual impairment, there is much less agreement about the need to treat the disease at its earlier stages or in patients with suspicious signs of glaucoma but no clear evidence of structural or functional damage. According to the American Academy of Ophthalmology preferred practice guidelines, the decision to begin treatment of the glaucoma suspect is 'complex and depends on ocular, systemic, medical, and psychosocial factors.' Recent results from multicenter clinical trials such as the Ocular Hypertension Treatment Study (OHTS)[4] and the European Glaucoma Prevention Study (EGPS)[5] have provided evidence about the incidence of glaucoma development in patients with ocular hypertension and the risk factors influencing it. Not all patients with ocular hypertension develop glaucoma. In fact, even when left untreated, the average proportion of patients with ocular hypertension developing early signs of damage to the optic nerve or visual field is less than 10% in five years. However, the risk of disease development seems to be highly variable according to certain risk factors and information about these factors has resulted in better evidence-based guidelines for the treatment of glaucoma suspects.

Even for patients who appear to have signs of glaucomatous optic neuropathy or visual field loss measured by standard automated perimetry, the decision for treatment should still take into consideration the rate of progressive disease. Although most glaucoma patients show some evidence of progression during the course of the disease, the rate of deterioration can be highly variable.[1, 6-8] While some patients progress slowly over the course of many years or decades with minimal impact on the quality of vision, others have aggressive disease with rapid rates of change that can eventually result in blindness or substantial impairment unless appropriate interventions take place. The evaluation of rates of change is therefore a fundamental aspect in the management of this disease, so that resources can be directed towards the patients who are most likely to develop substantial impairment.

Below, we review some of the evidence that guided the consensus statements about which patients with glaucoma or suspected of having the disease should be treated.

The efficacy of IOP reduction in delaying or preventing glaucoma development and progression

The efficacy of treatment in preventing disease development or progression is a fundamental consideration when deciding whether or not treatment should be

initiated for a particular condition. IOP reduction is currently the only available treatment that has been consistently demonstrated to significantly delay or prevent glaucoma progression. In recent years, the results of several multicenter clinical trials have provided evidence about the magnitude of the effect of IOP in preventing progressive structural and functional loss from glaucoma. Evidence of a beneficial effect of IOP reduction is now available throughout the spectrum of the disease, both decreasing the incidence of disease as well as its progression.

For patients with ocular hypertension, both the results of the OHTS[4,9] and EGPS[5,10] have demonstrated that IOP reduction could prevent or delay development of signs of glaucomatous optic neuropathy or visual field loss among glaucoma suspects. In the OHTS, 1636 patients were randomized to either observation or treatment and followed for a median time of 72 months. Ocular hypertension was defined based on the presence of qualifying IOP between 24 mmHg and 32 mmHg in one eye and between 21 mmHg and 32 mmHg in the other eye with gonioscopically open angles, normal visual fields and normal optic discs. Participants randomized to medication began treatment to achieve a target IOP of 24 mmHg or less and a minimum of 20% reduction in IOP from the average of the qualifying IOP and IOP at the baseline randomization visit. At baseline, mean IOP was 24.9 ± 2.6 mmHg and 24.9 ± 2.7 mmHg in the treated and observation groups, respectively. The average IOP reduction in the treated group was 22.5% ± 9.9% compared to 4.0% ± 11.6% in the observation group. At 60 months, the cumulative probability of developing primary open-angle glaucoma was 4.4% in the medication versus 9.5% in the observation group, which translates into a 54% relative reduction in the risk of glaucoma development with treatment.

The EGPS was also designed to investigate whether the onset of POAG could be prevented by treatment in ocular hypertensive patients. Inclusion criteria for the EGPS were similar to those of the OHTS. However, qualifying IOP had to be between 22 mmHg and 29 mmHg in at least one eye on two consecutive measurements taken at least two hours apart, with no inclusion/exclusion criteria with regard to the IOP in the fellow eye. The EGPS randomized 1081 patients to treatment with dorzolamide or placebo with mean planned follow-up of five years. However, only 64% of the patients in the treatment group and 75% in the placebo group completed the study. Mean IOP at baseline was 23.4 mmHg and 23.5 mmHg in the dorzolamide and placebo groups, respectively. Mean IOP reduction at five years was 22.1% in the dorzolamide group and 18.7% in the placebo group. At the completion of the study, there was no statistically significant difference between the two groups in the cumulative probability of developing glaucoma. Several reasons have been proposed to explain the apparent conflicting results between the OHTS and EGPS, including regression to the mean effects, lack of target IOP and selective loss to follow-up. However, despite the fact that the treatment with dorzolamide was not superior to placebo, the EGPS results were still compatible with higher IOP being a risk factor for glaucoma development. A 1-mmHg higher baseline IOP was associated with

18% higher risk of developing glaucoma, in a multivariable model containing age, presence of cardiovascular disease, CCT and presence of pseudoexfoliation.

For patients with glaucoma diagnosis, several clinical trials have provided evidence for a beneficial effect of IOP lowering in halting disease progression. The Early Manifest Glaucoma Trial (EMGT)[11] was designed specifically to evaluate the effect of IOP-lowering treatment on progression of glaucoma. The EMGT enrolled 255 newly diagnosed, previously untreated, open-angle glaucoma patients who had reproducible visual field defects at baseline. Patients were randomized to a fixed treatment protocol versus no treatment and were followed for a median of six years, with excellent retention. Mean IOP reduction was 25% in the treated group, with no changes in the control group. The proportion of patients who developed progression was significantly larger in the control versus the treatment group (62% versus 45%, respectively; hazard ratio [HR] = 0.50; 95% CI: 0.42 – 0.84; P = 0.003). Each 1 mmHg higher mean IOP during follow-up was associated with 13% higher risk of progression (HR = 1.13; 95% CI: 1.07-1.19; P < 0.001). Results were consistent in multivariable models adjusting for other risk factors.

The Collaborative Normal Tension Glaucoma Study (CNTGS)[12] enrolled 230 patients with unilateral or bilateral normal tension glaucoma characterized by glaucomatous cupping and a defined type of visual field defect and a median IOP of 20 mmHg or less in ten baseline measurements (with no recorded IOP above 24 mmHg).[12] Eyes were randomized to no treatment or to have IOP reduced by 30% by medical or surgical intervention. The study found that significantly fewer eyes progressed in the treated group versus the control group (12% versus 35%) in an analysis that changed the baseline to correct for the increased frequency of cataract in the treated group. The intent-to-treat analysis failed to show a beneficial effect of treatment, however.

Other prospective clinical trials have also provided some evidence that IOP reduction can slow glaucoma progression. However, it is important to note that these trials were not originally designed to specifically address the relationship between IOP reduction and glaucoma progression. The Advanced Glaucoma Intervention Study (AGIS)[13] was a long-term study designed to evaluate the clinical course of medically uncontrolled OAG by two surgical treatment sequences. Of 591 patients, 789 eyes were randomized to a treatment sequence of (1) argon laser trabeculoplasty, trabeculectomy and trabeculectomy (ATT); or (2) trabeculectomy, argon laser trabeculoplasty and trabeculectomy (TAT). One of the AGIS reports[13] examined the relationship between control of IOP and visual field deterioration. In the so-called Associative Analysis, eyes were divided according to the percent of visits for which the eye presented IOP less than 18 mmHg. Eyes were assigned to one of four categories: 100% (group A), 75% to less than 100% (group B), 50% to less than 75% (group C) and 0 to less than 50% (group D). Eyes in group A had mean changes from baseline in visual field defect score close to zero. Patients in groups B, C and D had progressively more changes in visual field compared to group A. In the analysis of predictive factors for progression of visual field loss in the AGIS, each 1 mmHg higher

mean IOP level at the first 18 months of follow-up was associated with a 0.10 increase in visual field defect score during the rest of follow-up (P = 0.002), after adjusting for race, assigned intervention sequence, age, diabetes, gender, reference IOP and reference visual field defect score.[13]

The Collaborative Initial Glaucoma Treatment Study (CIGTS)[14] randomized 607 patients with newly diagnosed OAG to medical versus surgical treatment. Each patient was assigned a target IOP that was a function of baseline IOP and a reference visual field, so that patients with more severe disease were required to have more IOP lowering. Patients assigned to the medical arm were treated with IOP-lowering treatments at the discretion of the treating physician, whereas patients assigned to the surgical arm underwent trabeculectomy (with 5-FU at the discretion of the surgeon). IOP was reduced, on average, by approximately 48% and 35% in the surgical and medical group, respectively. Visual fields were graded using a defined protocol (increasing scores reflecting increasing VF loss and ranging from 0 to 20). Both groups had, on average, minimal changes in visual field scores over time except during the last years of follow-up. The greater lowering of mean IOP in the surgically treated group apparently seemed to be of no further benefit in CIGTS patients except in a later analysis of longer-term results, which did reveal a better outcome for the surgical group in a subset of subjects with a greater degree of initial visual field loss.[15]

Risk factors for glaucoma development and progression

The decision to initiate treatment in a patient suspected of having glaucoma should depend on a careful analysis of the risk factors for development of the disease. Similarly, for patients with established signs of glaucomatous damage, the decision to initiate therapy also needs to take into consideration risk factors for further disease progression and visual impairment. The analysis of these risk factors needs to be performed in conjunction with an analysis of the potential side effects of treatment, life expectancy and presence of ocular and systemic co-morbidities.

Several studies have investigated the risk factors for development and progression of glaucoma. From the analysis of these studies, several factors emerge as having strong or moderate association with the risk of glaucomatous progression: higher IOP, older age, worse disease severity (for patients with established damage), optic disc hemorrhages, black race, and thinner corneas.[16] More recently, evidence has accumulated pointing to ocular perfusion pressure as another risk factor for progression of the disease.[17] For other factors, such as gender, presence of diabetes mellitus, arterial systemic hypertension, history of migraines and myopia, the evidence is weak or still insufficient. Although a significant risk factor for incidence of disease, presence of positive family history of glaucoma has an unclear relationship with risk of disease progression. Below we review some of the evidence with regard to the risk factors for glaucoma progression.

Intraocular pressure

As outlined above, there is strong evidence from several clinical trials to support higher mean IOP as a risk factor for development of glaucoma, as well as for progression of disease in individuals with manifest glaucoma. In EMGT, AGIS, OHTS, EGPS and the Canadian Glaucoma Study[18] each mmHg of increased IOP was associated with an increased risk for progression of 10-19%.

Age

There is strong evidence that older age is an independent risk factor for development and progression of glaucoma. This has been confirmed by several longitudinal clinical trials as well as by multiple population-based studies. The effect of older age increasing risk of glaucoma progression has to be analyzed in the context of life expectancy. Although older subjects have higher risk of progression, they may be at a lower risk for development of functional disability from the disease due to shorter life expectancy.

Corneal thickness

Corneal thickness is another factor that has been associated with the risk of glaucoma development and progression. In the OHTS,[9] EGPS[10] and Barbados Eye Study,[19] CCT was an important predictor of development of primary open-angle glaucoma. Corneal thickness has also been shown to be a risk factor for development of visual field defects in patients with glaucomatous optic neuropathy[20] and to be related to structural and functional abnormalities in glaucomatous patients.[21-23] A long-term follow-up report from the EMGT confirmed the role of corneal thickness as a risk factor for further progression in patients who already have glaucoma and elevated IOP, with the risk increasing 25% for each 40μm lower CCT.[17]

Disease severity

Several investigations have suggested that patients with worse severity of disease at baseline have higher risk of progression and development of blindness from glaucoma. In the EMGT,[17,24] patients with more severe visual field defects at baseline had significantly higher chance of progressing over time. It is important to note, however, that measures of disease severity cannot be considered strictly as risk factors for the disease, as they are part of its definition. However, their assessment and incorporation into predictive models has been proven to be helpful in predicting which patients are more likely to develop clinically important stages of disease in the future.[25-26] In fact, patients with ocular hypertension with larger cup/disc ratios or worse values of pattern standard deviation have been shown to be at increased risk for development of glaucoma. These predictive

factors have been incorporate in successful models for predicting risk of disease development in this population.

Black race

Individuals of African ancestry have higher incidence of POAG and tend to develop the disorder earlier in life, with higher rates of progression and blindness from the disease.[27-28] There are multiple factors that may contribute to the increased risk of progression and blindness from glaucoma in individuals of African ancestry, including lack of response and access to treatment. Also, individuals of African ancestry have been demonstrated to have larger optic discs with smaller rim areas, which may confer a biomechanical disadvantage with a lower reserve number of nerve fibers. They also have thinner corneas, which are a significant risk factor for the disease, as described above. Finally, they may have less access to medical examinations and care, are less aware of the risks for glaucoma, and may have differences in treatment adherence and persistence. However, there is evidence to indicate that despite differences in environment, education, and medical systems, there is an inherent disease risk that has been conserved in African-derived persons.

Optic disc hemorrhages

Optic disc hemorrhages have been associated with an increased risk of development and progression of POAG in multiple studies, including the OHTS[29] and EMGT.[30] Additionally, optic disc hemorrhages are associated with faster rates of disease progression.[31] These hemorrhages are probably a result either of ischemic infarction in the disc rim or of mechanical tearing of capillaries in the rim as nerve fibers atrophy and tend to disappear in a few months.

Family history

There is strong evidence from population-based studies for the familial nature of POAG. In the Rotterdam study, the lifetime absolute risk of glaucoma was nearly ten times higher for individuals having relatives with glaucoma than for control patients.[32] Importantly, all available family members were examined in that study, reducing the likelihood of potential recall bias and misclassifications from self-reported data. In the Barbados Family Study, family history was also identified as a major risk factor for glaucoma based on direct examination of the relatives of affected patients.[33] Although the OHTS and EGPS did not find family history to be a risk factor for glaucoma development, this was most likely related to methodological weaknesses of these studies. As no relatives of the study subjects were examined, investigators had to rely on self-reported family history with its potential inaccuracy.

The relationship between family history and risk of progression in patients with established glaucomatous damage is uncertain. It is possible that a history

of blindness from glaucoma in the family may indicate a higher risk of having a more severe form of disease with higher rates of progression. However, no studies are currently available to confirm this hypothesis.

Other risk factors

There is growing evidence indicating that reduced ocular perfusion pressure is a risk factor for glaucoma progression. In the EMGT, Individuals with systolic perfusion pressure lower than 125 mmHg had a 42% higher risk of progressing over time compared to patients with systolic perfusion pressure above 125 mmHg.[17] This effect was present even after adjustment for other risk factors.

Diabetes was routinely assumed to be a risk factor for POAG until the last 15 years, when it failed to show an association with POAG in several population-based studies and clinical trials. There is reason to believe that the past association between diabetes and glaucoma may have been partly derived from ascertainment bias, because diabetic patients might have more eye examinations. At the present moment, the relationship between diabetes and risk of glaucoma development and progression is uncertain.

In the CNTGS, history of migraines was significantly associated with risk of progression in normal-tension glaucoma patients, suggesting a vasoespastic component influencing the pathogenesis of glaucoma.[34] Other systemic manifestations of vasoespasm, such as Raynaud's phenomena, have not been found to be associated with glaucoma progression in other studies.

Myopia has been associated with glaucoma prevalence in population-based studies,[35] however, its precise relationship with risk of progressive damage in patients with established disease remains unclear.

The use of ancillary diagnostic tests in the evaluation of treatment decisions

To diagnose disease, a clinician integrates the constellation of symptoms and/or signs of a presenting patient and then assigns a level of certainty regarding its presence. In the case of glaucoma evaluation, the process generally starts with the medical interview and history. It is followed by clinical examination, which generally includes slit-lamp examination, intraocular pressure measurement and optic nerve examination. After this information is collected, the clinician hypothesizes about the chance that glaucoma is present and can order additional tests, such as the visual field. It is not unusual for a patient to present with suspicious appearance of the optic disc and normal or inconclusive visual field tests. In this situation, additional testing, such as optic disc and/or retinal nerve fiber layer (RNFL) imaging or function-specific perimetric tests can be conducted to try to minimize the margin of error regarding the uncertainty of diagnosis. Then, the test results are used to complement clinical evaluation to determine whether the patient with suspected glaucoma truly has disease or is likely a healthy subject. This information can then be used along with other

information about risk factors to decide whether a particular patient should be treated or not and to decide about need and frequency of follow-up. In order to evaluate the benefit of ancillary tests, it is essential to know their ability in predicting future development of functional loss in glaucoma.

Previous investigations have shown that cross-sectional baseline structural measurements, either by expert assessment of stereophotographs or objective imaging methods, are predictive of future development of visual field loss in glaucoma suspects, suggesting a potential role for these measurements in early detection of disease and influencing treatment decisions in glaucoma suspects.[26,36-41] As part of the OHTS Confocal Scanning Laser Ophthalmoscopy Ancillary Study, ocular hypertensive patients with thinner neuroretinal rim area measurements at baseline were shown to have higher risk of developing glaucoma during follow-up. Studies with scanning laser polarimetry and optical coherence tomography have also demonstrated that glaucoma suspects with thinner measurements of retinal nerve fiber layer (RNFL) thickness at baseline are at higher risk for progressing to established glaucomatous functional damage. However, measures of predictive ability reported in these studies have generally indicated a low accuracy of cross-sectional structural measures for predicting individual functional outcomes. For example, in the OHTS CSLO study, the positive predictive value of an abnormal result in the Moorfields Regression Analysis was only 14.1%, demonstrating the low accuracy of baseline measures to predict future individual outcomes.[37] This is likely due to the wide variation in the appearance of the optic nerve and RNFL, which makes it difficult to identify early signs of disease at a single point in time. Although detection of progressive optic disc change over time is likely to be a more specific indicator of the presence of structural damage from glaucoma and to correlate better with functional outcomes, the ability of progressive optic disc change in predicting functional outcomes in glaucoma patients has only been recently elucidated. Medeiros *et al*.[42] showed that patients suspected of having glaucoma at baseline and who had documented evidence of progressive optic disc change on stereophotographs during follow-up had almost 26 times higher chance of developing a visual field defect (HR = hazard ratio [HR]: 25.8; 95% CI: 16.0-41.7) compared to patients who did not show change on disc stereophotographs during follow-up. Presence of optic disc progression was the most important predictive factor for conversion, with an R^2 of 79%, well above that of any other known risk factor for development of glaucoma, such as IOP and corneal thickness. A recent work by Chauhan *et al*.[43] also suggested that progressive optic disc changes measured by the Topographic Change Analysis (TCA) software of the Heidelberg Retina Tomograph (Heidelberg Engineering GmbH, Dossenheim, Germany) were predictive of functional loss in a cohort of 81 patients, suggesting that imaging devices could also be used to monitor optic disc appearance.

Detection of progressive structural damage in glaucoma has significant clinical implications for patients. Recent analysis of population-based data has suggested that even mild visual field loss in glaucoma patients already carries

a significant negative impact in vision-related quality of life measures.[44] Also, assuming conservative treatment efficacy, over 10% of glaucoma patients who are diagnosed with early visual field damage and followed under treatment will still develop significant visual impairment or blindness from the disease during their lifetime.[45] This evidence seems to point to the need for early detection and treatment of glaucoma before significant visual field loss has developed. Therefore, monitoring of the optic nerve appearance for detection of change before substantial visual field damage occurs could potentially decrease rates of functional impairment associated with the disease.

Function-specific perimetric tests such as short-wavelength automated perimetry (SWAP) or frequency doubling automated perimetry (FDT) have also been suggested as tests that could assist in early detection of glaucomatous functional loss. Although initial evaluations of SWAP compared to Full-threshold perimetry showed promising results, more recent research has not shown a clear benefit of SWAP when compared to SITA standard perimetry.[46-48] For FDT, current research suggests that it may detect functional damage before SITA standard perimetry, however, there are only a few longitudinal studies available.[49-51] Additionally, it is still not clear what parameters a clinician should use when evaluating results from these tests and how to incorporate this information into treatment decisions.

The usefulness of predictive models in treatment recommendations

Although the information on individual risk factors may help clinicians in treatment decisions, it is frequently difficult to integrate the information on the several risk factors and provide a global assessment for a particular patient. In that situation, predictive models or risk calculators may benefit clinicians in providing a more objective assessment of risk. Mansberger *et al*. performed a survey of ophthalmologists to estimate their ability to predict the risk of glaucoma development in ocular hypertensive patients.[52] Ophthalmologists had the benefit of an oral review and written handouts summarizing the OHTS results. They found that ophthalmologists tended to underestimate the risk when compared to the actual risk found by a risk calculator. Ophthalmologists also had a large range of predictions, sometimes differing from the actual risk by 40%, illustrating the need for a more standardized method for risk assessment.

The development of predictive models requires a series of complex steps which initially involve the acquisition and analysis of data from one or multiple longitudinal studies that have carefully followed patients over time. In 2005, Medeiros *et al*.[26] published the results on the development and validation of a risk calculator to assess the risk of an ocular hypertensive patient to develop glaucoma. The risk calculator was derived based on the results published by the OHTS[9, 53] and incorporated the variables that were described by that study as being significantly associated with the risk of developing glaucoma over time. The risk calculator was designed to estimate the chance of an ocular hypertensive

patient to develop glaucoma if left untreated for five years. To simplify the use of the risk calculator, a point system and an electronic version of the calculator were made available for clinicians. In 2007, OHTS and EGPS investigators published results of the development and validation of a risk calculator for glaucoma based on the analysis of the combined OHTS/EGPS dataset.[41] The results were similar to the predictive model published in 2005, and the risk calculator contained the five variables significantly associated with the risk of glaucoma conversion: age, IOP, CCT, PSD and vertical cup/disc ratio.

A predictive model that is derived from a particular dataset is not guaranteed to work on a different group of patients. In fact, the performance of regression models (or risk calculators) used as diagnostic or prediction tools is generally better on the dataset on which the model has been constructed (derivation set) compared to the performance of the same model on new data. Therefore, before risk calculators can be successfully incorporated into clinical practice they need to be validated on different populations, that is, they need to be demonstrated to work satisfactorily for patients other than those from whose data the model was derived. The risk calculator published by Medeiros *et al*. in 2005 was validated in an independent population from the Diagnostic Innovations in Glaucoma Study (DIGS), showing good fit and predictive ability to identify patients who developed glaucoma. The risk model from the pooled OHTS/EGPS sample of over 1,100 ocular hypertension patients also demonstrated good fit with a c-statistic of 0.74 and good calibration. The OHTS/EGPS risk calculator is available on the web at http://ohts.wustl.edu/risk.

Predictive models for glaucoma progression

Estimation of the risk of patients with existing glaucoma of developing progressive damage over time is at least as important as estimating the risk of unaffected patient developing glaucoma. The development of predictive models for glaucoma progression could use the same principles as those used to develop and validate models for glaucoma development. Initially, longitudinal studies that followed patients with glaucoma would have to be reviewed to identify risk factors associated with progressive disease. A predictive model could theoretically be developed based on the results from longitudinal studies incorporating all the risk factors found to be significantly associated with progressive disease. Such a model would be helpful in estimating which glaucoma patients are at higher risk for developing progressive loss of visual function. It is important to emphasize that any predictive model would have to be validated on an independent population of patients, as described above for the risk calculators in ocular hypertension.

Limitations of predictive models

The use of predictive models in clinical practice has several limitations. Predictive models are based on restricted populations of patients that were selected based

on strict inclusion and exclusion criteria and that may not be representative of all patients seen at everyday clinical settings. Use of these models should be restricted to those patients who are similar to the ones included in the studies used to develop and/or validate it. It is also important to emphasize that although predictive models can provide a more objective evaluation of risk, their use does not replace the judgment of a clinician when making management decisions. For example, current risk calculators to estimate risk of glaucoma development do not include important information to guide treatment such as medical health status and life expectancy, patient's willingness to treatment, costs of medications and overall effect of treatment on quality of life. Also, it is important to emphasize that current risk calculators for glaucoma have been designed to estimate the risk of development of the earliest signs of disease, which do not necessarily have an impact on the quality of vision of the patient. Finally, as more evidence regarding risk factors for disease development and progression accumulates, newer and better-refined predictive models will be developed that should replace current existing ones.

The importance of assessing rates of disease progression for treatment decisions

The rate of disease progression is of fundamental importance in considerations of treatment for glaucoma patients. Treatment is indicated for patients whose rates of progression will most likely result in loss in vision-related quality of life over the projected remaining years of life.[8] As the rate of disease progression in individual eyes is quite variable, some patients may progress slowly and the disease will be expected to have only a minimal impact on the quality of vision. On the other hand, patients with aggressive and rapidly deteriorating disease may develop functional impairment during their lifetimes, resulting in significant decrease in quality of life.

Standard automated perimetry remains the 'gold standard' for the assessment of rates of functional loss in glaucoma. A recent report from the EMGT provided information on the natural history of open-angle glaucoma and rates of progression of visual field loss.[7] Patients with glaucoma were followed without treatment for an average of six years. The median rate of visual field loss was -0.4dB/year. However, there was a large variability in rates of progression among the eyes, with some eyes staying practically stable during follow-up with rates close to 0dB, while other eyes progressing very fast with rates faster than -5dB/year. The large variability in rates of change indicates the need for individual assessment of the velocity of disease progression for each patient.

Several studies have provided evidence that significant structural changes to the optic disc and RNFL may appear before detectable functional loss is identified on standard automated perimetry.[4,42,54-59] The relatively poor sensitivity of standard perimetry for detection of early disease may be related to the natural history of the disease or may reflect variability of measurements and the

logarithmic scaling of perimetric data. The logarithmic scaling may introduce an artifactual relationship between structural and functional measurements in glaucoma.[56-57,60-61] The logarithmic scale may accentuate sensitivity changes in the visual field at low decibel values and minimize changes at high decibel levels. Therefore, visual function changes would be less apparent in the early stages of structural damage giving the impression that structural losses occur first. This has implications for measuring rates of progressive disease. Rates of functional loss measured by SAP in early disease may be misleadingly slow, highlighting the importance of also assessing rates of structural progression.

Although optic disc stereophotographs have been considered the gold standard for evaluation of structural damage in glaucoma, assessment of rates of structural change using stereophotographs is difficult due to the qualitative and subjective nature of this assessment. The use of objective and quantitative structural measurements derived from imaging technologies has facilitated the assessment of rates of structural damage in the disease. Several studies have evaluated rates of glaucoma progression using imaging technologies, such as confocal scanning laser ophthalmoscopy,[62-64] scanning laser polarimetry[8,65-67] and optical coherence tomography.[68-69] Additionally, other studies have demonstrated that rates of progression as measured by imaging instruments are related to risk factors for the disease, such as intraocular pressure.[67] These results suggests that evaluation of rates of structural progression using imaging instruments can provide useful additional information to the evaluation of rates of progressive visual field loss with standard automated perimetry.

Other considerations

Cost effectiveness

The financial implications of initiating glaucoma treatment for the individual and society require careful evaluation as the gap between therapeutic possibilities and the resources available continues to enlarge. In recent years there have been more studies of cost-effectiveness of glaucoma treatment,[70] however, the main methodological issue with economic models is the absence of a clinically relevant long-term effectiveness measure. One such study using cost-utility analysis modeled a hypothetic cohort of people with ocular hypertension and different treatment thresholds from ‘treat no one’ to ‘treat everyone’.[71] The ‘treat everyone’ option costed more and was less effective than the other options. Treatment of patients with > 2% annual risk of the development of glaucoma was likely to be cost-effective. Some care providers have attempted to provide cost-effective strategies for glaucoma and ocular hypertension, however the evidence base for cost-effectiveness is limited.

Life expectancy and general health status

Life expectancy and general health status of the patient are important considerations when deciding whether to treat a patient. Using a model that calculates OAG incidence from age-specific prevalence, Broman *et al*.[72] estimated average life expectancy from age of glaucoma diagnosis to be 13.1 years in Europeans, 13.0 years in Hispanic, 10.5 years in Chinese and 15.4 years in African populations. Current risk calculators do not include critical information guiding treatment such as life expectancy and patient's willingness to commit to years of eye drops.[7] Incorporating mortality risk into estimates of five years glaucoma risk, Griffin *et al*.[73] reported how mortality risk (using the Charlson index) can be used in calculating an adjusted (and reduced) risk of developing glaucoma in one's lifetime. Additionally, it is important to ensure that patients can comply and persist with therapy.

Avoidance of harm

Patients need to have realistic expectations of the nature of the therapy which demands effective communication with the clinician. Glaucoma therapy may have consequences ranging from allergic conjunctivitis to a blinding complication of surgery. A misunderstanding that glaucoma treatment will improve vision may create barriers to compliance with treatment not only with the individual concerned but also among friends and family with whom the person engages, which may hinder uptake of glaucoma care among others. These issues need to be considered when deciding if and how to treat a given patient.

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2. TREATMENT GOALS. TARGET IOP*

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Consensus statements

1. The target IOP is the IOP range at which the clinician judges that the estimated rate of progression is unlikely to affect the patient's quality of life.
   Comment: Although recommended by most experts, there is insufficient evidence that using target IOP is associated with better clinical outcomes.
2. The determination of a target IOP is based upon consideration of the amount of glaucoma damage, the rate of progression, the IOP at which the damage has occurred, the life expectancy of the patient, and other factors including status of the fellow eye and family history of severe glaucoma.
3. The use of a target IOP in glaucoma requires ongoing re-evaluation and adjustment.
4. The benefits and risks of escalating treatment to reach a target IOP must be balanced.
   Comment: Uncertainties regarding the short- and long-term variations of IOP, accuracy of tonometer readings, patient's life expectancy, adherence to therapy and estimated progression rates remain unresolved.

* This chapter updates the section on target IOP from the 2007 WGA Consensus (Jampel H. Target IOP in clinical practice. In: Weinreb RN, Brandt JD, Garway-Heath D, Medeiros FA (Eds.). Intraocular Pressure. Kugler Publications, Amsterdam 2007; pp. 121-125).

Medical Treatment of Glaucoma, pp. 23-26
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5. Treatment goals include IOP, visual function and structural (optic disc, RNFL) outcomes and QOL.
   Comment: It is uncertain whether patient reported outcomes of glaucoma can be applied in clinical practice, and whether they capture clinically meaningful progressive changes.

Concept of target IOP

The target IOP is the IOP range at which the clinician judges that the estimated rate of progression is unlikely to affect the patient's quality of life.

Use of target IOP in clinical practice

Most clinicians use target IOP in clinical practice. The determination of a target IOP is based upon consideration of (1) the amount of glaucoma damage (according to structural and functional measures); (2) the baseline untreated IOP, *i.e.*, the level at which the damage has occurred (ideally several readings should be available); (3) the patient life expectancy (actuarial tables may be useful), with target IOP being lower in people with longer life expectancy and target IOP higher in elderly people; (4) the rate of progression at the current IOP level (using visual fields and/or structural tests); (5) status of the fellow eye (if the fellow eye is healthy, the potential impact of glaucoma in quality of life is reduced, but if the fellow eye is blind the probability of glaucoma progression should be more vigorously minimized); and (6) family history of severe glaucoma.

It is important to acknowledge that there is a subjective component and clinical expertise appears to be an important factor in the way target IOP is determined.

There are straightforward ways of setting target IOP, while other approaches used more complex formulae trying to capture all known relevant factors mentioned above. An example of a simple initial approach would be: reduce the IOP by 30% in all newly diagnosed patients with glaucoma. Another relatively simple method would be: mild glaucoma, high teens; moderate glaucoma: mid teens; advanced glaucoma: low teens.

Target IOP should have a degree of flexibility tailored to the patient's condition and changing ocular and general circumstances. Specifically, the risk associated with additional intervention to further lower the IOP needs to be considered when a clinician encounters an IOP outside the target. This is especially relevant when surgery is needed to further reduce the IOP, but generally speaking each treatment decision and change must balance the potential risk and benefits.

Target IOP may be more useful for some patients, *e.g.*, those with high risk of substantial vision loss and blindness. Perhaps among patients with low risk for visual loss (*e.g.*, ocular hypertension, mild normal tension glaucoma) the

emphasis could be on minimizing side effects of therapy rather than achieving a particular IOP.

Recording the target IOP

Most clinicians using target IOP in their clinical practice recommend recording it in the medical notes. This may be particularly useful when several clinicians are involved in patient care.

Re-evaluation of the target IOP

The definition of a target IOP is expected to change over time, depending on the patient's circumstances and outcomes. For example, if there is rapid disease progression when the initial target IOP has been met then it would need to be revised downwards. Revision may also be considered if the fellow eye has a substantial change in visual function. Similarly, if there is a deterioration of the general health and life expectancy or if the patient has been stable for a long period, the target IOP could be raised.

Use of target IOP in clinical trials

Target IOP may be a useful outcome in glaucoma trials. For example, if two alternative interventions are compared, a possible outcome measure could be how many patients reach a pre-determined target IOP. Target IOP can also be used to set a homogenous IOP level in a group of patients and observe its effect in the progression of the disease. Target IOP has been used in several glaucoma trials (*e.g.*, OHTS, CIGTS, CNTGS).

Limitations of using target IOP

There are important uncertainties in establishing a target IOP. One is the IOP measurement. Because of the short- and long-term variations of IOP, it is unknown whether a mean or a range of IOP should be chosen. In addition, the sub-optimal accuracy of tonometer readings and the influence of corneal biomechanical properties and thickness in IOP readings are additional limiting factors.

From the patient's perspective, life expectancy and adherence to therapy are difficult to predict. From the disease point of view, estimation of glaucoma progression rates in clinical practice is challenging. Glaucoma progression is typically measured with visual function tests (perimetry), but current methods to diagnose progression have different sensitivities and specificities, especially in detecting relatively early progression. The added value of structural tests for detecting progression is also being investigated.

There is lack of full understanding of the effect of glaucoma on patients' quality of life. Current patient-reported outcome measures and validated questionnaires may not capture clinically relevant changes in the condition. This is more likely to happen in earlier stages of the disease.

There is also a concern that using a fixed target IOP by inexperienced clinicians may lead to overestimate the benefits of IOP lowering and underestimation of risks associated with escalation of therapy.

Ultimately, the role of using target IOP should be evaluated in a randomized clinical trial in which one group of patients has a pre-determined target IOP level and the clinicians strive to reach it. The comparator would be a group of patients in whom there was no determination of a target IOP, or a group having different criteria for setting the target IOP. Clinical (progression of glaucoma) and patient-reported outcomes (quality of life measures) would be assessed over time. Because of the subjectivity in setting target IOP it would seem useful to evaluate the intra- and inter-observer agreement in establishing target IOPs at different stages of the disease.

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Paul Healey, Rupert Bourne and Tony Wells.

Robert Fechtner and Tony Realini.

Makoto Araie, Consensus co-Chair.

Doug Rhee and Malik Kahook.

3. DRUGS

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Consensus statements

1. All eye drops have the potential for systemic effects, which may be decreased with a lower concentration, reduced frequency of administration and using nasolacrimal occlusion or gentle eyelid closure.
   Comment: During pregnancy and lactation, the risks and benefits of these medications should be evaluated for each patient.
2. Topical cholinergic agents can effectively reduce intraocular pressure.
   Comment: In open-angle glaucoma, cholinergics enhance aqueous outflow through the trabecular meshwork by means of ciliary muscle contraction.
   Comment: Cholinergics may open the drainage angle in certain instances of angle closure by stimulating the iris sphincter muscle.
   Comment: The effects of pilocarpine are representative of this class. Pilocarpine has an additive hypotensive effect to β-blockers, alpha-2 adrenergic agonists, and carbonic anhydrase inhibitors. It can be additive to prostaglandin analogues in some patients.
   Comment: Common ocular side effects of pilocarpine, which limit its use, include brow-ache, induced myopia, and dimness of vision.
   Comment: TID or QID dosing is associated with poor adherence.
3. Indirect cholinergic agents are reserved for open-angle glaucomas in aphakic or pseudophakic eyes.
   Comment: Indirect cholinergic agents are cataractogenic and also may cause adverse systemic effects.
4. Topical β-blockers are effective IOP-lowering agents.
   Comment: Topical β-blockers decrease IOP by reducing aqueous humor formation. All non-selective β-blockers have comparable IOP-lowering efficacy.

Medical Treatment of Glaucoma, pp. 29-126
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Comment: Topical and systemic β-blockers are poorly additive with respect to lowering IOP.

Comment: Although some β-blockers have intrinsic sympathomimetic activity (ISA) or α-blocking properties, their clinical properties are similar to those of other non-selective β-antagonists. However, ISA may reduce respiratory and cardiovascular side-effects related to β-blockade.

5. Timolol, and possibly all other β-blockers, have minimal IOP-lowering efficacy during sleep.

   Comment: Non-selective topical β-blockers are contraindicated in patients with asthma, chronic obstructive pulmonary disease (emphysema and bronchitis) some cases of congestive heart failure, bradycardia, and heart block.
6. The IOP-lowering efficacy of betaxolol, a relatively selective β-1-blocker, is less than that of non-selective β-blockers.

   Comment: Betaxolol is relatively safer than a non-selective β-blocker in patients with known reactive airway disease.
7. Carbonic anhydrase inhibitors (CAIs) are effective IOP-lowering agents.

   Comment: CAIs reduce IOP by suppressing aqueous humor production through inhibition of the isoenzyme carbonic anhydrase II.

   Comment: CAIs are the only category of drugs available commercially in both topical and systemic formulations to lower IOP.

   Comment: For systemic CAIs, major side effects include paresthesia, malaise, gastrointestinal disturbances, renal disorder, blood dyscrasia, and metabolic acidosis.

   Comment: For topical CAIs, side effects include ocular burning, stinging, bitter taste, superficial punctuate keratopathy, blurred vision, tearing, headache, and transient myopia.

   Comment: CAIs may increase ocular blood velocity; however, there is insufficient evidence for any clinical benefit of this effect for glaucoma patients.

   Comment: Topical CAIs and systemic CAIs are poorly additive with respect to lowering IOP.
8. Systemic CAIs are contraindicated with sulfonamide allergy, with depressed sodium and/or potassium blood levels, and in metabolic acidosis.
9. The non-selective adrenergic agonists, epinephrine and its pro-drug (dipivefrin) are effective IOP-lowering agents.

   Comment: Adrenergic agonists reduce IOP by decreasing aqueous formation and increasing outflow.

   Comment: Adrenergic agonists are contraindicated in infants and children because of systemic side effects.

   Comment: IOP lowering efficacy of adrenergic agonists is less than that with timolol. This class is often additive to prostaglandin analogues but not to non-selective β-blockers.

   Comment: Local side effects include hyperemia and blepharoconjunctivitis. Systemic circulatory effects include hypertension and tachyarrhythmias.

10. Selective alpha-2 adrenergic agonists reduce IOP by suppressing aqueous inflow and increasing outflow. They also may affect episcleral venous pressure.
    Comment: Systemic side effects with selective alpha-2 adrenergic agonists include dry mouth, drowsiness and hypotension.
11. There is insufficient evidence for neuroprotection by selective alpha-2 adrenergic agonists in humans.
12. Bunazosin, a selective α1A antagonist, increases uveoscleral outflow.
    Comment: Although it is well-tolerated, the hypotensive effect of topical bunazosin is weaker than that of topical timolol.
13. Prostaglandin analogues (PGAs) are the most effective IOP-lowering agents of all topical glaucoma medications, and generally are first line therapy.
    Comment: PGAs lower IOP by increasing uveoscleral aqueous humor outflow, and may also have an effect on outflow facility.
    Comment: Common side effects of prostaglandin analogue drops include conjunctival hyperemia, reversible increase of eyelash length, thickness and pigmentation, irreversible increase of iris pigmentation, and increase of eyelid skin pigmentation. Rare side effects include uveitis, reactivation of herpetic keratitis and cystoid macula edema.
    Comment: PGAs are systemically safe, but are relatively contraindicated in pregnancy, as are all glaucoma medications.
14. Preservatives used for multi-dose topical ophthalmic medications can cause ocular surface changes.
    Comment: Benzalkonium chloride (BAK), in particular, has been associated with ocular surface changes in chronic use. Alternative preservative systems are increasingly used in multi-dose bottles in an effort to decrease the potential for deleterious effects on ocular surface. However, direct comparisons between these agents are lacking.
    Comment: Preservative free systems, in the form of unit dose packages, are a viable alternative to traditional multi-dose bottles. In theory, they may have fewer ocular surface effects, however, direct comparisons with preserved agents are lacking.

I Cholingergic Agents

Changwon Kee, Takeshi Yoshitomi, Neeru Gupta

Mechanisms of action

Cholinergic agents were the first class of drugs applied to the eye for the treatment of glaucoma.[1] These drugs improve outflow facility through tension on the trabecular meshwork as a biomechanical consequence of ciliary muscle contraction, and ciliary muscle disinsertion from the sclera and meshwork areas abolished this effect.[2]

Contraction of the ciliary muscle is mediated by muscarinic-receptor activation. Direct acting parasympathomimetic agents, such as pilocarpine and carbachol, stimulate muscarinic receptors, while indirect acting agents, such as echothiophate iodide and physostygmine, promote muscarinic receptor activity by increasing acetylcholine availability. Five different subtypes of mAChRs have been identified and classified according to their different G protein coupling properties.[3] The human ciliary body contains M1, M2 and M3 muscarinic receptor subtypes,[4-8] and the latter seems abundant. M4 and M5 subtypes have not been studied in the ciliary body.[9,10]

Direct acting agents

Pilocarpine

Pilocarpine is derived from the plant *Pilocarpus microphyllus*, in which the drug occurs as the isomer isopilocarpine. Pilocarpines are prepared as solutions, gels, and membrane-controlled delivery systems (Ocusert). The solutions, which are most commonly used, are available in concentrations ranging from 0.25% to 10%. As the pilocarpine concentrations greater than 4% do not generally increase the ocular hypotensive effect, the 1% to 4% solutions are most commonly used.[11,12]

Pilocarpine is prescribed for use four times daily to lower IOP. It is recommended to start with the lowest concentration of pilocarpine, typically 1%, and increase the dose until the desired pressure-lowering effect is obtained. Pilocarpine binds to melanin in the iris and ciliary body, and iris color may influence IOP response. Eyes with darkly pigmented irides may require higher concentration of pilocarpine for maximum effect.[13] Pilocarpine shows an additive hypotensive effect when used in conjunction with β-blocking agents, alpha-2 adrenergic agonists, carbonic anhydrase inhibitors, and prostaglandin analogues.[14-19] Pilocarpine constricts the pupil and pulls the iris out of the angle and may therefore may be useful for the treatment of acute angle closure or widening of the angle in the plateau iris syndrome.[20]

Local side effects

Ocular side effects of cholinergic medications relate to muscarinic cholinergic receptors found in the iris, causing iris sphincter muscle contraction. In patients with cataract, pupillary constriction may worsen visual acuity and predispose to posterior synechiae, and in those with glaucoma, may aggravate visual field constriction. Anterior movement of the iris/ciliary body diaphragm may predispose to angle closure and transient worsening of myopia. In the young patient, ciliary body contraction can induce problematic fluctuating accommodative myopia and in many instances, brow ache or headache depending on individual tolerability.[21] Headaches may disappear with continued application.[21] Instillation of 2% pilocarpine causes an average accommodative myopia of 5.8 diopters in young patients. Increased permeability of the blood-aqueous barrier can result in severe inflammation when the drug is used postoperatively and in other inflam-

matory conditions.[22,23] Other ocular side effects include conjunctival hyperemia, dermatitis around the eyelids, retinal detachment, and annular ciliochoroidal detachment.[24-26]Attempts to minimize these effects have been made by altering drug formulations or delivery systems.

Systemic side effects
Muscarinic receptors are also located in the gastrointestinal tract, sweat glands, cardio-pulmonary system, and urinary tract. Thus, rare systemic side effects after topical administration of cholinergic agents may include nausea, vomiting, diarrhea, sweating, bradycardia, bronchial spasm, pulmonary edema and urinary frequency.[27-29]

Indications
Pilocarpine can be used for treating both primary open-angle glaucoma and primary angle-closure glaucoma following laser iridotomy.

Contraindications
Pilocarpine decreases the IOP through increasing trabecular outflow facility, therefore, applying this agent to the angle-closure glaucoma with 360 degrees of PAS in the angle is ineffective. As pilocarpine causes breakdown of blood aqueous barrier, it should not be used in the secondary glaucoma associated with uveitis. If it is used in the neovascular glaucoma, the contraction of iris and ciliary muscles by pilocapine produces severe ocular pain without any effect on decreasing the IOP. Pilocarpine may be contraindicated in eyes predisposed to rhegmatogenous retinal detachment.

Aceclidine

Aceclidine is a parasympathomimetic drug acting directly on the motor end-plate.[30,31] It induces contraction of longitudinal ciliary muscle more than circular ciliary muscle, increasing outflow facility with less accommodation than pilocarpine.[21,30-33] Aceclidine hydrochloride used topically in a strength of 2 or 4% is available in Russia, France, Italy and in several other countries of Europe, but not in the USA and Asian countries.

Efficacy
Aceclidine is less effective in decreasing IOP than pilocarpine on a concentration basis (*e.g.*, 4% aceclidine has the same ocular hypotensive effect as 2% pilocarpine).[34] Aceclidine is thought to induce less ciliary muscle spasm and accommodation than pilocarpine. It is less toxic than pilocarpine.[34] Aceclidine was found to produce slightly more powerful moisis than pilocarpine.[35]

Acetylcholine

Acetylcholine (often abbreviated ACh) is a neurotransmitter in the autonomic nervous system. Although not used for the medical treatment of open angle glaucoma, acetylcholine chloride (Miochol in the USA, Ovisot in Japan) is used intraocularly to induce rapid miosis during ocular surgery. Acetylcholine is supplied in a sterile vial contains dehydrated acetylcholine chloride. The diluent (usually sodium chloride) is mixed with the acetylcholine just before use because of the compound's instability.

Injection of 0.5 to 2 ml of 0.1 to 1% concentration of acetylcholine intracamerally produces miosis within a few seconds, it acts directly at the muscarinic receptor in the iris and ciliary smooth muscle very fast. However, cholinesterase in the anterior chamber also quickly inactivates it by hydrolysis, which makes this drug's acting time very short. It also has no effect as an eyedrop for medical treatment of glaucoma because of hydrolysis during penetration of the cornea. Administration of acetylcholine during cataract surgery not only induces miosis, but also reduces postoperative intraocular pressure elevations.[36-38]

Systemic and local side effects

Corneal edema, corneal clouding, and decompensation have been reported with the use of intraocular acetylcholine.[39] Systemic effects such as hypotension, sweating, bradycardia, and flushing occasionally have been noted.

Carbachol

Carbachol which was first synthesized in 1932 has been used for treatment of glaucoma.[40,41] Carbachol is different from pilocarpine in structure, but their actions are greatly similar. Carbachol is less permeable to cornea[42] and more resistant to hydrolysis by the cholinesterases than pilocarpine and gives it a longer duration of action. Carbachol has most of the same local side effects as pilocarpine, but they are somewhat more severe. Carbachol often is less well tolerated than pilocarpine. Carbachol is primarily used as eyedrop, but it is also used during ophthalmic surgery. Intraocular carbachol requires about two to five minutes to achieve maximum miosis and maintains it longer than acetylcholine. Intraocular carbachol not only produces prolonged miosis, but also results in a significant reduction in postoperative intraocular pressure after cataract surgery.[43]

Local side effects

Corneal clouding, bullous keratopathy, and increased postoperative iritis have been associated with the use of intraocular carbachol.[44] Intraocular carbachol can be toxic to the corneal endothelium and should be avoided in cases involving compromised endothelium.[45]

Indirect acting cholinergic agents

Indirect cholinergic agents inhibit acetylcholinesterase found in human ocular tissue.[46] The mechanism of improved outflow facility is presumed similar to that discussed for pilocarpine. Physostigmine is a reversible inhibitor, and available as an ointment. Echothiophate Iodide is an irreversible cholinesterase inhibitor and has a prolonged duration of action.[47] This advantage however is offset by adverse reactions such as systemic toxicity related to cholinesterase depletion with chronic therapy, including respiratory paralysis during general anesthesia with muscle relaxant use.[48] Local adverse effects include cataracts with anterior and posterior subcapsular changes that appear to be dose-related,[49] though the mechanism is unclear. Iris cysts may occur in children, and ocular inflammation and corneal toxicity are not uncommon in addition to effects common to cholinergic agents. For these reasons, indirect agents are usually reserved for patients who are pseudophakic or aphakic, if other options are not available.

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II Beta-blockers

Non-selective β-blockers

John H.K. Liu

There are three subtypes of β-adrenergic receptors; β-1, β-2, and β-3 receptors.[1] β-1 receptors are located mainly in the heart. Stimulation of β-1 receptors in the heart increases the rate and force of cardiac contraction. β-2 receptors are located in the bronchial, vascular, gastrointestinal, and genitourinary smooth muscles. Stimulation of these β-2 receptors causes relaxation of smooth muscles. β-3 receptors are found in adipose tissues and they are involved in lipolysis. Ocular β adrenergic receptors largely consist of the β-2 receptor subtype.[2]

β-adrenergic antagonists (β-blockers) are competitive inhibitors against the agonists for the β-adrenergic receptors. A β-blocker can be characterized as selective or non-selective based on the relative affinities for the specific receptor subtypes. While a selective β-blocker preferentially binds with one receptor subtype, the selectivity is not absolute. Selective β-blockers for a specific receptor subtype at high concentrations can bind with other β-receptor subtypes. Non-selective β-blockers, such as propranolol and timolol, bind equally well with both the β-1- and β-2-receptor subtypes. Most available β-blockers have a low affinity for the β-3-receptor subtype.

When an agonist binds with any β-adrenergic receptor subtype, a regulatory G-protein on the cell membrane is activated. This stimulates the enzyme of adenylate cyclase to convert adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP). Intracellular cAMP concentration increases, which acts as a second messenger in signal transduction via the protein kinase A pathway for specific cellular functions. One such cellular function in the ciliary processes is the production of aqueous humor. It has been demonstrated that adding a non-selective β-blocker to ciliary processes reduces intracellular cAMP concentration and inhibits aqueous humor formation.[3] Endogenous sympathetic tone provided by local catecholamines probably controls aqueous humor formation and exogenously given β-blockers interfere with aqueous humor formation and reduce IOP.[4]

The lowering of IOP through intravenous or oral administration of propranolol, a non-selective β-blocker, in glaucoma patients was first reported in 1967.[5] Potential development of propranolol as a topical IOP-lowering drug was limited by unwanted corneal anesthetic property. Instead, the development of another topical non-selective β-blocker, timolol, for lowering IOP took place.[6] Timolol maleate was approved for clinical use in the United States in 1978. Compared with common glaucoma medications available at that time, timolol eye drops demonstrated better efficacy, infrequent dosing, and minimal ocular side effects.[7,8] However, topical timolol treatment can cause severe systemic side effects.[9] With three decades of experience in the use of non-selective β-blockers including timolol, levobunolol, and metipranolol, their IOP-lowering efficacies are well established and the associated local and systemic side effects are well characterized.[10,11]

Efficacy

The non-selective β-blocker was the drug of choice for lowering IOP for many years until the introduction of prostaglandin analogues in the late 1990s. Today, the non-selective β-blocker remains a popular alternative for initial therapy and a choice for adjunctive therapy to lower IOP. Non-selective β-blockers can be used for virtually all forms of glaucoma and the IOP-lowering efficacy is additive to prostaglandin analogues, α-adrenergic agonists, carbonic anhydrase inhibitors, and cholinergics.

Mechanism of action

Non-selective β-blockers reduce aqueous humor formation. The rate of aqueous humor formation can be reduced as much as 50% during the day.[12-15] Resistance to aqueous humor outflow does not appear to be affected. It is known that nighttime aqueous humor formation is approximately half the daytime rate.[4] While timolol reduces daytime aqueous humor formation, it has very little effect on the already slow aqueous humor formation during the sleep period.[16] This specific

mechanism on aqueous humor formation translates to the IOP response accordingly; timolol does not significantly reduce nighttime IOP.[17-20]

Local side effects

Clinically available β-blockers should not cause corneal anesthesia.[21] Upon installation with topical β-blockers, burning and stinging occur to various extent. Transient blurred vision is common. Longer blur is expected for a gel-forming preparation such as Timoptic-XE. In addition, patients may be hypersensitive to certain components in the drug formulations.

Systemic side effects

After topical installation, β-blockers are absorbed via the nasal mucosa into the systemic circulation.[22] Blockage of β-adrenergic receptors in the heart by the circulating β-blockers leads to bradycardia, lower blood pressure, decreased myocardial contractility, and slower conduction time.[9,23-25] Compared to the use of timolol solution, plasma concentration and bradycardia associated with the use of gel-forming timolol preparation are reduced.[26-28] In addition, the systemic absorption and related side effects of a β-blocker can be reduced by nasolacrimal occlusion.[29]

Contraindications

Systemic adverse effects of β-blockers deserve serious clinical attention.[9,25,30,31] A careful review of the medical history is needed before prescribing a β-blocker to lower IOP. Patients with reactive airways disease (asthma, chronic obstructive pulmonary disease, etc) congestive heart failure, bradycardia, and heart block should not be treated with non-selective β-blockers. Communication among medical care providers can identify potential drug-drug and other drug-disease interactions.

Individual non-selective β-blockers

Timolol

Timolol lowers IOP in normal, ocular hypertensive, and glaucomatous eyes.[6,32-34] The onset of IOP effect after installation of timolol solution is about 30 minutes with the maximal IOP effect after two hours.[32,33] A significant IOP-lowering effect can persist for 12 hours with a measurable effect for 24 hours.[33] Topical timolol can cause significant contralateral IOP-lowering due to systemic absorption.[32,33,35] In patients who are already on the therapy with oral beta-blockers, timolol eye drops may produce little IOP-lowering effect.[36]

The IOP-lowering efficacy of timolol may decrease over time (tachyphalxis). A short-term escape in efficacy within a period of weeks may occur probably

due to the up-regulation of local β-adrenergic receptors. Over a longer period of months or years, the effect of timolol can taper off in some patients. It is unclear whether a poor adherence to the daily timolol treatment is involved in this long-term drift in IOP-lowering efficacy. After stopping timolol eye drops, the IOP-lowering efficacy of timolol may persist for many days. A 'washout' period of four weeks is generally required to eliminate any residual IOP effect.

In the United States, available timolol preparations include timolol maleate 0.25% (Timoptic), timolol maleate 0.5% (Istalolol, Timoptic), timolol hemihydrate 0.5% (Betimol), and gel-forming timolol maleate 0.25% and 0.5% (Timoptic-XE).[11] Timolol 0.1% is available in both solution and gel forms outside the United States. The pharmacodynamics and the profile of adverse effects are generally considered similar for different timolol preparations.[37] Timoptic-XE and Istalolol are recommended for once daily use. Other preparations are prescribed for once or twice daily. Although timolol 0.5% is commonly used, lower concentrations may be equally effective.[38] The 0.5% concentration may be needed to reach a full effectiveness in some patients with dark irides.[39] Although timolol can be used twice daily, once daily use is probably equally effective and preferable clinically.[40] In practice, starting with a lower timolol concentration, once daily dosing, and using nasolacrimal occlusion techniques may decrease systemic side effects.

Levobunolol

Levobunolol hydrochloride (Betagan) is a non-selective β-blocker available since 1985. Similar to timolol, levobunolol decreases IOP in eyes with elevated IOP.[41] The IOP effect begins within one hour and the maximal effect occurs in two to six hours.[42] Significant IOP-lowering effect can last for 24 hours.[42] Levobunolol is available in 0.25% and 0.5% concentrations. Once-daily levobunolol may be as effective as twice-daily treatment.[43,44] A metabolite of levobunolol, dihydrobunolol, has β-blocking activity and may explain the sustained effect of levobunolol.[45]

Metipranolol

Metipranolol 0.3% (OptiPranolol) is another non-selective β-blocker available since 1991. Its affinities for the β-1- and β-2-adrenergic receptors are about equal.[46] The IOP-lowering efficacy is similar to other non-selective β-blockers.[47,48] Onset of action is within 30 minutes, the maximal effect appears at two hours, and a detectable IOP-lowering effect persists for 24 hours.[49] Like levobunolol, an active metabolite of metipranolol, deacetylmetipranolol, may contribute to the prolonged IOP-lowering effect.[49]

Selective β-1-blocker

Betaxolol

Efficacy
Betaxolol, a selective β-1 blocker, is effective for lowering IOP.[50-53] However, the IOP reduction may be less than the non-selective β-blockers.[54-58] Due to the weaker efficacy in lowering IOP, the use of betaxolol is more likely to require adjunctive therapy. Betaxolol hydrochloride was introduced originally as a 0.5% solution in 1985 (Betotopic). Betaxolol 0.25% formulated as a suspension (Betoptic S) has been available since 1991 to provide a longer duration in IOP reduction. This preparation has the same IOP-lowering efficacy and may cause less ocular irritation than the betaxolol 0.5% solution.[59]

Mechanism of action
Betaxolol reduces aqueous humor formation and has no effect on the outflow resistance.[15,60]

Systemic side effects
Since β-adrenergic receptors on bronchial smooth muscles are the β-2 receptor subtype, betaxolol has a more favorable pulmonary side effect profile than non-selective β-blockers.[61,62] In patients with known reactive airway disease, the use of betaxolol is considered relatively safer than the non-selective β-blocker. However, the selectivity is relative and betaxolol still can cause pulmonary complications.

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III Alpha- and Beta-adrenergic Antagonists

Atsuo Tomidokoro

Some α1-adrenergic antagonists, as well as α2 agonists, have the potential to reduce intraocular pressure (IOP). Alpha 2 agonists primarily influence aqueous formation, while α1 antagonists have little effect on either aqueous formation or conventional outflow,[1] suggesting that α1 antagonists reduce IOP through an increase in uveoscleral outflow. Some β-adrenergic antagonists, including amosulalol, aritinolol, labetalol, carvedilol, bucindolol, and nipradilol, are known to have α-adrenoceptor blocking action and many of them are widely used as systemic medications for hypertension or heart failure. Among them, 0.25% topical nipradilol has reported IOP reducing effects and nipradilol has been registered as an antiglaucoma ophthalmic solution since 1999 in Japan. Levobunolol, which is a more globally used antiglaucoma β antagonist, has been reported to show α1 blocking activities in rabbits.[2-3]

Nipradilol

Nipradilol has non-selective β-receptor and selective α1-receptor blocking properties[4-5] with a nitric oxide (NO) donative action.[6]

Mechanism of action

Nipradilol has β-blocking action which reduces aqueous formation in the ciliary body and α-blocking action which further reduces IOP through an increase in uveoscleral outflow.[7-8]

Efficacy

The IOP lowering effect of nipradilol is comparable with that of topical 0.5% timolol and plays a similar role in glaucoma management.[7-10]

Local and systemic side effects

The incidence of local side effects of nipradilol is similar to that of timolol.[11] The results of pharmacokinetic analysis for systemic β1 and β2 receptors after topical instillation of nipradilol (27% and 9%, respectively)[12] were considerably lower than those of other usual β-blockers (ex. 62% and 82% for timolol),[13] suggesting lower risk of systemic side effects of nipradilol.

Indications and contraindications

Indications and contraindications are basically same as those of other non-selective β-blockers.

Possible effects on neuroprotection and ocular blood flow

Nipradilol has been reported to have a neuroprotective effect *in vivo* and *in vitro*[14,15] It also increases blood velocity in the optic nerve head (ONH) evaluated with the laser speckle method[8,16] Topically instilled nipradilol can reach the posterior periocular tissue at pharmacologic concentration (equivalent concentration = 140 ng/g in the periocular tissues around the optic nerve insertion 60 minutes after the instillation in monkey[16] and 320 ng/g in the retina-choroid 30 minutes after the instillation in rabbits.)[14] However, a recent randomized controlled trail including 146 normal-tension glaucoma patients confirmed that no significant differences between the nipradilol-treated and timolol-treated arms were found in either IOP reduction or visual field progression over the three-year study period.[9]

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Beta-Blockers with intrinsic sympathomimetic activity

Allison Ungar, Gadi Wollstein and Joel S. Schuman

Carteolol

Mechanism of action (MOA)

Carteolol is a non-selective β-adrenergic antagonist with intrinsic sympathomimetic activity (ISA). This drug inhibits aqueous secretion at the ciliary epithelium by blocking the β-adrenoceptors. The proposed mechanism of ISA from human studies is through the β2-adrenoceptors. There is some debate over

whether carteolol's main metabolite, 8-hydroxy-cateolol, contributes to the ISA.[1] In theory, carteolol's ISA should be advantageous in lessening the respiratory and cardiovascular effects from β-blockade after systemic absorption. The ISA may also be helpful locally by maintaining or improving ocular blood flow through vasodilatation or minimization of vasoconstriction.[2]

Standard vs. long-acting formulation

The long-acting formulation has the same mechanism of action. However, the long-acting formulation utilizes alginic acid resulting in increased precorneal residence time.[3]

Efficacy

Reduction of IOP: Carteolol is well established to significantly reduce IOP, and has been reviewed thoroughly. It is effective in this regard for both ocular hypertension and primary open-angle glaucoma.[4]

Carteolol vs. other ocular β-adrenoceptor antagonists

Carteolol has similar IOP lowering effects and efficacy at preventing visual field loss as timolol[5-8] and metipranolol.[8] In contrast, levobutnolol has shown to have a greater age-adjusted IOP-lowering effect than carteolol.[9]

Combination therapy

In a study of patients with primary open-angle glaucoma and normal-tension glaucoma, combining carteolol with latanoprost was more effective at lowering IOP than was latanoprost alone or nipradilol with latanoprost.[10]

Long-term treatment

A seven-year longitudinal study demonstrated that in newly diagnosed POAG patients, carteolol maintains visual fields with similar efficacy to timolol and betaxolol.[11]

Standard vs. long-acting formulation

The once daily carteolol alginate shows equivalent IOP lowering to that of the standard formulation.[12] Troughs for standard and long-acting formulations at 12 and 24 hours, respectively were equivalent.[1]

Ocular blood flow

Some studies have shown carteolol to increase blood flow velocity in the posterior ciliary artery, the ophthalmic artery, and the central retinal artery when used to treat primary open angle glaucoma[13,14] and normal-tension glaucoma.[15]

Systemic side effects

Cardiovascular – blood pressure/heart rate
Ocular carteolol has shown to decrease both systolic and diastolic blood pressure and heart rate. Notably, carteolol is less likely than timolol to induce nocturnal bradycardia and cause cardiovascular adverse events overall.[16]

Respiratory
Ocular carteolol has shown to decrease vital capacity and FEV_1 in asthmatics. Most clinical trials have excluded individuals with respiratory disease.[1] One comparative study examining FEV_1 found no difference from baseline or between the groups treated with carteolol, timolol, and meipranolol.[8]

Lipids
Ocular carteolol has not shown to have deleterious effects on the lipid profile.[17-19]

Other systems – digesitive, metabolic, nervous, special senses, urogenital
No significant differences have been shown between carteolol and timolol in regards to the digesitive, metabolic, nervous, special senses, or urogenital systems.[16]

Standard vs. long-acting formulation
There are no significant differences between the two formulations in regards to cardiovascular and respiratory changes.[11]

Local side effects

Carteolol vs. other ocular β-adrenoceptor antagonists
Ocular carteolol has shown similar local side effects such as burning, stinging, tearing, ocular pain, blurred vision, itching, and conjunctical hyperaemia when compared to timolol, meripranolol, and levobunolol.[1] One study reported the overall frequency of reported ocular symptoms to be significantly greater with timolol than with carteolol.[5]

Standard vs. long-acting formulation
The two formulations have been found to have similar ocular side effect profiles.[12] Notably, the long lasting formulation has a low incidence of blurring, which can be problematic with other long-acting formulations.[3]

Indications and dosing

Carteolol is a first-line agent for treating primary open-angle glaucoma and ocular hypertension. Standard carteolol is available in 1 or 2% concentration dosed twice daily. Long-acting carteolol is dosed once daily.

Contraindications

Individuals at risk for bronchospasm should avoid using carteolol.

Pindolol

Mechanism of action

The mechanism of pindolol is similar to that of carteolol (see above). It is also a non-cardioselective β-adrenergic blocking agent with ISA.

Efficacy

Several small studies have shown ocular pindolol to decrease intraocular pressure as well as timolol.[20,21] In another small study, on average pindolol decreased IOP by 2.79% more than saline.[22]

Systemic side effects

In a small clinical study, serum levels of pindolol were undetectable after treatment.[21] No changes in heart rate or blood pressure have been reported after administration of ocular pindolol.[22,23]

Local side effects

Pindolol has not been found to affect pupil motility or corneal sensitivity.[24]

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Carbonic anhydrase inhibitors

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Mechanism of action

The several carbonic anhydrase (CA) isoenzymes in the body catalyse the hydration and dehydration of carbon dioxide. In the eye, CA is a key enzyme in aqueous humour production. Two isoenzymes of CA (II and IV) are present in the ciliary processes. CA catalyzes the primary reaction in the following sequence:

$$CO_2 + H_2O \rightarrow H_2CO_3 \rightarrow H^+ + HCO_3^-$$

HCO_3^- provided by this reaction sequence is essential for the active secretion of aqueous humor. It has been demonstrated that inhibition of the production of HCO_3^- leads to an inhibition of active transport of Na^+ across the non-pigmented epithelium, thereby reducing active aqueous humor formation.[1] Thus, inhibition of the CA activity in the ciliary processes causes decreased aqueous humour secretion, which in turn leads to lowering of the intraocular pressure (IOP).[2,3] Inhibition of > 99.9% of the activity of isoenzyme II of carbonic anhydrase in ciliary epithelium is required to achieve adequate IOP reduction. When systemic acetazolamide is given orally, the IOP decrease is already detectable at 30 minutes after administration, reaches its peak at two hours and lasts at least for six to eight hours. The washout time of the systemic CAIs is three days.[4] In contrast to the relatively non-selective acetazolamide, the topical CAIs (dorzolamide and brinzolamide) have a special affinity for CA II.[2,5,6] The selectivity of the topical CAIs for CA II is considered to be the explanation for their smaller IOP-lowering efficacy as compared to that achieved by acetazolamide, which acts non-selectively on both CA II and IV isoenzymes.

Drug formulation, indications and efficacy

Five different CAI molecules have been used in clinical practice to reduce elevated IOP in glaucoma (Table). Acetazolamide, methazolamide, and dichlorphenamide are administered systemically (orally or intravenously).[2,3] Brinzolamide and dorzolamide are applied topically.[2] For more than 50 years, this category of medication has been an important option in some glaucoma patients who

remain resistant to alternative treatment. It is the only category that can be administered as either a topical or a systemic agent. The availability of topical CAIs has significantly diminished the use of systemic CAIs in the last decades; however, systemic CAIs are still important and useful in specific circumstances, such as the very young who are awaiting surgery, when the administration of topical medication may be problematic for elderly patients, and when the urgent IOP reduction is needed. The indications for topical CAIs are broader than the indications for systemic CAIs. In most cases, topical CAIs work well as adjunctive agents rather than first-line agents. However, topical CAIs could be considered as first-line agents in special instances when first-line agents are not well tolerated.

Table. Dosage and administration of carbonic anhydrase inhibitors

Drug	Tradenames		Route
Acetazolamide	Diamox, Diamox Sequels, Diamox Retard	125-, 250-mg tablet 500-mg slow release capsule	Oral/intravenous
Methazolamide	Neptazane	25-, 50-mg tablet	Oral
Dichlorphenamide	Daranide, Antidrasi	50-mg tablet	Oral
Brinzolamide	Azopt	1%	Topical
Dorzolamide	Trusopt	2%	Topical

Systemic CAIs: acetazolamide, methazolamide and dichlorphenamide

Acetazolamide (*e.g.*, Diamox™) is formulated for oral use (250 mg/tablet) and for intravenous administration (500 mg/ml). It is also prepared in 500 mg slow drug-release capsules (Diamox Retard™ or Sequel™) which can be given once daily. Methazolamide (Neptazane™) tablets (50 mg) are less frequently used than acetazolamide. The usual daily dosage of methazolamide varies between 100 and 150 mg. Dichlorphenamide (Daranide™) is produced in 50-mg tablets. The daily dosage of this rarely-used molecule is 100 to 150 mg.[3]

Topical CAIs: dorzolamide and brinzolamide

Dorzolamide hydrochloride 2% (Trusopt™) was the first topically-applied CAI.[2,5] It is formulated in a solution of acidic pH (pH = 5.6), which is necessary for good ocular absorption. Cosopt™ is the fixed combination of dorzolamide 2% and timolol 0.5%.[7]

Brinzolamide 1% (Azopt™) is highly lipophilic, which promotes its corneal penetration. In Azopt™ the active ingredient (brinzolamide) is dissolved in a viscous ophthalmic suspension (carbomer), which allows a long contact-time with the ocular surface, with close to physiological values for pH (pH = 7.5) and osmolality (300 mOsm/kg). Azarga™ is the fixed combination of brinzolamide 1% and timolol 0.5%.[8,9]

Table 1. The clinically most important characteristics of dorzolamide and brinzolamide BAC; benzalkonium chloride

	Dorzolamide	Brinzolamide
Formulation	solution	suspension
Concentration	2%	1%
Number of daily instillations	2 to 3	2 to 3
pH	5.6	7.5
Osmolality	data not available	300 mOsm/kg
BAC concentration	0.0075%	0.01%
Site of the ocular absorption	cornea	cornea
Washout duration	1 week	1 week

Use of acetazolamide is generally restricted to the above-mentioned situations where it is necessary to achieve acute IOP reduction; however, in intractable glaucoma its long-term use may become necessary.[3,10] The required daily dosage varies between one and four tablets (up to 1000 mg per day). The maximum acetazolamide-induced IOP decrease is approximately 40%. To prevent systemic hypokalaemia consequent to increased diuresis, acetazolamide may be given together with oral potassium supplementation. For long-term therapy, topical CAIs are preferred.[2]

The IOP decrease provided by dorzolamide and brinzolamide is very similar. In monotherapy, the peak IOP reduction (at two hours after instillation) varies between 16.3% and 22.9%, and the 12-hour trough reduction is between 13.2% and 18.9% in primary open-angle glaucoma and ocular hypertension.[2] A meta-analysis of randomized clinical trials showed that the reductions of IOP from baseline were -22% (range, -24% to -20%) for 2.0% dorzolamide as a peak reduction and -17% (-19% to -15%) at trough, -17% (range, -19% to -15%) for 1.0% brinzolamide as a peak reduction and -17% (-19% to -15%) at trough. These are generally lower than with other commonly-used classes of IOP lowering drugs. IOP reductions from baselines for 0.5% timolol were peak, -27% (-29% to -25%), and trough, -26% (-28% to -25%); for 0.5% betaxolol were peak, -23% (-25% to -22%), and trough, -20% (-23% to -17%); and for 0.005% latanoprost were peak, -31% (-33% to -29%), and trough, -28% (-30% to -26%).[11] In another meta-analysis, the rank of glaucoma drugs was studied according to their intraocular pressure (IOP)-reducing effect in POAG and OH.[12] At peak, the rank order from high to low in terms of the mean IOP reduction reached was bimatoprost, travoprost, latanoprost, brimonidine, timolol, dorzolamide, betaxolol, and brinzolamide. At the trough, this rank order was bimatoprost, latanoprost, travoprost, timolol, betaxolol, dorzolamide, brinzolamide, and brimonidine. A similar result was reported in NTG.[13] These results show that the efficacy of dorzolamide and brinzolamide are similar and comparable to betaxolol, but are less effective compared to timolol and prostaglandin analogues in POAG, OH, and NTG. The long-term IOP lowering efficacy of topical CAIs is stable; no long-term drift phenomenon has been reported. Topical CAIs are most frequently used in fixed or unfixed combinations with topical beta-receptor blockers.[2,3,14,15]

Additivity of topical CAIs to other IOP lowering drug classes is summarised in Table 2. It has been reported that as adjunctive therapy to latanoprost, brinzolamide produced significantly lower IOP than timolol.[16] This may be related to the mechanism of action of the prostaglandin derivatives, which increase the uveoscleral outflow but also increase the activity of CA in ciliary epithelium with a secondary increase in aqueous humor secretion. Topical CAIs may be effective as adjunctive therapy with a prostaglandin by blocking prostaglandin-mediated aqueous production.[17]

Table 2. Additive effects of topical CAIs used with other IOP-lowering drugs[7]

Topical CAI added to	**Additivity**	**Comment**
Topical beta-receptor blockers	YES	Clinically useful combination Combined preparation available
$PGF_{2\alpha}$ analogues	YES	Clinically useful combination
Pilocarpine 1% or 2%	YES	Small additional IOP decrease
Systemic CAIs	NO	No additional IOP decrease

Clinical benefits of the influence of CAIs on ocular blood flow

Because CAIs could give rise to metabolic acidosis with secondary vasodilatation and improvement of blood flow, considerable attention has been paid to the effects of CAIs on blood flow. Systemic acidosis can occur in the setting of oral CAI therapy, and local acidosis within ocular tissues is theoretically possible with topical CAI therapy, with the potential for a local increase in ocular blood flow.[18] Because systemic acidosis can promote sickling of red blood cells in persons with sickle cell anaemia, these drugs should be used with caution in such individuals.

Several animal studies indicated that intravenous acetazolamide increases blood flow in the retina and choroid.[19,20] In normal subjects, intravenous acetazolamide was also reported to improve retinal blood flow;[21] conversely, other studies in normal subjects indicated little ocular perfusion effects despite decreased IOP after acetazolamide administration.[22,23] As for the ocular perfusion effects of topical CAIs, reported effects in experimental animals, normal subjects, and primary open-angle (POAG) and normal-tension glaucoma subjects are conflicting: dorzolamide was reported to show significantly beneficial effects in some studies, while insignificant effects in other studies.[20] Though two color Doppler imaging studies failed to find significant effects of dorzolamide and brinzolamide on the retrobulbar hemodynamics in both normal and POAG subjects,[24,25] it has been reported that brinzolamide showed increased retinal oxygen saturation in POAG subjects.[25] In the European Glaucoma Prevention Study (EGPS), a multicenter, randomized, prospective study to explore the conversion from ocular hypertension to glaucoma, the preventive effect of 2% dorzolamide was studied. Although dorzolamide reduced IOP by 15% to 22% throughout the five-year follow-up period, there was no statistically significant difference be-

tween medical therapy and placebo in reducing the incidence of POAG among a large population of OHT patients at moderate risk for developing POAG.[26]

A beneficial effect of dorzolamide has been reported for treatment of cystoid macular edema (CME) in patients with retinitis pigmentosa (27-29). It is thought that acidification of the subretinal space induced by CAIs is responsible for the increase in fluid resorption from the retina through the RPE into the choroid (30). Dorzolamide was shown to be effective in improvement of cystoid macular edema, and it is noteworthy that topical CAIs have effects on both retinal and retinal pigment epithelial cell function. However, oral acetazolamide was reported to be more effective than dorzolamide in managing macular edema and improving visual acuity (27). In conclusion, although CAIs have been suggested to be able to improve ocular perfusion, no evidence-based information is available at present to suggest any clinical benefit related to ocular perfusion effects of CAIs in glaucoma.

Contraindications and side effects

Systemic contraindications

Since all CAIs are sulfonamide derivatives, cautions and contraindications against sulfonamides are relevant for CAIs.[2,3] Thus, CAIs are contraindicated in cases of known sulfonamide allergy. CAIs are excreted predominantly by the kidney. Therefore, in patients with severe renal impairment (CrCl < 30 ml/min) caution is indicated, especially when systemic CAIs are given.[10] CAIs are contraindicated in situations in which sodium and/or potassium blood levels are depressed (*e.g.*, kidney and liver dysfunction, suprarenal gland failure, and hyperchloremic acidosis). Pregnancy and lactation represent a relative contraindication against the use of CAIs, since no adequate studies have been conducted on pregnant and nursing women. The CAIs are excreted with the milk,[2] and therefore they may influence the red blood cell CA activity in the newborn. The potential influence of severe hepatic impairment on the CAI metabolism needs to be clarified.[2]

Systemic side effects

The systemic side-effects of CAIs can appear in acute form due to hypersensitivity (*e.g.*, Stevens- Johnson syndrome), or can develop gradually, due to dose-dependent systemic alterations which can be reversible after the CAI medication is stopped. CAI-induced severe blood dyscrasia (agranulocytosis, thrombocytopenia, aplastic anaemia or pancytopenia) has reportedly resulted in 120 lethal cases over 40 years[2,31,32] These reactions are attributed to systemic CAIs; but thrombocytopenia has also been reported in a very small number of patients using topical dorzolamide.[33] In these cases the outcome was less severe than reported in connection with acetazolamide, and the thrombocyte production recovered after cessation of the topical CAI treatment. In order to be able to detect the above-mentioned potential side-effects in good time, repeated

haematological laboratory testing may be of benefit during chronic treatment with systemic CAIs. The less serious adverse effects (fatique, paraesthesia, headache, gastrointestinal side effects, taste perversion, bitter taste feeling, decreased appetite, renal stone formation, malaise and acidosis) are common during long-term systemic CAI medication, but are relatively rare and less severe under topical CAI treatment.[2,30] Even topically applied CAIs accumulate in red blood cells and inhibit approximately 21% of the CA II content of the cells.[2] In newborns or premature newborns with foetal haemoglobin, it may lead to acidosis.[35] Thus, administration of topical CAIs in newborns requires special caution. In diabetes mellitus, acetazolamide-induced acidosis may worsen the hyperosmolar status.[36] Additive side effects or increased toxicity have been reported for systemic CAIs taken together with systemically administered cyclosporine, digitalis, lithium, aspirin (increased toxicity) and diuretics (increased potassium loss). Systemic acetazolamide decreases the effects of oral antidiabetics, and diminishes cholinesterase activity.[1,37] The most important systemic side effects are summarised in Table 3.

Table 3. Systemic side effects of the systemic and topical CAIs

Type of the side effect	**Systemic CAIs**	**Topical CAIs**
Blood dyscrasia	YES	Rare, less severe
Bitter taste	YES	YES
Gastrointestinal complaints	YES	Rare, less severe
Paraesthesia	YES	Rare, less severe
Renal stone formation	YES	Rare, less severe
Acidosis	YES	YES, in immature newborns

Ocular side effects

Choroidal detachment and transient myopia are known infrequent side effects of the sulfonamide derivatives, which can occur under either systemic or topical CAIs medication. A rare allergic complication of topical dorzolamide is marginal keratitis, which resolves spontaneously after withdrawal of dorzolamide. Periorbital contact dermatitis and allergic conjunctivitis are much more common complications of topically applied dorzolamide.[38] Though periorbital dermatitis and allergic conjunctivitis recover soon after the dorzolamide exposition is stopped, it reappears if a CAI is later introduced in the topical medication. Thus, periocular CAI allergy in the history represents a contraindication against any topical CAI medication. Due to reduction of the corneal CA II activity, topical CAIs can show an adverse effect on corneal endothelial cell function by inhibiting the bicarbonate pump and worsen the status of the compromised corneas with decreased endothelial cell number and function (*e.g.*, in Fuchs' dystrophy, decreased endothelial cell density due to complicated cataract surgery). It is reported that the corneal thickening was induced by topical CAIs application in patients with a compromised corneal endothelial cell layer.[39] This can lead

to manifest cornea decompensation which is not necessarily reversible after the withdrawal of the CAI molecule from the treatment.[2]

To optimize solubility, dorzolamide is formulated in a solution with a pH of 5.6; as a result, the primary ocular adverse event reported with its use is transient stinging and burning of the eyes upon instillation. Brinzolamide is formulated as a suspension with a neutral pH; its primary ocular adverse event is transient blurred vision upon instillation. Both drugs are associated with a transient bitter aftertaste.

Pregnancy and pediatiric patients

In pregnancy, systemic and topical CAIs (as with any drug) are only to be used if the potential benefit justifies the potential risk to the fetus or the infant. In children, it is reported that oral CAIs administration can cause growth retardation and metabolic acidosis.[40] A study of pediatric glaucoma patients (3 to 12 years of age) showed that both systemic acetazolamide and topical dorzolamide were effective at lowering IOP (36% vs. 27%).[41] Topical CAI treatment is preferred unless systemic administration is found to be more effective or adverse reactions occur.

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IV Alpha-adrenergic Agents

Non-selective alpha-adrenergic agonists

Atsuo Tomidokoro, Makoto Araie

Alpha-adrenergic receptors are widely distributed in the human body and 3 alpha-1 adrenoceptor subtypes (α1A, α1B and α1D), 3 alpha-2 adrenoceptor subtypes (α2A, α2B and α2C) have been cloned and all these receptors conform to the G protein-coupled receptor paradigm.[1] In binding studies, α1A and α2A adrenoceptors were dominant subtypes in ocular tissues.[2-5] Non-selective alpha agonists, including epinephrine and its prodrug form (dipivefrin), are glaucoma medical therapies with long history of more than a century. Though their use has been gradually waning due to the development of new medications showing greater intraocular pressure (IOP) reduction, the drugs are still commercially available and are employed for open-angle glaucoma patients in many countries.

Dipivefrin is the prodrug form of epinephrine, in which two pivalyl acid chains are esterified with epinephrine to increase the lipophilicity of the molecule. The passage of dipivefrin through the cornea into the anterior chamber is 17 times higher than epinephrine.[6] Because of the lipophilicity, less epinephrine is contained in each drop of dipivefrin, resulting in fewer external and systemic side effects.

The mechanism of IOP reduction by non-selective alpha agonists is still controversial in spite of their long histories. The IOP reduction should be achieved through the balance between the stimulation of alpha receptors and that of beta receptors in the processes of aqueous formation and its outflow. The alpha stimulation causes vasoconstriction in the ciliary process and reduces the ultrafiltration pressure, resulting in reduction in aqueous formation. On the other

hand, the beta stimulation in the ciliary epithelium can increase the aqueous formation.[7,8] In the aqueous humor outflow system, non-selective adrenergic agonists increase in both conventional[9,10] and uveoscleral[7,8] outflow, resulting in lowering of IOP. Several studies suggest that these mechanisms should be associated with productions of prostaglandins[11-13] and cAMP.[14]

Onset of IOP reduction by topical epinephrine occurs at 1 hour with a peak effect at 4 hours. The effect usually continues 12 hours, and thus twice daily dosing schedule is recommended. Because many patients show a maximal IOP reduction with lower concentration of epinephrine,[15,16] the therapy should be started with a lower concentration and increased if necessary for achieving sufficient IOP reduction. At the initiation of the epinephrine therapy, a monocular trial may be beneficial since the drug has a slight IOP reducing effect on the contralateral untreated eye.

When adding epinephrine to non-selective beta-adrenergic antagonists, additive IOP lowering effects are reportedly little compared to monotherapy of the beta-blockers.[17,18] On the other hand, the concomitant use of epinephrine with a beta-1-selective blocker, betaxolol, shows significant additive IOP reduction, though the combined effect is less than the sum of the IOP reduction by either agent alone.[19-21] The combination of non-selective alpha agonists and prostaglandin analogues can be also useful. Dipivefrin has additive effect on IOP when adding to monotherapy of latanoprost.[22,23]

It is reported that at least 50% of glaucoma patients with use of topical epinephrine become intolerant to the therapy[24] mainly due to its external adverse effects. The most common side effects are hyperemia, tearing, irritation, and hypersensitivity blepharoconjunctivitis. Hyperemia results from an initial vasoconstriction by a rebound vasodilation. Some patients who develop epinephrine-related hypersensitivity blepharoconjunctivitis can often tolerate dipivefrin without similar symptoms,[25] while others demonstrated cross-sensitivity.[26] Adrenochrome deposits, which are a kind of black melanin pigmentation, are often found in patient using topical epinephrine for a long term. Cystoid macular edema is reportedly observed in approximately 10 to 20% of aphakic eyes after topical epinephrine therapy.[27-29] A case of macular edema after topical dipivefrin therapy in a phakic eye was also reported.[30] Though dipivefrin is more stable in solution and produces a lower incidence of external side effects compared to epinephrine, it can also develop external side effects including giant follicular bulbar conjunctivitis.[31]

Topically instilled epinephrine can cause systemic side effects, including tachycardia, palpitations, arrhythmias, and hypertension because of its systemic absorption. It is reported that cardiac side effects and headache were found in 25%[32] and 10%[24] of patients, respectively, who were receiving topical epinephrine therapy. To reduce the systemic side effects, the lowest concentration of the drug possible for IOP reduction should be initially prescribed and punctual occlusion and gentle eye lid closure after instillation should be also useful. Topical epinephrine is contraindicated in patients with severe hypertension, cardiac diseases, and thyrotoxicosis. Dipivefrin may cause fewer systemic side

effects compared with epinephrine because of the lower concentration of drug administrated.

As to clinical indications, epinephrine and dipivefrin are usually used as adjunctive therapy when the initial therapy is not satisfactory in IOP reduction or used in patients in whom other glaucoma medications are contraindicated. Epinephrine and dipivefrin can be used in patients with asthma, in young patients intolerant of miotics, and in those with cataract since larger pupil may improve the view around the lens opacities.

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Selective alpha-adrenergic agonists

Arthur Sit

Selective alpha-adrenergic agonists are differentiated from non-selective alpha-adrenergic agonists by their relative binding affinity for one of the receptor types. For glaucoma medications, the alpha-2 receptor type is the target for alpha-agonists. Three selective alpha-adrenergic agonists have been used for the treatment of glaucoma: clonidine hydrochloride, apraclonidine hydrochloride, and brimonidine tartrate. While each of these medications is relatively selective for the alpha-2 receptors, they do retain some alpha-1 activity. However, the degree of selectivity for alpha-2 compared with alpha-1 receptors is high-

est with brimonidine, followed by clonidine and apraclonidine. Radio-ligand binding assays and tissue bath assays indicate that ratio of alpha2-binding to alpha1-binding for brimonidine, clonidine and apraclonidine was 1812, 183, and 72 times, respectively.[1]

Mechanisms of action

The primary mechanism of action for IOP reduction with selective alpha-adrenergic agonists appears to be reduction of aqueous humor production. Lee et al. found that clonidine reduced aqueous humor flow by 21% in clonidine 0.125% treated eyes as compared to fellow placebo-treated eyes.[2] Apraclonidine also reduces aqueous flow, but the degree of reduction appears to vary significantly based on the individual study. Toris *et al.* found that aqueous flow was reduced by 12%, while Brubaker and colleagues found that aqueous flow was reduced by 35-44% compared with baseline. Brimonidine has also been demonstrated to reduce aqueous flow, with the magnitude of reduction ranging from 20% to 48% in various studies.[3-8] Reduction of aqueous flow in animal models has been shown to be even greater, with rabbits having a 70% reduction.[1, 9]

Although reduction of aqueous flow appears to be the main mechanism for IOP reduction with alpha-2-agonists, other mechanisms have been demonstrated as well. Krieglstein *et al*.[10] demonstrated a reduction in episcleral venous pressure (EVP) with clonidine. Interestingly, topically applied clonidine appeared to reduce EVP in both the ipsilateral and contralateral eyes, suggesting a central as well as peripheral effect. Toris *et al*.[11] found that apraclonidine increased outflow facility calculated from fluorophotometry, and decreased EVP, as well as decreasing aqueous flow. In contrast, Maus *et al*.[5] did not find any difference in flow resistance with either apraclonidine or brimonidine. An increase in uveoscleral outflow has also been reported in some studies with brimonidine, in both human subjects[4] and animal models.[1]

Neuroprotection

In addition to reduction of IOP, selective alpha-2-agonists (and brimonidine in particular) have been suggested as having direct neuroprotective effects. Alpha-2 adrenergic receptors (Alpha-2a subtype) have been identified in the human retina, indicating the presence of a plausible target.[12,13] Using a chronic ocular hypertensive rat model, in which the episcleral and limbal veins are photocoagulated, subcutaneous injection of brimonidine improved retinal ganglion cell survival without significantly reducing the IOP.[14,15] Similar promising results have been demonstrated in rat models of ischemia induced RGC death, in which the ophthalmic vessels are transiently ligated,[16] and optic nerve crush models.[17] Proposed mechanisms for neuroprotection include inhibition of pro-apoptotic mitochondrial signaling, and activation of anti-apoptotic pathways.[13] At the present time, no clinical trials have demonstrated a neuroprotective effect of brimonidine in humans beyond the effect of IOP reduction.

Efficacy

All three selective alpha-adrenergic agonist medications have demonstrated significant reductions in IOP compared to controls.

Clonidine

Harrison *et al*.[18] compared the effects of a single drop of clonidine 0.125% and 0.25% against a placebo and pilocarpine 2% in a double-masked cross-over study of 21 open-angle glaucoma patients. Clonidine 0.125% and 0.25% had onset of effect starting at 154 minutes and 135 minutes, with a duration from onset of 201 minutes and 270 minutes, respectively. The peak IOP reduction for clonidine 0.125% and 0.25% was 6.8 mmHg and 7.6 mmHg at 203 minutes and 238 minutes from baseline, respectively.

Hodapp *et al*.[19] also demonstrated a significant IOP reduction with clonidine, with a slightly greater reduction using 0.25% than with 0.125%. The duration of action was at least six hours for the 0.125% and at least 8 hours for the 0.25%. The authors also reported a small contralateral reduction in IOP independent of reduction in blood pressure when using clonidine 0.25% every 8 hours. Based on diurnal measurements of IOP, the maximum IOP reduction with clonidine 0.25% was 4.4 ± 6.1 mmHg occurring at mid-day, after correcting for effects from placebos.

Apraclonidine

Robin[20] evaluated the short-term effect of apraclonidine 1% and found an onset of action within one hour, with a peak IOP reduction of 6.5 ± 4.3 mmHg (37.3% ± 20.4%) occurring between three to five hours after administration. In a longer term study, Abrams *et al*. evaluated the efficacy of apraclonidine 1% given twice daily for one month.[21] After 12 hours, the trough effect was still significant, with a reduction of IOP between 20-30% from baseline.

Brimonidine

Derick *et al*.[22] assessed the dose response of brimonidine 0.08%, 0.2%, and 0.5% during a one-month double-masked placebo controlled study. They found that the maximum mean IOP decreases from baseline for the 0.08%, 0.2%, and 0.5% doses were 20.8%, 27.2%, and 30.1%, respectively, using twice a day dosing. However, the authors recommended the 0.2% concentration since it was close to the top of the dose response curve with fewer systemic and local side-effects. All of the concentrations of apraclonidine showed a decrease in efficacy over time, stabilizing after about 14 days. A subsequent study by Katz *et al*.[23] compared twice daily brimonidine 0.2% with timolol 0.5% over a period of one year. The authors found that using twice daily dosing of brimonidine 0.2% resulted in a peak (two hours after dose) IOP reduction of 6.7 mmHg while

the trough (12 hours after dose) IOP reduction was 4.3 mmHg. Brimonidine is currently approved by the United States Food and Drug Administration for three-times-daily usage.

Systemic and local side effects

Local side effects with selective alpha-agonists are common.[24,25] Conjunctival blanching occurs due to binding on the alpha-1 receptors of blood vessels. Mild lid retraction likely occurs due to the alpha-1 stimulation of Müller's muscle. Mydriasis may also occur in a portion of eyes treated with apraclonidine. In contrast, topical Clonidine can produce a significant miosis in treated eyes as well as contralateral.[2]

Allergic conjunctivitis and dermatitis are the most common reasons for discontinuing chronic therapy with selective alpha-adrenergic agonists. Apraclonidine appears to have a higher rate of allergy with chronic use compared with brimonidine. Some studies have found that the rate of follicular conjunctivitis as high as 36% with apraclonidine 0.5%.[24] In comparison, long-term studies with brimonidine 0.2% were found to have ocular allergy rates of 12.7%.[23] As well, lower allergy rates have been reported with brimonidine 0.15% using Purite (Allergan, Irvine, CA) as the preservative instead of benzalkonium chloride.[26]

All the selective alpha-agonists can produce systemic side-effects. These include dry mouth, sedation, systemic hypotension and bradycardia. Dry mouth is likely a local effect due to direct absorption through the nasolacrimal system causing vasoconstriction of the nasal and oral mucosa.[24] Other systemic side effects are likely due to medication crossing the blood-brain barrier. The potency of these effects appears to be related to the lipophilic nature of the medication. Both clonidine and brimonidine are highly lipophilic and can easily cross the blood-brain barrier resulting in significant sedation, hypotension and bradycardia. These systemic side effects are less frequent with brimonidine than clonidine.[22,23] In contrast, apraclonidine is lipophobic and systemic side-effects uncommon, occurring at a similar rate to placebo.[20] Because of the rapid onset of action and minimal systemic side-effects, apraclonidine is commonly used to treat IOP spikes after laser trabeculoplasty or peripheral iridotomy.

Brimonidine is the most widely used of the three existing selective alpha-adrenergic agonists. However, it is not approved for use in children and systemic side-effects appear to be common, with one study reporting lethargy in 76% of patients.[27] Other authors have reported similar results with cases of severe somnolence in younger children.[28]

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Alpha-adrenergic antagonists

Makoto Araie

Although only one α adrenoceptor antagonist (α-1 adrenoceptor antagonist, bunazosin) is currently used clinically for glaucoma therapy in Japan,[1,2] several α-adrenoceptor antagonists have been examined in an attempt to show promise for clinical use and others has been used diagonistically or to the constrict pupil or to reverse mydriasis.

Bunazosin

Bunazosin is a potent and selective α-1-receptor antagonist showing similar affinity to each α-1 adrenoceptor subtypes as prazosin[3-5] and has been in clinical use for systemic hypertension in several countries.[6] Studies in rabbits showed that topical application of 0.05% bunazosin for four weeks reduced the IOP without tachyphylaxis.[7] Application of a high concentration (0.3%) of bunazosin reduced the IOP in normal humans by about 3 mmHg, but at this concentration topical bunazosin also caused miosis, ptosis and conjunctival hyperemia.[8]

Several studies, including phase-II studies, indicated that the concentration of 0.01% may be used as a clinical dose with duration of ocular hypotensive action of 12 hours,[9-11]and a phase-III study and a long-term one-year study carried out in Japan demonstrated that 0.01% topical bunazosin reduced the IOP in subjects with primary open-angle glaucoma (POAG) or ocular hypertension (OH) without tachyphylaxis.[1,2] The ocular hypotensive effect of 0.01% bunazosin was found to be, however, less potent than that of 0.5% timolol[1] and was thought to be equivalent to that of 0.1% dipivefrin[12] or 2% dorzolamide, if we may use the ocular hypotensive effect of 0.5% timolol as a standard for comparison.[13] Topical bunazosin was reportedly effective in reducing the IOP in POAG with normal range IOP (normal-tension glaucoma, NTG),[14] primary angle-closure glaucoma[15] or secondary glaucoma[16] and induced a small, but significant further IOP reduction when added to latanoprost or timolol therapy.[17,18]

A study in normal humans showed that topical bunazosin caused no significant effects on the fluorophotometrically determined aqueous flow rate, tonographic outflow facility or episcleral venous pressure, suggesting that topical buanzosin reduce the IOP by increasing uveoscleral outflow.[19] In fact, a study in rabbits demonstrated that topical bunazosin increased uveoscleral outflow facility as measured by a two-level constant pressure infusion method, but showed no significant effects on the fluorophotometrically determined aqueous flow rate or outflow facility (outflow facility to systemic circulation not attributable to

uveoscleral outflow).[20] The somewhat different mechanism of action of bunazosin from that of 5-methylurapidil, an α-1A adrenoceptor antagonist with 5HT 1A agonistic activity, may be attributed to the difference in the 5HT 1A agonistic activity.[26] Although bunazosin significantly influenced metabolism of extracellular matrix (ECM) in rat conjunctival and subconjunctival tissues,[22] it caused no significant effects on matrix metalloproteinase (MMP) activities in cultured monkey ciliary muscle cells, but inhibited phenylephrine-induced constriction of bovine ciliary muscles.[23] This mechanism action of bunazosin probably explains both uveoscleral outflow-increasing effect of bunazosin[19,20] and a small, but significant its additive effect to ocular hypotensive effect of latanoprost in patients and monkeys.[17,18,23]

Studies using rabbits showed that topically instilled 0.01% bunazosin penetrated to the posterior parts of the ipsilateral eye by local diffusion at pharmacological levels and ameliorated intravitreal phenylephrine or endothelin-1 (ET-1) induced vasoconstriction of retinal vessels[24,25] or intravitreal ET-1 or systemic nitric oxide synthase (NOS)- induced blood flow reduction at the optic nerve head or visually evoked potential (VEP) changes.[26,27] Further, bunazosin reportedly reduced glutamate-induced neurotoxicity in rat primary retinal cultures by inhibiting Na^+ influx at 1μM.[28] These experimental facts may suggest a possibility that topical bunazosin has direct beneficial effects on the posterior ocular tissues relating to glaucoma in addition to its ocular hypotensive effects, but clinical implication of these findings is unknown at present time of investigation.

Topical 0.01% bunazosin caused no significant effects on pulse rate, but a small, but significant reduction of systolic (-3.2 mmHg) and diastolic (-1.9 mmHg) blood pressure.[1] Its local adverse effects such as hyperemia or foreign body sensation are less frequently encountered than 0.5 % timolol.[1] A long-term use of topical 0.01% bunazosin also caused a small, but significant miosis of 0.2 mm in pupillary diameter.[1] Intra-operative floppy iris syndrome is often encountered in patients taking α-1A adrenoceptor antagonists such as tamsalosin for treatment of prostate hypertrophy,[29,30] but this complication is not reported in patients using bunazosin.[30] This apparent paradox may be explained as follows. Historically, α1 adrenoceptors have been pharamacologically classified into two subtypes, that is, one showing high affinity to prazosin (α1H) and the other with low affinity to prazosin (α-1L).[31,32] Since no genes cloning α-1L could be found, it has been proposed that the α-1A adrenoceptor has two phenotypes, that is α-1H receptor with high affinity to prazosin and α1L receptor with low affinity to prazosin.[33-36] Effects of bunazosin on the IOP, that is, on the ciliary muscle,[23] is thought to be mediated by α-1H receptors with high affinity to prazosin,[37] while iris dilator muscle of humans mainly has α-1L receptors,[38] and α-1A adrenoceptor antagonists used for treatment of prostate hypertrophy such as tamusulosin are thought to act through α1L receptors in prostate.[39] Dissociation of the effects of bunazosin on the IOP and pupil is also explained by low affinity of bunazosin to α-1L receptors of the iris dilator muscle.

Topical bunazosin appears to have no systemic contraindications and to be indicated in ocular hypertension, primary open angle glaucoma, primary angle

closure glaucoma or secondary glaucoma, but its effect in developmental glaucoma has not been examined. It is usually used as an additional eye drop when the effects of topical prostaglandin-related drugs, β antagonists or carbonic anhydrase inhibitors are considered unsatisfactory.

Other selective α1 receptor antagonists

Prazosin is the prototype of α-1 adrenoceptor antagonists of quinazoline class showing selective α-1 adrenoceptor antagonistic activity and has similar potencies at α-1A, α-1B and α-1D subtypes.[40] Topical prazosin at concentrations of 0.0001%-0.1% reduced the IOP in rabbits dose-dependently for six to eight hours with maximum effect at two hours,[41] without affecting outflow facility, episcleral venous pressure, blood pressure or ocular blood flow.[42,43] Tonography and measurement of posterior chamber aqueous ascorbate levels suggested decreased aqueous flow by topical prazosin.[42]

The effect of α-1 adrenoceptor antagonist on aqueous humor dynamics was studied in more detail using corynanthine and thymoxamine, other selective α-1 adrenoceptor antagonists, and fluorophotometry. Topical corynanthine reduced IOP in monkeys without affecting aqueous flow rate and tonographic outflow facility, suggesting uveoscleral outflow-increasing effect of an α-1 adrenoceptor antagonist.[44] Topical corynanthine reduced IOP in ocular hypertensive subjects in single dose studies, but caused tachyphylaxis in multiple dose studies at one, two and three weeks.[45] Thymoxamine had no significant effects on the IOP, aqueous flow rate, blood-aqueous barrier permeability or outflow facility[46,47] and did not alter the aqueous flow rate-increasing effect of epinephrine in humans,[48] although it may reduce the IOP in rabbits.[49] Since thymoxamine induces miosis without affecting accommodation, the central anterior chamber depth[47] or systemic conditions,[50] this drug may be used to break pupillary block, to reverse phenylephrine-induced mydriasis or to reduce iris-zonular contact in pigmentary dispersion syndrome or glaucoma.[50-55] In open-angle glaucoma, however, thymoxamine may be useful only in differentiating mild angle-closure glaucoma from open-angle glaucoma as an adjunct to gonioscopy.[56]

Dapiprazole which showes high affinity to α-1A and α-1D adrenoreceptor subtypes[57,58] reportedly reduced the IOP in rabbits,[59] but clinical usefulness of this drug is in the miosis-related effects, that is, reversal of phenylephrine-induced mydriasis,[60-65] reversal of mydriasis after cataract surgery,[66-68] stabilization of the iris in pigmentary dispersion syndrome or glaucoma[69-72] or reduction in night haloes.[73] Recent studies indicated that brimonidine, a selective α-2 adrenoceptor agonist, is more suited to be used to constrict the pupil because of fewer local side effects than dapiprazole.[74,75]

Alpha-2 adrenoceptor antagonists

Although topical application of rauwolscine, yohimbine or WB-4101 SK & F 86466 was reported to show ocular hypotensive effects in rabbits,[76,77] potential

of α-2 adrenoceptor antagonists as an ocular hypotensive agent for treatment of glaucoma is not established at present time of investigation.

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V Prostaglandins

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Background

Prostaglandin analogues have now been in use as ocular hypotensive agents for more than a decade and are generally considered as a reasonable alternative for first-line treatment. Initial studies on rabbits, cats and monkeys demonstrated that prostaglandin F_{2alpha} (PGF_{2alpha}) probably is the most potent ocular hypotensive agent among the naturally occurring prostaglandins.[1-3] It has also later been shown that the effect is mediated by the FP receptor.[4-5] However, PGF_{2alpha} is not a highly selective agonist for the FP receptor and can be expected to have some effect also on e.g. the EP-receptors. These tend to mediate ocular inflammation, and the analogues in clinical use today have been developed in order to be more selective for the FP-receptor than PGF_{2alpha}.[6-9]

Mechanism of action

Presently there are five prostaglandin analogues in clinical use; latanoprost (Xalatan®), travoprost (Travatan®), bimatoprost (Lumigan®), unoprostone (Rescula®) and tafloprost (Taflutan®, Saflutan®, Taflotan®, Tapros®). All reduce IOP by increasing outflow. Aqueous flow is, if anything, slightly increased.[10-11] The main effect on outflow is an increase in uveoscleral flow. This has been clearly demonstrated in monkeys for latanoprost,[12] travoprost,[13] and tafluprost.[8] In human eyes indirect calculations, based on determining intraocular pressure (IOP), aqueous flow, and clinical outflow facility, have demonstrated that increased uveoscleral flow is the major explanation for IOP reduction also in human eyes for latanoprost,[14] bimatoprost,[15] and travoprost.[16] No human studies on mechanism of action have yet been reported for tafluprost. Unoprostone, an analog of a metabolite of PGF_{2alpha}, seems to act differently from the other compounds. Independent of FP receptor stimulation, it opens maxi-K channels, which are potassium channels that reach an activation threshold only during depolarization and/or at high intracellular Ca^{2+} concentrations.[17] Unoprostone mainly increases conventional outflow[18] following calcium dependent tissue contraction,[19] but the relationship between the activation of maxi-K channel and IOP reduction still remains unclear. Also, unlike the others, unoprostone should be given twice a day.

A small effect on outflow facility in human eyes has been reported also for latanoprost,[14] bimatoprost[15] and travoprost.[16] Thus, for all three analogues a combined effect on conventional and uveoscleral outflow is a possibility;[11] this is supported by the observations that FP receptors are present in both ciliary body and trabecular meshwork,[4,20,21] The inability of clinical tonography to clearly separate between the two outflow routes makes this question difficult to resolve, but it seems clear that the major effect is on uveoscleral flow.

The increase in uveoscleral flow is due to a re-structuring of the ciliary muscle with increased spaces between the muscle bundles.[22] Stimulation of the FP-receptor increases the amount of metalloproteinases (MMP) in the ciliary muscle[23] and the change in collagen turnover results in loss of collagens.[24,25] Interestingly, in the ciliary body, but not the trabecular meshwork, the induction of MMP exceeded the induction of TIMPs,[26,27] which is the inhibitor of MMPs. This might explain that most, or all, of the effect on outflow is on uveoscleral outflow. Still, some effect on conventional outflow and/or effects not based on restructuring of the ciliary muscle cannot be ruled out. An almost maximal effect on IOP is seen already after 8-12 hours,[14] while one would expect that tissue remodeling would require more time. Taken together, there are still some questions to answer concerning the mechanism of IOP reduction by PG analogues.

It is clear that the FP-receptor is crucial for the effect on IOP by the prostaglandin analogues used today. None of them has any effect on IOP in FP-receptor deficient mice.[28-30] Still, other prostanoid receptors may also mediate some reduction of the IOP. In monkey eyes stimulation of the EP_2 receptor increases uveoscleral flow,[31] while stimulation of the EP_4 receptor increases outflow facility through the trabecular meshwork.[32] Stimulation of EP_2 and EP_4 receptors also mediate an IOP reduction in mice.[33] As PGF_{2alpha} also has some affinity for EP receptors one might then expect that PGF_{2alpha} would be a more potent drug than the FP selective agonists used today. This seems to be the case in non-human primates, where the effect on IOP of PGF_{2alpha} could only be matched with a combination of FP receptor and different EP-receptors agonists.[34] For human eyes a similar approach can be expected to induce more ocular irritation and side effects. In fact, studies of the effect of PGF_{2alpha} -isopropylester eye drops on the human eye suggested that such side effects would prevent its use in many eyes.[35]

Latanoprost, travoprost and tafluprost are all esterified pro-drugs and hydrolyzed to the pharmacologically active free acids when they pass through the cornea. Bimatoprost is also a prodrug but with an ethyl amide instead of an isopropyl ester on the alpha-chain. The free acid differs from latanoprost acid by a double bond. Like the other pro-drugs bimatoprost has no affinity for the FP-receptor, but the free acid, 17-phenyl-$PGF_{2alpha,}$ is a FP-receptor agonist with high efficacy. Bimatoprost is partially hydrolyzed by amidase to its free acid, and the amount of the free acid found in the anterior chamber is likely to be sufficient to explain its effect on IOP.[36] Recent studies also report an action of the amide on FP receptor variants,[37] but it is not clear if that is involved in the effect on IOP.

Efficacy

A summary of the five prostaglandin analogues is presented in Table 1. As a group, prostaglandin analogues are the most potent of the commonly used glaucoma drugs with peak and trough reductions of IOP of 31-33% and 28-29% respectively for latanoprost, travoprost and bimatoprost.[38] There are no com-

parable reports for tafluprost, while unoprostone has been reported to induce an IOP reduction of about half of that of latanoprost.[39-41] The IOP lowering effect of latanoprost has been shown to be stable over several years with no long-term drift.[42]

Indication

According to the product labels all prostaglandin analogue eye drops are primarily indicated for IOP reduction in open-angle glaucoma or ocular hypertension, but they can be used also in chronic angle-closure glaucoma and different forms of secondary glaucomas.

Side effects of the prostaglandin analogues

The general side effect profile of the different PGF2α analogues is similar (Table 2), but there are differences in the frequency of certain individual side effects.[43]

Conjunctival hyperaemia

Animal studies have demonstrated that the conjunctival hyperemia seen in some eyes during treatment with prostaglandin analogues is due to release of nitric oxide.[44,45] Published studies show a large variation (between 5% and 50%) in the frequency of hyperaemia.[46] It is of practical importance to know that the hyperaemia rate is usually much higher in treatment-naive eyes or after a long washout period, as seen in randomised controlled clinical trials,[47-56] than it is in previously-treated eyes; especially when the previous treatment included a PGF2α analogue eyedrop, as is seen in real-life studies.[57-63] The hyperaemia induced by PGF2α analogues is minimal (trace, or of mild severity) in the majority of cases;[47-62,64-68] and a clear tendency for a time-dependent decrease of severity is typical.[60,69] Therefore, discontinuation of successful treatment with a PGF2α analogue because of conjunctival hyperaemia in the early days or weeks of the treatment is not recommended. In the short term, latanoprost induces significantly less hyperaemia than do bimatoprost or travoprost.[70,71] According to the product labelling,[46] the frequency of conjunctival hyperaemia is 5 to 15% for latanoprost, 10 to 25% for unoprostone, 12% for tafluprost (based on combined evaluation of data on preserved and unpreserved preparations), 5 to 45% for bimatoprost and 35 to 50% for travoprost.

Increase of iris pigmentation

Darkening of the iris is an irreversible side effect of all topical PGF2α analogues. Iris darkening is caused by increased transcription and increased activity of tyrosinase in the iris stromal melanocytes, which is stimulated by clinical dosage of topical PGF2α analogues.[72-75] Iris darkening does not involve mitotic activity of the melanocytes;[73,76] thus it does not represent an increased risk for development

or progression of uveal malignant melanoma.[77] Eyes with mixed-colour irides containing brown areas are especially susceptible to colour change.[42] More than three-quarters of green-brown and yellow-brown irides treated with latanoprost were found to be affected.[42] Iris darkening in blue-grey or brown irides is rare, or less visible.[42,78] After six to twelve months of travoprost treatment, the incidence of iris colour change (independent of iris colour) varied between 1.0% and 3.1%.[49,55,79] At the same length of treatment, iris darkening was noted in 5.1 % to 10.1% of eyes for latanoprost users[47,49] and in 1.1% to 1.5% for bimatoprost users.[52,64] Compared to the use of the above-mentioned PGF2α analogues, iris darkening has been consistently reported to be less frequent among unoprostone users.[40,80-83] Currently, little information is available on iris pigmentation under tafluprost treatment. Increased iris pigmentation usually appears in the first months of the PGF2α analogue medication, and develops in the first year of treatment in nearly all those eyes with iris darkening in five years.[42]

Eyelash changes

Increase of the length and thickness of the eyelashes (hypertrichosis), as well as darkening of the eyelashes occurs in all races.[79,84-87] Reported frequency of eyelash changes varies between zero and 25% for latanoprost,[42,48,49] between 0.7% and 52% for travoprost,[49-51] and between 3% and 36% for bimatoprost.[51,52] But in the same population, and using identical criteria for the changes, in studies with a follow-up duration up to six months, the rate was similar for all these three PGF2α analogues.[48,53] Eyelash changes associated with the use of unoprostone seem to be similar to those observed with latanoprost.[88] Though registered as a side effect, less than 1% of patients complain about hypertrichosis,[79] and many patients in fact prefer the longer lashes, for cosmetic reasons. However, hypertrichosis can lead to complaints if it is unilateral, in case of unilateral use of PGF2α analogues.[85] If the topically applied PGF2α analogues are in contact with the eyelids and the malar region, hypertrichosis and hyperpigmentation of the vellus hairs can occur.[85,86] Discontinuation of PGF2α analogue treatment results in reversal of eyelash pigmentation and hypertrichosis after spontaneous shedding of the lashes or following epilation.[86] As a rare eyelash alteration, poliosis has been described in chronic use of bimatoprost, latanoprost and travoprost.[89]

Increase of eyelid skin pigmentation

Increase of eyelid skin pigmentation is not a common complication of topical PGF2α analogues. In a one-year treatment study this side effect was registered in 1.5 %, 2.9 % and 2.9 % of the latanoprost, bimatoprost and travoprost users, respectively.[48] This side effect is reversible after discontinuation of PGF2α analogue medication.[90-92]

Ocular surface problems, blepharitis, ocular pain, and visual disturbance

The frequency of eye irritation, blurred vision, eye pain, dry eye feeling, eye pruritus, itching, burning, discharge, tearing, blepharitis, eyelid oedema and allergy varies between 1% and 6% in bimatoprost, latanoprost and travoprost users in the first year of treatment.[48,55] In other studies,[49,52,64] some figures are higher (itching in 13.9% to 14.6%, burning in 5.8% to 7.0% and eye dryness in 8% with bimatoprost; pain, ocular discomfort, foreign body sensation and pruritus in 7.0% to 8.5% with travoprost). Corneal epithelial erosions were noted in 9.6% of eyes with chronic latanoprost medication.[93] These erosions are usually mild and sporadic events. Their frequency is similar under bimatoprost, latanoprost and travoprost treatment.[94] Corneal sensitivity temporarily decreases after the instillation of any of these three PGF2α analogues, and the short-term decrease of sensitivity correlates with the Schirmer test score and the tear film break-up time.[95] This might be explained by preservative toxicity (for those drugs which contain BAK), since no stimulation of inflammatory pathways was measured after exposure of conjunctiva specimens to the above three PGF2α analogue eye drops.[96] With the unoprostone 0.15% preparation burning and/or stinging occurs in 18%, eye irritation in 20% and eye pain in 15%.[40,81] Discontinuation of the PGF2α analogue medication may become necessary because of the side effects discussed in this paragraph.

Damage of blood aqueous barrier, inflammation and cystoid macular oedema

Clinically detectable inflammatory side effects of the prostaglandin analogues (onset or recurrence of uveitis, cystoid macular oedema or recurrence of herpetic keratitis) are complications which occur only rarely.[97-103] These side effects usually occur on eyes which are susceptible to inflammation because of previous or low grade ongoing uveitis, herpetic keratitis, or macula diseases associated with cystoid macular oedema (*e.g.*, complicated cataract surgery, or epiretinal membrane, retinal vein occlusion in the presence of an open or missing posterior lens capsule after cataract surgery).[97,99-101,103] The time of onset of these side effects varies between one day to several months after starting treatment. All these side effects are reversible if the PGF2α analogue therapy is discontinued soon after the development of the symptoms.[97,99,100.103] Re-challenging with a PGF2α analogue leads to recurrence of the complication.[97,99,101-103]

Systemic safety

Topical PGF2α analogues have been consistently reported safe in respect of the cardiovascular and respiratory function.[70,104-107] Headache is a rare side effect of this drug class; it may resolve spontaneously without any change in the medication, or it may reverse after the PGF2α analogue therapy is discontinued.[47,49,50,55,84,109] According to the product labelling, pregnancy and lactation are contraindications for use of the topical PGF2α analogues, since systemi-

cally applied (much higher) doses of prostaglandins induce abortion in animals. There are no controlled clinical trials in this field, but case reports show that this kind of complication has not been detected in clinical practice.[110,111] If use of a PGF2α analogue is necessary during pregnancy and lactation, correct instillation technique and punctual compression can further decrease the risk of systemic absorption.

Rare side effects

Few cases of reversible deepening of the lid sulcus during prostaglandin analogue treatment have been reported.[112] Development of an iris cyst during latanoprost treatment, and disappearence of the cyst after discontinuation of latanoprost has been described in two cases.[113,114] In few cases, abdominal cramp has been reported under the use of topical prostaglandin analogues.[47-49,115]

Table 1. Main characteristics of prostaglandin analogue eye drops used to reduce IOP in clinical practice

Trade name*	**Lumigan®**	**Xalatan®**	**Taflotan® Saflotan®**	**Travatan®**	**Rescula®**
Active molecule*	Bimatoprost	Latanoprost	Tafluprost	Travoprost	Unoprostone
Concentration	0.03%, 0.01%	0.005%	0.0015%	0.004%	0.12%, 0.15%
Preservative (%)	BAK (0.005%)	BAK (0.02%)	No preservative, unidose formulation	BAK (0.015%), Alternative preservation system available	BAK (0.01%)
Administration frequency	*1/ day*	*1/ day*	*1/day*	*1/day*	*2 times/day*
Recommended as first line medication in OAG	*yes*	*yes*	*yes*	*yes*	*No*
Available in fixed combination with timolol 0.5%	yes	yes	no	yes	No

* in alphabetical order based on the original product; generic products may be also available

Table 2. Most important side effects of the prostaglandin analogue eye drops

Side effect	Frequency	Severity	Predisposing conditions	Reversibility
Eyelash changes	up to 52 %	mild	not known	Yes
Eyelid pigmentation	up to 3 %	mild	not known	Yes
Conjunctival hyperaemia	up to 50 %	typically mild (rarely, moderate or severe)	treatment-naive eyes	Yes
Ocular surface problems and eye irritation	up to 14 %	mild to moderate	Unknown	Yes
Iris darkening	up to 10 %	mild	mixed iris colour (green-brown or yellow-brown)	No
Uveitis	rare	severe	previous or ongoing uveitis or herpetic keratitis	Yes
Cystoid macular oedema	rare	severe	complicated cataract surgery, diabetic retinopathy, epiretinal membrane, retinal vein occlusion	Yes

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VI Fixed-combination Preparations of IOP-lowering Agents in Open-angle Glaucoma

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Introduction

The need for combination therapy

In the treatment of open-angle glaucoma (OAG) or ocular hypertension (OHT), patients who fail to achieve their respective individualized IOP targets with a single pressure-lowering agent often require treatment with additional agents.[1] In general, treatment with a combination of agents of different classes provides additional IOP reduction over that achieved with monotherapy,[2] and the magnitude of this additional benefit will depend on the agents combined. When treating to a target, combination therapy is frequently required: after 6 years in the Ocular Hypertension Study (OHTS), approximately 40% of 653 patients in the treatment group required two or more topical IOP-lowering agents to a achieve IOP reduction $\geq$ 20%.[3] In another study, over five years, over 50% of 153 patients treated with beta-blockers required additional medication or surgery.[4] Guidelines from the European Glaucoma Society (EGS) recommend that in patients responsive to initial monotherapy but not attaining their target IOP, a second agent should be added.[1] Similarly, guidelines from the American Academy of Ophthalmology (AAO) state that 'if a single medication is effective in lowering IOP but the target pressure is not reached, combination therapy or switching to an alternative therapy may be appropriate'.[5]

Problems associated with combination treatment

There are, however, potential problems associated with combination treatment, particularly relating to adherence.[1] Adherence, as defined by the EGS, has two components: compliance and persistence.[1] Compliance describes taking a medication as directed, with the correct dose, administration technique and dosing

intervals. Persistence refers to the continuity of treatment, which may be measured by the number of prescription refills over a period of time. It is well known that adherence in glaucoma is poor,[6] even in patients who are aware that their medication usage is being monitored.[7] There is an association between adherence and the number of medications prescribed, with patients prescribed fewer agents being more adherent,[8] and patients preferring simplified regimens over complicated ones.[9] There is also an association between dose frequency and adherence: in an interview study of 100 patients using glaucoma medications, significantly more patients using eye drops more than two times daily reported that they missed doses compared with those using eye drops one to two times daily.[10] There seems to be a closer relationship between adherence and number of drops per day than between adherence and number of medications.[6] Fixed combinations (FCs) would appear to be an elegant solution to this problem.

Benefits of fixed over unfixed combinations in terms of adherence

FCs are stable preparations of multiple active agents in a single bottle. In general, FCs are equally efficacious as the unfixed combinations of their components.[11] In some cases, FCs may be better tolerated than the unfixed combinations of their components, because of a reduction in exposure to preservatives or due to the action of the beta-blocker timolol. There is also a potential for a reduced 'washout', an effect associated with instillation of multiple drops in which the second drop is partly lost through drainage. The efficacy and tolerability of individual FC products are discussed in detail in subsequent sections.

A major benefit of FCs is their potential for improved adherence over unfixed combinations. In an observational, six-month study of 1052 glaucoma patients switching to FC therapy from either monotherapy (29%) or multiple concurrent therapies (71%), patients more frequently reported behaviors or views associated with good adherence when using the FC compared with when they were using their previous therapy (Fig. 1). This study suggests benefit, but self-reported adherence tends to be higher than that measured by objective measurements such as electronic medication monitoring.[7] Moreover, patient attitudes to treatment may well be affected by the simple act of switching to any medication. More robust data supporting the use of FCs come from a study of a retail pharmacy claims database in the USA.[12] Three cohorts of glaucoma patients were defined according to the number of bottles (not medications) prescribed in month 1, and these patients were followed over a period of 12 months. Patients in cohort 1 (n = 14,742) were prescribed a single FC, those in cohort 2 (n = 18,411) received two bottles (a beta-blocker and another ocular hypotensive), and those in cohort 3 (n = 4826) were prescribed three bottles.

At each month over the 12-month study period, there were statistically significant differences in the percentage of patients continuing on the treatment started in month 1 between all three cohorts (Fig. 2). The proportion of patients completing the year without discontinuing was 35% in cohort 1 (patients receiving a single FC), 27.2% in cohort 2, and 23.9% in cohort 3 ($p < 0.0001$). Overall, adherence decreased as number of bottles increased.

It is worth noting that this study examined the influence of the number of bottles on adherence, rather than the impact of FCs *per se*: some patients in cohorts 2 and 3 received FCs alongside other agents. Nevertheless, as FCs allow combination treatment while reducing the number of bottles, the link between number of bottles and adherence appears to support the use of FCs. Patients who were switched from their original medication (for example, because of lack of efficacy) were counted as having not persisted with therapy. This study was conducted only in one country, and it may be difficult to generalize the results to other settings. For example, the range of FCs available is quite different in the US compared with many other developed countries, the main difference being a lack of lipid-based FCs. Secondly, owing to the variety of ways in which medication is paid for in the US, adherence is likely to be affected by financial considerations in some cases, whereas this is less likely in health services that provide subsidized medication. With these caveats in mind, the data presented in this study suggest that a management regimen consisting of as few bottles as possible may enhance persistence, an important component of treatment adherence, and FCs appear to be a good means of reducing the number of bottles.

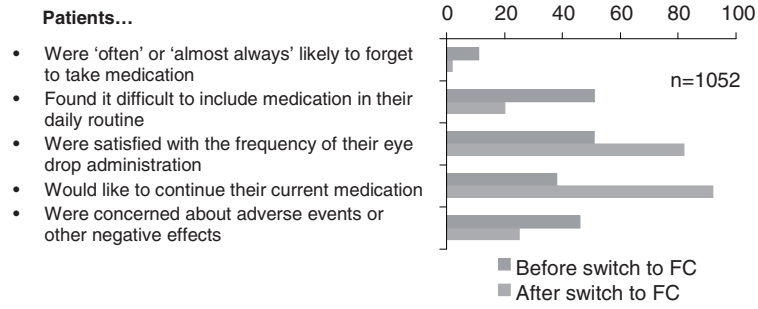

Fig. 1. Percentages of patients reporting views / behaviors related to adherence before and after a switch to FC therapy. All comparisons of before switch vs. after switch: $p < 0.01$.

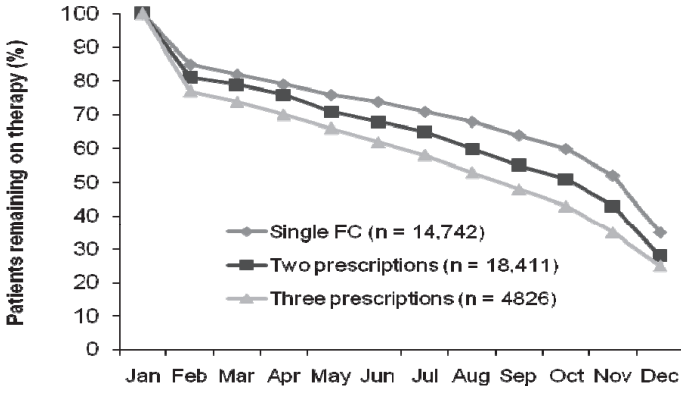

Fig. 2. Percentage of patients remaining on therapy in retail pharmacy claims database study. All between-group comparisons, $p < 0.0001$.

Recommendations regarding use of FCs

The EGS guidelines state that the FCs have 'many advantages, particularly the potential for improved patient compliance and fewer side effects because of a reduced level of preservatives.' Regarding combining treatment, the EGS recommends the following:

- 'Multiple topics treatment should be avoided if possible as compliance is likely to suffer '
- 'When available, fixed combination preparations may be preferable to two separate instillations of the same agents'

While the AAO preferred practice plan states that combination therapy 'may be appropriate'in those requiring further IOP-lowering therapy, it is silent on the use of FCs.

FCs are neither licensed nor recommended for use as first-line treatment, and in general should be prescribed when IOP is not sufficiently controlled with monotherapy. Overmedication exposes the patient to unnecessary risks of adverse events. Although not stated in international guidelines, it is the opinion of the authors of the current article that, in some cases, patients may benefit from early aggressive treatment with FCs. Examples of such patients include those with particularly high IOP levels, severe VF defects and/or high rates of progression.

Review methodology

In the following sections, studies comparing the major FC products will be reviewed. Studies included in this review are randomized, controlled, comparative trials of the FCs in patients with open-angle glaucoma (OAG) that evaluated efficacy in terms of IOP parameters, published in English. 'Switch studies' (non-comparative studies investigating the effect on IOP of replacing one medication with another) and retrospective studies were excluded. Studies comparing FCs with unfixed combinations or monotherapies other than their components were excluded. The review concentrates on the IOP-lowering effects of FCs, and therefore data on effect of FCs on parameters of ocular blood flow and IOP-independent effects were outside the scope of this review.

PubMed was searched with the search terms given in Table 1. For trials in progress or undergoing analysis, the FDA clinical trials registry was consulted (www.clinicaltrials.gov).

Table 1. PubMed search ter

PubMed search terms	Limits
dorzolamide [TI] AND timolol [TI] AND trial NOT blood flow [TIAB]	English
dorzolamide AND timolol NOT blood flow [TIAB]	English, Clinical trial or Meta-analysis
dorzolamide AND timolol AND (unidose OR preservative)	English
brinzolamide [TI] AND timolol [TI] AND trial NOT blood flow [TIAB]	English
brinzolamide AND timolol NOT blood flow [TIAB]	English, Clinical trial or Meta-analysis
brimonidine [TI] AND timolol [TI] AND trial NOT neuroprotec* [TIAB]	English
brimonidine AND timolol NOT neuroprotec* [TIAB]	English, Clinical trial or Meta-analysis
latanoprost [TI] AND timolol [TI] AND trial	English
latanoprost AND timolol	English, Clinical trial or Meta-analysis
bimatoprost [TI] AND timolol [TI] AND trial	English
bimatoprost AND timolol	English, Clinical trial or Meta-analysis
travoprost [TI] AND timolol [TI] AND trial	English
bimatoprost AND timolol	English, Clinical trial or Meta-analysis

Non-lipid-based FCs

Overview of the non-lipid-based FCs

Non-lipid FCs include combinations of beta-blockers with an alpha-agonist, carbonic anhydrase inhibitor (CAI), or pilocarpine. Non-lipid FCs are approved for use throughout the world, and no other category of FCs is available in the US.

Dorzolamide

Dorzolamide is a CAI and dorzolamide/timolol fixed combination (DTFC, Cosopt, Merck and Co. Inc., NJ, USA) is administered as one drop twice daily. It is more efficacious than dorzolamide monotherapy, and equally well tolerated.[13,14] In registration trials, DTFC showed equivalent efficacy and tolerability compared with the unfixed combination.[15,16] In theory, DTFC should be better tolerated than the unfixed combination of timolol and dorzolamide, because dorzolamide is often administered three times daily and, even compared with dorzolamide twice daily, the FC involves reduced exposure to preservatives. However, no clear benefits in terms of tolerability are evident from randomized clinical trial data, with both the DTFC and the unfixed combination being most frequently associated with bitter taste, blurred vision and ocular burning.[15] DTFC is available as a unidose (preservative-free) formulation in some countries, but at the time of writing there were no clinical studies demonstrating benefits in terms of tolerability over multidose DTFC. The patent for DTFC has expired in the USA; its patent in most European countries expires in 2013.

Brinzolamide

Brinzolamide is also a CAI and brinzolamide/timolol fixed combination (BzTFC, Azarga, Alcon Laboratories, Hünenberg, Switzerland) is the FC most recently launched in Europe. BzTFC is administered as one drop twice daily. BzTFC is more efficacious than brinzolamide monotherapy.[17] In the registration trial, BzTFC was associated with numerically lower rates of bitter taste than brinzolamide monotherapy, but rates of other adverse events were comparable between treatments, with ocular burning and blurred vision being among the most frequently reported.[17] A search of PubMed provided no published comparisons of BzTFC with the unfixed combination, and therefore we conclude that no benefit (e.g. in terms of tolerability) of BzTFC over the unfixed combination has been demonstrated.

Brimonidine

Brimonidine is an alpha-agonist and brimonidine/timolol fixed combination (BrTFC, Combigan, Allergan Inc., Irvine, CA, USA) is administered as one drop twice daily. BrTFC provides superior efficacy in terms of mean reduction from baseline in IOP compared with brimonidine monotherapy.[18] The most frequently reported adverse event with both brimonidine and BrTFC is ocular allergy, but BrTFC is associated with reduced ocular allergy compared with brimonidine.[18] It has been hypothesized that the improvement in tolerability observed with BrTFC arises because timolol inhibits the shrinkage of the corneal epithelial cells that occurs after application of adrenergic agonists.[19] Addition of timolol to brimonidine may therefore help maintain the natural barrier of the conjunctiva and protect against allergic reactions, although this hypothesis requires testing.[19] Compared with the unfixed combination, BrTFC provides comparable efficacy and tolerability.[20]

Several FCs containing pilocarpine with timolol, metipranolol or carteolol are available. These are now rarely used and studies of these products will not be covered.

Comparisons of the non-lipid-based FCs as sole therapies

Data comparing DTFC with BzTFC

DTFC was compared with BzTFC in a one-year multi-center, randomized, double-masked parallel-group trial conducted in 437 patients with OAG or OHT who required further IOP-lowering despite previous therapy.[21] IOP assessments were performed at 08.00 and 10.00 at week 2 and months 3 and 9, and at 08.00, 10.00, and 16.00 at months 6 and 12. At 6 months, there were no statistically significant differences between treatment groups in mean IOP at any of the three timepoints. Over 12 months, mean IOP was 16.7-18.8 mmHg with BzTFC and 16.9-19.3 mmHg with DTFC. Upper 95% confidence limits of treatment group differences were within +1.5 mmHg at all timepoints, signifying that, in terms of

effect on mean IOP, BzTFC was non-inferior to DTFC. Compared with DTFC, BzTFC was associated with a significantly lower rate of all adverse events and of eye irritation. There were only slight differences in the rates of any individual adverse event. Ocular irritation and ocular pain were each reported at a higher incidence in patients treated with DTFC versus patients treated with BzTFC. Patients treated with BzTFC reported a higher incidence of blurred vision versus patients treated with DTFC. The most common nonocular adverse reaction was dysgeusia (characterized as a bad taste) reported at a similar incidence in patients treated with either study medications.

The tolerability benefits suggested in the 1-year trial are also suggested by two 'comfort studies'.[22,23] In a two-day comfort study, 127 patients with OAG or OHT were randomized to receive one drop in both eyes of either BzTFC or DTFC on day 1.[22] On day 2, the allocations were reversed. Ocular discomfort was rated one minute after instillation using a 10-point scale and preference was recorded on day 2. Ocular discomfort scores were significantly lower with BzTFC compared with DTFC. Ocular pain and discomfort were reported more frequently with DTFC while blurred vision was more common with BzTFC. In a similar comfort study, patients were randomized to receive two drops daily of either BzTFC or DTFC for one week.[23] Ocular comfort was rated on a 5-point scale. At one week, mean ocular comfort scores were significantly lower with BzTFC compared with DTFC and 49% of BzTFC-treated patients reported no ocular discomfort compared with 15% of DTFC-treated patients.

Data comparing BrTFC with DTFC

Nixon and colleagues reported the pooled results of two randomized, investigator-masked, three-month parallel-group studies comparing BrTFC with DTFC in patients with OAG or OHT.[24] A total of 101 patients received the FC as sole therapy and 79 received it as an adjunct to a prostaglandin derivative (PG) and IOP was measured at 10.00 h at months 1 and 3. At month 3, when provided as sole therapy, BrTFC was associated with a further 7.7 mmHg mean IOP reduction from baseline (measured at 10.00 h) compared with 6.7 mmHg in DTFC-treated patients ($p = 0.040$). In the analysis of adverse events, there were no significant differences between treatment groups in the incidence of any adverse event. Tolerability was also assessed through the use of an ocular comfort questionnaire, which asked patients to rate on a 5-point scale the severity of burning, stinging and unusual taste. This element of study design was biased against DTFC, which is generally associated with these three adverse events, and it is not surprising that mean scores for stinging, burning and unusual taste, as well as 'overall comfort' were significantly lower in those receiving BrTFC than in those receiving DTFC.

An interesting study by Sáenz-Francés *et al.,* recently presented at the 2009 International Symposium on Ocular Pharmacology and Therapeutics (ISOPT), reported superior IOP-lowering of BrTFC compared with DTFC in a crossover trial of six-week treatment periods.[25] However, conclusions regarding these results cannot be drawn until their full publication in a peer-reviewed journal.

Several studies suggest that BrTFC and DTFC are associated with comparable levels of efficacy. A prospective, multicenter, observer-masked, crossover trial with four-week treatment periods that enrolled 30 patients was conducted in Brazil by Arcieri *et al.*[26] IOP was measured at 08.00, 12.00 and 16.00 at baseline and at the end of each treatment period. There were no statistically significant differences between treatment groups in mean IOP at any timepoint, nor in mean diurnal IOP, and no significant difference in the incidence of all ocular adverse events, although the incidence of stinging was significantly higher among those treated with DTFC. Hatanaka *et al.*[27] compared the hypotensive efficacies of BrTFC and DTFC in 210 patients in terms of effect on circadian IOP curve, IOP diurnal peaks, and IOP peak in response to a water-drinking test.[27] After eight weeks of treatment, BrTFC and DTFC were found to be comparable in terms of all of the above parameters.

This issue continues to be evaluated. A 12-week tolerability study being conducted by Allergan / DBYAN Medicine Professional Corporation is currently recruiting (clinicaltrials.gov identifier: NCT00621335). In addition, a crossover study with two-month treatment periods comparing the two products has been completed at the Aristotle University of Thessaloniki (clinicaltrials.gov identifier: NCT00972257).

Data comparing BrTFC with BzTFC

At the time of writing, there are no published studies comparing BrTFC with BzTFC as sole therapies.

Comparisons of the non-lipid-based FCs as sole therapies: conclusions

As sole therapies, DTFC and BzTFC are associated with similar levels of efficacy.[21] Results from a single randomized controlled trial[21] and two short-term 'comfort studies,[22,23] suggest BzTFC is associated with better ocular comfort than DTFC, but additional data may be needed, as the very short durations of these latter studies make it difficult to draw conclusions regarding tolerability in long-term treatment. BrTFC is associated with superior or equivalent efficacy compared with DTFC. [24,26,27] The side effect profiles of these agents are difficult to compare: BrTFC is mainly associated with ocular allergy; DTFC with burning, stinging and unusual taste.

Comparisons of the non-lipid-based FCs as adjuncts to prostaglandin therapy

In patients failing to achieve individualized target IOP with dual therapy, incisional surgery, laser surgery and therapy with three agents are potential options. The term 'maximal medical therapy (MMT)' refers to the combination of different classes of glaucoma medication to produce the optimal therapeutic effect on IOP. MMT is reached when further escalation of medical treatment would yield no significant therapeutic benefit.[28,29] This trade-off point will vary

among patients; in practice, concomitant use of three topical medications often constitutes MMT.[28] Patients who may benefit from MMT include those who are considered likely to be adherent, and who continue to have uncontrolled IOP and/or show evidence of continued progression. Such patients need to be seen more frequently than the average glaucoma patient, perhaps every two to four months.[30]

The link between adherence and number of drops per day becomes even more important in the context of MMT. If MMT is made up of individual medications, then a daily regimen of at least five instillations will be required. This is inconvenient for the patient, and, as seen above, there is an association between the number of drops per day and adherence,[8] as well as an association between number of medications included in the regimen and adherence.[6] EGS guidelines recommend against using more than two topical medications unless one is a FC,[1] and therefore, FCs are useful if MMT is to be considered.

Data comparing BrTFC with DTFC as adjuncts to prostaglandin therapy

One option for MMT is the combination of a non-lipid-based FC with a PG therapy. A pooled analysis of two randomized, investigator-masked, three-month parallel-group studies comparing BrTFC with DTFC included 79 patients who received the therapy as part of MMT, that is, as an adjunct to a PG.[24] At month 3, the mean (± SD) decrease from baseline in mean IOP (measured at 10.00 h) was 6.9 ± 4.8 mmHg (29.3% decrease) with BrTFC and 5.2 ± 3.7 mmHg (23.5% decrease) with DTFC. This trend towards superior efficacy of BrTFC did not reach statistical significance.

Other trials comparing non-lipid FCs as adjuncts to prostaglandin therapy

A clinical trial comparing BrTFC with BzTFC on a background of PG therapy is being conducted by Alcon / University of Thessaloniki, and is ongoing (clinicaltrials.gov identifier: NCT00981786). At time of writing, there were no studies comparing DTFC with BzTFC on a background of PG therapy.

Comparisons of the non-lipid-based FCs as adjuncts to prostaglandin therapy: conclusions

As adjuncts to a PG therapy (i.e. as part of MMT), both BrTFC and DTFC provided additional, clinically significant reductions in IOP,[24] suggesting that these are effective options in patients who require further IOP-lowering despite therapy with two agents.

Lipid-based FCs

Overview of the lipid-based FCs

PG therapy is now increasingly used as first-line therapy, owing to advantages over older treatments in terms of dosing schedule, tolerability and efficacy.[1] A meta-analysis has shown PGs to be the most efficacious monotherapies in terms of mean IOP reduction from baseline.[31] Among the PGs, all are effective in lowering IOP, but a meta-analysis comparing latanoprost, travoprost and bimatoprost suggested that bimatoprost was associated with the greatest ability to lower IOP overall.[32] IOP reduction from baseline was statistically significantly greater with bimatoprost than latanoprost at all time points. The IOP difference was between 0.5 to 1.17 mmHg at noon. IOP reduction from baseline was statistically significantly greater for bimatoprost than for travoprost at 8:00 AM and 12:00 PM. This trend was also seen at 4:00 PM and 8:00 PM, but the difference was not statistically significant at the former time point and borderline at the latter time point.

Some meta-analysis data suggest a superior efficacy of bimatoprost over latanoprost and travoprost[33] or a superior efficacy of bimatoprost and travoprost over latanoprost in terms of effect on mean IOP and response rate.[34] However, another meta-analysis of 12 articles including 3048 patients concluded that there were minimal differences in terms of efficacy between the PGs.[35] Overall, it seems reasonable to conclude that claims of superiority of one PG over another are not really proved when the data of the trials are analyzed precisely. Clinical endpoints may include mean diurnal IOP levels, mean IOP levels at each measurement time, mean IOP reductions from baseline at each time point, and/or percent IOP reductions from baseline at various time points. The conclusions may be based on only one parameter without considering others, and that can explain different conclusions.

The active ingredients of the lipid-based FC products are a PG (either bimatoprost, latanoprost or travoprost) in combination with the beta-blocker timolol. All are dosed once daily. At the time of writing, there was no available FC containing tafluprost. Lipid-based FCs have been licensed for use in most countries in Europe and Australia, as well as in Canada and Latin America, but not in the US. Patients responsive to PG monotherapy, but who fail to achieve their individualized IOP target should, according to international guidelines, receive a PG in combination with another agent (*e.g.*, a beta-blocker).[1] The popularity of PGs as first-line treatment mean that a lipid-based FC is a common second-line therapy in countries where they are available.[36-38]

Registration trials have shown that the lipid-based FCs are associated with superior efficacy compared with their individual components as monotherapies.[39-42] The fact that, when using lipid-based FCs, timolol is dosed once daily rather than twice daily appears not to affect the efficacy of the combination.[39-42] Lipid-based FCs appear to be associated with reduced rates of conjunctival hyperemia compared with the PG monotherapy.[41] The reasons for this are unclear:

timolol may exert an anesthetic effect or an effect on corneal epithelial tight junctions. Alternatively, timolol may block NO production by the β-adrenoceptor pathway, which might reduce hyperemia. A further hypothesis is that timolol potentiates vasoconstriction by endogenous catecholamines, thereby reducing the vasodilation of hyperaemia.[41]

Bimatoprost/timolol-fixed combination (BTFC, GANfort, Allergan Inc., Irvine, CA, USA) has been shown in a pooled analysis of two identical, three-month registration trials to provide superior efficacy over bimatoprost monotherapy in terms of percentage of patients achieving mean IOP < 18 mmHg at all time points at all study visits (week 2, week 6, and month 3) and percentage of patients achieving a mean IOP reduction > 20% at all visits.[41] BTFC was also associated with reduced incidence of conjunctival hyperemia compared with bimatoprost monotherapy. In another registration trial, BTFC was shown to provide equivalent efficacy and tolerability compared with the unfixed combination of its components.[43]

Latanoprost/timolol-fixed combination (LTFC, Xalacom, Pfizer Inc, New York, USA) was the first lipid-based combination product available in many countries. LTFC has been shown to provide superior efficacy compared with latanoprost monotherapy in terms of mean IOP reduction from baseline[44] and effect on diurnal IOP curve.[39] In a 12-week study comparing LTFC (administered in the morning) with the unfixed combination in 190 patients with controlled IOP, LTFC (am administration) was effective in reducing IOP from baseline.[45] However, the difference in mean diurnal IOP between treatment groups was 1.1 mmHg, favoring the unfixed combination. LTFC (am administration) was therefore not shown to be non-inferior with respect to this outcome.

Following on from this study, the same group conducted a similar 12-week, randomized, double-masked, multicenter study comparing LTFC (administered in the evening) with the unfixed combination of its components (also administered in the evening) in 517 patients with OHT, OAG, pigmentary or exfoliation glaucoma.[46] IOP was measured at 08.00, 12.00 and 16.00 at weeks 6 and 12 and at any time at week 2. Mean baseline IOP levels were approximately 25 mmHg in both treatment groups, and the reduction from baseline in mean diurnal IOP was 8.7 mmHg with LTFC (evening administration) and 9.0 mmHg with the unfixed combination. In this instance, the between-group difference was 0.3 mmHg and the upper limit of the 95% confidence interval was < 1.5 mmHg, signifying that LTFC (pm dosing) was noninferior to the unfixed combination, $p = 0.015$. At week 12, LTFC demonstrated noninferiority with respect to IOP reduction from baseline at all three timepoints. In addition, there were no statistically significant differences in the percentages of patients achieving ≥ 20% reduction in mean diurnal IOP or in the percentages of patients reaching mean diurnal IOP ≤ 18 mmHg. Throughout treatment, both regimens were well tolerated, although LTFC was associated with a reduced incidence of any adverse event, any ocular adverse event, and of any treatment-related adverse event. These results demonstrate that time of dosing can have an impact on the efficacy of LTFC.

As well as efficacy and tolerability, cost of medication may be a consideration in treatment decisions. In much of Europe, the patent on LTFC will expire before that on BTFC or TTFC, with the earliest patent expiring in 2011.

Travoprost/timolol-fixed combination (TTFC Alcon Laboratories, Hünenberg, Switzerland) has been shown to provide superior efficacy compared with travoprost monotherapy in terms of mean IOP reduction from baseline,[42] and equivalent efficacy and tolerability compared with the unfixed combination.[47]

Comparisons of the lipid-based FCs with non-lipid-based FCs

Data comparing LTFC with a non-lipid-based FC

Two small trials have evaluated LTFC and DTFC. In a single-center crossover trial with six-week treatment periods that enrolled 32 patients, there were no significant differences between DTFC and LTFC in mean IOP at any of the five diurnal timepoints, and no significant differences in the incidence of any adverse event.[48] In a similar crossover trial with eight-week treatment periods that compared LTFC with DTFC, there were no significant differences in mean IOP at any of the seven timepoints.[49] In this latter study, bitter taste was more frequently reported with DTFC, while hyperemia was more common with LTFC.

Data comparing BTFC with a non-lipid-based FC

At the time of writing, there were no studies comparing BTFC with any non-lipid-based FC.

Data comparing TTFC with a non-lipid-based FC

A six-week, prospective, multicenter, double-masked, randomized clinical trial compared TTFC with DTFC in 319 patients with POAG or OHT.[50] At six weeks, mean (± SD) diurnal IOP was 16.5 mmHg ± 0.23 in patients receiving TTFC and 17.3 mmHg ± 0.23 in those receiving DTFC, $p = 0.011$. Mean IOP was significantly lower in the TTFC group than in the DTFC group at the 09.00 h time point at week 2 and week 6. No other statistically significant differences between treatments were observed.

Comparisons of the lipid-based FCs with non-lipid-based FCs: conclusions

Small-scale trials suggest that LTFC is associated with an ability to lower IOP comparable to that of DTFC,[48,49] but these results should be interpreted with caution, as they evaluated the treatments over relatively short periods and in small study populations. One short-term trial suggests that TTFC is marginally more efficacious than DTFC in terms of effect on morning IOP.[50] The tolerability profiles of DTFC and lipid-based FCs are difficult to compare: adverse events associated with DTFC include bitter taste, stinging and blurring while hyperemia is the adverse event most associated with lipid-based FCs.

Comparisons of the lipid-based FCs

Owing to the current competitive environment in which the manufacturers of the lipid-based FCs operate, there have in recent years been a number of trials comparing these products in head-to-head trials.

Data comparing LTFC with TTFC

LTFC and TTFC have been evaluated in a 1-year, randomized, double-masked, multicenter, parallel group trial enrolling 408 patients.[51] IOP was measured at 09.00 only at week 2, week 6, month 3 and month 9, and at 09.00, 11.00 and 16.00 at months 6 and 12. TTFC was associated with lower mean IOP values at the 09.00-h time point at week 2 and month 6, but not at any other time points. When the mean IOP values recorded at a particular timepoint were averaged across all treatment visits, TTFC was associated with a 0.6 mmHg lower IOP at the 09.00-h timepoint ($p = 0.0235$) but not at 11.00 or 16.00 h. Hyperemia was reported in a higher proportion of patients receiving TTFC compared with LTFC.

Data comparing BTFC with LTFC

Given that bimatoprost is associated with a greater overall ability to lower IOP compared with either latanoprost or travoprost,[32] it is of interest whether the FC containing bimatoprost is more efficacious than LTFC or TTFC. Centofanti *et al.* reported the results of a prospective, randomised, multicentre, investigator-masked clinical study in which 82 patients were randomised to either BTFC ($n = 47$) or LTFC ($n = 45$) once at night for 12 weeks.[52] IOP was measured at 10.00, 12.00 and 16.00 h at one month and at three months. BTFC was associated with significantly greater mean IOP reduction compared with LTFC at all three timepoints at month 1 and at two of three timepoints at month 3. At three months, the percentage reduction in mean diurnal IOP was 21.4% with BTFC and 13.7% with LTFC, $p < 0.001$. There were no statistically significant between-group differences in terms of incidence of hyperaemia or indeed of any adverse event.

The results from the study by Centofanti *et al.* are supported by those of smaller trials.[53,54] In a four-week trial of 36 patients, BTFC was associated with superior IOP reduction compared with LTFC at all three time points at week 4.[53] Similarly, in a 12-week crossover trial of 54 patients, BTFC was associated with significantly superior IOP lowering compared with LTFC at five of seven time points at week 12.[54]

Data comparing BTFC with TTFC

Given the putative superiority of bimatoprost in terms of IOP reduction over travoprost,[32] one might expect BTFC to be associated with a greater ability to lower IOP than TTFC. A crossover trial (12-week treatment periods) was

presented by Rossetti *et al.* at the National Congress of the Ophthalmological Society of South Africa (OSSA), 2010.[55] The presented results suggested superior efficacy of BTFC compared with TTFC, but until publication of data in a peer-reviewed journal, any conclusions regarding the relative efficacies of BTFC and TTFC remain speculative.[55] Kelly-Rigollet *et al.* presented interesting data at the European Glaucoma Society Congress in 2008 and later at the World Glaucoma Congress 2009 from a trial comparing the three lipid-based FCs.[56] The data suggested that BTFC was associated with similar or greater IOP-lowering efficacy compared with LTFC or TTFC. Again, one should await full publication of these results before drawing firm conclusions.

Data comparing lipid-based FCs: conclusions

Randomized controlled trial data suggest that the lipid-based FCs LTFC and TTFC are associated with approximately comparable efficacies with small differences at certain timepoints.[51] They are also associated with comparable tolerability profiles. Compared with LTFC, BTFC may be associated with a slightly greater ability to lower IOP at various timepoints and equivalent tolerability.[52-54] This phenomenon may be not very surprising, given the fact that timolol is common to the three lipid-based FCs (and the only pharmaceutical difference is the PG) and that bimatoprost seems to have at least a similar, and maybe a slightly superior efficacy to latanoprost and travoprost in terms of IOP-lowering activity. Compared with TTFC, BTFC may provide greater reductions in IOP, but this remains speculative and needs further scientific support.

Use of FCs in practice

Survey data show that, in Europe, use of FCs, and in particular, lipid-based FCs are now common treatment choices in for patients failing to achieve individualized IOP targets.[36-38,57] In a study of 1583 patients treated in Italy in 2002, FCs of a CAI and a beta-blocker were prescribed in 8.3% of patients (lipid-based FCs were not available during the time of data collection). In an analysis of the records of 853 patients treated in private practice in Germany during 2005 and 2006, 29.5% of all patients were receiving dual therapy and 10.5% of all patients were receiving a lipid-based FC.[37]

Survey data also reveal that among clinicians working in Europe, FCs are looked on favorably, mainly because of perceived advantages over unfixed combinations in terms of adherence.[58] Among 50 respondents to a survey of ophthalmologists, FCs were usually used as second- or third-line therapy. The most popular FC as first-line therapy was DTFC while the most popular FC in the second-line setting was LTFC. Overall, 98% of respondents believed FC therapy improved patient care because it improved adherence. Most respondents stated that there was a difference in efficacy between the FC products, with the most effective being BTFC. A smaller proportion (68%) stated that there were differences in terms of tolerability between the available FCs.

Triple FCs

Fixed combinations of three IOP-lowering agents are available in some countries and are in development in others. For example, Sophia Laboratories have developed a combination of brimonidine/dorzolamide/timolol. Phase II results suggest that it has superior efficacy compared with either BrTFC or DTFC.[59] Manufacturers are developing triple fixed combinations including PGs for launch in the near future. These triple FCs may be useful alternatives to incisional and laser surgery in patients requiring further IOP lowering following failure to achieve target IOP with dual therapy.

Summary and conclusions

Combination treatment is frequently required in patients who fail to achieve their individualized target IOP.[3] There are significant clinical problems associated with treatment with multiple bottles: the number of instillations is negatively related to adherence,[10] and for this reason international guidelines recommend that multiple bottles should be avoided if possible.[1] FCs appear to be elegant solutions to this problem. The literature generally shows global clinical equivalence of the FCs compared with unfixed combinations, though slight differences in IOP-lowering efficacy may be seen in some cases .[11] FCs are appear to be associated with improved adherence compared with unfixed combinations,[12,60] although current data on this issue are scarce and further research is to be encouraged. FCs also have some other theoretical advantages over unfixed combinations, including reduced exposure to preservatives and reduced 'washout effect'. The simplification of treatment is a key issue for glaucoma patients, since the disease remains silent for a long period of time and that compliance is not natural for many patients. With FCs, there is no wash-out effect and the treatment regimen is greatly simplified, enhancing the medication's efficacy and potentially improving the patient's compliance. One bottle also reduces the risk of confusion between two treatments.

Drug regimens comprising multiple bottles have been identified by glaucoma patients as a barrier to therapeutic compliance and available data suggest a reduction in compliance in patients on multiple IOP-lowering medications compared to those on single-drug regimens. FCs of IOP-lowering medications provide the efficacy of multiple active agents with the convenience of a one-bottle regimen. FC therapies have other potential benefits as well, including reduction in exposure to preservatives and elimination of the washout effect. These benefits are balanced against the cumulative side effects of multi-drug therapies.

Non-lipid-based FCs (dorzolamide/timolol-fixed combination [DTFC], brinzolamide/timolol-fixed combination [BzTFC] and brimonidine/timolol fixed combination [BrTFC]) are options for patients who fail to achieve IOP target with monotherapy. DTFC and BzTFC are associated with similar effects on IOP, and trials suggest that BzTFC may be better tolerated than DTFC.[21] BrTFC is

associated with superior or equivalent efficacy compared with DTFC.[24,26,27] The side effect profiles of BrTFC and DTFC are different and difficult to compare.

Lipid-based FCs (bimatoprost/timolol fixed combination [BTFC], latanoprost/timolol fixed combination [LTFC] and travoprost/timolol fixed combination [TTFC]) are also effective and well-tolerated options for patients who fail to achieve IOP targets on monotherapy. According to the EGS guidelines, patients who fail to achieve IOP targets on PG therapy should be prescribed a combination of a PG with another agent.[1] As PG therapy is increasingly used as a first choice for first-line treatment, lipid-based FCs are common choices in second-line treatment in countries in which they are available.[36-38,57] Small-scale trials suggest that LTFC is associated with an ability to lower IOP comparable to that of DTFC.[48,49] One trial suggests that TTFC is marginally more efficacious than DTFC in terms of effect on morning IOP.[50] Current data also suggest a significant superiority of the lipid-based FCs when compared to their individual components. The comparison of the three lipid-based FCs showed small differences in IOP-lowering activity, though BTFC may appear more effective than the two others at some timepoints.[52,55] This has to be confirmed since the published papers on this topics are lacking. Furthermore, the observed IOP differences between the three lipid-based FCs are usually inferior to 1 mm Hg and most health agencies consider clinical relevance to be a between-treatment difference greater than 1.5 mm Hg. Each patient may ultimately get the drug he/she does best on, and the choice must be a balancing act between efficacy and tolerability in each case.

The need to use more than one hypotensive drug complicates the management of glaucoma, but such complications can be reduced by the use of FCs. In Europe, about one-third of patients are receiving combination therapy. Of these, two thirds are treated with a FC. Until recently, recommended practice was to prescribe separate instillations for better individual dosing of each drug, but the problem of compliance and tolerability are so important that it is more reasonable to prescribe a simplified treatment – specifically, an FC. Nevertheless, FCs are not first-line medications and they are only indicated in patients which need adjunctive therapy, when IOP is not sufficiently controlled by a single medication. If patients are not carefully selected, there is a risk to overmedicate a great number of patients, with the risk of exposure to some patients to two medications, without need.

In conclusion, FCs are useful options in the treatment of OAG and may aid the achievement of long-term IOP control in patients requiring therapy with more than one agent.

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VII Investigational and Future Drugs

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Currently, there are six classes of drugs on the market for the treatment of elevated IOP. Despite the variety of choices, there remain large numbers of patients who do not respond well to these drugs and blindness results. A variety of investigational drugs from a growing number of classes are being developed and tested for their IOP lowering efficacy and side effect profile. These classes are summarized below.

Prostaglandin analogs

Prostaglandin EP_2/EP_4 analogs

The prostanoid EP_2 receptor agonist, butaprost,[1] an EP_4 agonist (ARVO 2010 abstract #151) and a mixed EP2/4 agonist (ARVO 2010 abstract #2007) have recently been reported to lower intraocular pressure in monkeys to a level similar to FP agonists such as latanoprost. This IOP effect is accomplished in monkeys by increasing uveoscleral outflow. Similar studies[2] of another selective EP_4 receptor agonist, 3,7-dithia PGE_1 showed a significant increase in outflow facility without an effect on uveoscleral outflow. These IOP-reducing effects are similar to FP agonists that have been reported sometimes to have no effect on outflow facility but other times to increase outflow facility.[3] EP_2/EP_4 analogs can be classified as outflow drugs with IOP efficacy at least as good as FP agonists,[4] although hyperemia and stinging and burning seem to be greater.

Nitric oxide donating prostaglandin analogs

PF-3187207, a nitric oxide donating prostaglandin analog lowers IOP in glaucomatous beagles, in rabbits with saline induced transient ocular hypertension, and in monkeys with laser induced glaucoma. The IOP reduction with this compound was more than with latanoprost alone presumably as a consequence of a contribution by NO in addition to its prostaglandin activity (ARVO 2009 abstract #1471). Its IOP-lowering mechanism of action has not been elucidated to date. The compound is now in clinical development for the treatment of ocular hypertension.

Serotonin agonists

Serotonin, (5-hydroxy tryptamine, 5-HT) is an important endogenous neurotransmitter in the mammalian central nervous system and it is found throughout the eye, which has led some investigators to consider serotonin agonists as a potential class of IOP-lowering drugs. $5HT_{2A}$ agonists effectively lower IOP in normotensive and hypertensive eyes of monkeys.[5] R-DOI decreased IOP in ocular normotensive monkeys by increasing uveoscleral outflow.[6] Of the many 5HT receptors, $5HT_2$ appears to be the one most involved in the maintenance of IOP.[5]

Dopaminergic agonists and antagonists

Cabergoline is an interesting dopaminergic agonist at D2/3 receptors with some serotonergic activity at $5HT_2$ and $5HT_{1A}$ receptors. Cabergoline and other ergot derivatives (bromocriptine, lergotrile, lisuride and pergolide) reduce IOP in research animals.[7] The $5HT_2$ and dopaminergic agonist activities of cabergoline probably mediate the IOP reduction in monkeys by increasing uveoscleral outflow.[7]

Angiotensin AT1 receptor antagonists

Recent evidence suggests that components of the renin-angiotensin hormone system are involved in the regulation of IOP. The angiotensin II AT_1 receptor is one of two receptor subtypes able to bind angiotensin II. AT_1 receptors are localized in ocular tissues of rabbits and humans. These receptors mediate vasoconstriction and extracellular matrix formation, two factors that can affect aqueous humor dynamics. An early study in monkeys found an IOP lowering effect of the angiotensin converting enzyme inhibitor, enalaprilat. The drug appeared to promote the formation of endogenous prostaglandins which in turn modified the outflow pathway and caused an increase in outflow facility, thus explaining the IOP effect.[8] Topical AT_1 receptor antagonists (sartans) reduce IOP in ocular hypertensive monkeys. One of these antagonists, olmesartan lowered IOP in ocular hypertensive rabbits by increasing uveoscleral outflow with no effects on aqueous flow and outflow facility.[9,10] Olmesartan also appeared to decrease IOP and increase uveoscleral outflow in monkeys but, as in rabbits, the effect was small.[11] The currently available AT1 receptor antagonists do not appear to be efficacious enough to be developed for clinical use.

Cytoskeletal drugs

The actin cytoskeleton and associated cellular-adhesion proteins are attractive targets for novel therapeutic approaches for glaucoma.[12,13] No commonly employed therapies directly target and enhance outflow facility through the conventional outflow pathway (through the trabecular meshwork (TM) and Schlemm's canal (SC)). This pathway can account for 50% to 75% of aqueous humor outflow.[13]

New therapies are in early clinical trials that target the structures and enzymes involved in maintaining actin associated cell-cell, cell shape and cell-ECM interactions.[12,13] These compounds are intended to reduce the resistance to outflow by affecting cellular and tissue contractility/relaxation in the outflow pathways.

Direct perturbation of the actin microfilament system (by cytochalasins, latrunculins, etc.)[14,15] or acto-myosin contractility of trabecular meshwork cells (by myosin light chain kinase or rho kinase inhibitors or by over-expression of caldesmon)[16-19] dramatically reduces outflow resistance in live monkeys and/or in human/monkey organ cultured perfused anterior segments. Morphological studies show that the common effects of these agents is the relaxation of TM, JCT and IW cells, as well as the TM overall. Cellular relaxation leading to a 'relaxed' tissue configuration may be the geometrically/biomechanically critical event and may be the fundamental endogenous control mechanism for outflow resistance, providing some validation of this as a therapeutic target for resistance reduction in glaucomatous eyes.[12,13]

Potential issues with some agents in this class are adverse corneal epithelial or endothelial effects due to altered permeability, and conjunctival hyperemia or hemorrhage.[20,21] Dose and delivery refinements could help overcome these issues. Novel gene transfer approaches that would over-express cytoskeleton-relaxing proteins such as caldesmon in the TM are attractive delivery options for producing long-term therapeutic effects.[13]

ROCK inhibitors

Rho GTPase and its effector, ROCK (Rho-associated coiled coil-forming kinase) participate in signaling pathways that regulate actin stress fiber formation, focal adhesion, cell shape, cell motility and smooth muscle contraction. Recent investigations showed significant intraocular pressure (IOP)-lowering effects of ROCK inhibitors.[17] The IOP-lowering effects are attributed to improved outflow facility, possibly caused by rearrangement of the actin cytoskeleton and resultant relaxation of cells in the conventional outflow pathway.[18,21] Clinical trials revealed IOP-lowering effects of ophthalmic solution of a selective ROCK inhibitor with no systemic adverse events in humans.[22] The most frequent adverse event after instillation of ophthalmic solution of a selective ROCK inhibitor was transient bulbar conjunctival hyperemia. Also, the potential risk of conjunctival hemorrhages has been suggested[21] ROCK inhibitors have been shown to inhibit scar formation in animal models of glaucoma surgery, suggesting utility as effective anti-scarring agents after filtration surgeries.[23] Taken together, the findings suggest that ROCK inhibitors may be effective treatments for open-angle glaucoma and ocular hypertension.

Endothelin

Endothelin, produced by endothelial cells, is a potent vasoconstrictor that plays a major role in ocular physiology and pathology, including glaucoma. Two recep-

tors for ET-1, ETA and ETB, mediate vasoconstriction through the regulation (increase) of intracellular calcium levels.[24] The ETB receptor acts as a vasoconstrictor when found on smooth muscle vasculature as well as a vasodilator, through the production of NO, when found on the surface of endothelial cells.[25] The biological effect of endothelin on the vasculature results from the balance of ETA and ETB effects.[26]

Endothelin is associated with many different pathologic conditions, including glaucoma. Vascular dysregulation and altered ocular blood flow may lead to ischemic damage to the optic nerve head and retinal ganglion cells. The role of endothelin in these processes remains under intense study. ETA and ETB receptors on both the ciliary body and trabecular meshwork contribute to contractility and outflow resistance.[27,28] Changes in outflow resistance, directly affects IOP. ET-1 has been implicated in the loss of RGCs and linked to astrogliosis, extracellular matrix remodeling and nitric oxide induced damage. ET-1 contributes to the disruption of anterograde axonal transport. ET-1 may also mediate ECM remodeling at the level of the ONH, possibly contributing to increased collagen deposition, reduced aqueous humor outflow facility and progressive damage to the optic nerve head.[29]

Several ET-1 receptor antagonists have been tested in animals and humans. In glaucomatous monkeys, avosentan (SPP 301), an ETA receptor antagonist, significantly reduced IOP.[30] In a clinical trial, a dual ETA/ETB receptor blocker, bosentan, significantly increased blood flow to the retina, choroid, and optic nerve head but had no effect on IOP.[31]

Sulfisoxazole a non-selective ET-1 receptor antagonist reduced ET-1 induced elevation of NO. Additionally, sulfisoxazole reduced the number of GABA positive neurons, used as a measure of toxicity, by 41%. This evidence shows that ET-1 blockage can have a protective effect on the retinal ganglion cells of the optic nerve head.[32]

ET-1 is present and involved in a vast array of processes within the eye, and many may be directly related to the pathophysiology of glaucoma. The ET-1 pathway appears to show promise as a target for glaucoma therapies other than IOP reduction.

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VIII Preservatives in Topical Ophthalmic Medications

Malik Y. Kahook

Many different preservatives are currently used in multi-dose topical ophthalmic preparations. While benzalkonium chloride (BAK) remains the most commonly used preservative, other systems have been introduced and are becoming more prevalent both in the United States and abroad.[1] A primary motivation for introducing alternative preservatives has been the desire to achieve effective protection for multi-dose bottles (as required by regulatory agencies) while still trying to minimize the effects of detergent preservatives, such as BAK, on the ocular surface of treated patients.[2,3] There has also been a recent push towards eliminating preservatives entirely from topical ophthalmic preparations, beyond the currently available preservative free beta blocker timolol, by the use of bottles with inherent antimicrobial properties (surface coatings and one way valves) or by using unit doses, such as timolol or tafluprost (Merck & Co., Inc., Whitehouse Station, N.J., U.S.A & Santen Pharmaceutical Co., Ltd. Osaka, Japan), that do not require a preservative system.

Historical perspectives

BAK is a detergent quaternary ammonium compound with a broad range of antimicrobial activity. It was first introduced as a germicidal in the 1910s and became more widely used in the 1940s.[4] BAK was first introduced in ophthalmology

in the 1940s to preserve hard contact lens solutions. BAK concentration in common ophthalmic formulations ranges from 0.004% to 0.02%.

Benefits of using BAK as a preservative include:

1. Excellent efficacy in combating microbial contamination of bottles.
2. Ability to break cell-cell junctions in the corneal epithelium thus allowing for anti-hypertensive drops to enter the anterior chamber in greater concentration.
3. Familiarity of industry members with the product.

Drawbacks of using BAK as a preservative include:[5-8]

1. BAK is known to induce cell necrosis (at concentrations of 0.05-0.1%) and cellular apoptosis (at concentrations of 0.01%) by way of disturbing the cellular membrane in bacterial cells.
2. The effects of the detergent are cumulative and become more severe with more concentrated and frequent exposures.
3. BAK may lead to a break down of cell-cell junctions on the ocular surface with possible downstream effects on the basal cell layers and stromal nerve endings in the cornea.
4. High concentrations of BAK can reduce tear break-up time by causing disruption of the lipid component of the tear film and hence tear film instability.
5. Allergies to BAK have been reported.

While BAK remains the main preservative used in multidose ophthalmic medications, alternative molecules have been used in the past and present with some notable recent introductions.

Classification of preservatives

Detergent preservatives

Detergents are compounds that cause bacterial cell death by way of interrupting the lipid component of cell membranes leading to instability of the microbial cell wall, extrusion of cell contents and subsequent cell death.

Oxidizing preservatives

Oxidative preservatives penetrate cellular membranes and alter the DNA, protein, and lipid components leading to metabolic dysfunction and eventual cell death.[9] These molecules were developed because of their reduced toxicity to human ocular epithelial cells in comparison to detergent preservatives. While toxicity to ocular surface cells is less than the predating BAK system, oxidizing

preservatives may still lead to cell injury with chronic therapy as evidenced by preclinical animal studies and in vitro testing.[10]

Ionic buffered preservatives

Ionic-buffering systems are a class of ophthalmic preservatives recently incorporated into topical medicines. An example of an ionic-buffered preservative is sofZia (Alcon, Fort Worth, TX, USA), which is a combination of boric acid, zinc, sorbitol, and propylene glycol. The use of these preservative systems has been limited to specific countries and they are currently not available in European markets. This preservative system has, however, been shown to be effective at protecting multidose bottles with fewer deleterious effects on human epithelial cells compared to detergent preservatives.[11] Both in vitro and in vivo studies have shown a decreased rate of toxicity to corneal and conjunctival epithelial cells when compared to BAK containing glaucoma medications.[12,13] It is important to note that these differences, compared to BAK, have not been shown in prospective human clinical studies to date.

Specific preservatives[14]

Cetrimonium Chloride

Cetrimonium is a detergent-type preservative found in artificial tear preparations such as Civigel (Ciba Vision Ophthalmics, Duluth, GA). It has been shown to cause keratinization and inflammatory infiltrates at the limbus and within the conjunctival stroma and epithelium.

Chlorobutanol

Chlorobutanol is a detergent preservative which was formerly used as a preservative agent in artificial tears, where it has been documented to cause keratitis and irritation to the ocular surface. Human corneal epithelial cells exposed to chlorobutanol display decreased amount of mitoses and deterioration of overall cell integrity. One advantage for its use in artificial tears is that it does not affect the stability of the lipid component of the tear film. This agent becomes unstable when stored at room temperature for extended periods of time leading to limited use by manufacturers of ocular therapeutics.

Edetate disodium (EDTA)

EDTA is a chelating agent that gained use in ophthalmic solutions due to its ability to bind metals. For example, it has been used therapeutically to remove calcified plaques that occur in the superficial cornea in band keratopathy. EDTA also has preservative effects based on its ability to chelate and has been shown to inactivate trace amounts of heavy metals, which aids in the preservation of

stored solutions. Ophthalmic solutions that have employed EDTA in the past include Acular and Betagan

Polyquaternium-1 (Polyquad)

Polyquad is a detergent type preservative related to BAK and was initially developed for use in contact lens solutions. Polyquad offers the advantage of not becoming concentrated in contact lenses (as opposed to BAK.which does accumulate in contact lenses). Although traditionally classified as a detergent, Polyquad has unique properties compared to BAK. Bacterial cells attract it, yet human corneal epithelial cells tend to repel the compound. Drops that contain Polyquad include Tears Naturale II (Alcon) and Opti-Free Express Multi-Purpose Disinfecting Solution (Alcon). The main reported detriment associated with Polyquad is its tendency to reduce the density of conjunctival goblet cells potentially leading to altered tear film stability.

Polyhexamethylene Biguanide (PHMB)

PHMB has been used in contact lens solutions such as ReNu (Bausch & Lomb, Rochester, NY, USA). It has known antimicrobial activities against Acanthamoeba and bacteria. It has been shown to be non-irritating to human corneal cells; but is limited by poor antifungal activity. PHMB employs its microbial activity by integrating into bacterial cell walls and has been shown to lethally alter the transcription of bacterial DNA.

Stabilized oxychloro complex (SOC / Purite)

SOC is an oxidative-type preservative and introduced under the trade name Purite (Allergan, Irvine, CA, USA). Sodium chlorite, a main derivative, has been used in water purification systems since the 1940's. It is currently used in many topical drops, including Alphagan-P (Allergan) and Refresh Tears (Allergan). SOC has been shown to be well tolerated by the ocular surface and, even at very low concentrations (0.005%), has broad antimicrobial activity against both fungus and bacteria. Chemically, it is a mixture of chlorine dioxide, chlorite, and chlorate and when exposed to light, SOC dissociates into water, oxygen, sodium, and chlorine free radicals. It is the chlorine free radicals that are thought to inhibit microorganism protein synthesis within cells by glutathione oxidation leading to cell death.

Sodium perborate (GenAqua)

Sodium perborate, also known as GenAqua, is an oxidizing preservative used in lubricants such as Genteal eye drops (Novartis Ophthalmics, NJ, USA). It was one of the first of the oxidative-type preservatives and alters protein synthesis within bacterial cells by oxidizing cell membranes and altering membrane-bound

enzymes leading to enzymatic inhibition. It is catalyzed into hydrogen peroxide, water, and oxygen, upon exposure to an aqueous environment and the resulting hydrogen peroxide effectively kills microbes.

SofZia

SofZia is an ionic buffered preservative system found in travoprost Z (Travatan Z, Alcon, Fort Worth Texas). SofZia is deemed inactive when exposed to cations found in the normal human tear film, theoretically leading to less cytotoxicity to the ocular surface compared to more conventional preservatives. Both in vivo and in vitro studies appear to show that travoprost with sofZia is less deleterious to ocular tissues as well as the tear film although there are no prospective randomized trials to confirm this belief.

Human data

Sherwood *et al*. investigated changes in conjunctival and Tenon's capsule biopsies from two patient groups undergoing primary trabeculectomy surgery. The first group had not history of topical medication use and the second group without had received at least two types of antiglaucoma topical medication, for a minimum of one year (mean, 7.7 years) before surgery.[15] A significant increase in the number of macrophages, lymphocytes, mast cells and fibroblasts was noted in the conjunctiva and Tenon's capsule of those who received previous topical therapy compared to those who did not. A significant decrease in the number of epithelial goblet cells was also noted in those previously exposed to topical drops. The authors concluded that chronic topical therapy resulted in these changes and that this may have an effect on future surgical outcomes. There was no clear separation between effects from the active ingredients versus effects from preservatives in this study. Broadway and colleagues also reported on the effect of various long-term topical drop therapy on the cell population profile of the conjunctiva.[16] They noted a significant drop in goblet cell numbers in patients treated long term with multiple topical drops.

Baudouin *et al*. studied conjunctival and trabecular meshwork changes in 61 patients undergoing trabeculectomy.[17] This group represented 1) patients treated with two or more drugs for at least 1 year; 2) patients treated with a beta blocker for one year; and 3) patients who underwent primary surgery without history of topical drop use. Inflammatory cell infiltrates and fibroblasts evaluated in biopsy samples revealed a higher rate of abnormal cell infiltration in tissue samples from patients exposed to multiple preserved glaucoma medications compared to those exposed to monotherapy or patients who underwent primary surgery. The authors concluded that detergent-preserved medications were, in part, responsible for the inflammatory changes.

Malvitte and colleagues examined the inflammatory response to the chronic use of preserved topical glaucoma therapy in humans through sampling of tear cytokine levels using multiplex bead analysis.[18] They noted an increase in pro-

inflammatory cytokines (IL1-b, IL-6, IL- 12, tumor necrosis factor a) in samples obtained from those patients using chronic glaucoma therapy compared with healthy controls. They concluded that proinflammatory cytokine secretion by conjunctival cells is increased due to topical treatments for glaucoma and they implicated BAK as the culprit. It is noteworthy, however, that the cytokine concentration in tears was not significantly correlated with the number of daily instillations and thus not correlated with the exposure to either active ingredients or preservatives.

Conclusions

While effectively protecting multi-dose bottles from contamination by common pathogens, all preservatives appear to have variable effects on ocular surface cells with in vitro testing. *In vivo* data correlating the findings from *in vivo* studies are still lacking. There are few clinical reports showing that the number of detergent preserved medications taken by glaucoma patients may be correlated with specific indicators of ocular surface disease.[15-19] For this reason, a balance between anti-microbial efficacy and maintaining ocular safety is ideal when exploring possible new preservatives for ophthalmic preparations. Furthermore, it appears to be important for clinicians to minimize the exposure to detergent preservatives when possible and to treat ocular surface disease early and aggressively if these changes manifest with chronic topical therapies for glaucoma and other ophthalmic conditions. The development of new metrics might allow for more precise comparisons between medications and their preservatives in the future and to correlate *in vitro* data with what is observed clinically. Additionally, the introduction of preservative free formulations may allow for effective IOP lowering without the potential for compromising ocular surface health.

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IX Applying Pharmacogenomics to Improve Open-Angle Glaucoma Treatment Outcomes

Stephen G. Schwartz, Tomomi Higashide, Sayoko E. Moroi

Abstract

At present, pharmacogenomics is an evolving discipline in medicine. Within ophthalmology, some of the earliest candidate gene-based investigations have occurred in relation to open-angle glaucoma. Two important classes of drugs used to treat open-angle glaucoma are β-adrenergic receptor antagonists and prostaglandin analogs. One small clinical trial has suggested an association between polymorphisms in the β_1-adrenergic receptor gene with clinical response to betaxolol. A second small clinical trial has suggested an association between polymorphisms in the prostaglandin $F_{2\alpha}$ receptor gene and clinical response to latanoprost. A small pilot study based on intraocular pressure elevation following treatment with intravitreal triamcinolone acetonide did not find an association with polymorphisms in the glucocorticoid receptor gene. At present, we lack of markers that are predictive of pressure response to certain glaucoma drug

classes and side effects, such as steroid-induced glaucoma. The application of pharmacogenomic approaches to understand inter-patient variability in response to certain glaucoma treatments will lead to targeted treatments based on genetic profiles that are predictive of drug response. Such targeted therapy will minimize non-responders, which will lead to improved treatment outcomes. Furthermore, pharmacogenomic research focused on glaucoma may lead to development of novel treatments.

Introduction

Based on the results of the randomized clinical trials, intraocular pressure (IOP) reduction has been validated to delay progression of open-angle glaucoma. Among the choices from five major drug classes, there are the more commonly used prostaglandins and beta-blockers compared to alpha-adrenergic agents and carbonic anhydrase inhibitors, and the least used are the cholinergics. The optimal treatment should lower IOP maximally, have minimal side effects, and be affordable. However, a major clinical challenge remains because there are clearly some patients who are 'non-responders'.[1] A secondary data analysis of pooled data from phase three clinical trials comparing 0.5% timolol twice daily versus 0.0005% latanoprost daily and demonstrated that 28% of patients treated with timolol, and 18% of patients treated with latanoprost were non-responders.[2] We cannot predict those individuals who are non-responders nor can we predict the efficacy of IOP-lowering which is relevant to achieve the appropriate target IOP range for the patient.

Interestingly, the issue of 'unresponsiveness' to topical beta-blockers was acknowledged in a design and power calculations of a masked, randomized, five-year clinical trial that assumed a '10% rate of unresponsiveness to timolol'.[3] The mechanisms for this variable response rate remain are largely unknown. There have been suggestions of variations in medication efficacy based on race. For example, travoprost may be relatively more effective in patients of African descent, while timolol may be relatively less effective in these patients.[4] However, in the Ocular Hypertension Treatment Study (OHTS), there were no statistically significant differences in IOP response to non-selective beta-blockers or prostaglandin analogues between self-identified African American and white individuals.[5]

Therefore, initiation of glaucoma medication is carried out in a 'trial and error' fashion. Clinicians need to evaluate the IOP responses of the prescribed drugs, and, if the effects are lower than expected, switching or addition of drugs should be considered. However, determination of IOP responses is not an easy task. A number of factors including IOP fluctuations, error in IOP measurements and compliance of patients may modify the post-treatment IOP value and make the true IOP response difficult to know. Furthermore, the true IOP response may vary over time.[6] A one-eye trial of glaucoma medication, where the untreated eye serves as a control to subtract the IOP fluctuations, has been advocated to assess the IOP responses.[7] However, the limitation of clinical usefulness of the

one-eye trial has been questioned by several reports due to asymmetrical IOP fluctuations, especially in glaucoma patients.[8,9] Also, a one-eye trial is not suitable for drugs with contralateral effects, such as beta blockers. Therefore, IOP measurements at several time points before and after treatments are thought to be necessary to estimate the true IOP responses on average, which require considerable time and efforts for both clinicians and patients.

If pharmacogenomics helps us to predict the IOP response correctly, we can avoid prescribing a drug with low efficacy, and we do not need to worry about if the patient is a non-responder or not. Selection of glaucoma medication can be individualized based on the predicted drug efficacy determined by genetic backgrounds of each patient[10,11] At this time, the published pharmacogenomic reports have based on a 'candidate gene' approach that focused on genes related to β-adrenergic antagonists and prostaglandin analogs. In addition, preliminary efforts have investigated the steroid response associated with intravitreal triamcinolone acetonide (IVTA).

Beta-adrenergic antagonists

The β-adrenergic antagonists include several non-selective agents (β_1- and β_2-antagonists), such as timolol maleate, and one β_1-selective agent, betaxolol hydrochloride. In the US, the non-selective agents are more widely used, primarily because of their greater efficacy.[1] Although timolol appears relatively less effective in African American patients,[12,13] this was not replicated in a later study.[5] Similarly, the difference in efficacy between the non-selective and selective β-antagonists has also never been fully explained and has, perhaps, negatively impacted the development of other β_1-selective medications. The interpatient variability in response seen with betaxolol appears similar to the interpatient variability long observed with systemic β_1-blockers used in the treatment of systemic hypertension.[14]

The β-AR is a cell surface receptor member of the superfamily of guanine nucleotide-binding regulatory proteins (G protein coupled receptors).[15] There are three β-ARs, β_1-AR, β_2-AR and β_3-AR are encoded by the genes *ADRB1, ADRB2*, and *ADRB3* located at 10q24-26, 5q31-32, and 8p12-p11.2, respectively.[16] Among these three β-ARs, the β_1-AR and β_2-AR are relevant to aqueous humor dynamics. Of interest, the β_1-AR gene contains two well-characterized single nucleotide polymorphisms (SNPs)[17] and the β_2-AR gene contains four.[18] Among these SNPs, some are of interest because they change an amino acid that has the potential to alter protein function.

Beta$_1$-adrenergic receptor

At nucleotide 145, an A→G substitution leads to a serine→glycine (Ser→Gly) exchange at codon 49, within the extracellular amino terminus, resulting in increased basal and agonist-promoted adenyl cyclase activity.[19] The minor allele, Gly145, occurs in about 14% of people of both Caucasians and African Americans.[20]

At nucleotide 1165, a C→G exchange leads to an arginine→glycine (Arg→Gly) substitution at codon 389, within the intracellular portion of the molecule, near the carboxyl terminus, with a proposed G protein-binding domain.[21] The Arg389 variant exhibits an increase in agonist-promoted desensitization and higher basal and agonist-induced adenyl cyclase activity.[21,22] The minor allele, Gly389, occurs more frequently in African Americans (42%) than in Caucasians (27%).[20] This discrepancy may be clinically significant, given the greater prevalence of primary open-angle glaucoma among African Americans.[23]

The first demonstration of an ophthalmologic pharmacogenomic relationship with the β_1-AR was published in 2005.[24] In a prospective, nonrandomized clinical trial, 48 consecutive normal volunteers were treated with betaxolol for six weeks. The Arg389 homozygote genotype was associated with a significantly higher baseline IOP and a significantly greater magnitude of response to betaxolol therapy. Using multivariable linear regression, the Arg389 homozygote genotype was independently associated with a higher baseline IOP and a greater magnitude of response to betaxolol therapy, even after adjusting for baseline IOP. There were no statistically significant associations found with respect to the polymorphisms at codon 49. It is important to note that this study was performed on normal volunteers and may not be applicable to patients with open-angle glaucoma or ocular hypertension. Similarly, this study may not be applicable to the more widely used non-selective β antagonists, such as timolol. Nevertheless, this was the first demonstration of a pharmacogenomic relationship regarding clinical efficacy of a glaucoma medication.

In a prospective study of 19 glaucoma patients and 18 normal volunteers treated with timolol, Ser49 homozygotes demonstrated lower heart rate, higher systolic arterial pressure, and higher diastolic arterial pressure than Gly49 carriers under the conditions evaluated.[25]

Beta$_2$-adrenergic receptor

In a region corresponding to the leader cistron, a regulatory 19 amino acid peptide, at nucleotide –47, a T→C exchange leads to a cysteine→arginine (Cys→Arg) substitution at codon 19.[26] The Cys19 variant is associated with increased receptor density in culture.[27] At nucleotide 46, a G→A exchange leads to a glycine→arginine (Gly→Arg) substitution at codon 16. The Gly16 variant associates with increased agonist-induced downregulation of the β_2-AR.[28] At nucleotide 79, a C→G exchange leads to a glutamine→glutamic acid (Gln→Glu) substitution at codon 27, which associates with absent agonist-induced downregulation of the β_2-AR.[29] At nucleotide 491, a C→T exchange leads to a threonine→isoleucine (Thr→Ile) substitution at codon 164, in the ligand-binding pocket, which associates with decreased coupling to Gs protein and subsequent lower adenyl cyclase activity.[28]

In a prospective study of 89 normal volunteers treated with timolol, no association was found between clinical efficacy of timolol and the Arg16/Gln27, Gly16/Gln27, and Gly16/Glu27 variants.[30] In a large and well-powered primary

open-angle glaucoma (POAG) case-control study comparing white versus black African ancestry, there were no differences in *ADRB2* alleles and haplotypes between the POAG cases and control groups, whether analyzed together or by ancestry. Previously described ancestry-based differences in allele frequencies were found, as well as the expected ancestry-based differences in ADRB2 haplotypes. Thus the ADRB2 gene is not a glaucoma susceptibility locus, and can be studied for its role in variation of IOP and response to topical beta blockers.[31]

Prostaglandin analogs

Similar to the β-adrenergic antagonists, the prostaglandin analogs have shown a variable rate of non-responders. For example, one small, retrospective survey reported a 25% incidence of patients with a poor response to latanoprost.[32] Latanoprost is a highly selective agonist against the prostaglandin $F_{2\alpha}$ (FP) receptor.[33] The FP receptor gene is located on chromosome 1p31.1, and belongs to the family of G protein coupled receptors.[34,35]

The first demonstration of a pharmacogenomic relationship with the FP receptor was published in 2007.[36] In a prospective, nonrandomized clinical trial, 100 normal volunteers were treated with latanoprost for one week. The authors studied ten polymorphisms, of which two were novel. The polymorphisms rs3753380 and rs3766355 showed statistically significant associations with the magnitude of response to latanoprost in this study. The promoter assay revealed that the C allele of rs3766355 and T allele of rs3753380 were associated with lower transcriptional activity of the FP receptor gene, which was in agreement with the differences of IOP response to latanoprost based on genotypes of these SNPs.

The FP receptor is involved in IOP regulation via a pathway consisting of various proteins, including prostaglandin transporter (PGT), fatty acid amide hydrolase (FAAH) that is responsible for the activation of all prostaglandin prodrugs,[37] prostaglandin F2α receptor regulatory protein (FPRN)[38] and MMPs[39-41] As a preliminary experiment, the correlation between percent IOP reduction and the following polymorphisms that were reported previously was examined: T396A in PGT,[42] P129T in FAAH,[43] T277S, N576K, and I837V in FPRN [NCBI database], -1607 insG in MMP-1,[44] C-1306T in MMP-2,[45] -1171 delA in MMP-3,[46] and C-1562T[47] and CA repeats (-131~-90) in MMP-9.[48] However, no significant correlation was found between genotypes of these SNPs and IOP responses to prostaglandin analogs. It remains possible that new SNPs that are associated with IOP reduction by latanoprost will be identified in these genes.[36]

Corticosteroid-induced glaucoma

A subset of patients will develop increased IOP and secondary open-angle glaucoma when exposed to corticosteroids.[49] The etiology of this steroid response has never been fully explained, although a genetic determinant has long been suspected.[50,51]

Off-label injection of intravitreal triamcinolone acetonide (IVTA) has gained in popularity to treat a variety of retinal diseases, including exudative age-related macular degeneration[52] and macular edema secondary to diabetes mellitus[53] retinal vein occlusion,[54] and other causes. Clinically significant elevation of IOP has been reported in about 40% of patients.[55]

The dramatic up-regulation in expression of the myocillin gene (*MYOC*) in cultured trabecular meshwork cells exposed to dexamethasone was initially demonstrated as the trabecular meshwork inducible glucocorticoid response (*TIGR)* gene. Mutations in MYOC are estimated to cause open-angle glaucoma in both juvenile onset and a proportion of POAG cases.[56] There is no statistically significant evidence of a link between *MYOC* mutations and steroid-induced ocular hypertension.[57] A recent study of cadaver eyes found that exposure to timolol reduced *MYOC* RNA levels from trabecular meshwork cultures in one of three patients. Exposure to timolol did not affect *MYOC* induction by dexamethasone.[58]

Glucocorticoid receptors are present on the surface of trabecular meshwork cells, providing a possible mechanism for corticosteroid action on intraocular outflow pathways.[59] There are six well-known polymorphisms in the human *GR* gene, making this a reasonable gene for candidate gene analysis.[60-64] However, in a pilot study comparing short-term IOP fluctuations following IVTA with the *GR* genotype, there were no statistically significant associations detected between any of the 6 studied polymorphisms and IOP response following IVTA.[65] [Gerzenstein, S.M. et al. 2008].

Future directions

Despite the recent advances in ophthalmic genetics, there is still much that remains to be elucidated with pharmacogenomic applications to glaucoma therapeutics. For example, to our knowledge, there are currently no peer-reviewed data regarding possible pharmacogenomic relationships affecting other medications used in the treatment of glaucoma, such as carbonic anhydrase inhibitors, α_1-agonists, and cholinergic agents.

Even within the systems described here, there are many additional candidate genes and pathways for future association studies. With newer molecular methods, genome-wide approaches will encompass the logical candidate genes, but provide potentially added information relevant to the pathways involved in these targets and aqueous humor dynamics.[11] Both the β-adrenergic receptor and the prostaglandin $F_{2\alpha}$ receptor pathways utilize a second messenger system, interacting with a G-protein, a primary effector, a secondary messenger, and secondary effectors. Elements of these pathways, as well as their regulatory components, are reasonable candidates for future analysis. These are summarized in Table 1. For example, within the β-AR pathway, the gene *GNAS1* codes for the G protein and contains a silent polymorphism in the region encoding the α subunit. This T→C substitution at base position 393 associates with systemic β-blocker response.[66]

In addition, timolol is metabolized by the cytochrome P450 enzyme CYP2D6; the gene CYP2D6 contains polymorphisms that associate with variations in the biodisponsibility of the drug.[25] The CYP2D6 phenotype can be classified according to the level of CYP2D6 activity; poor, extensive, intermediate, and ultra-rapid metabolizers. Poor metabolizers are at risk of drug side effects due to a sustained high plasma level of the drug. In case of timolol, poor metabolizers in healthy subjects had a suppression of increase in heart rate in response to maximal exercise after treatment with aqueous timolol.[25,67] Another recent study reported a significant relationship between a SNP, Arg296Cys, in CYP2D6 gene and timolol-induced bradycardia in patients with primary open-angle glaucoma.[68] However, in that study, the effect of genotype of SNPs in CYP2D6 gene on IOP-lowering effects of timolol remained inconclusive. The information of genotype of SNPs in CYP2D6 gene may be useful to identify poor metabolizers who are at risk of systemic side effects of timolol.

Conclusions

The challenge of genomics is to determine if we can predict disease risk, disease progression and treatment outcome, despite the intricate biological and physiological interactions among expression of drug target genes, drug metabolizing enzymes, and disease genes. Using candidate gene approach, early pharmacogenomic studies related to glaucoma treatments show some evidence that polymorphisms in the β_1-AR and the prostaglandin $F_{2\alpha}$ receptor affect clinical response to, respectively, betaxolol and latanoprost in normal volunteers. These preliminary results need to be investigated in patients with ocular hypertension or open-angle glaucoma. In contrast, there is currently no convincing evidence of a pharmacogenomic relationship with respect to steroid-induced glaucoma. However, newer molecular methods using a genome-wide approach will lead to discovery of potential pharmacogenomic associations in patients who are steroid responders, which could lead to a molecular drug target for future therapy of steroid-induced glaucoma, as well as a better understanding of the steroid response.

Identification of genetic markers of ‘poor IOP responders’ has the potential to target those patients with disease to more appropriate treatment, such as surgery, to lower IOP more effectively thus minimizing progressive optic nerve damage and visual field loss. Such genetic markers will need to be tested in stratified patient populations for predictive value, and then validated in separate cohorts. A cost-benefit analysis with economic modeling will also need to demonstrate the health benefits and long-term cost savings to improve treatment outcomes and thereby decrease disease morbidity. The coverage of genetic testing will be determined through the process of technology assessment by national insurance and private payors.[69,70] The future application of such a genetic profile could lead to fewer return office visits for follow-up for changed medical therapy, thus improving treatment outcomes.

Table 1. Candidates genes for future association studies

Pathway	B-adrenergic receptor	Prostaglandin $F_{2\alpha}$
Transducer	Gs protein	Gq protein
Primary effector	Adenyl cyclase	Phospholipase C
Secondary effector	Protein kinase A	Protein kinase C

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Norbert Pfeiffer, Arthur Sit and Remo Susanna.

Norbert Pfeiffer.

Arthur Sit.

Jost Jonas and Leo Schmetterer.

Ivan Goldberg, Consensus co-Chair.

Tarek Shaarawy.

4. SELECTION OF DRUGS

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Consensus statements

1. Only the IOP lowering effect should be considered to define the comparative efficacy of an ocular hypotensive agent.
2. Initiation of therapy: prostaglandin analogues (PGA) are recommended as first choice agents for most eyes with glaucoma.
3. IOP reduction with initial monotherapy should be at least 20% from baseline.
   Comment: IOP reduction of less than 10% should be considered as non-response.
   Comment: Switching drugs within the PGA class may, upon occasion, provide greater IOP lowering.
4. Adjunctive therapy is indicated when existing therapy fails to reach the target IOP.
   Comment: Adjunctive therapy should be limited to one drug from each class.
   Comment: The efficacy of a drug when used as monotherapy is usually less when used as an adjunctive agent.
5. Provided the use of the combination product is as efficacious as the two components administered independently, fixed-combinations are preferred when possible over the use of two separate bottles due to convenience, reduced amount of preservative instillation and possible improved adherence.
   Comment: Evidence is lacking that fixed combination products provide better outcomes than the individual components delivered separately.
6. Surgery is indicated when medical therapy fails to adequately lower the intraocular pressure or prevent progression, the risk of progression remains too high despite the use of medical therapy, or is not possible due to allergy, intolerance, poor adherence or lack of availability.

Lowering intraocular pressure (IOP) is the only proven treatment that is able to halt or delay the visual field loss and the progression of glaucomatous optic neuropathy. Lowering IOP also reduces the risk of conversion to glaucoma in

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eyes at risk for the disease. Although laser and incisional surgery can effectively reduce IOP, treatment with topical eye drop medications remains the preferred initial treatment worldwide because of its favorable risk-benefit profile.

Although the effectiveness in lowering IOP is a key criterion for drug selection, other factors also need to be considered. As is the case for initiation of drug treatment for any disease, an evaluation for patient-specific ocular and systemic contraindications, interference by and with systemic medications, and cost are additional factors that need to be considered for both initial and adjunctive therapy. Nevertheless, only the extent of IOP lowering should be considered to define the efficacy of an anti-glaucoma agent because IOP lowering is, as mentioned above, the only proven treatment for glaucoma.[1] Non-IOP lowering benefits claimed for some medications are insufficiently supported by data to warrant current consideration when making treatment decisions.[2]

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Initial therapy options

Christopher Girkin, Ivan Goldberg

Of the variety of available medical therapy options, prostaglandin analogues (PGA) are the optimal and recommended first-line agent in most settings where these agents are available. PGAs provide the best sustained IOP-lowering profile over 24 hours when compared to other classes of eye drops, have a maximal once-daily dosing frequency, and enjoy widespread patient acceptance because of their ease of use, ocular tolerability, and lack of systemic side effects, all of which compare favorably with other agents. PGAs should be used as first-line therapy unless other issues, such as PGA-specific contraindications or availability, are an issue.

Although any approved drug may be used as initial therapy for an individual patient, a non-selective beta-adrenergic antagonist is the preferred alternative to a PGA. They are useful particularly if PGAs are unavailable in a specific location because of regulatory issues, cost, or availability or if PGAs are not preferred by a patient due to possible side effects (*e.g.*, iris discoloration). Topical beta-blockers offer the advantages of once-daily dosing and excellent local tolerability, although they are generally less effective at reducing IOP, pose systemic safety risks in susceptible individuals, and appear to be ineffective during the nocturnal period.

Adjunctive therapy

Fabian Lerner, Ivan Goldberg

Treatment with a single IOP-lowering agent (monotherapy) may not provide sufficient IOP reduction to adequately slow the process of glaucomatous neurodegeneration. In this circumstance, most physicians will alter treatment to provide further IOP reduction. Indications for therapy advancement include progression of the disease, even at the pre-determined target IOP range and/or failure to reach or maintain the target IOP. The risks, benefits, costs and alternatives of additional treatment should be assessed on an individual basis. In general, the risk-benefit and cost-benefit of providing adjunctive medical therapy favors increased treatment, particularly when optic nerve or visual field progression has been documented.

Therapeutic options when initial monotherapy is deemed insufficient include switching medications to a new form of monotherapy (to keep the number of drugs used to a minimum), adding medications (adjunctive therapy), or laser or incisional surgery.

Switching medications

Switching a medication is indicated if initial therapy fails to reduce IOP or the reduction is insufficient (there is a non-response). One definition employed by many physicians is that an IOP reduction of ≤ 10% suggests a non-response to that agent. Assessment of the effectiveness of an agent usually requires more than one IOP measurement after starting treatment. MEDICATIONS THAT DO NOT LOWER THE IOP SHOULD BE DISCONTINUED. If the initial therapy reduction is 10-20%, the drug may be switched. Further, the moderate effect should be documented in the chart for this drug, since it may be tried again as an adjunctive agent if additional therapy is needed in the future.

Switching to different monotherapy may be done using a drug from a different class of medications (*e.g.*, switching from a beta-blocker to a PGA) or within the class if the initial drug was a PGA (*e.g.*, switch a PG analog to another PG analog). There is widespread consensus that switching monotherapy within medication class for medications other than PGAs is not effective.

Adjunctive therapy

If initial therapy has reduced the IOP, but further lowering is needed, a second drug may be added. The efficacy of the two drugs acting together will depend on the class of drugs and their mechanisms of action. No additivity is expected when using two agents from the same class, *i.e.*. two beta-blockers or two PGAs. Therefore, adjunctive treatment should be limited to one drug from each class, for example adding a beta-blocker to a PGA. Drugs may be additive even when the mechanism of IOP-lowering is similar. For example, both a topical CAI and a beta-blocker lower IOP by reducing aqueous humor formation, but the IOP

reduction when used concomitantly is greater than when either medication is used alone.[1-3] The same happens with two drugs that enhance outflow; there can be an additional pressure-lowering effect, albeit often minimal, when a cholinergic agent and PGA are used together.[4]

Typically, the efficacy of a drug as monotherapy is reduced when used as adjunctive therapy. The adverse effects of two adjunctive drugs are generally, but not always, the same as the adverse effects of the two drugs separately (there are no 'new' adverse effects when both drugs are used together).

Selection of an adjunctive drug

Selection of an adjunctive drug to initial therapy with PGAs

Most other classes of medications provide additional IOP lowering when used as adjunctive agents to PGAs. The most commonly used adjunctive agents are beta-blockers (timolol), topical CAIs (dorzolamide or brinzolamide) and alpha agonists (brimonidine).

Various studies have shown a statistically significant reduction of the IOP when adding a beta-blocker, either once or twice a day, to a PGA,[5-8] although this effect may be blunted in patients using oral beta-blockers for systemic diseases. A recent retrospective review calculated the additional IOP-lowering effect of several drugs at one to three months after at least a two-week run-in phase of latanoprost.[9] Brimonidine added to latanoprost reduced mean diurnal IOP an additional 2.1 mmHg, similar to the reduction produced by dorzolamide.[10] The addition of brinzolamide to travoprost produced a statistically lower IOP when compared to the addition of brimonidine to travoprost, although the clinical significance of this difference between added drugs is unclear (2.1 mmHg additional mean IOP reduction for brimonidine versus 2.7 for brinzolamide).[11] Conversely, Tabet *et al*. evaluated the additivity of different agents to PGA[12] and found that lowering efficacy of available adjunctive agents to PGAs is limited; regardless of which agent was chosen, less than 15% of added lowering in IOP was achieved. Brinzolamide provides additional 24-hour IOP lowering when added to latanoprost as compared with timolol, and a CAI may be particularly advantageous when added to a PGA as an adjunctive agent.[13]

Selection of an adjunctive drug to initial therapy with beta-blockers

Fixed combination agents containing beta-blockers (timolol-CAI, timolol-PGA, timolol-alpha agonist) are discussed in another section.

Adjunctive agents generally used in conjunction with beta blockers are PGAs (latanoprost, travoprost or bimatoprost), topical CAIs (dorzolamide or brinzolamide) and alpha agonists (brimonidine).

In two studies, latanoprost added to timolol produced a significantly reduction of IOP (2.9 mmHg difference,[14] while travoprost added to timolol reduced

the IOP an average of 2 mmHg after three months.[15] A similar reduction was obtained when adding bimatoprost to timolol.[16]

Adjunctive therapy with a topical CAI

Both dorzolamide and brinzolamide provide an additional reduction of IOP when added to timolol. Dorzolamide has been reported to reduce the IOP an additional 11-16% at trough and 20-22% at peak when added twice a day to timolol (also used twice a day).[17,18] Brinzolamide twice a day also produced an additional lowering of IOP when added to timolol twice daily of 14.2% at trough and 21.9% at peak.[19]

Adjunctive therapy with an alpha agonist

In a study comparing the use of timolol twice a day vs brimonidine thrice daily vs the fixed-combination timolol/brimonidine twice a day, there was a 2.0-2.3 mmHg lower mean difference of IOP in the fixed-combination group[19] compared to the timolol-alone subjects.

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Combination therapy – fixed-dose combination (FC)

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Fixed-dose combination (FC) eye drops are the fastest growing segment of the IOP lowering topical medications; in most countries prostaglandins or topical CAIs or alpha2 agonists or pilocarpine, each combined with timolol, are available as FCs. Currently, all FC contain beta-blockers, and all share the same contraindications with beta-blockers.

Fixed-dose combinations

Many practitioners are using fixed combinations as first choice, especially when a lower target IOP is desired initially. However, one should recall that there is a difference between *first-choice treatment* and *first-line treatment*. First-choice treatment refers to a drug that a physician prefers to use as initial IOP-lowering therapy,[1] while first-line drug treatment is one that has been approved by an official controlling body (*i.e.*, EMEA, CPMP or FDA) for initial IOP-lowering therapy.[1] It should be noted that no official body has yet approved any FC as first-line treatment. Although theoretically FCs offer significant benefits for

patients, there is insufficient evidence that these perceived advantages translate into real advantages.[2-10]

When combination treatment is needed, *i.e.*, two or more active molecules are to be used to try to obtain adequate IOP lowering, FCs may offer the following advantanges (in no particular order):

1. Reduced inconvenience for the patients because of
   a. one bottle rather than two;
   b. a reduced number of total drop instillations;
   c. no need for a time gap between drops so as to reduce dilution and to maximize penetration (no proof of this in humans nor of the minimum minutes of interval, five to ten minutes generally accepted);
   d. reduced cost (needs to compare with generics in separate bottles);
   e. increased compliance, adherence (no proof exists yet regarding FCs).
2. Less exposure to preservatives, due to decreased number of instillations (difficult to compare with adjunctive therapy since an increasing number are now preservative-free).
3. Better effect on IOP than separate instillation of the same two products (no proof exists yet).
4. At least the same effect on IOP as separate instillation of the same two products.

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Surgery and medications

There are several indications for advancing to surgery from medical treatment. These are summarized below. It should be kept in mind that chronic medical therapy may have a negative effect on the success of incisional surgery.[1,2] Moreover, even after surgery, patients should be advised that restarting medical therapy is always possible.[3]

Indications for advancing to surgery from medical treatment

- IOP is likely to cause disease progression despite maximal tolerable medical therapy.
- Visual loss has been demonstrated, or is highly likely, despite best efforts with medical therapy.
- Non-adherence, non-persistency and/or dyscompliance have been demonstrated, even without documented progression.
- Medical therapy has to be discontinued due to ocular allergic or toxic effects, or due to systemic adverse effects.
- Medical therapy is unavailable or inaccessible to the patient; in such cases surgery may be warranted as a primary therapeutic strategy.

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5. MEDICAL TREATMENTS OF OTHER TYPES OF OPEN-ANGLE GLAUCOMA

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Consensus statements

1. PG analogs are first choices for monotherapy in pseudoexfoliative glaucoma and pseudoexfoliation syndrome with ocular hypertension when treatment is required.
   Comment: Pilocarpine can reduce iris movements in eyes with pseudoexfoliation and, therefore, may reduce deposition of exfoliation material or pigment in the trabecular meshwork.
2. PGAs are first choices for monotherapy in pigmentary glaucoma.
   Comment: Pilocarpine can be effective in pigmentary glaucoma in reducing reverse pupillary block and diminishing iris movements.
3. Medical treatment of inflammation is first line treatment for uveitic glaucoma.

Medical treatment of exfoliative (*i.e.*, pseudoexfoliative) glaucoma

Exfoliation syndrome (XFS) is an age-related, generalized disorder of the extracellular matrix (ECM) characterized by the production and progressive accumulation of a fibrillar extracellular material in many ocular tissues. It is the most common identifiable cause of open-angle glaucoma worldwide, accounting for the majority of cases of this disease in some countries. It is associated systemically with an increasing number of vascular disorders, hearing loss, and Alzheimer's disease. The characteristic fibrils, composed of microfibrillar subunits surrounded by an amorphous matrix comprising various glycoconjugates,

Medical Treatment of Glaucoma, pp. 141-154
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contain predominantly epitopes of elastic fibers, such as elastin, tropoelastin, amyloid P, vitronectin, and components of elastic microfibrils, such as fibrillin-1, fibulin-2, microfibril-associated glycoprotein (MAGP-1), and latent TGF-ß binding proteins (LTBP-1 and LTBP-2), the extracellular chaperone clusterin, the cross-linking enzyme lysyl oxidase, and other proteins. Two common single nucleotide polymorphisms (SNPs) in the coding region of the lysyl oxidase-like 1 (LOXL1) gene located on chromosome 15 are specifically associated with XFS and XFG in many populations. In Japan, one SNP is the same and one is different. Lysyl oxidases are essential for the formation, stabilization, maintenance, and remodelling of elastic fibers. LOXL1 protein is a major component of exfoliation deposits and appears to play a role in its accumulation and in concomitant elastotic processes in intra- and extraocular tissues of XFS patients. This discovery should open the way to new approaches and directions of therapy for this protean disorder.

Mechanism of open-angle glaucoma

Friction between the iris and the exfoliation material (XFM) covering the lens surface leads to disruption of the iris pigment epithelium at the sphincter and pigment liberation. Just as the iris scrapes XFM from the lens surface, the material on the lens causes rupture of iris pigment epithelial cells at the ruff and sphincter region with concomitant dispersion of pigment into the anterior chamber. Blockage of aqeous outflow by a combination of pigment and XFM deposited in the intertrabecular spaces, and XFM in the juxtacanalicular meshwork, and beneath the endothelium of Schlemm's canal is believed to be the major cause of elevated IOP. Although exfoliative glaucoma (XFG) is characteristically a high-pressure disease, pressure-independent risk factors, such as an impaired ocular and retrobulbar perfusion and abnormalities of elastic tissue of the lamina cribrosa, may be present and further increase the individual risk for glaucomatous damage.

Epidemiology

The prevalence of XFG increases steadily with age, although there are wide racial or ethnic differences. More than half of XFG is diagnosed unilateral, but microscopic examination showed that pseudoexfoliation material exists prior to the clinically visible appearance of exfoliation material in the fellow eye.[1]

Patients with XFG have a higher risk of converting from ocular hypertension to glaucoma and the prognosis of XFG is more severe than that of primary open-angle glaucoma (POAG).[2,3]

XFG shows greater intraocular pressure (IOP), greater 24-hour IOP fluctuation, greater visual field loss, and optic disc damage at the time of detection than POAG. XFG also has a poorer response to medications, more rapid progression, and greater need for surgical intervention than POAG.

Medical management

The fundamental approach to the medical treatment of eyes with XFG is similar to POAG. Medical or laser treatment is usually recommended as first line therapy. However, ophthalmologists need to recognize that XFG is more likely to be recalcitrant to medical treatment and require surgical treatment than POAG.

Prostaglandin analogue

The most effective therapy for XFG is IOP reduction and initial medical treatment is a topical prostaglandin (PG) analogue because of the excellent hypotensive performance, including 24-hour IOP reduction and suppression of IOP fluctuation.[4] The mechanism of XFG IOP elevation is the production and progressive accumulation of a fibrillar extracellular material in the trabecular meshwork, resulting in resistance of outflow facility. It has been reported that suppression of aqueous humor production leads to worsening of trabecular function.[5] From a clinical point of view, it is a controversial point if aqueous humor suppression for XFG worsens trabecular meshwork function. PGs are rational choice for treatment of PXF glaucoma, because PGs enhances uveoscleral outflow to reduce IOP. Latanoprost treatment had a marked effect on the aqueous concentration of TGF-ß1, MMP-2, and TIMP-2 in XFG patients.[6]

Latanoprost provided a narrower range of diurnal IOP fluctuation compared to timolol.[7] Bimatoprost and travoprost may provide a statistically greater IOP reduction than latanoprost.[8,9] However, further investigations are necessary to conclude this due to the limited number of reports.

Miotics

Cholinergic agents have multiple beneficial actions in eyes with XFS. Not only do they lower IOP, but they should enable the TM to clear more rapidly, by increasing aqueous outflow and by limiting pupillary movement, and slow the progression of the disease. Becker proposed suggestive evidence that treatment with aqueous suppressants leads to worsening of trabecular function.[10] Theoretically, miotics should be the first line of treatment. The use of miotics, unfortunately, has almost disappeared from use in glaucoma on the basis that they are considered a q.i.d. drug and because many patients have nuclear sclerosis and miotics may reduce visual acuity or dim vision sufficiently to create difficulty. Pilocarpine has also been shown to blunt an early morning IOP spike which often occurs in the supine position after a night's sleep.[11] The long-term use of miotics may lead to the development of posterior synechiae in patients with XFS. However, 2% pilocarpine q.h.s. sometimes can provide sufficient limitation of pupillary mobility without causing these side effects.

Aqueous suppressants

Aqueous suppressants do not interfere with the mechanism of the cause of progression of trabecular meshwork damage, *i.e.,* iridolenticular friction and disruption of the iris pigment epithelial cells. Aqueous suppressants reduce IOP, although suppression of aqueous humor production theoretically has a possibility of worsening of trabecular function. Beta-blockers have equal[12] or greater[13] ocular hypotensive effect in eyes with XFG than those with POAG. Dorzolamide is almost as effective as timolol and is additive when combined with it.[14] There is no clear evidence that indicates aqueous suppressants increase iridolenticular friction and disruption of the iris pigment epithelial cells of eyes with XFG.

Other anti-glaucoma drugs

There are no contraindicated anti-glaucoma medications for eyes with PXF glaucoma. A greater additive effect of epinephrine with timolol has been reported in XFG than in POAG.[15]

Apraclonidine 0.5% adjunctively used with timolol maleate 0.5% reduced IOP of PXF glaucoma as same as POAG.[16]

Remarks

Sudden IOP elevation

PXF glaucoma sometimes showed sudden IOP elevation especially within the first two years after treatment.[17] Frequent and careful observation is necessary.

Future therapy

For most of the twentieth century, glaucoma was equated with elevated IOP, and all therapy has been guided at lowering IOP. There was little incentive to attempt to distinguish between various open-angle glaucomas if the treatments were essentially the same. However, this view also prevented the application of directed therapy in those instances in which such was available and applicable.

Drugs which affect the integrity of the cytoskeleton of the TM may be a boon to the treatment of XFS and XFG, although they have not yet been examined for this purpose. Over thirty years ago, Kaufman and Bárány showed that intracameral cytochalasin B caused an increase in outflow facility in eyes of cynomolgus monkeys.[18] Use of such agents never came to fruition in patients because of potential toxicity, particularly to the cornea, but it can be seen that a washout of extracellular material from the TM might be a breakthrough approach to the treatment of XFS if the blockage to the TM could be removed and have a long-lasting effect. The serine-threonine protein kinase inhibitor H-7 was shown to have a similar effect on the TM by a different mechanism, probably by inhibiting cell contractility, cytoskeletal support, and cell-cell adhesions in the TM.[19]

Topical latrunculin B increases aqueous outflow facility by a similar mechanism without affecting the cornea.[20,21] Latrunculins bind to the free actin in the cell, preventing it from polymerizing into microfilaments. The existing actin cytoskeleton gradually degenerates, leading to a large increase in outflow facility.[22]

Potential therapy aside from lowering IOP

Understanding the mechanisms leading to elevated IOP in XFS could stimulate new, more logical approaches to therapy. The eventual goal is to prevent the development of XFM, thus effectively curing this disease. A treatment which would eliminate the formation of XFM or depolymerize it once formed should be a prime goal. Possible approaches include finding a means to prevent it from aggregating initially, prevent it from cross-linking, disaggregating the fibrils, and depolymerizing the microfibrils.

Homocysteine (HCY)

Mild hyperhomocysteinemia (HHCY), a common recognized cardiovascular risk factor, may result from a variety of causes affecting HCY metabolic pathways HHCY in animals is associated with disruption of the elastic fiber component of the ECM, with resulting vascular complications.[23] Elevated HCY levels are present in blood, aqueous humor, and tear film in patients with XFS.[24-29] The systemic abnormalities associated with XFS are also associated with HHCY, which appears to be a common thread extending through both XFS and the systemic disorders associated with it.

In a large study of 24,968 healthy women, HCY levels were inversely associated with intake of folate and vitamins B2, B6, and B12.[30] Treatment with folic acid and vitamins B6 and B12 reduce HCY concentrations in patients with coronary artery disease.[31] HCY might be a modifiable risk factor for XFS. Decreased serum concentration of vitamins B6 and B12 and folate has been reported in patients with XFS.[24] Because of the strong association with elevated HCY levels, one must also consider the possibility that these patients may benefit from lowering of plasma HCY by supplemental vitamins B6, B12, and folic acid.

Folate deficiency leads to altered expression of genes involved in cell signaling, the cytoskeleton and the ECM.[32] Actin disrupting agents, such as latrunculin B, reversibly increase the proportion of receptors on the cell surface and increase 33 the rate of 5-methyltetrahydrofolate delivery.[34]

Inflammation

C-reactive protein is a marker of inflammation and a predictor of cardiovascular disease, while interleukin-6, a regulator of C-reactive protein, plays a key role in the intitiation of inflammation. Patients with HHCY have elevated levels of these compounds.[33] There is evidence that XFS is accompanied by low-grade inflammation.[35]

Lysyl oxidase

Lysyl oxidase in vascular endothelia is inhibited by high concentrations of HCY. This downregulation impairs the endothelial barrier function and could be involved in HCY-induced endothelial dysfunction.[36] Endothelial dysfunction induced by tumor necrosis factor-alpha (TNF-α) is also associated with a decrease of lysyl oxidase expression or activity.[37] HHCY in animals is associated with disruption of the elastic fiber component of the ECM, with resulting vascular complications.[23]

TGF-ß1 also interacts with lysyl oxidase to influence the formation of elastic tissue,[38] and levels of TGF-ß1 are significantly elevated in the aqueous humor of eyes with XFS and are believed to be both responsible for overproduction of ECM and an important causative factor for the production of XFM.[39] TGFß-1 and ß-2 contribute to conjunctival scarring after filtering surgery.[40] Modification of TGF-ß1 activity may improve both the disease itself and the surgical treatment necessitated by it.

An eventual goal is to prevent the development of XFM, thus effectively curing this disease. A treatment which would eliminate the formation of XFM or depolymerize it once formed should be a prime goal. Possible approaches include finding a means to prevent it from aggregating initially, prevent it from cross-linking, disaggregating the fibrils, and depolymerizing the microfibrils.

Interactions between lysyl oxidase, HCY, TGF-ß1, and their effect upon elastic tissue in XFS require clarification. How do the different polymorphisms of the LOXL1 gene affect these interactions and alter elastogenesis? Will mutations in LOXL1 be discovered? Different mutations may lead to greater or lesser disease severity. In the future, will we be able to modulate LOXL1 gene activity to alter the course of XFS? These and other questions are now open to further exploration in an attempt to manage this very common and severe glaucoma.

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Medical treatment of pigmentary glaucoma

Pigment dispersion syndrome (PDS) is a genetically inherited disorder consisting in disruption of the iris pigment epithelium with liberation of pigment granules. Reverse pupillary block, in which aqueous humour pressure is greater in the anterior chamber than in the posterior chamber, is a contributing cause to iris concavity, a characteristic of this condition. The triggering mechanism of pigment liberation is rubbing of the epithelial sheath of the iris against zonular fibers during pupil movements.[1] These granules accumulate in anterior segment structures and may lead to dysfunction of the trabecular meshwork causing ocular hypertension and glaucoma.[2,3] The estimates of risk of developing pigmentary glaucoma (PG) from pigment dispersion syndrome are highly variable. Currently it is believed to be of 10% at five years and 15% at 15 years.[4] Young, myopic men are most likely to have PG. Retinal detachment may occur in as many as

6-7% of individuals with PDS/PG [5-7] and lattice degeneration can be found in 20% of the eyes.[8]

Although there is no consistent evidence on which is the preferable class of drugs to begin treatment in PDS-related OH and in PG, it is generally assumed that increasing aqueous outflow is better than decreasing inflow. The former may reduce fluctuation and IOP spikes and the latter may lead to less aqueous washing through the TM, which might be counterproductive (no evidence available).

Prostaglandin analogs may be therefore a rational first choice for some, because they are potent ocular hypotensive agents, enhance uveoscleral outflow and also offer the advantage of once daily administration. In one prospective, comparative one-year trial latanoprost has been shown to be more effective than timolol in reducing IOP in PG patients.[9] PGAs have no effect on the pigment-releasing process. The increased iris pigmentation observed in eyes submitted to their use does not lead to increased pigment dispersion because it primarily affects the iris stromal melanocytes and not the iris pigment epithelium.[10,11]

Since PG analogs do not reduce continued liberation of pigment granules, others prefer pilocarpine instead, which seems at first glance almost ideal for first choice in this condition because it increases outflow, reduces reverse pupillary block and also diminishes iris movements and, therefore, allegedly, may stop granule liberation and granule deposits in the trabecular meshwork.

For pilocarpine use in PDS-associated OH and PG, it is mandatory, due to the high rate of retinal lesions and of retinal detachment, to carry out a complete examination of peripheral retina prior to its indication and to repeat it in the long term. Other disadvantages of pilocarpine (instillation frequency, refractive changes, QoL deterioration in patients with an importantly damaged VF and syecheiae and cataract formation making the use of pilocarpine less common in pigmentary glaucoma.

To overcome some of the disadvantages of pilocarpine use in PDS-associated OH and PG, a once-daily 2%-pilocarpine instillation has been suggested (R Ritch-unpublished data), but this is unproven. At that dosage and concentration the process of liberation and deposition of pigment granules may be stopped while synechiae and accommodation disturbances may be not affected (no substantial evidences supporting this). If pilocarpine is not sufficient for IOP control, another medication should be added. Although there may be some in vivo antagonism in IOP lowering effect between PG analogs and pilocarpine,[12,13] PG analogs should not be excluded as a possible addition in pilocarpine-treated individuals.

Although having been used as monotherapy in PDS-associated OH and PG, beta blockers and carbonic anhydrase inhibitors, both aqueous suppressants are less promising than the above-mentioned medications because their efficacy is inferior to PG analogs and they do not have specific anti-pigment dispersion effects like pilocarpine.

Alpha-agonists (as adrenergic compounds) are traditionally good companions to pilocarpine, as shown by clinical experience with epinephrine and dipivefrin, and their hypotensive efficacy is also better in PG than in other types of

glaucoma.[14,15] The use of brimonidine in this condition should be evaluated in controlled trials.

Fixed combinations of timolol plus a CAI or brimonidine may be chosen as an acceptable option instead of PGAs in case of important adverse effects, of non-response to them or as part of combined therapy.

The use of topical alpha-adrenergic inhibitors (thymoxamine, dapiprazole) has also been proposed for PDS/PG because they may produce miosis and reversal of posterior iris bowing without the ciliary muscle contraction and unwanted accommodation produced by pilocarpine.[16,17] These medications also reduce exercise-induced IOP rises.[18] Their use in PDS/PG should still be evaluated with controlled trials.

Argon laser trabeculoplasty (ALT), another therapy that increases outflow, has proven to be efficacious in this condition with open, heavily pigmented angles, especially in younger patients, and the effect decreases with age 19-21. In comparison with POAG patients submitted to the same procedure, the hypotensive effect in PG individuals is of shorter duration.[19,20] Available evidence on Selective Laser Trabeculoplasty (SLT) in PG is scarce since the largest SLT studies have included few eyes with the condition. McIlraith *et al.*,[22] at one-year follow-up, have found no differences in effect based on angle pigmentation. Harasymowycz *et al.*,[23] in a study on 167 SLT-treated patients, found out that four out of six eyes with heavily pigmented angles did not respond. They speculated that the pigment or pseudoexfoliation material accumulating at the angle may prevent prevent the low-energy laser beam from reaching the trabeculum cells. A marked and sustained IOP elevation in spite of prevention with topical brimonidine has been observed in four eyes with heavily pigmented angles in this same study. Caution with levels of energy and with distance between spots should be recommended in such eyes.

Laser peripheral iridotomy (LPI) may reduce reverse pupillary block by flattening the concave iris root.[24] Thus far, LPI proved effective in decreasing the incidence of IOP-increase (*i.e.*, the need for medical treatment) over a ten-year follow up in one randomized controlled clinical trial only, performed on PDS eyes (*i.e.*, well before the onset of an actual pigmentary glaucoma): the eyes had normal IOP on enrollment, a concave iris root and released pigment granules into the anterior chamber upon medical dilation. The effect proved greater in patients aged < 40 years.[25,26]

In summary, there is moderate evidence (level B) that LPI can decrease the incidence of progression from PDS to PG in selected phenotypes. Once PG occurs, there is no evidence that LPI offers any benefit by either slowing the progression rate or decreasing the strength of the treatment schedule.

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Medical treatment of uveitic glaucoma

The first line in medical treatment of uveitic glaucoma is treatment of the uveitis itself. If an underlying systemic diagnosis is found, this should be treated accordingly. In most cases, anti-inflammatory therapy involves the use of corticosteroids, either local (topical, periocular or intraocular), systemic or both. IOP elevation in patients with uveitis is often corticosteroid-induced[1] and in severe uveitis, immunosuppressive agents such as mycophenolate, cyclosporin, tacrolimus, and methotrexate, as well as anti-TNF monoclonal antibodies should be considered and may permit lower doses of corticosteroids to be used. Joint management with a uveitis specialist is essential in these circumstances. It is a false economy to restrict corticosteroid treatment in active uveitis in an attempt to avoid corticosteroid-induced IOP elevation. It is better to control the inflammation as required and deal with the secondary IOP elevation on its merits.

Most IOP-lowering medications may be used in the medical treatment of hypertensive uveitis or uveitic glaucoma. Topical beta blockers are usually the first-line, providing there are no contraindications. Topical carbonic anhydrase inhibitors (tCAIs) may also be used as a first or second line. The hypotensive effect of tCAIs may be unpredictable in uveitic eyes, ranging from no response, to a profound IOP reduction in some eyes that have had severe chronic inflammation and consequent ciliary body damage.[2] Topical brimonidine is less often used, partly because the resultant conjunctival injection is undesirable in eyes with ocular inflammation, prolonged use occasionally produces quite severe granulomatous anterior uveitis,[3] and also because its efficacy may be compromised by concomitant use of non-steroidal anti-inflammatory agents.[4] Fixed-combination therapies (beta blocker and tCAIs or beta blocker and brimonidine) may be used to improve compliance, and decrease exposure to preservatives.

The use of topical prostaglandin analogues (PGA) in patients with elevated IOP and uveitis is still the subject of some controversy. There are reports suggesting a causal relationship between the use of PGA and anterior uveitis, however, the evidence is weak.[5-8] It has been reported that bimatoprost had no influence on the degree of aqueous flare in patients with uveitic glaucoma.[9] In a randomized, prospective, crossover study, the degree of aqueous flare was unaffected by latanoprost, travoprost and bimatoprost, in phakic patients with glaucoma or ocular hypertension.[10] In that study each patient was treated for four weeks, followed by a four-week washout between different drugs.

This supports the findings of a previous study that failed to show a significant effect on the permeability of the blood aqueous barrier after 12 months use of

latanoprost.[11] In that study, the lens status of enrolled patients is not reported, which is of significance in that a previous randomized controlled study has reported increased aqueous flare after PGA treatment of pseudophakic and aphakic eyes.[12] It is worth pointing out that the above studies were carried out in eyes of patients with glaucoma rather than uveitis. A retrospective study comparing the frequency of anterior uveitis and cystoid macular edema in eyes with uveitis and elevated IOP (n = 280) treated with PGA or other agents, found no difference in the frequency of anterior uveitis between both groups.[13]

A summary of the available evidence would suggest that PGA can produce an idiosyncratic anterior uveitis reaction in approximately 1% of non-uveitic patients, but there is little evidence that it exacerbates established uveitis. A greater concern in uveitic patients with pre-existing macular edema is that this may be exacerbated by PGA. In addition, in patients with elevated natural PGs from the inflammation, topically applied PGs may be less efficacious, although there are no studies testing this assumption. There is minimal evidence that the effect of latanoprost may be reduced by concomitant use of non-steroidal anti-inflammatory drugs.[14]

If inflammation is well-controlled, a trial of PGAs can be initiated as a second or third line in eyes with no history of macular edema. Moreover, caution should be exercised to monitor the condition for exacerbation of the inflammation. Miotics should not be used in eyes with elevated IOP and uveitis, as they may exacerbate inflammation.[15] ALT is not indicated in uveitic glaucoma.[16] Transcleral diode cyclophotocoagulation or endocyclophotocoagulation may be an alternative when trabeculectomy with MMC and surgery with a drainage device fails.

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6. DRUG DELIVERY

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Consensus statements

1. Poor adherence / perseverance / dyscompliance are major problems in glaucoma. Patients taking fewer doses than prescribed are at risk of having worse outcomes than those taking a higher proportion.
   Comment: On average, most studies of glaucoma patients estimate that about 70% of doses are taken. This may vary depending on duration of treatment, number of medications taken and severity of the disease.
2. Patient self-report of adherence is often overestimated.
   Comment: Physicians do not accurately predict which patients are poorly compliant.
   Comment: While not readily available, better systems to reliably and easily monitor patient drop taking behavior are desirable since they would provide feedback for physicians to better identify patients with difficulty adhering to drop regimens.
3. Risk factors for lower adherence rates have been identified and include younger and older age, race/ethnicity, and depression.
   Comment: While poor adherence can occur in all patients, additional efforts may be required in patients with these risk factors.
4. Patients often have difficulty properly administering drops to their eyes.
   Comment: Efforts to improve adherence should address physical barriers.
   Comment: Observation of patient eye drop administration can detect patients that are unable to instill them.

Medical Treatment of Glaucoma, pp. 157-164
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5. For at least the next several years, topical IOP-lowering medication will remain the mainstay for glaucoma treatment.
   Comment: Despite limitations (inconvenience, dependence on the compliance of the patients and well-described adverse events in particular on the conjunctiva), topical anti-glaucomatous medication is (relatively) cheap, easily available, and generally safe, and it is reversible, should side effects arise.
6. A change in the preservatives of eye drops to a less toxic and more tissue-friendly formulation, and/or the development of preservative free drug delivery systems is needed to reduce the preservative related side-effects and tissue toxicity while delivering enough drug to control the intraocular pressure.
7. Non-IOP dependent therapy for glaucoma and also new drug delivery systems remain a high priority unmet medical need in glaucoma management.

Adherence/Perseverance/Dyscompliance

David Friedman, David Greenfield and Ivan Goldberg

Definitions

The literature on adherence to medical therapy has always suffered to some extent by an inconsistent use of terminology. What is meant by ‘compliance?’ What is the implication when this term is used as opposed to ‘adherence?’ These are not trivial questions since the nomenclature used influences how patients and doctors think about the issues involved and how they communicate with each other.

The most recent trend is to use the term adherence since this is less judgmental as it does not imply that the patient who fails to take medications is in some way failing to be a good person (as is implied with the term compliance). But what is adherence? Is it taking 100% of doses? Most clinicians would accept less than perfect drop taking as adherence, so when does a patient become ‘non-adherent’ or ‘poorly adherent.’ Unfortunately, there are no published studies documenting the level of adherence that are clinically important. We therefore rely on our clinical judgment about what is good enough to help keep our patients safe.

For the purposes of this discussion, we will define ‘adherence’ as the degree to which a patient follows the prescribed treatment instructions during a defined period of time. An alternative measure that has been used is ‘persistence.’ It is a measure of continuous use. Again, how do we know when a patient has run out of medication? In general the number of drops in a bottle are known, and therefore the number of days that a bottle can last can be calculated. However, some patients use more than one drop at each dosing, and this means that far fewer days are available in a bottle. Persistence is less frequently used as an indicator of overall drop taking behavior as many appear to stop for periods of time but still continue to use their medications. Another term used is the

'medication possession ratio' which is an indication of how much of the prescribed course of therapy was used. It is calculated by dividing the amount of medication the patient actually used by the total prescribed and is frequently applied to pharmacy claims data.

Strategies for determining adherence

Patient interviews

Several approaches have been used to identify patient adherence to treatment. One of the most common ones is to ask patients directly whether or not they take eyedrops as prescribed. Unfortunately, patients frequently overestimate their level of adherence. In one study, patients administered a mean of 76% of the prescribed pilocarpine doses, as recorded by an electronic eye drop monitoring device. However, when these patients were interviewed they reported administration of a mean of 97% of the prescribed doses.[1] The authors also noted that ophthalmologists do a poor job of detecting which patients are poorly adherent. Similar discrepancy was also noted in a recent study using an electronic monitor in patients who knew they were being monitored:[2] the mean adherence rate was 71% based on the monitoring device, compared to 95% according to patients self-report. Others also reported higher rates on non-adherence to timolol therapy using data on dispensed eye drops compared to data from questionnaires (51% and 24%, respectively).[3] Researchers in other fields have also reported that electronic monitor data and patient self-report are poorly correlated.[4] These findings call into question studies that rely on interviews with patients to determine which ones are adherent and which are not. That said, a recent study found that admitting to any missed doses in the last week was associated with lower refill rates and lower adherence when monitored electronically.[6]

Pharmacy claims data

Pharmacy claims data have limitations,[7] especially when considering the use of eyedrops which do not come in fixed quantities as is the case with pills. Some patients are using medications in one eye, and may deliver more than one drop when putting drops in the eyes, and others may hoard medications or may rely on samples. Estimates based on pharmacy claims are likely only an approximation. However, pharmacy claims data are a reasonable estimate of drop taking behavior and should on average be able to separate those taking most of their drops from those taking far less.

Several studies using pharmacy claims data have reported on glaucoma therapy and in general report that about 70% of doses are taken.[7,10-12] The first study of this type assessed Medicaid recipients in New Jersey, who were given free medications and reported that 23% had not refilled a prescription over a 12-month period.[11] The same author reported that 25% of this population failed to fill 80% or more of their prescriptions over time. Others reported lower rates of

medication possession,[10,12] at any given point in time, with rates being around 50%. Using the medication possession ratio, one group reported that about 65% of doses were available.[7] These data and the large number of studies published on hypertension and lipid lowering therapies using pharmacy claims data indicate that a large proportion of doses are not taken.[13]

Electronic monitoring

Electronic monitoring allows researchers to know exactly how many doses are administered by the patient, although it does not confirm that the drops actually went into the eye. The use of monitoring devices to assess adherence was initially reported in the 1980s in studying adherence to pilocarpine treatment,[14,15] and later in studies with timolol.[1] More recently others have evaluated adherence to treatment with prostaglandin analogs using electronic monitors.[2] In regard to pilocarpine, 41% of the patients omitted at least 10% of the prescribed doses, and 20% omitted at least 20% of the prescribed doses.[14] Others reported that 34% of patients on pilocarpine omitted at least 25% of the prescribed doses, and 15% omitted at least 50% of the prescribed doses.[15] Adherence to treatment by nonadherent patients tended to increase just before the return visit in this study and a more recent publication.[2]

Electronic monitoring studies of adherence to prostaglandin analogs have had variable findings. One study using a MemsCap device reported that 97% of doses were taken when patients were on monotherapy and this decreased to 86% when a second medication was required.[5] In contrast, others using the Travatan Dosing Aid, reported that 44% of the patients used their eye drops less than 75% of the time. The overall mean adherence rate was 71%.[2]

Electronic monitoring remains a gold standard approach to monitoring adherence, but few methods exist for monitoring eye drops with this technology. Subjects being monitored are also frequently aware of this fact and this may influence drop taking behavior and this may bias the findings.

Prevalence and risk factors for less-than-ideal adherence

The title of this section is intentionally wordy and poorly stated, because we have almost no clear way to define what is ‘poor adherence.’ As noted above, several methods have been used to evaluate patients’ adherence to therapy: questionnaires, interviews, the use of health insurance claims data or health plan database, and the use of electronic dose-monitoring device. Regardless of the method used, all adherence studies show that many patients do not take their medications as prescribed. The prevalence of non-adherence varies considerably among studies, and ranges between 23-85% in the larger-scale studies. Electronic monitoring studies in glaucoma and most other chronic asymptomatic diseases find that on average patients take about 70% of prescribed doses.

There is a large literature in chronic disease on risk factors for low adherence. In addition, several reports in the last decade have looked at this specific ques-

tion. Unfortunately, many of those relied on self reported adherence and these studies suffer from two major design issues. First, those who admit to failing to take medications as prescribed may be different from those who do not take medications but refuse to admit they do not take them. What makes one person more willing to be honest with the interviewer than the other? This difference, and not the risk of not taking drops, may be what is being assessed in these interview-based studies. Second, the group identified as 'adherent' in these studies likely includes many who are not taking the medications as prescribed. This will tend to reduce the power that these studies have to detect real differences.

A major review summarized known associations with poor adherence in all chronic diseases and found depression and cognitive impairment were strongly associated.[16] Adherence was worse with asymptomatic diseases and barriers to obtaining medications, complex treatments, high cost of medications, and a poor doctor-patient relationship were all found to be risk factors. Several of these have been found to be associated with lower adherence rates in glaucoma. A model for thinking about the issues that might influence adherence to therapy includes patient factors, medication factors, provider factors and environmental factors. Patient factors that have been associated with lower adherence include patient concern about glaucoma and those who are younger or older and African Americans.[6] Medication factors include the cost of medications, depression, the complexity of the regimen, and side effects. Provider factors include communication and poor understanding of the consequences of glaucoma. Environmental factors include travel away from home and not having somebody to help with eye drops. Additionally, several studies have found that those who report missing drops are more likely to have poorer adherence.

Several previous reports have found that patients frequently fail to instill a drop in the eye when attempting to do so, and a recent report evaluated videotapes of patients experienced in using topical glaucoma drops and found that the majority touched the bottle to the eye, and the average number of drops administered at each dosing was 1.8, with nearly a quarter of the subjects squeezing a stream of medication on the eye.[8] Furthermore, about 20% of patients completely failed to administer a drop to the eye.

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Delivery systems

Jost Jonas, David Greenfield and Ivan Goldberg

Consensus statements

1. Anti-glaucomatous drug delivery systems in the near-term future (less than five years):
   Topical medication will remain the foundation for delivery of anti-glaucomatous therapy. Despite limitations that include inconvenience, dependence on patient adherence, and both local and systemic adverse reactions, topical anti-glaucomatous medication is relatively inexpensive and readily available. Topical therapy is generally safe; should adverse reactions occur they are often reversible. Candidate drug delivery systems include: intravitreal injection of soluble or crystalline drugs;[1,2] intravitreal implantation or injection of a bioerodible drug reservoir with slow-release modality;[3] intravitreal implantation of a non-resolvable slow-release device;[4] trans-sclerally fixated drug release devices (coated micro needles);[5] transscleral or transconjunc-

tival iontophoresis;[6] genetic engineering using transfected intraocular cells to produce a drug of choice; use of siRNA to silence the expression of deleterious genes; subconjunctival or sub-Tenon injection/implantation of a slow release drug; intraocular cell-encoated drug production;[7,8] formulation of nano-drugs with enhanced transcorneal passage;[9] intraocular lens-derived drug delivery systems;[10] lacrimal insert reservoir with controlled release of medical therapy; and contact lens associated drug delivery.[11]

2. Limitations of intraocular drug injection or delivery systems in glaucoma
   - The risk of injection-related infection is approximately 1:2000.[12] In contrast to glaucoma, a highly effective topical treatment for macular diseases, such as exudative age-related macular degeneration or diffuse diabetic macular edema, has thus far not been an alternative to intravitreal drug application.
   - An important difference between retinal disease and glaucoma is the '50% rule' in glaucoma that implies that approximately 50% of all subjects using anti-glaucomatous medication may not need the therapy or may not have the disease. This is in contrast to the '100% rule' in macular disease that suggests that all patients need treatment. It is easier to justify a potentially severe advese effect under the assumptions of the 100% rule as compared to the 50% rule.
3. Preservatives in topical anti-glaucomatous medicationDevelopment of preservatives with less tissue toxicity is needed to reduce local adverse affects on the ocular surface. Development of preservative-free drug delivery systems suspended in a nano-particle formulation that may be delivered in a spray or suspension and applied once daily is needed.
4. Intraocular lymphatic drainage system
   - It remains inconclusive so far whether the recently described rich lymphatic network in the human ciliary body contributes to aqueous and protein drainage from the eye, and whether it can be used as a target for glaucoma treatment.[13,14]
5. Non-IOP dependent anti-glaucomatous therapy
   - Non-IOP dependent therapy for glaucoma, in combination with novel drug delivery systems, remains a high priority unmet medical need in glaucoma management.

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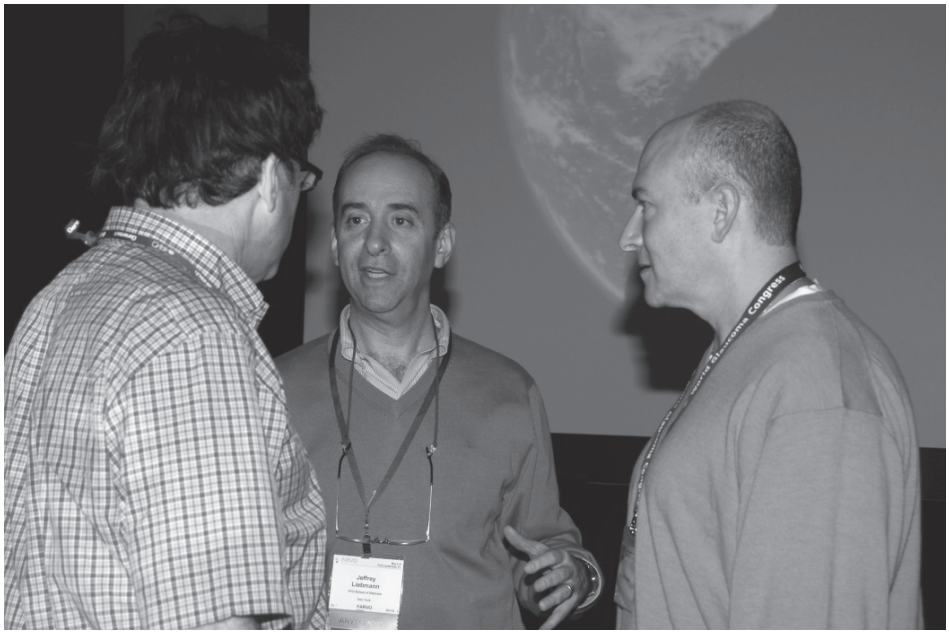

Robert N. Weinreb, Jeffrey Liebmann and David Greenfield.

7. HEALTH ECONOMICS

Ronnie George, Anne Coleman, Steven Kymes

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Consensus statements

1. There are wide variations in reported costs of glaucoma therapy across nations.
   Comment: There is little information from developing countries.
   Comment: With the exception of the US, the differences in costs of therapy are largely related to the level of economic development in various regions of the world.
2. Cost of one time surgery is substantially greater than medication in the short term, but lower in the long term.
   Comment: Changes in medication costs may alter this.
   Comment: Surgical failure may alter this because of the need for additional medication and/or surgery.
3. Generic drugs potentially can reduce direct treatment costs.
   Comment: More studies are needed comparing generic and branded drugs.
4. Side effects of glaucoma medications have minimal economic impact.
5. There do not appear to be significant differences in the cost of fixed combination products compared with individual components.
6. Failed medical therapy is defined differently in each country and depends on the cost and availability of medical therapy and surgical alternatives in that country.
   Comment: Pricing of glaucoma medications is not transparent.

There is little information about the benefit (Quality adjusted life year (QALY)) of an intervention in terms of reduction per mm of Hg. This limits our ability to compare different treatment strategies, different medication groups or generics and branded products comparisons. Most studies on efficacy of treatment have used outcomes for eyes and not binocular vision. Data on assessing QALY, as-

Medical Treatment of Glaucoma, pp. 167-173
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sumes that that cost and quality of life are driven by best eye or worst eye. The hypothesis that these are driven by best or worse or binocular vision has not been tested and lack of this data does impair our ability to assess cost effectiveness.

The disease and its costs / the treatment and its costs

There are wide variations in disease costs reported from developed countries, with similar variations seen in direct patient costs.[1-4] Wide variations are also seen by disease stage. Most studies estimate direct costs since indirect costs are relevant only to patients or when the societal perspective is mandated; most payors or providers will not be concerned with indirect costs. Unfortunately there do not appear to be any available data from developing countries, but patients are much more likely to be directly paying these costs in these locations. Quick *et al*. reported that 50-90% of population of developing countries have to pay from their pocket.[5] Indirect costs are likely to be a significant factor in developing countries, but this is unknown.

Most of the evidence seems to indicate that there are very important differences in the cost of glaucoma and its treatment between nations, because the differences are largely a function of the level of economic development in the nations (the one exception being between the U.S. and other developed nations).[2] Global costs, as in multinational estimates of costs, have little meaning because of the underlying heterogeneity between nations (see above).

For countries with lower levels of economic development, it would also depend upon whether generic versions of medications are available in the country.

There are no estimates regarding the cost of secondary glaucoma; costs may differ from the available information on POAG.

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Cost of medical treatment and comparison with other therapies for glaucoma (and how medical treatment fits in with the other modalities)

When viewed on a 'one time basis' the cost of surgery is of course much larger than the cost of medication.[1] The cost of managing surgical complications should be incorporated into the cost of the surgery. However, while it is likely that the cost of managing surgical complications from glaucoma surgery is likely to be significant, the probability of such events seems to be rather low. Properly, the analysis of something like surgery where there is a (relatively) large upfront payment whose benefit is enjoyed over time would be to amortize it over the period during which the benefits are enjoyed. Similarly, the cost of side-effects of surgery or medication should be recognized by multiplying the probability of the side-effect and the cost of that side-effect. This is easily addressed using the decision analytic methods we typically use for conducting cost-effectiveness studies.

However, over time, the cost curves merge (unpublished, Kymes *et al*.) with the long-term cost of surgery being lower than medication. This will likely change, however, as prostaglandin analogues become generic, with medication gaining an advantage in both the short and long term.

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Generics and how these will affect cost of glaucoma management throughout the world (including formulation of generics vs. brand drugs and is there any real difference between/ or do we know?)

The introduction of generic prostaglandins will likely reduce the cost of medical treatment of glaucoma from about $1000/year to a few hundred in the U.S. (a bit above the cost of generic Timolol). It will probably reduce the degree of differences we currently see in the cost of prostaglandins between countries.[1,2]

There is little published evidence regarding the comparative efficacy of generic glaucoma medication versus the original molecule. In a randomized cross over trial in India that compared Xalatan versus one Indian generic latanoprost, Xalatan had better IOP control and lesser side effects.[3] On switching there was an increase in IOP by 0.89 mm when switched from Xalatan to the generic and a decrease by 1.1 mm on switching from the generic to Xalatan. From unpublished data from India (courtesy R. Parikh) that studied the effect of switching to a generic medication after the patient was controlled on Xalatan, mean IOP increased by 1.8 mmHg at the end of three months, when subjects were on the generic.

The issue of safety and efficacy of generics is hampered by the non availability of information regarding its cost effectiveness in terms of preventing disease progression. There have been a plethora of studies that have been published on the cost of treatment and the burden of the disease. But the cost of treatment (and burden of disease) only has meaning in the context of what it is being compared to. In assessing if generics are less effective or less safe than branded drugs, we must be consider it in the context of a comparison. What is the value of a mmHg? None of us know because that is a cost-effectiveness question that considers the rate of progression, and we do not have good information on progression currently.

Whether differences in efficacy would influence overall disease costs is a cost-effectiveness question that considers the rate of progression, and we do not have good long term information on progression currently. The EMGT gives us, however, some guidance to this. Basically, if the new medication is no better than a placebo (not likely) we would expect to see a reduction in progression similar to that seen in the EMGT placebo group.[4] To the extent that it was simply less effective, we would see a 10% risk of progression for each millimeter of effectiveness lost. Unpublished data (courtesy Steven Kymes) show that given the slowly progressing nature of the disease, it takes considerable loss of efficacy to make an impact on costs alone on a population basis. This might not be true for an individual who has fast progressing visual field loss. The difference in cost is not near as important as the rate of progression or the impact on quality of life in determining the cost-effectiveness of treatment.[5] Calculation of utility values would be influenced by cultural differences. Perhaps the most dramatic example came from Gupta *et al*. which showed that among people with glaucoma in India, they were willing to accept a greater risk of death to cure their illness, than they would accept of becoming blind. Meaning that among this sample, being blind was worse than being dead. Another important issue in determining how cost varies by country is who is paying the bill. In most of the industrialized world, there is a third party payor. While in the developing world, the payor is often the patient him/herself. This substantially changes the way in which costs are measured.

In India, an estimate would be that more than 85% people pay from their pocket and in that scenario, patient's paying capacity becomes a very important issue in determining or changing therapy. Basically for 35% of population it would be the choice between the cost of the basic necessities of life versus a prostaglandin/prostaglandin analogue to lower eye pressure.

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Glaucoma medical therapy – what are the other costs to consider?

There are a number of other costs potentially associated with the use of glaucoma medications. These include the cost of managing side effects, potentially increased frequency of office visits as compared to surgical therapy and other costs such as caregiver, travel costs and time.[1]

On a population basis, the cost of managing side-effects of medication are negligible. The cost involves additional office visits and changes in medication choice. This does not add substantially to the total cost of treatment. From the patient's perspective, Jampel reported the willingness of patients to pay for a side-effect free medication.[2] Except for sexual or cardiac side-effects, the amount patients were willing to pay was relatively minor.

Even if patients on medical therapy have an increased frequency of office visits this is not likely to significantly affect the difference in the costs of treatment unless these differences are very large (*i.e.*, two to three visits/year). Again, as the prostaglandins move to generic, more visits will be able to be absorbed. These cost differences may be significant in areas with poor access to eye care where patients have to travel long distances to access eye care. Whether one considers these indirect costs would depend on the perspective of the decision maker. It will also vary by nation/culture. For instance, in the U.S. and most developed nations, there is virtually no incremental cost associated with the travel and time to obtain medication because the medication is either delivered to their home directly or is obtained at the same/time and vendor where they may obtain other items such as groceries. It should also be noted that when we talk about the cost of caregivers, the importance is only relevant to the extent that it is different from the cost of surgery. National differences do exist as Sleath *et al*. report, in a survey of glaucoma patients from South India, 38% had to travel for half an hour or longer to purchase their medication and 9% traveled more than two hours to purchase their medications.[3] The majority of those who participated in this study (60%) were urban residents; the access to pharmacies is likely to be much poorer in rural India.

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Combination dugs – is the cost worthwhile?

There do not appear to be significant differences in the cost of combination drugs as opposed to their individual components.[1] Since use of combination therapy is likely to improve compliance, its effect on cost was considered. However, there is no published evidence that show empirically that improved compliance results in improved outcomes, and more importantly, whether this relationship is linear, curvilinear etc. Therefore, there is currently no evidence that could help evaluate the cost-benefit of medication compliance.

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Failed medical therapy

With regard to failed medical therapy it is apparent that the threshold for surgery or ALT varies from country to country. Kobelt *et al*. report that among those on monotherapy followed up over a two-year period across nine countries, the rates for ALT/surgery showed wide variations from 11% for Germany to 52% for UK.[1] The study was carried out in the pre-prostaglandin era and surgical rates are likely to be lower now across the developed world. Lee *et al*. report a surgical/ALT rate of 35% over a five-year period in the US and 28% in Europe over similar time frame.[2] Patients in this study were nearly equally distributed over disease severity groups. In developing countries, a good proportion of the glaucoma population would be advised to have surgery for socioeconomic reasons. Uncontrolled IOP on a single beta blocker (typically costing one USD) may be an indication for surgical intervention. It is apparent that the definition of failed medical therapy differs from region to region.

One of the confounders is assessing costs in combined cataract and glaucoma surgery since many of these would not qualify as failed medical therapy.

The perspective of the decision being made should be taken into account. If the primary purpose of the surgery is to improve vision, the incremental cost/charge of glaucoma surgery over that for cataract surgery should be assigned to the glaucoma surgery, and vice-versa. In modeling, if the patient is taken off medical therapy that would be treated as a benefit. If the combined procedure is done in response to a failure of medical therapy, the incremental cost/charge of cataract surgery over the glaucoma surgery shall be charged to the cataract surgery. However most studies have not reported costs from this perspective.

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Health economics of medical therapy in developing countries
(including pricing of medications in the U.S. and the high cost of developing new medications)

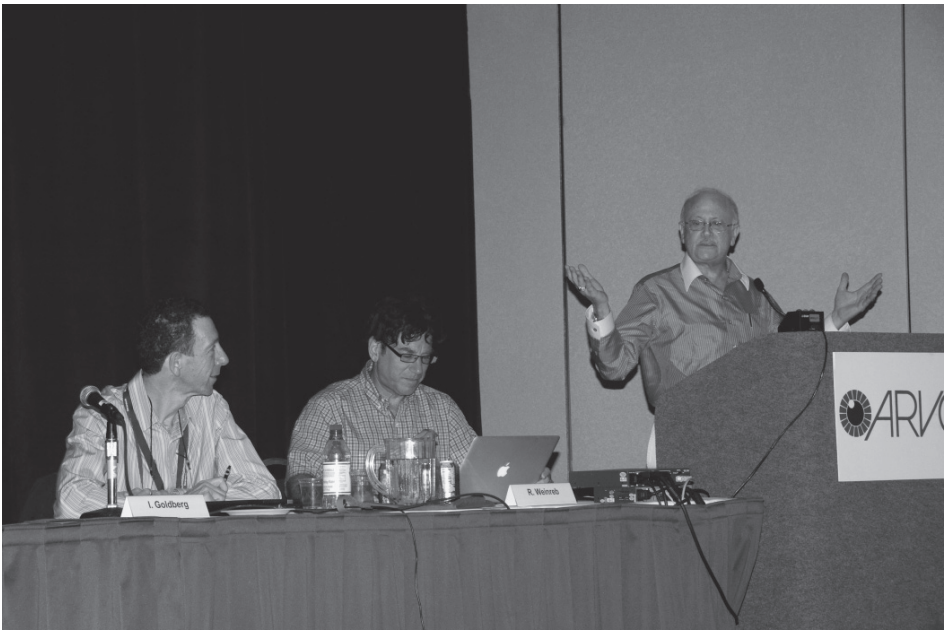
There are a few reports on cost of glaucoma from developing countries. In the absence of reliable estimates it was felt that medical therapy in developing countries is likely to be heavily influenced by drug pricing. Most participants felt that cost was an important consideration in deciding on surgical intervention. Therapeutic options could be limited to the lowest priced medications.

For the developed country markets, the pharmaceutical industry has been able to survive/grow due to 'cost and pricing shifting' within the international market (*i.e.*, higher prices and profit margins obtained from US and other developed country markets helping to subsidize new business opportunities but lower margins in developing countries). This strategy may not be viable in the long term (given the current health care debate in the U.S.). It is also our opinion that 'branded medical therapy' may not be a viable option for some/many glaucoma patients in developing countries if 'discounted' pricing is not provided by these companies (especially if medical therapy consists of two or more different drops). The pricing of medication in the U.S. does not appear to be directly correlated to the development costs (but targeted to whatever price the market will bear). Since the market in the U.S. is demanding lower overall costs, then prices for medications will have to decrease in the U.S., thereby putting tremendous pressure on the companies. One solution for industry would be to reduce their development costs (thereby increasing the process of farming out clinical trials to the developing countries). Anticipated returns from the market may influence whether new drugs are actually marketed.

Gabor Holló, Alfonso Anton and Stefano Gandolfi.

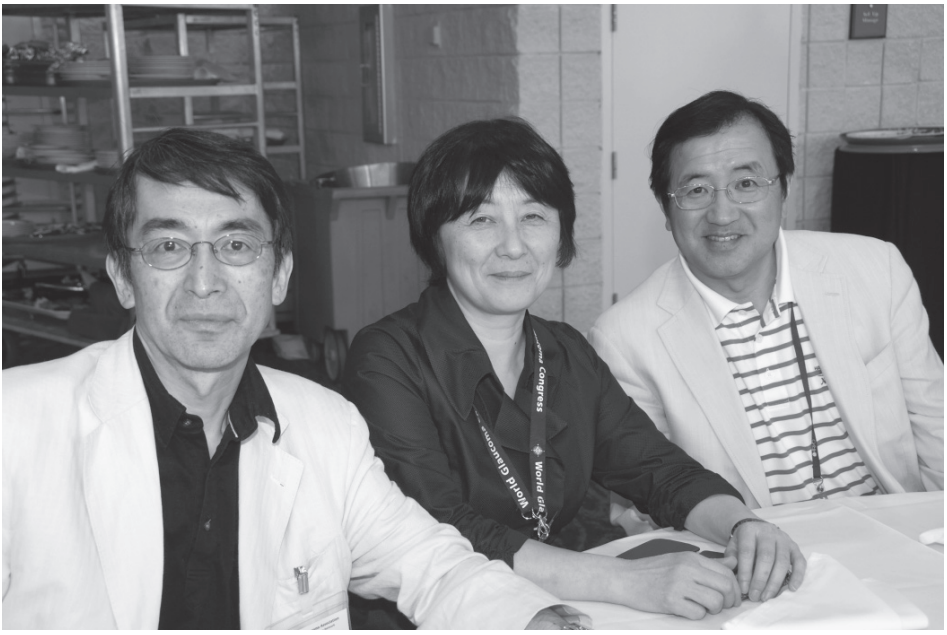
Mauro Leite, Ivan Goldberg, Harsha Rao, Chris Girkin, Fabian Lerner, David Friedman (left to right) Michal Schwartz and Jeffrey Liebmann (background).

David Greenfield and Carlo Traverso.



Ivan Goldberg, Robert N. Weinreb and Bob Ritch.

Bob Ritch, Section leader.



Makoto Araie, Aiko Iwase and Kazuhisa Sugiyama.

8. NON-PHARMACEUTICAL MEDICATIONS AND APPROACHES

Section leaders: Makoto Araie, Robert Ritch, Clement Tham
Contributors: Makoto Aihara, Aiko Iwase, Sandra Fernando, Michael S Kook, Simon Law, Robert Nussenblatt, Vincenzo Parisi, Nathan Radcliffe, Douglas Rhee, Kwok-Fai So, Raymond Chuen-Chung Chang, He Wei, Lori Ventura

Consensus statements

1. There is a paucity of clinical trial information examining neuroprotective effects of non-pharmaceutical compounds (alternative or complementary therapies) for glaucoma.
   Comment: Bio-availability of these natural compounds has not been well studied, and clinical studies of their efficacy and safety are needed.
2. Exercise reduces IOP, but the extent, duration and clinical significance are unclear.
   Comment: Exercise also can increase ocular blood flow, but the significance of this is unknown.
3. Acupuncture has been reported to lower IOP and increase ocular blood flow.
   Comment: The reported results are inconsistent and additional studies are needed before it is employed in clinical practice.

Quercetin and quercetin glycosides

Makoto Aihara

Background

Flavonoids comprise a large family of plant-derived compounds widely distributed in fruits and vegetables.[1,2] Here is growing evidence from human nutrition studies that the absorption and bioavailability of specific flavonoids is much higher than originally believed.[2,3] Flavonoids are believed to exert protective and/or beneficial effects on multiple disease states, including cancer, cardiovascular disease, and neurodegenerative disorders.[2-5] These physiological benefits of flavonoids are generally thought to be derived from their antioxidant activity and free radical scavenging.[6]

Quercetin is an important flavonoid and is ordinarily present bound to a sugar as a glycoside. For example, quercetin 3-O-rutinoside (rutin) is one of the

Medical Treatment of Glaucoma, pp. 177-258
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quercetin glycosides, which is rich in buckwheat and tartary buckwheat, commonly ingested in Japan and other Asian countries, and amazingly accounting for as high as 1% of the total weight of buckwheat and tartary buckwheat.[7,8]

RGC death in glaucoma is believed to be induced by apoptotic mechanisms triggered by multiple stimuli, including ischemia, oxidative stress, or elevation of glutamate levels.[9,10] Numerous studies have demonstrated that excessive glutamate induces RGC death in vitro and in vivo,[11] and that the glutamate receptor antagonists MK801 or memantine can ameliorate RGC death caused by elevated intraocular pressure.[12-16] Oxidative stress induced either by increased levels of reactive oxygen species (ROS) or mitochondrial dysfunction is also implicated in glaucomatous, ischemic, and hereditary optic neuropathies.[17,18] Accordingly, flavonoids including quercetin may also have neuroprotective potential in glaucoma.

Neuroprotection in non-retinal neurons

In *in vitro* culture studies, Quercetin showed an ameliorating effect on oxidative stress-induced PC12 cell death[19] or midbrain culture of rat,[20] and also other kinds of stress-induced cell death, such as beta-amyloid induced PC12 cell death[21] or kainite/NMDA induced rat neuronal death.[22] Quercetin also induced neuroprotective effect by modulating inflammatory responses in astroglia by IL1beta.[23] *In vivo*, quercetin was effective in rat brain trauma model[24] and cerebrovascular insults.[25]

Neuroprotection in retinal neurons

Only five studies describing the potential effects of flavonoids on RGC death induced by oxidative stress or pressure stress using RGC-5 transgenic cell lines or in vivo rodent models have been reported.[26-30] Liu *et al.* reported a neuroprotective effect of quercetin on pressure-induced RGC-5 death.[30]

Drug delivery of quercetin and quercetin glycoside

A few reports have indicated that repeated intake of several hundred milligrams of quercetin-rutinoside resulted in a plasma concentration of 100nM or higher.[31-33] Moreover, flavonoids can penetrate into the central nervous system through the blood-brain barrier.[34] Interestingly, quercetin itself may not be effective in neurodegenerative disease such as Parkinson disease model rat,[35] because it penetrates the blood brain barrier less efficiently than quercetin glycosides.[25] This may be the reason for its beneficial effects in rat brain trauma or cerebrovascular insults.[24,25]

Mechanism of neuroprotective action

Although the precise mechanism of action remains unclear, the beneficial activity of flavonoids is generally attributed to their antioxidative efficacy.[8,22,24] The antioxidant capacity of flavonoids depends on the arrangement of functional groups surrounding the flavonol nucleus, which may directly affect glutathione metabolism, antioxidant capacity, or the ability to maintain low Ca^{2+} levels despite high levels of reactive oxygen species.[1,8]

Conclusion

Quercetin and its glycosides have neuroprotective effect and may have applications for glaucomatous optic neuropathy. However there was no clinical evidence to use them as a neuroprotective agent. The major concerns of quercetin intake as a supplement are its poor penetration into the retina[25,34] and its specific inhibitory effect on HSP72 induction,[36,37] which may lead to deteriorate neuroprotective effect by HSP72. Further studies are needed using glaucoma[9] animal model and human studies.

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Methylcobalamin

Makoto Aihara

Background

Methylcobalamin is an active form of Vitamin B12 (cyanocobalamin). Vitamin B12 deficiency is well known to cause megaloblastic anemia and neuropathy. Humans have two vitamin B12-dependent enzymes (*i.e.*, methionine synthase and methylmalonyl coenzyme mutase). Neuropathy occurs because of lack of methionine synthase and not by a lack of activity by methylmalonyl coenzyme mutase. Methylcobalamin is effective in enhancing myelinization in neural axons. Several reports have indicated enhancement of axonal regeneration or post-synaptic field potentials.[1-3] In rat cultured cortical neurons, methylcobalamin protected against glutamate-induced cell death.[4] Vitamin B12 has until now been used primarily for diabetic neuropathy and peripheral neuropathy in humans.

Ocular studies

In the eye, vitamin B12 deficiency induces optic nerve atrophy in monkeys.[5] Also, in a patient with methionine synthase deficiency resembling methylcobalamine deficiency, the visual system was disturbed.[6] Thus, methylcobalamin may have a neuroprotective effect on optic neuropathy, including glaucoma. However, only a few studies have been reported in ophthalmology. In rat retinal culture, methylcobalamin protected against glutamate-induced cell death.[7] In *in vivo* experiments, only one report showed methylcobalamine to ameliorate optic nerve degeneration in the optic nerve crush rat model.[8] There was no evidence of a beneficial effect of methylcobalamin in glaucomatous optic neuropathy.

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Curcumin

Makoto Araie

Pharmacological basis of curcumin

Curcumin is a yellow coloring agent present in the commonly used spice, turmeric (*Curcuma longa*), which has been used in Indian cuisine to add color and as a preservative and also in traditional medicine to treat various common diseases.[1] In 1815, Vogel and Pelletier first isolated curcumin and in 1910 Milobedzka and Lampe determined its chemical structure, diferuloylmethane [1,7-bis (4-hydroxy-3-methoxyphenyl) -1, 6-heptadiene-3,5dione] (Fig. 1).

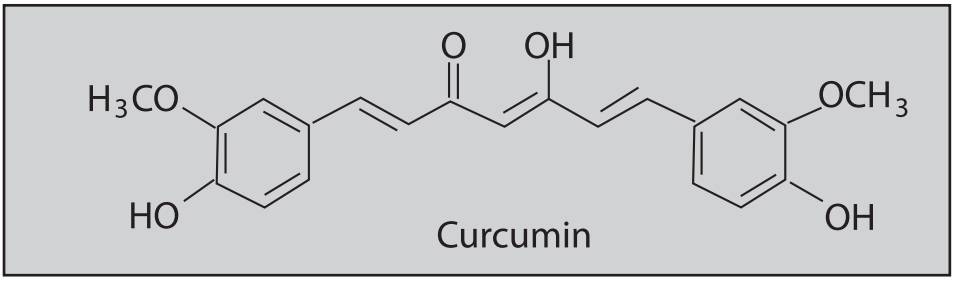

Fig. 1

Studies of curcumin have increased exponentially in recent years and over 2000 papers have been published since 2000.[2] These studies demonstrated that curcumin has antioxidant, antibacterial, antiviral, antifungal, anti-inflammatory, antiproliferative and pro-apoptotic effects.[3] Potential therapeutic effects of this compound on various diseases, including neurodegenerative, cardiovascular, pulmonary, metabolic or immune-related diseases, malignancies and infectious disease (including HIV-AIDS), have been suggested.[4-7] Diseases for which there are ongoing clinical trials with curcumin include Alzheimer's disease (AD), psoriasis vulgaris, multiple myeloma, pancreatic cancer, familial adenomatous polyposis, and sporadic adenomatous polyps of the colon.[5]

The biology of the effects of curcumin has been under intensive study and curcumin is now known to have numerous molecular targets. Reported targets with which curcumin directly interacts are glycogen synthase kinase (GSK)-3ß, β-amyloid, toll-like receptor (TLR) 4, 5-lipoxygenase (LOX) of which binding constants (IC_{50}) to curcumin are at nanomolar levels, cycloxgenase (COX)-2, xanthine oxidase, phosphorylase-3 kinase, N-aminopeptidase, DNA polymerase, autophosphorylation activated protein kinase, focal adhesion kinase (FAK), thioredoxin reductase (Trx R), topoisomerase II, ubiquitin isopeptidase, pp60 src tyrosine kinase, albumin, glutathione, tubulin, P glycoprotein or human α1-acid glycoprotein.[2] Further, curcumin binds with divalent metal ions such as Fe, Cu, Mn and Zn with relatively high affinity to Fe and Cu with dissociation constants of micromolar levels. Molecular targets of which activity curcumin reportedly modulates indirectly or secondarily include transcription factors such as NF-κB, p53 or CHOP, enzymes such as glutathione reductase or protein kinase, growth factors such as EGFR, antiapoptotic proteins such as Bcl-2 or Bcl-xL, inflammatory mediators such as TNF-α, IL-1 or IL-6, invasion and angiogenesis biomarkers such as MMP-9 or VEGF, some of chemokines and chemokine receptors or cell-cycle regulatory proteins.[2]

Open-angle glaucoma and curcumin

Open-angle glaucoma (OAG) is a neurodegenerative disease characterized by characteristic structural change of the optic nerve head and slowly progressive death of retinal ganglion cells mainly by apoptosis.[8] In addition to mechanical insult caused by elevated intraocular pressure (IOP), several mechanisms are thought to be involved in the development and progression of OAG that could be targets for pharmacological intervention.[9] Such possibly interrelated mechanisms include ischemia/hypoxia due to insufficient perfusion[10-12] oxidative stress[13,14] local or systemic abnormalities in the nitric oxide system[14,15] primary or secondary mitochondrial dysfunction,[16,17] excitotoxicity,[18] aberrant immunoregulation in which heat shock proteins may play an important role,[19-22] neurotrophin deprivation[23] or abnormal TNF-α signaling.[24]

It is interesting to note that curcumin has shown possible beneficial effects in most of the above mechanisms.[2,7] Beneficial effects of curcumin at various doses (30-300 mg/kg, i.p., 1-2 mg/kg, i.v., or 30 mg/kg, p.o.) on focal cerebral ischemia in rats have been reported[25-31] These effects were thought to be primarily attributable to its potent anti-oxidative effects[32-35] and partly to protection against hypoxia-induced decrease in beta-III tubulin content.[36] Antioxidant activity of curcumin reportedly includes several mechanisms, *i.e.*, upregulation of defensive genes and proteins such as HO-1 or catalase[37-40] inhibition of heavy metal-catalyzed lipid peroxidation by chelating toxic metals,[41-43] or reduction of nitrite levels.[29,44,45] In vitro studies demonstrated that curcumin at relatively high concentrations (10-100 μM) inhibited lipopolysaccharide (LPS)-induced NO synthase activity[46-48] by suppressing activation of NF-κB.[49] Curcumin also attenuates mitochondrial dysfunction by reducing reactive oxygen species.[50-52]

Further, curcumin was reported to inhibit mitochondrial proton F0F1-ATPase/ ATP synthase at a relatively high concentration. (45 μM).[53]

Curcumin was reported to be effective in the kainic acid-induced hippocampal cell death in mice[54] and in the NMDA-induced damage of cultured retinal cells[55] Manganese complex curcumin may be more effective than the parent compound, curcumin, in reducing kainic acid-induced damage in hippocampal cells in the rat.[56] Curcumin was also reported to be effective against glutamate toxicity in rat cerebral cortical neurons, attributed to increased brain-derived neurotropic factor (BDNF) levels and activation of Trk B.[57] Oral administration of curcumin (10-20 mg/kg) increased hippocampal neurogenesis in chronically stressed rats probably by preventing stress-induced decrease in BDNF and 5-HT (1A) expression in the hippocampal subfields.[58] Curcumin also increased viability of cultured rodent cortical neurons by up-regulating the BDNF/Trk B pathway.[59]

The effects of curcumin on pro-inflammatory cytokines have been well documented.[3] Curcumin reportedly inhibits effects of high glucose on lipid peroxication and secretion of cytokines such as TNF-α, IL-6, IL-8 or MCP-1 by cultured monocytes at 0.01-1.0 μM; pretreatment with curcumin (100 mg/kg) decreased blood levels of TNF-α, IL-6 or MCP-1 in streptozosin (STZ)-induced diabetic rats.[60] Tumor-induced oxidative stress is thought to play a role in loss of proper cell-mediated immunity and reduced effector T-cell population and thymic atrophy. Curcumin was reported to prevent tumor-induced thymic atrophy by restoring the perturbed activity of NF-κB and TNF-α signaling pathway.[61] Further, curcumin is known to have various immunomodulatory effects such as those on lympoid cell populations, antigen presentation, humoral and cell-mediated immunity and cytokine production.[62-64] Cryopreservation of islets with curcumin at 10 μM resulted in better islet viability and functionality associated with heat shock protein (Hsp) 90 and HO-1.[65]

In Alzheimer's disease (AD), a neurodegenerative disorder of the elderly characterized by deposition of β-amyloid plaque, NF-κB and apolipoprotein E are involved in the associated neuroinflammation, while reactive oxygen species and activated microglial cells contribute to neural loss.[4,7,66] It is interesting to note that a possible link between glaucoma and AD has been suggested.[67-71]

Curcumin affects β-amyloid peptide, suppressing oxidative damage and inflammatory signaling pathways.[4,7] Age adjusted AD prevalence and incidence in an area with high curcumin (rural India) was much lower than in western countries, including the USA.[72] Curcumin may also be effective in other neurodegenerative conditions, such as Parkinson's disease, Huntington's disease, tauopathies, cerebrovascular disease, head trauma, alcohol-induced neurotoxicity or aging of the brain.[4,7] It is possible that some of the mechanisms of action of curcumin in these neurodegenerative disorders also apply to OAG, and this field of investigation deserves study.

Although curcumin is thought to be safe, biphasic responses to it must be kept in mind. In tumor cells, curcumin suppresses survival and proliferation and activates apoptosis.[2] Examples are its pro-apoptotic effects on human hepatoma

G2 cells or cervical carcinoma cells[73,74] or those on N18 mouse-rat hybrid retinal ganglion cells.[75,76]

Effects of curcumin in ocular tissues

Effects of curcumin have been examined in corneal epithelial cells, lens and retina. Corneal epithelial cells cultured in a hyperosmotic medium as a model for dry eye disease increased production of IL-1β, IL-6, while TNF-α levels and p38 MAP kinase, JNK MAP kinase and NF-κB were also activated. Pretreatment with 5μM curcumin abolished phosphorylation of p38 MAP kinase, increased activation of NF-κB and increased production of IL-1β, suggesting its usefulness in ameliorating inflammatory processes in the ocular surface in dry eye disease.[77] Curcumin also suppressed IL-1β or TNF-α-induced disruption of simian virus 40-transformed human corneal epithelial barrier function by inhibiting NF-κB activity,[78,79] and inhibited the angiogenic response induced by implantation of an FGF-2 pellet in the rabbit cornea by inhibiting expression of gelatinase B.[80]

Curcumin at a dose of 75mg/kg *in vivo* or at 200 μM *in vitro* was reported to ameliorate cataract formation in rats caused by selenium-induced oxidative stress, probably by preventing free-radical-induced accumulation of Ca^{2+} in the lens.[81,82] It was also reported that the lens removed from the rat treated with curcumin at a dose of 75 mg/kg for 14 days was much more resistant to cataractogenesis by a product of lipid peroxidation, 4-hydroxy-2-trans-nonenal (4-HNE) than controls.[83] Rats treated with naphthalene and kept on a diet supplemented with 0.005% curcumin showed significantly less lens opacification than controls treated only with naphthalene.[84] This effect was attributed to attenuation of apoptosis caused by naphthalene-induced oxidative stress.

A diet supplemented with 0.002% curcumin was also reported to be effective against cataract induced by galactose or STZ-induced hyperglycemia in rats.[85,86] The effect of curcumin against STZ-induced cataract was attributed to prevention of the loss of chaperone-like activity of α-crystallin.[86] A diet supplemented with curcumin was also reported effective in ameliorating retinal damage caused by diabetes. In STZ-induced diabetic rats kept on a diet supplemented with 0.05% curcumin, diabetes-induced decrease in the antioxidant capacity of the retinal tissue and increase in the oxidatively modified DNA and nitrotyrosine were prevented and diabetes-induced increase in the IL-1β, VEGF and NF-κB levels were inhibited.[87] VEGF levels were reported to be inhibited at lower dose of curcumin, that is, 0.01% curcumin supplement.[88] On the other hand, a higher dose of supplemental curcumin (0.2% in diet) was suggested to be necessary to protect retinal cells from light-stress-induced damage, the mechanism of which involves inhibition of NF-κB activation and down-regulation of cellular inflammatory genes.[89] Pretreatment with curcumin also protected cells of retina-derived cell lines from H_2O_2-induced damage by up-regulating cellular protective mechanisms such as HO-1 and thioredoxin.[89] As briefly mentioned above, curcumin was also effective against NMDA-induced damage in rat retinal cell cutures at 15 μM, but not 1 or 5 μM. This effect against NMDA-mediated

excitotoxic damage was associated with decrease in NMDA-induced Ca^{2+} rise and reduction in the level of phosphorylated NR1 subunit of the NMDA receptor, suggesting curcumin-induced modulation of NMDA receptor activity.[55] On the other hand, curcumin was reported to cause DNA damage and inhibited expression of DNA repair genes such as ATM or DNA-PK and induced apoptosis through intrinsic pathway and caspase-3-dependent and –independent pathways in mouse-rat hybrid retinal ganglion cell line N18 cells at concentrations of 10 μM or higher.[75,76]

Bioavailability of curcumin

Oral curcumin has poor bioavailability due to poor absorption attributable to high hydrophilicity, rapid metabolism and rapid systemic elimination.[64,90] Curcumin is thought to be metabolized through conjugation leading to the formation of curcumin glucuroride and sulfates and reduction leading to the formation of tetra-, hexa- or octa hydrocurcumin,[91,92] and these metabolites are also biologically effective.[93] In one study, 15 patients with advanced colorectal cancer received oral doses of curcumin extract of 440 to 2200 mg/day containing 36 to 180 mg curcumin for up to four months.[63,64] Although the oral extract was well tolerated without significant toxicity, neither curcumin nor its metabolites were detected in blood or urine, while curcumin was recovered from feces. In another study in 25 patients with high-risk or pre-malignant lesions, oral curcumin was given at a starting dose of 500 mg and the dose was increased to another level in the order of 1000, 2000, 4000, 8000 and 12000 mg/day. There was no curcumin-related toxicity up to 8000 mg/day and the concentration of curcumin in the serum peaked at one to two hours, averaging 0.51, and 1.77 μM after oral intake of 4000 and 8000 mg of curcumin, respectively.[94] It was also reported that a daily oral dose of 3600 mg of curcumin resulted in detectable levels in colorectal tissue, which might be sufficient to be pharmacologically active.[91,95]

In spite of its lower bioavailability, effects of diet supplemented with curcumin have been documented in various rat models as described above, and an epidemiological study also suggested effectiveness of dietary curcumin in preventing Alzheimer's disease.[72] Thus, enhanced bioavailability of curcumin in the near future may bring more promising results.[63,64] Bioavailability of curcumin may be increased by concomitant administration of curcumin with piperine.[96] by making curcumin nanoparticles, liposomes or phospholipid complexes.[97-100] Bis-0-demethylated curcumin, which has more potency than curcumin due to a higher number of phenolic groups, is reported to be safe in rats and this compound may also deserve future studies.[101]

Although curcumin is thought to be safe in animals and humans in spite of its numerous pharmacological effects,[5] and it is 'generally regarded as safe' according to FDA,[4] its long-term use in rats at high doses was not free from toxicity. According to the evaluation of National Toxicology Program, daily administration of 2600 mg/kg of turmeric oleoresin containing about 80% curcumin in rats caused moderate toxicological effects including relative increase

in liver weight or stained fur at 13 weeks, and severe toxicological effects such as ulcers, hyperplasia of the cecum or intestinal cancer at two years.[102]

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Ginkgo biloba extract

Robert Ritch

Ginkgo biloba extract (GBE) contains over 60 known bioactive compounds, about 30 of which are found nowhere else in nature. The standardized extract used most widely in clinical research, EGb 761 (Dr Willmar Schwabe GmbH & Co, Karlsruhe, Germany), contains 24% ginkgo flavone glycosides (flavonoids), 6% terpene lactones (ginkgolides and bilobalide), approximately 7% proanthocyanidines, and other, uncharacterized compounds.[1]

GBE has been claimed effective in a variety of disorders associated with aging, including cerebrovascular disease, peripheral vascular disease, dementia, tinnitus, bronchoconstriction, and sexual dysfunction. GBE appears to have many properties applicable to the treatment of non-IOP-dependent risk factors for glaucomatous damage.[2] GBE exerts significant protective effects against free radical damage and lipid peroxidation in various tissues and experimental systems. Its antioxidant potential is comparable to water soluble antioxidants such as ascorbic acid and glutathione and lipid soluble ones such as alpha-tocopherol and retinol acetate.[3] The antioxidant properties of are due to its direct free radical scavenging activity. Proteasome inhibitory properties of anthocyanins may contribute to their antioxidative, anti-inflammatory and neuroprotective activities, rationalizing their use in neurodegenerative disorders.[4]

GBE preserves mitochondrial metabolism and ATP production in various tissues and partially prevents morphologic changes and indices of oxidative damage associated with mitochondrial aging.[5-9] In contrast to other antioxidants, gingko has the capacity to enter the inner mitochondrial membrane, thus making it an effective antioxidant at the mitochondrial level.[10] It can scavenge nitric oxide[11] and possibly inhibit its production.[12]

Substantial experimental evidence exists to support the view that GBE has neuroprotective properties in conditions such as hypoxia/ischemia, seizure activity, cerebral edema, and peripheral nerve damage.[13,14] GBE protects against glutamate toxicity.[15,16] It can reduce glutamate-induced elevation of calcium concentrations[17] and can reduce oxidative metabolism in both resting and calcium-loaded neurons.[18] Neurons in tissue culture are protected from a variety of toxic insults by GBE, which inhibits apoptosis.[19-22]

GBE improves both peripheral and cerebral blood flow. It is effective in treating Raynaud's disease, which is strongly associated with normal-tension glaucoma.[23,24] It has been reported to protect myocardium against hypoxia and ischemia-reperfusion injury[25,26] and to relax blood vessel walls.[27] GBE is a strong

inhibitor of platelet activating factor.[28] There is mixed evidence for functional improvement in patients with Alzheimer's-type and multi-infarct dementias. Preliminary data suggest that GBE may increase the probability of survival in the elderly population.[29]

It has been suggested that alterations in systemic NO and ET-1 activity (endothelial dysfunction) are involved in vascular dysregulation in glaucoma.[30-33] GBE reportedly attenuates endothelial dysfunction[34] and improvement of peripheral circulation by GBE is at least partly attributable to its effects on the NO-pathway or endothelium-dependent vasodilation.[35,36] Further studies of GBE on the ocular circulation and progression of normal-tension glaucoma are warranted.

In the eye, GBE may have a protective effect against the progression of diabetic retinopathy[37] and reduces ischemia-reperfusion injury in rat retina.[38] GBE protects retinal photoreceptors against light-induced damage by preventing oxidative stress in the retina.[39,40] Chloroquine-induced ERG changes were prevented by simultaneous treatment with GBE.[41] In a rat model of central retinal artery occlusion, GBE reduced edema and necrosis and blocked the reduction in b-wave amplitude.[42]

Jia *et al.* found that GBE suppressed dexamethasone-induced IOP elevation in rabbits.[43] It reduced the dexamethasone-associated accumulation of extracellular materials within the cribriform layers of the trabecular meshwork and achieved better meshwork cellularity. In cultured human trabecular cells, GBE substantially reduced dexamethasone-induced myocilin expression.[43,44] investigated the dosage dependence of intragastral GBE versus saline on RGC survival in the rat optic nerve crush model. The mean survival rate increased significantly ($P < 0.001$) from $58.4 \pm 9.0\%$ in the saline group to $74.2 \pm 6.8\%$ in the high-dosage GBE group. The same group found that intraperitoneal administration gave similar results.[45]

GBE has been reported to improve automated visual field indices.[46,47] In one clinical cross-over study of low-dose, short-term treatment in normal volunteers, GBE increased ophthalmic artery blood flow by a mean of 24%.[48] A more recent study, however, failed to confirm these results.[49]

A systematic review of case reports concluded that 'the causality between ginkgo intake and bleeding is unlikely.'[50] A systematic review of eight randomized controlled trials concluded that the 'available evidence does not demonstrate that GBE causes significant changes in blood coagulation parameters.'[51] The idea that the combination of ginkgo and anticoagulant or antiplatelet drugs might represent a serious health risk is based on several case reports but not supported by clinical trials.[52]

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Grape seed extract

Robert Ritch

Grape seed proanthocyanidins have a broad spectrum of pharmacological and medicinal properties against oxidative stress. Grape seed proanthocyanidin extract (GSE) provides excellent protection against free radicals in both in vitro and in vivo models.[1] GSE-induced improvement in myocardial ischemia-reperfusion injury in vitro has been reported.[2-4] Activin, a new generation antioxidant derived from grape seed proanthocyanidins, reduces plasma levels of oxidative stress and adhesion molecules (ICAM-1, VCAM-1 and E-selectin) in patients with systemic sclerosis.[5] Supplementation of a meal with GSE minimizes postprandial oxidative stress by increasing the antioxidant levels in plasma, and, as a consequence, enhancing the resistance to oxidative modification of low density lipoproteins.[6] Grape seed proanthocyanidins have also been reported to have activity against HIV-1 entry into cells.[7] Grape seed extract has recently been shown to inhibit the growth of prostate cancer cells in mice.[8] In the eye, GSE inhibits key components of cataractogenesis by reducing oxidative stress within lens epithelial cells.[9] and significantly prevents and postpones development of cataract formation in rats with hereditary cataracts.[10]

Resveratrol

Robert Ritch

Resveratrol (3,5,40-trihydroxystilbene), a powerful polyphenolic antioxidant, is found largely in the skins of red grapes and berries and came to scientific atten-

tion as a possible explanation for the low incidence of heart disease among the French, who eat a relatively high-fat diet (the French paradox). Many studies suggest that consuming alcohol (especially red wine) may reduce the incidence of coronary heart disease (CHD). Grape juice, which is not a fermented beverage, is not a significant source of resveratrol. A large number of studies in the past few years suggests its benefit in vitro and in vivo in a variety of human disease models, including cardioprotection, neuroprotection, immune regulation, and cancer chemoprevention. For an extensive review, see reference 11. Substantial data show that actions of resveratrol include inhibition of lipid peroxidation and platelet aggregation, metal chelating (primarily copper), free radical–scavenging activity, anti-inflammatory activity, modulation of lipid metabolism, antifungal properties, and anticancer and estrogen-like activity.[11]

Resveratrol increases the lifespan of the yeast, *Saccharomyces cerevisiae*, the nematode, *Caenorhabditis elegans*, and the fruitfly, *Drosophila melanogaster*. It was later shown to extend the lifespan of the short-lived fish, *Nothobranchius furzeri*,[12] and has now been shown to significantly increase the health and survival of mice on a high-calorie diet, pointing to a new approach to treating diseases of aging.[13] Among its multiple functions, resveratrol activates sirtuins (silent information regulator proteins), a family of proteins that play an important role in DNA repair, gene silencing, chromosomal stability and longevity.[14]

The physiologic effects of resveratrol appear to be related to its ability to regulate nutrition and longevity genes.[11] Resveratrol is an effective antioxidant.[15-17] It inhibits lipid peroxidation of low-density lipoprotein (LDL), prevents the cytotoxicity of oxidized LDL, and protects cells against lipid peroxidation.[16] Resveratrol protects against the degeneration of neurons after axotomy.[18] A single infusion of resveratrol can elicit neuroprotective effects on cerebral ischemia-induced neuron damage through free radical scavenging and cerebral blood elevation due to nitric oxide release.[19] Its antiapoptotic activity has led to the suggestion that resveratrol may make a useful dietary supplement for minimizing oxidative injury in immune-perturbed states and human chronic degenerative diseases.[20]

Levels of intracellular heme (iron-protoporphyrin IX), a pro-oxidant, increase after stroke. In neuronal cell cultures, resveratrol induces heme oxygenase 1, suggesting that increased heme oxygenase activity is a unique pathway by which resveratrol can exert its neuroprotective actions.[21]

Resveratrol directly inhibits CYP1B1. The versatility of RSV lies in its diverse targeting of membrane and intracellular receptors, signaling molecules, biogenesis enzymes, oxidative systems, DNA-repair mechanisms, and transcription factors, and it can activate or repress a number of signal-transduction pathways found throughout the cell [11]

There appears to be an association between aging and neurodegenerative diseases, such as Alzheimer's, and that modulation by both caloric restriction and drugs which mimic caloric restriction, such as resveratrol, can ameliorate these diseases.[22] Resveratrol reduces the levels of secreted and intracellular amyloid-ß peptides by proteosomal degradation.[23]

In the eye, resveratrol suppresses selenite-induced oxidative stress and cataract formation in rats.[24] The authors suggested that the presence of oxidative stress in selenite cataract development and its prevention by resveratrol support the possibility that high natural consumption of resveratrol in food can help prevent human senile cataract. Resveratrol also induces dilation of retinal arterioles, suggesting a potential benefit for this compound in the treatment of retinal vascular disease.[25] Sirtuin-1 activators (such as resveratrol) demonstrate neuroprotective properties in mouse models of optic neuritis and multiple sclerosis.[26]

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Pycnogenol

Robert Ritch

Pycnogenol, an extract of French maritime pine bark (*Pinus pinaster*), is primarily composed of procyanidins and phenolic acids and is a potent antioxidant with strong free radical-scavenging activity against reactive oxygen and nitrogen species. Procyanidins are biopolymers of catechin and epicatechin subunits, which are important in human nutrition.[1]

Pycnogenol is effective in patients with venous microangiopathy[2,3] and accelerates healing in leg ulcerations from chronic venous insufficiency[4] and diabetes.[5] In chronic venous insufficiency, pycnogenol reduced lower leg circumference and symptoms of pain, cramps, nighttime swelling, feeling of 'heaviness', and reddening of the skin.[6] Pycnogenol can protect vascular endothelial cells from Aß-induced injury.[7] It reversed elevation of serum creatinine, BUN, LDH, IL-1beta, IL-6, and TNF-alpha levels in ischemia reperfusion injury in unilaterally nephrectomized rats.[8]

Pretreatment with pycnogenol reduces smoke-induced platelet aggregation.[9] Pycnogenol significantly reduces LDL-cholesterol levels.[10] A randomized controlled trial reported it effective for erectile dysfunction.[11] It has also been reported to improve symptoms of jet lag.[12] It inhibits not only HIV-1 binding to host cells, but also its replication after entry in susceptible cells *in vitro*.[13] It has been reported to increase urinary catecholamines and ameliorate attention deficit hyperactivity disorder in children.[14]

After oral administration of pycnogenol, plasma samples significantly inhibited NFkB activation and MMP-9 release from human monocytes, indicating that it exerts anti-inflammatory effects by inhibiting proinflammatory gene expression.[15]

Glutamate inhibits cyclo-oxygenases 1 and 2.[16] This cytotoxicity was inhibited by both GBE and pycnogenol.[17] Pycnogenol not only suppresses the generation of reactive oxygen species, but also attenuates caspase-3 activation and DNA fragmentation, suggesting protection against Aß-induced apoptosis.[18]

Pycnogenol has also been reported to inhibit angiotensin-converting enzyme and to enhance the microcirculation by increasing capillary permeability.[19] It inhibits progression of preproliferative diabetic retinopathy[20] and may reduce the risk of formation of both diabetic retinopathy and cataract.[21] More recently, in patients with mild to moderate retinal edema, pycnogenol treatment significantly improved both the edema and retinal thickness as measured by high resolution ultrasound.[22] Laser Doppler flow velocity measurements at the central retinal artery showed a statistically significant increase from 34 to 44 cm/s in the Pycnogenol group as compared to marginal effects in the control group.[22]

Steigerwalt *et al*.[23] evaluated the effects of the food supplement Mirtogenol (Mirtoselect and Pycnogenol on IOP and ocular blood flow in 20 subjects versus 18 controls. After three months of treatment, the IOP was lowered compared to that of untreated controls from a baseline of 25.2 mmHg to 22.0 mmHg ($p < 0.05$). Ocular blood flow (central retinal, ophthalmic, and posterior ciliary arteries) improved both in the systolic and diastolic components as measured by Color Doppler imaging.

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Fish oil and omega-3 fatty acids

Sandra Fernando

Pharmacology

Omega-3 fatty acids, found most notably in fish oil, include docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). These are long-chain polyunsaturated fatty acids (PUFAs) with an 18-carbon chain precursor that cannot be synthesized by mammals. Therefore, these fatty acids must be obtained through diet or supplementation. Once omega-3 fatty acids are ingested, they undergo elongation and desaturation to form long-chain metabolites that can eventually become incorporated into cell membranes.[1] DHA has many diverse functions at the cellular level including enzyme regulation, membrane fluidity, regulation of ion channels and signal transduction.[2]

Aqueous production involves membrane-bound pumps and receptors. Omega-3 deficiency can affect membrane-bound protein activity in rats[3] and therefore may affect aqueous production. Increasing dietary omega-3 in mice reduces IOP by increasing outflow facility[4] and diets with increased omega-3 and decreased omega-6 PUFA's may favor increased synthesis of PG-F2.[5] In rabbits, intramuscular cod liver oil lowered IOP by 3 mmHg at 0.2 ml/day, and 6.5 mmHg at 1 ml/day. When treatment with cod liver oil was stopped, IOP rose to baseline levels.[6] However, human studies investigating dietary fat consumption and primary open-angle glaucoma (POAG) showed that a high ratio of dietary omega-3 to omega-6 polyunsaturated fat consumption appears to increase the risk of POAG.[7] The trabecular meshwork in glaucoma is also affected by oxidative stress related changes such as cell loss, increased accumulation of extracellular matrix (ECM), and cellular senescence, which are minimized with prostaglandin analogue application in vivo.[8]

DHA and EPA play a role in red cell fluidity, deformability, and aggregability.[9] POAG patients are hypothesized to have enhanced platelet aggregation,[10-12] and EPA is a precursor to eicosanoids, which have vasodilator and antiaggregatory effects.[13,14] Reduced plasma EPA and DHA were found in glaucoma patients compared to siblings without glaucoma, and it was postulated that EPA and DHA play a role in modulating impaired systemic microcirculation and ocular blood flow in POAG.[15]

In the retina, DHA has been implicated in modifying enzyme activity in photoreceptor cells and providing an environment for conformational changes in rhodopsin. Decreased retinal DHA content affects visual function in monkeys[16,17] and a combination of DHA, vitamin E, and vitamin B were reported to improve contrast sensitivity and visual field indices.[18] In addition, DHA protects cells from oxidative stress by modulating levels of pro- and anti-apoptotic proteins of the Bcl-2 family, which protects photoreceptors from oxidative stress.[19]

DHA is also enriched in retinal pigment epithelial cells and is a precursor of neuroprotectin D1 (NPD1), which inhibits retinal pigment epithelial cell apoptosis and inhibits oxidative-stress-mediated pro-inflammatory gene induction.[20] DHA also reduces the activation of kainate receptors in retinal reperfusion after ischemia, and is proposed to have a neuroprotective effect in ischemia-induced retinal injury. In rabbits, intraperitoneal DHA was effective in protecting the retina against IOP-induced transient ischemia.[21] In addition, oral administration of DHA in rats counteracted kainic acid-induced retinal neurotoxicity[22] and DHA protected against ischemia-reperfusion related retinal cell death in monkeys, partially by inhibiting the formation of hydroxyl radicals.[23] In rodent eyes with laser photocoagulation-induced increased IOP, glial cell activation was significantly lower and protective effects on retinal structures was significantly higher in animals fed with an omega-3 and omega-6 PUFA combination diet compared to controls and those fed a single supplementation (omega-3 or

omega-6) diet.[24] Lastly, DHA combined with lutein and zeaxanthin promotes rat photoreceptor survival after oxidative damage.[25]

Dosage and side effects

There are many types of nonprescription dietary supplements of omega-3 fatty acids available. However, none are regulated by the same standards as pharmaceutical agents.[26] In 2004, the FDA approved a formulation of omega-3-acid ethyl esters to reduce high triglyceride levels, which is a combination of omega-3-acid ethyl esters (P-OM3). It contains concentrated forms of EPA (465 mg), DHA (375 mg) and other omega-3 fatty acids (60 mg) for a total of at least 900 mg of omega-3 fatty acids per each one-gram capsule.[27] In patients with documented coronary heart disease, the American Heart Association recommends one gram of DHA and EPA for cardiovascular protection.[28] The best dietary sources of EPA and DHA include fatty fish such as salmon, herring, mackerel, halibut and tuna[29] and also some fresh-water fish such as lake herring, lake trout, freshwater salmon and whitefish.[30](USDA)

The most common drug-related adverse events associated with omega 3 fatty acid supplementation include dyspepsia and belching.[31] There are no known, clinically significant drug interactions; however, some reports suggest that omega-3 fatty acids may impair platelet aggregation and increase bleeding times.[32,33] Omega-3 fatty acid supplementation has also been attributed to increased levels of liver transaminases,[31] and a transient increase in glucose levels.[27]

In conclusion, omega-3 fatty acids play an important role in reducing oxidative damage in the retina, improving ocular blood flow and protecting against retinal ischemia induced by increased IOP.

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Alpha-lipoic acid

Sandra Fernando

Background and pharmacology

Alpha-lipoic acid is a cofactor in the mitochondrial dehydrogenase complex that catalyzes the oxidative decarboxylation of α-keto acids, such as pyruvate and α -ketoglutarate.[1,2] In this decarboxylation process, alpha-lipoic acid is reduced to dihydrolipoic acid and the two substances operate as a redox couple. Lipoic acid and dihydrolipoic acid also chelate transition metals and assist in the regeneration of other antioxidants, such as glutathione, α-tocopherol, and ascorbate.[3] Normally, alpha-lipoic acid is present in small amounts in mammalian tissue (5-25 nmol/g) and is bound to an enzyme that makes it unavailable as an antioxidant. However, unbound exogenous alpha-lipoic acid has antioxidant effects and can act as a substitute for glutathione.[4] Exogenous administration of alpha-lipoic acid has been shown to reduce ischemic-reperfusion injury in rodent cerebral cortex,[5] heart[6] and peripheral nerve.[7]

Alpha-lipoic acid and the eye

Alpha-lipoic acid exerts potent antioxidant effects in the lens and retina. In the lens, alpha-lipoic acid reduces the iron pool from the cytoplasm of lens cells, which increases the cells' defense against oxidative damage.[8] It also may prevent or slow progression of cataract through mechanisms such as decreasing lens aldose reductase activity and increasing lens glutathione levels.[9-11]

In the retina, alpha-lipoic acid decreased the amount of leukostasis in the retinal capillary endothelium in diabetic rats.[12] In experimental diabetes, it corrects decreased retinal ion demand[13] and may increase retinal oxygenation.[14] In the diabetic rat retina, abnormal mitochondrial NAD+/NADH ratios and increased 4-hydroxyalkenal levels indicative of hypoxia are ameliorated by treatment with alpha-lipoic acid.[15]

New hypotheses have emerged about the specific effect of alpha-lipoic acid therapy on the pathogenesis of glaucoma. Osborne proposed that decreased blood flow to the optic nerve in glaucoma leads to a compromise in retinal ganglion cell energy requirements, causing the cells to be more susceptible to injury by oxidants (nitric oxide, TNFα) released from astrocytes.[1] These effects eventually lead to ganglion-cell death because of the inability of mitochondria to maintain normal function. Therefore, agents that specifically enhance ganglion cell mitochondrial energy production and decrease oxidative stress should theoretically be beneficial in a disease such as glaucoma.

Alpha-lipoic acid improved visual function in 45% of glaucoma patients supplemented with lipoic acid[16]and two months of alpha-lipoic acid supplmentation was found to increase aqueous glutathione levels in POAG patients.[17] In addition, alpha-lipoic acid supplemenation with vitamin C is believed to increase aqueous humor drainage by reducing the viscosity of trabecular meshwork hyaluronic acid.[18]

Dosing, bioavailability, and side effects

Alpha-lipoic acid is absorbed by the gastrointestinal tract in a variable manner. After administration of 200 mg alpha-lipoic acid in humans, only 20-40% is absorbed, which is lowered by its administration in food.[19] After absorption, it rapidly traverses cell membranes in a pH-dependent manner and acts as a substrate for an Na^+-dependent multivitamin transporter. Its transport is inhibited by benzoic acid and medium-chain fatty acid[2] and undergoes renal excretion. Alpha-lipoic acid transiently accumulates in the liver, heart, and skeletal muscle, and also crosses the blood-brain barrier.[20]

Dietary sources of alpha-lipoic acid include muscle meats, heart, kidney, liver, and certain fruits and vegetables.[21] However, it is not likely that a Western diet can achieve levels equivalent to dietary supplements, which range from 50-600 mg.[2]

Alpha-lipoic acid supplementation is not correlated with significant side effects in humans or animals. However, rats were reported to show signs of sedation and apathy after administration of > 2 g/kg.[22] In humans, a number of clinical trials used alpha lipoic acid supplements up to 2400 mg/day with no reported adverse effects compared to placebo.[2]

Conclusion

Alpha-lipoic acid has powerful antioxidant effects, and can be useful in blocking pathological processes in glaucoma caused by ischemia and oxidation.[16] However, the lack of clinical trials investigating the benefits of neuroprotective supplements such as alpha-lipoic acid in glaucoma limits its current use.[23]

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Soy sauce

Aiko Iwase

Soy sauce is a widely used fermented seasoning in Asian countries and more recently, worldwide. Phytochemicals, as antioxidants and anti-inflammatory agents, may help prevent or delay the progression of age related changes.[1] Isoflavones are the flavonoids of soy beans, and are reported to significantly reduce serum total cholestrerol and tryacylglycerol and significantly increase HDL cholesterol.[2] These beneficial attributes of isoflavone have been adopted for the preventive strategies against cardiovascular and arterioscrelotic disease. Studies using nuclear magnetic resonance and electrospray-ionization time-of-flight mass spectrometry analysis suggest that carbohydrate-containing pigments such as melanoidins are the major contributors to the high antioxidant capacity of dark soy sauce.[3]

Various soybean materials obtained in soy processing and products (miso, natto, soy sauce, etc.), include five isoflavones – daidzin, glycitin, genistin, daidzein and genistein – but soy sauce contains little of them, while soy sauce oil richly contains daidzein and genistein.[4] Deregulated apoptotic mechanisms have been implicated in many pathologic human neurological disorders, including glaucoma. In cerebellar granule cells, genistein and daizein suppressed low potassium-dependent apoptosis at doses of 0.1-20 μM, and survival was about 70% in the presence of 20 μM genistein and about 60% in the presence of 20 μM daizein.[5]

The manufacturing process and the composition of the starting ingredients differs between countries, and it is likely that differences in the raw materials, fermentation time and heating processes used during the manufacture of soy sauce may affect the composition and antioxidant activity of the final products.[6] Soy sauce should be considered as a flavoring or seasoning, but not as a functional food, since it contains a relatively high concentration of sodium chloride, but little isoflavone.[7]

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Green tea

Aiko Iwase

The botanical name of the tea plant is *Camellia sinensis*. The small-leaf Chinese variety is named *Camellia sinensis* var. sinensis and the large-leaf black tea discovered in India is named *Camellia sinensis* var. assamica. In the eighth century, during the Tang Dynasty, Buddhist monks or Japanese envoys are thought to have brought the small-leaf Chinese variety to Japan and thus tea trees cultivated in Japan are *Camellia sinensis* var. sinensis.[1] Green tea produced in Japan is mainly produced by steaming and is unfermented, while oolong tea is half-fermented and black tea is full-fermented. Major chemical components (% of dry weight) of green tea are catechins (9.4-16.2%), theanine (0.5-2.4%), caffeine (2.1-4.0%) and vitamin C (0.1-0.4%).[2]

Theanine

Theanine is a glutamate analogue. A high concentration of theanine (500 μM) reduced glutamate-induced death of cultured rat cortical neurons, suggesting a neuroprotective effect of on glutamate toxicity.[3] In postischemic neuronal death in field CA1 of the gerbil hippocampus, theanine solution given at a dose of 125 and 500 μM significantly suppressed CA1 neuron damage by 60 and 90%, respectively.[1] The mechanism of this neuroprotective action may be at least partly attributed to its mild affinity to NMDA and /or AMPA /kainate receptors.[4]

Since IC_{50} values for theanine to these receptors are relatively high, other mechanisms, such as effects on the glutamate transporter, were suggested.[1] Theanine is absorbed in the intestinal tract, reaching a peak at 0.5-2 hours after oral administration.[5,6] A recent study showed that oral intake of l-theanine at a dose of 2 and 4 mg/kg attenuated Abeta(1-42)-induced memory impairment in mice, possibly by suppression of ERK/ P38 and NF-kB, as well as the reduction of oxidative damage.[7]

Catechins

Catechins are the main bioactive constituents of green tea leaves and consist of eight polyphenolic flavonoid-type compounds; (+)-catechin (C) (-)-epicatechin(EC), (+)-gallo-catechin(GC), (-)-epigallocatechin(EGC), (+)-gallocatechin(GC), (-)-epigallocatechin(ECG), (+)-gallocatechin gallete(GCG), and (-)-epigallocatechin gallate(EGCG).[8] EGCG is the most abundant of tea catechins and thought to be responsible for the most of biological activity of green tea.[9] According to Kuroda and Hara, green tea contains C, EC, ECG, EGC and EGCG at concentrations of 21, 98, 90, 411 and 444 mg/L respectively.[10]

Epidemiological studies have suggested potential relationship between green tea drinking and many types of cancer.[11-14] Further, green tea drinking was reportedly inversely associated with coronary atherosclerosis[15] and cerebrovascular diseases.[16] However, it must be noted that there are conflicting reports on whether the most effective source of catechins is tea or fruit.[17,18]

The mechanism of catechin action includes free radical scavenging / antioxidant actions (see reference 2 for review). Among catechins, ECG and EGCG were reported to be the most potent free radical scavengers.[19-23] In addition to direct antioxidant effects, catechins also indirectly increase endogenous antioxidative capacity by increasing levels of such enzymes as superoxide dismutase, catalase, glutathione peroxidase and reductase,[24] by preventing endogenous antioxidants being depleted by lipid peroxidation,[22] or by inhibiting xanthine oxidase.[25] EGCG was reported to inhibit many points of apoptotic sequence including caspase 3.[26,27] and reportedly modulates the expression of proapoptotic genes such as Bax, while inducing antiapoptotic genes such as BCl-2.[28]

Because of the above mentioned free radical scavenging, antioxidant, gene modulating activities, together with the ability to cross the blood-brain barrier,[29] green tea catechins may potentially act as neuroprotectants *in vivo*. In fact, epidemiological studies suggest that green tea catechins many reduce the risk for Parkinson's disease.[30,31] Green tea catechins were also reported to protect neuronal death from the Parkinsonian trigger MPTP in animal models.[32-34] EGCG also inhibits catechol-O-methyltransferase and may conserve synaptic dopamine in Parkinson's disease.[35] Green tea catechins, especially EGCG, protect the central nervous system in animal models of stroke.[36,37] In animal models of Alzheimer's disease, some green tea catechins specifically bind with and help to clear amyloid-beta.[34,38] In cultured hippocampal cells from rat brain, green tea catechins, especially EGCG, at concentration of 5-10 μM, inhibited formation of amyloid-beta fibrils implicated in neuronal death in Alzheimer's disease.[34]

Ocular effects of green tea catechins

Oral intake of EGCG (0.4% in drinking water) was reported to attenuate the light-induced photoreceptor damage in albino rats as measured by the a- and b-wave amplitude and expression of various proteins involved in apoptosis such as caspase-3, caspase-8, Bcl-2 and Bad.[39] Beneficial effects of oral intake of EGCG (0.5% in drinking water) was also demonstrated in a rat ischemia / reperfusion model, which mainly injures the retinal ganglion cell layer. EGCG siginificantly attenuated the change in a- and b-wave amplitudes, activation of caspases and other ischemia/reperfusion-induced changes *in vivo*. Further, EGCG inhibited light- induced apoptosis of cultured RGC-5 cells which was caspase-independent almost completely at 10 μM.[40]

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Non-pharmaceutical approaches to the treatment of glaucoma
Coffee, chocolate, and cocoa

Michael S. Kook

Glial activation and oxidative stress have been increasingly implicated in glaucoma. For instance, unstable ocular blood flow and/or perfusion pressure causing repeated ischemia and reperfusion appears highly relevant in inducing oxidative stress.[1-12] This in turn may lead to damage to a variety of macromolecules, such as proteins, lipids, sugar residues, or DNA, and thereby to cell death, such as that of retinal ganglion cells. Natural anti-oxidants may thus be important therapeutic modalities.

Coffee beans contain about 8% phenolic compounds, with anti-oxidative effects due to their free radical scavenging and metal-chelating activities.[13-17] The compound 3-methyl-1,2-cyclopentanedione (MCP), isolated from the coffee extract, is a selective scavenger of peroxynitrite.[18] MCP donates a proton to peroxynitrite to neutralize it through the chemical conversion of one of its carbonyl groups, which becomes reduced to a hydroxyl group. Polyphenols in coffee inhibit lipid peroxidation and protect against mutagenicity.[19] Despite much debate on the effects of coffee on glaucoma, its antioxidant potential deserves further research.

Chocolate is derived from cocoa beans from the seed of *Theobroma cacao*.[20,21] It contains a class of flavonoids, flavan-3-ols and their oligomers (procyanidins), Dark chocolate generally contains at least twice as much cacao, and thus twice the polyphenols as milk chocolate. In addition, the milk in milk chocolate may reduce absorption of cacao. The anti-oxidative capacity of cacao is higher than that of wine or green tea because of much higher levels of phenolic phytochemicals.[22] Several in vivo studies have provided support that the consumption of cacao-rich food, such as dark chocolate, is associated with a reduced risk of vascular disease.[23,24] The mechanism is due to the action of flavan-3-ols, which augment endothelial NOS, and thereby nitric oxide, to improve endothelium-dependent vasorelaxation.[25,26] Ingestion of cacao also decreases both systolic and diastolic blood pressure, improves insulin sensitivity, reduces LDL oxidation susceptibility (thereby increasing the serum total antioxidant capacity and HDL-cholesterol concentrations),[27] and reduces platelet adhesiveness and clotting.[28,29] Because of these multiple beneficial effects, chocolate also deserves further research and may prove of value in the treatment of glaucoma.

Cocoa pods from the cocoa tree (*Theobroma cacao*) are harvested and the beans removed and fermented. Dried and roasted beans contain about 300 chemicals, including caffeine, theobromine, and phenethylamine. Chocolate liquor is prepared by finely grinding the nib of the cocoa bean and is the basis for all chocolate products.

Cocoa powder is made by removing part of the cocoa butter from the liquor. Bittersweet chocolate, or dark chocolate, contains at least 15% chocolate liquor but may contain as much as 60%, with the remainder being cocoa butter, sugar, and other additives. Milk chocolate is the predominant form of chocolate

consumed in the U.S. and typically contains 10-12% chocolate liquor. Therefore, cocoa like dark chocolate contains both a high quantity and quality of phenol antioxidants.[30] The consumption of polyphenolic flavonoids from cocoa decreased the risk of heart disease in a cross-cultural epidemiological study.[30] This antioxidant activity may exert beneficial effects and may prove valuable in the non-pharmaceutical treatment of glaucoma.[27,31]

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N-acetyl cysteine

Robert Nussenblatt

N-acetylcysteine (NAC) is an acetylated variant of L-cysteine and has several medical indications. Its use is based on its proposed mechanism of influencing both anti-oxidant and nitric oxide systems, which can be very active during infections and stress. Glutathione is one of the body's major anti-oxidants[1] and helps to detoxify substances that harmful during inflammatory and infectious processes. Glutathione is composed of glutamate, glycine and cysteine. Cysteine is present in cells in the lowest concentration of the three.[2] Since glutathione production is dependent on the presence of these three substrates, a low concentration of cysteine may inhibit rapid production of gluthathione when needed. Therefore, exogenously administered NAC could help in meeting this anti-oxidant need. A second mechanism of action is as a vasodilator by its effect on nitric oxide.[3]

Perhaps its best known indication is as an antidote for acetaminophen overdose. NAPQI is the toxic metabolite of acetaminophen. NAC replenishes glutathione, which then binds directly to the toxic metabolite. This enhances a nontoxic sulfate conjugation in the liver cell.[4] NAC has also been evaluated in another clinical adverse event, contrast induced nephropathy, which occurs in about 2% of cases with normal serum creatinines. However, patients with serum creatinine levels above 2.0 mg/dL or with diabetes are at high risk to develop this complication.[5] An initial prophylactic trial using NAC showed a positive result.[6] A large number of controlled studies ensued with varied findings, the majority either showing an effect or the result being inconclusive.[7] NAC is not used standardly as prophylaxis.

Several studies have evaluated NAC in treating chronic obstructive pulmonary disease (COPD). In an open label study of almost 1400 patients, NAC resulted in clear clinical improvement.[8] There was a decrease in the viscosity of phlegm and decreased coughing shortness of breath. Another trial showed a decrease in the deterioration of the FEV1 in older patients treated with NAC.[9] In addition, there have been several randomized trials with the majority showing a clinical benefit to NAC therapy.[7]

In another pulmonary disorder, pulmonary fibrosis, a study randomizing patients to either NAC (600mg TID) and placebo also showed that the deterioration of lung function was slowed in those patients receiving the active therapy.[10] In one randomized controlled trial, NAC was useful in attenuating and preventing the signs and symptoms of influenza in a frail population.[11]

Side effects at doses 1200 mg BID or lower have been minimal with mostly gastrointestinal problems along with skin rashes. At the higher doses used to treat acetaminophen toxicity, there can more severe adverse events including tinnitus, headache, rash, chills, fever, and an allergic reaction.

The potential use of NAC in ocular disorders has been suggested in several studies, both of the retina and the trabecular meshwork. One study emphasized the importance of neuroprotection in glutamate induced cytotoxicity.[12] In this study using rat RGC-5 cells, glutamate treatment resulted in RGC-5 cell death. Pretreatment of these cells with NAC resulted in a reversal of the cytotoxic effects. A second model evaluated the glaucoma associated mutant optineurin in the induced death of RGC.[13] Plasmids expressing either the wild type or various optineurin mutants were inserted into a variety of cells lines. In the E50K mutation of optineurin-induced RGC death, reactive oxygen species were produced with the expression of E50K. The addition of NAC inhibited the cell death. Finally, a recent study evaluated the potential role of antioxidants in defects potentially leading to POAG. He et al. suggested that a mitochondrial complex 1 defect is associated with trabecular cell degeneration.[14] Cultured trabecular cells from POAG patients had significantly higher reactive oxygen species levels compared to controls. Anti-oxidants, including NAC, protected against cell death by inhibiting ROS generation and cytochrome-C release.

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Taurine

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Taurine (2-aminoethanesulfonic acid) is the decarboxylation product of cysteine, and is mainly obtained from diet. It is a free sulfur ß-amino acid found in animal tissue and is one of the most abundant low molecular weight compounds, present in the micromolar range per gram wet weight. While the body can make taurine from sulfur precursers, it is produced endogenously in the liver from methionine and cysteine. Enzymes that are needed for taurine production include cysteine sulfinic acid decarboxylase, which is the rate limiting step in the cascade leading to taurine.[1] However, the amount produced is insufficient

and dietary sources are needed. Taurine is found freely in the cytosol and is found particularly in the heart, retina, brain and blood.

Taurine has been associated with many different physiologic activities, including calcium transport, antioxidation, neurotransmission, and regulation of protein phosphorylation.[2] It should be added that the dominant role of taurine still needs to be determined. Significant changes in plasma and tissue levels occur in aging rats.[3] These decreases are noted in the eye as well[4] and may be due to a decrease in liver biosynthetic enzymes. Of interest is that withdrawing taurine from the diet of animals does not enhance the decrease; yet augmenting the exogenous amount of taurine helps to resolve the deficit. However these observations are in the rat. In the human, the data is less robust. What has been shown is that taurine concentrations increase in the cerebrospinal fluid of aging humans,[5] and by upwards of 30%.

As with other tissues, taurine is found in high concentrations in phagocytic cells. It is believed to provide protection against inflammatory cytotoxicity, anti-oxidant activity, and membrane stabilization. Taurine appears to mediate these effects by eliminating highly toxic HOCL and generating non-toxic TauCl. TauCl appears to suppress the production of many inflammatory mediators, including NO, TNF-alpha, IL-1, Il-2, and IL-6. It appears to suppress production of IL-10 as well, which is a downregulatory cytokine.[6,7] It would appear that taurine in phagocytes prevents chronic inflammatory processes. The underlying mechanisms in macrophages appears to be the inhibition of NO by the suppression of the activation of several factors, including Ras, ERK1/2, and NF-kB. In neutrophils, taurine appears to exert an inhibitory effect by inhibiting p47phox and the assembly of the NADPH-oxidase complex.[7]

Taurine appears to play an important in ocular development. It appears structurally similar to the neurotransmitters GABA and glycine. Taurine plays a role aslo in the formation and maintenance of neural tissue. Kittens given taurine-deficient diets exhibited retinal degeneration and CNS defects.[8] Interestingly, taurine increased the numbers of rod photoreceptors in retinal culture.[9] It appears to act in retinal progenitors via the GlyRa2 subunit containing glycine receptors.[10] As noted above, levels in animals decrease with aging, and specific ERG changes in rats can be associated with these decreased tissue levels, reflecting the fact that the retina has a decreased ability to deal with oxidative stress.[1] Exogenous taurine administration may be helpful in preventing age related changes in the retina.[1] Taurine concentrations seem to be markedly decreased in injured photoreceptors of dogs with glaucoma.[11] Taurine transformed rat retinal ganglia are protected from hypoxia-induced apoptosis, probably through the prevention of mitochondrial dysfunction.[12] One report in a small number of rabbits suggested that when topically applied 0.5% timolol was mixed with several amino acids, including taurine, the IOP decrease in the rabbit eye was greater than with timolol alone.[13]

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Citicoline

Vincenzo Parisi

The natural history of glaucoma involves the early impairment of the innermost retinal layers, which may precede the onset of visual field defects,[1] subsequently followed by damage due to transynaptic degeneration in post-retinal visual pathways and, in particular, at the level of the lateral geniculate nucleus.[2] Glaucoma must not be considered exclusively as a disease involving ocular structures, but a pathology in which regions of the brain involved in vision are also compromised.

The possibility of inducing an improvement of glaucomatous visual function pharmacologically with cytidine-5'-diphosphocholine (citicoline) was suggested in 1989.[3] A similar treatment was used in different brain disorders ascribed to vascular, traumatic or degenerative processes.[4,5]

Citicoline (exogenous CDP-choline) is a nontoxic and well-tolerated substance that acts as an intermediary in the synthesis of phosphatidylcholine, a

major phospholipid in the neuronal membrane, through activation of the biosynthesis of structural membrane phospholipids. It increases the metabolism of cerebral structures and inhibits phospholipid degradation. Enhancement of phosphatidylcholine synthesis may counteract neuronal apoptosis and provide neuroprotection.[6] Citicoline has been reported to have a neuroprotective effect on kainic acid-induced neurotoxicity in the retina.[7]

Citicoline may therefore have potential neuroprotective and neuromodulator roles, as demonstrated in conditions of cerebral hypoxia and ischemia.[8,9] In addition, it induces an increase in the levels of different neurotransmitters and neuromodulators, including noradrenaline, in the central nervous system. Several studies suggest that citicoline successfully increases the level of consciousness in different brain disorders ascribed to vascular, traumatic or degenerative processes.[4,5] When administered, citicoline is rapidly transformed to cytidine and choline, which are believed to provide neuroprotection by enhancing phosphatidylcholine synthesis; a similar effect may occur in glaucomatous retinal ganglion cells.[6]

The first studies reported that treatment with citicoline could induce an improvement of glaucomatous visual field defects.[3] Subsequent studies questioned whether this improvement was related to a real enhancement of ganglion cell function and neural conduction along the visual pathways, or whether it was due to the associated effects of citicoline on the level of consciousness and attention.[5]

To explore these hypotheses, further studies evaluated the effects of oral (1600 mg/die) or intramuscular (1000 mg/die) citicoline treatment, administered for 60 days, on retinal function and neural conduction in the visual pathways of glaucoma patients with moderate visual defects; these studies used an electrophysiological approach, pattern electroretinograpy, to evaluate ganglion cell function and visual evoked potentials to evaluate neural conduction along visual pathways.[10,11] Oral or intramuscular treatment with citicoline induced an improvement of both PERG and VEP responses, with an increase in amplitudes and a shortening in times-to-peaks.

Nevertheless, the beneficial effects of citicoline were treatment-dependent. In particular, 300 days after the end of treatment, no differences were detected with respect to pre-treatment conditions. When a second period of citicoline administration was performed, it was observed that even after a long period of wash-out (120 days), the improvement in visual function was once again evident, suggesting that repeated treatments may inhibit the development of the visual impairment.[10,11]

The effects of citicoline on the neural visual system were revealed by improvement in visual acuity,[12] in VEP responses, and in contrast sensitivity in amblyopic subjects after treatment. Since similar results were obtained in amblyopic subjects with levodopa,[13] and in studies of patients with Parkinson's disease, citicoline was recommended as a complement to levodopa therapy.[14] The addition of CDP-choline to patching therapy was no more effective than patching alone after 30-days, but that adding CDP-choline to patching stabilised the effects

obtained during treatment of amblyopia.[15] A dopaminergic-like activity could be suggested to explain PERG and VEP results after treatment with citicoline.

These results raise an interesting question: can oral or intramuscular citicoline effects be considered as 'neuroprotective', preventing the development of glaucoma? Considering that after the first period of washout there were no differences with respect to pre-treatment conditions, one cycle of treatment with citicoline is not sufficient to induce changes in the natural history of glaucoma. On the other hand, we observed that the second treatment period with oral citicoline induced an improvement which persisted after 120 days of washout.

The results obtained in the first study[16] were further explored in a restricted cohort of selected patients (12 OAG patients only), in which a series of 60 day-periods of treatment each followed by 120 days of wash-out, were carried out during a total period of eight years.[17] This study showed that after eight years, glaucomatous patients subjected to citicoline treatment displayed a stable or improved electrophysiological and visual field condition compared to pre-treatment (eight years before), while in similar glaucoma patients without citicoline treatment, there was worsening of the electrophysiological and visual field impairment with respect to pre-treatment conditions (eight years before).

Indeed, the data observed in glaucoma patients treated with beta-blockers plus several periods of treatment with intramuscular citicoline with respect to results in glaucoma patients treated with beta-blockers only may suggest the potential use of citicoline in order to obtain the stabilisation or improvement of visual function in glaucoma. In agreement with similar studies,[8,9,10,12,17] an important aspect is the lack of adverse pharmacological side effects in all participating subjects, even after long-term administration of the drug. This indicates the potential use of citicoline in the medical treatment of glaucoma, as a complement to hypotensive therapy, with a possible direct neuroprotective effect.

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Carnosine

Vincenzo Parisi and Robert Ritch

Carnosine (beta-alanyl-L-histidine) has been suggested as supplementary therapy in several ocular disorders. In particular, cataract patients treated with carnosine showed improved visual function.[1,2] it should be noted that Dr Babizhayev is CEO of Innovative Vision Products (IVP), the holder of patents for the use of N-Acetylcarnosine.

The rationale for the potential use of carnosine in glaucoma is once again based on the analogies between glaucoma and Alzheimer's disease. In fact, advanced glycation end products (AGEs) may contribute to the Alzheimer pathology and carnosine, a natural antioxidant and transition-metal ion sequestering agent, may inhibit the formation of AGEs.[3] In addition, carnosine seems to have a neuroprotective effect in animal models in which cerebral ischemia was induced.[4]

In rats with ischemic acute renal failure, two weeks of prior feeding of a diet containing L-carnosine- attenuated the ischemia/reperfusion-induced renal dysfunction, while histologic renal damage, such as tubular necrosis, was significantly reduced.[5] Slowing of the rate of cataract formation has been reported in rats.[6]

Since there is lack of information in the literature regarding the use of carnosine in glaucoma, experimental studies in glaucomatous animal models treated with

carnosine and subsequent controlled clinical trials performed in glaucomatous patients could shed light on its possible therapeutic role.

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Carnitine

Vincenzo Parisi and Robert Ritch

Carnitine, an amino acid derivative found in high energy demanding tissues (skeletal muscles, myocardium, liver), is essential for the intermediary metabolism of fatty acids. It plays an important role in such ocular tissues as the ciliary body, where muscle cells are present and may be an important energy reserve.[1] After carnitine treatment, patients with Alzheimer's disease improved on psychometric testing,[2-4] and patients with chemotherapy-induced peripheral neuropathy showed amelioration of sensory amplitude and conduction velocity.[5]

In animal models, carnitine protects against selenite-induced cataract[6] and ischemia-reperfusion retinal injury.[7] It protects RPE cells against hydrogen peroxide-induced oxidative damage.[8] Patients with early age-related macular degeneration showed improved visual function and fundus alterations after carnitine treatment.[9]

Carnitine prevents glutamate neurotoxicity in primary cultures of cerebellar neurons.[10] and, by increasing the level of ATP, may improve mitochondrial function.[11,12] Considerable evidence suggests that mitochondrial dysfunction and oxidative damage may play a role in the pathogenesis of Parkinson's disease and that acetyl- L-carnitine is beneficial in animal models of the disease.[13] Mitochondrial dysfunction has been observed in patients with glaucoma.[14] Thus, one could hypothesize that improved ganglion cell function and neural conduction along the optic nerve could occur after carnitine treatment in glaucoma patients.

At present there is lack of information regarding controlled clinical trials performed in glaucomatous patients treated with carnitine.

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Coenzyme Q10

Nathan Radcliffe

Coenzyme Q10 (CoQ10), also known as ubiquinone, is a membrane bound mitochondrial antioxidant cofactor that participates in the electron transport chain. CoQ10 has been shown to improve mitochondrial function and is currently being evaluated in clinical trials for Alzheimer's disease, Parkinson's disease and Huntington's disease.[1,2] In humans with Parkinson's disease, there is evidence that CoQ10 can slow the rate of functional decline compared to placebo.[3]

CoQ10 has received interest in glaucoma because it is a free radical scavenger and inhibits apoptosis by blocking Bax.[1,4] Mitochondrial dysfunction and

oxidative stress have been implicated in the development of glaucomatous optic neuropathy.[5] In a rat model of pressure-induced retinal ischemia/reperfusion injury, CoQ10 administration inhibited glutamate increases and prevented retinal ganglion cell (RGC) apoptosis.[6] Guo and Cordeiro have shown that CoQ10 inhibits staurosporine induced RGC apoptosis as visualized with the detection of apoptosing retinal cells technique.[7] As a result of these and other studies, CoQ10 has received recent attention for a potential role for neuroprotection in glaucoma.[8] However, there are no randomized clinical trials showing that CoQ10 is effective for glaucoma neuroprotection in humans, nor are there any experimental ocular hypertension/glaucoma animal studies demonstrating a neuroprotective effect of CoQ10.

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Folic acid

Nathan Radcliffe

Folic acid is an essential vitamin that is involved (in its active form tetrahydrofolate) in nucleotide biosynthesis and homocysteine (HCY) remethylation. Folate is found in green, leafy vegetables and in many breads and cereals fortified with folate. Folic acid deficiency (as well as certain medications and enzymatic deficiencies) can result in elevated levels of HCY. Hyperhomocysteinemia (HHCY) is a strong risk factor for atherosclerotic and thromboembolic disease. Elevated HCY levels are associated with several neurodegenerative diseases, including Alzheimer's disease.[1,2] Supplemental folic acid, combined with other B-vitamins (B-6 and B-12) can lower HCY levels by at least 30%.[3] A number of large,

randomized trials investigating the effects of lowering HCY with folate and B vitamins on cardiovascular and cerebrovascular endpoints have been performed without any strong evidence of benefit to HCY lowering.[4] Additionally, a recent large scale randomized trial showed that high-dose B vitamin supplements did not slow cognitive decline in individuals with mild to moderate AD.[5]

Homocysteine is toxic to retinal ganglion cells (RGCs) through stimulation of N-methyl-D-aspartate (NMDA) receptors and this excitotoxic damage is possibly potentiated by simultaneous elevation of HCY and glutamate.[6] An *in vitro* study of the effects of toxic concentrations of HCY on rat retinal tissues found HCY to be damaging to RGCs as well as to the outer and inner nuclear layers.[7] These findings raise the question of whether HHCY could be involved in the pathophysiology of glaucomatous optic neuropathy.

While the findings about HCY levels in POAG are somewhat conflicting, they have not been consistently found to be higher than controls.[8-11] Levels of HCY are elevated in exfoliation glaucoma while folate, vitamin B12 and B6 levels are reduced in this condition.[8,10-13] In summary, while there are intriguing connections between glaucoma and folate deficiency/elevated HCY, there is currently no evidence from experimental animal studies or human clinical trials to substantiate folate supplementation for glaucoma, we do advocate treating those patients, particularly those with exfoliation syndrome, in whom HCY levels are elevated. Furthermore, the lack of an observed benefit to HCY lowering with folate and B-vitamin supplementation in large cardiovascular trials raises the possibility that HCY may be a marker, rather than a cause, of these pathologies.

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Glutathione

Nathan Radcliffe

Glutathione is an antioxidant tripeptide of glutamate and a major intracellular antioxidant which neutralizes free radicals and reactive oxygen species. While glutathione depletion was initially thought to be a by-product of oxidative stress during apoptosis, current evidence suggests that glutathione may be involved in the regulation of apoptosis.[1]

In monkeys with experimental glaucoma, Müller cells have increased extracellular glutamate, likely due to increased transport and metabolism of glutamate.[2] In DBA/2J mice which develop glaucoma, glutathione depletion occurred, but this depletion was blocked by administration of the antioxidant alpha-luminol, suggesting that oxidative stress, including glutathione depletion, may play a role in glaucomatous neuronal damage.[1] In mice with deficiencies of the glutamate transporters GLAST or EAAC1, spontaneous retinal nerve fiber and optic nerve degeneration occurred in the absence of elevated IOP, and the administration of a glutamate receptor blocker prevented RGC loss.[3] However, in a glaucoma model of mice with these glutamate transporter deficiencies, there was no accumulation of glutathione in Müller cells, as has been previously observed in experimental glaucoma. The investigators proposed that these mice represent the first animal model of normal pressure glaucoma.

Glutathione deficiency and oxidative stress have been hypothesized to play a role in both anterior segment glaucoma pathophysiology (trabecular meshwork function) as well as in optic nerve apoptosis.[4,5] In particular the trabecular meshwork may be more sensitive to oxidative damage than the cornea or iris.[6] Patients with POAG have been shown to have low levels of circulating serum glutathione.[7] Furthermore, Turkish patients with POAG are more likely to poses the null genotype in the glutathione S-transferase M1 gene, though this finding was not replicated in a subsequent study.[8,9] Several additional Glutathione S-transferase deficiencies were more prevalent in Arab patients with glaucoma, suggesting that the role of glutathione transfer in glaucoma deserves further attention.[10] In summary, there is animal model evidence that glutathione may play a role in glaucoma. This pathway represents a potential target that will require further study before a therapeutic approach in humans can be explored.

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Melatonin

Nathan Radcliffe

Melatonin is an antioxidant regulatory compound produced by the pineal gland and by the retina, where it acts as a free radical scavenger and as a regulator of rod outer segment disc shedding.[1,2] Melatonin is also a neurohormone that binds to plasma membrane receptors (MT1/MT2) and is available over the counter as a dietary supplement in the United States. Melatonin has received attention in stroke, Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis and has been suggested to be potentially neuroprotective through its inhibition of the hamster retinal nitridergic pathway.[3-5] Furthermore, melatonin suppresses nitric oxide mediated retinal damage, including apoptosis in the rat retina.[6] Melatonin may also reduce apoptosis in astrocytoma cells through inhibition of phospholipase C.[5] Melatonin is protective against retinal ischemia/reperfusion injury in guinea pigs and specifically in RGCs of rats.[7,8] There is no experimental evidence for a protective role of melatonin in glaucoma in either humans or animal models. Further study is required to determine the potential value of this antioxidant compound in glaucoma.

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Salvia miltiorrhiza

Douglas Rhee

Introduction

Salvia miltiorrhiza (red sage, Chinese sage, dan shen) is a perennial flowering plant, approximately 30-60 cm high, that is native to China and Japan. In traditional Chinese medicine, red sage is believed to improve circulation and is used to treat hypertension and cardiovascular disease, especially acute myocardial infarction and strokes.

In patients with glaucoma, one report claimed to stabilize the visual field in moderate to advanced glaucoma.[1] The mechanism was presumed to be independent of IOP.

Possible beneficial mechanisms of action

There has been little direct study with red sage and glaucoma. In an experimental model of elevated IOP in rabbits, intravenous red sage resulted in near complete preservation of RGC compared to controls.[2] The same group also found less reduction of axoplasmic flow in this rabbit model in red sage treated group (intravenous); this beneficial effect was potentiated by concurrent use of topical timolol.[3]

Although there has been little direct study of glaucoma, there has been extensive study of red sage in other areas, with over 1,000 studies listed during on-line search (www.ncbi.nlm.nih.gov; search term ‘salvia miltiorrhiza’) in March 2010. Many of these studies have focused on the anti-oxidant and

anti-inflammatory properties attributed to red sage or Tanshionone IIA (Tan IIA), its principle active ingredient, in cardiovascular, tumor, and acute hepatic injury research. In these studies, several proteins and pathways that have been associated with glaucoma have been affected, albeit in different cell types. A brief review is presented.

Anti-oxidant and redox scavenger

The predominant activity that is believed to be conferred by red sage is as an antioxidant. In atherosclerotic lesions, smooth muscle cells grow in response to oxidative stress, such as homocysteine. In a rat model of atherosclerosis, an extract of red sage inhibited the growth of vascular smooth muscle cells and decreased the intracellular reactive oxygen species concentration.[4] By surveying several different signaling pathways, the investigators determined that the red sage was acting through the protein kinase C/ mitogen-activated kinase (PKC/MAPK). Although the receptor is unknown, they used two-dimentional immunoblotting and mass spectrometry to compare the protein extracts from cells treated with homocysteine compared to those receiving homocysteine and red sage to show significant change in cytoskeleton and chaperone proteins. Red sage exerted its protective effect through scavenging of reactive oxygen species and modulation of protein carbonylation to inhibit cell proliferation.[4] In a separate study, red sage directly lowered total plasma homocysteine by increase the activity of trans-sulphuration enzymes that metabolize homocysteine.[5]

Tan IIA alleviated oxidative damage induced by glutathione-induced hyper-stimulation of the NMDA receptor (*i.e.*, excitotoxicity) in human neuroblastoma SH-SY5Y cells.[6] There is some evidence indicating a direct effect mitigating NMDA receptor excitoxicity.[7]

Red sage has been reported to have some protective effective effect on hepatic damage, apparently through an antioxidant mechanism.[8] Red sage was protective against reperfusion injury in liver through inhibiting oxidation and also antagonizing TNF-a.[9]

Anti-inflammatory effects

In an experimental model of myocardial infarction, Tan IIA blocked nuclear factor-kappaB2 (NF-kappaB2) and transforming growth factor beta-1 (TGFb1) secretion in rat cardiac cells.[10] In liver injury models, Tan IIA reduced levels of interleukins-2, -4, (tumor necrosis factor alpha (TNFa), and interferon-gamma.[11] In a prospective randomized controlled trial of an extract containing red sage, along with *panax notoginseng* and *dryobalanops camphor*, in 106 patients who had an ischemic stroke or TIA were managed with conventional therapy with or without this extract, the experimental group had a lower rate of recurrent stroke/TIA.[12]

Effect on blood viscosity

In beagles, intravenously administered salvianolic acid B (another active compound found in red sage), decreased blood viscosity, while oral administration had no effect.[13] In humans, red sage can potentiate the effects of warfarin, leading to bleeding complications.[14]

Vasodilatory effects

In rat cardiac arterioles, red sage induced vasodilation by increasing production of nitric oxide from the endothelial cells either directly, or from a locally produced cytochrome P450 metabolite, via calcium-activated potassium channels.[15]

In rats, whole red sage extract given intravenously can lower blood pressure.[16] Further studies with Tan IIA showed it lower systemic blood pressure in rats with spontaneous elevated blood pressure via ATP-sensitive potassium channels to lower intracellular calcium.[17]

Effect on extracellular matrix modulation

Tan IIA inhibits proliferation and induces apoptosis of tumor cells in breast and colon cancer cells, *in vitro*.[18,19] Although seemingly unrelated to the pathogenesis of glaucoma, Tan IIA suppressed NF-kappaB signaling and reduced urokinase plasminogen activator and matrix metalloproteinases (MMPs)-2, -9, and increased tissue inhibitors of metalloproteinases (TIMPs)-1 and -2.(Hung YC 2010) In an experimental model of acute myocardial infarction, salvianolic acid regulated MMP-9 enzyme levels in cardiac cells.[20] *In-vitro* testing of pure extracts of MMPs, red sage blocked rat MMPs-1, -2, and -9 activity.[21]

In hepatoma HepG2 cells, red sage extract inhibited cell invasion by modulating smad2/3 signaling of TGFb1.[10] In a rat model of diabetic nephropathy, Tan IIA decreased TGFb1 and collagen IV deposition.[22] In rate mesangial cells, red sage decreased production of plasminogen activator inhibitor-1 (PAI-1) by antagonizing angiotensin II.[23]

Red sage and the eye

Red sage has been reported to be beneficial for the preservation of visual field in a single report via an IOP-independent mechanism. Using a rabbit model of ocular hypertension, Zhu and Cai implicate the anti-inflammatory and vasodilatory effects of red sage. Using modern molecular techniques in non-ocular tissues and animal models, red sage affects several pathways that may be involved in the pathogenesis of glaucoma.

Despite the failure of memantine to demonstrate a clear therapeutic advantage, NMDA-receptor mediated excitotoxicity still has significant experimental evidence implicating it as a contributor to secondary RGC death.[24] Oxidative stress has been implicated in the pathogenesis of open angle glaucoma, particularly

exfoliative glaucoma.[25,26] Furthermore, TGFß1 levels are increased in aqueous humor and deposits of exfoliation material in patients with exfoliative glaucoma.[27,28] The relationship between TGFß1 and exfoliation syndrome is more complicated than a simple mutational one.[29] TGFß1 likely contributes to the formation of deposits seen in the trabecular meshwork. Red sage has been shown to antagonize TGFb1. Downregulating NF-kappaB in RGC confirms protection against apoptosis.[30,31]Capillary vasodilation and decreasing blood viscosity may confer increased blood flow to the optic nerve. However, caution should be applied as red sage can induce bleeding complications in patients on anti-coagulant therapy.

The effect on MMP and TIMP balance could be deleterious to IOP as the shifting of this balance toward greater MMP activity correlates to IOP lowering.[32] Red sage has a tendency to shift the MMP/TIMP balance towards decreased MMP activity.

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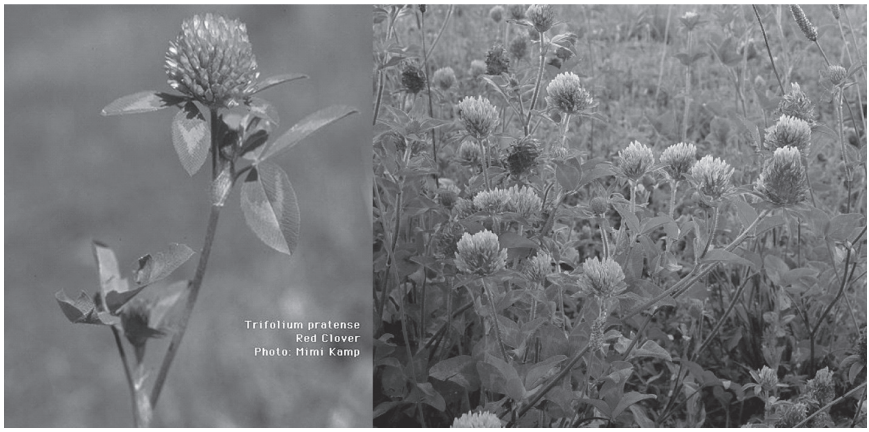
***Trifolium pratense* (red clover)**
Douglas Rhee



Introduction

Trifolium pretense is a species of clover, native to Europe, western Asia and Africa, but present in many other regions. It is a perennial, growing to approximately 20-80 cm tall. There are seven varieties of *T. pretense* and it is both the state flower of Vermont and the national flower of Denmark.

Traditionally, red clover has been used for irregular menses, menopause, and fertility. For ocular use, folklore and supplementation advertisements extol its use for 'sore eyes' and conjunctivitis. The chemically active compounds in red clover are primarily isoflavones, but there is also a weak amount of coumarin and cyanogenic glycosides. There is significant evidence that these isoflavones act as 'phytoestrogens', hence their effect on menopausal symptoms etc.[1,2] One of the components from red clover, puerarin, was reported to have an IOP lowering effect.

Potential beneficial mechanisms of action

There are numerous different individual compounds that are considered isoflavones. In particular, puerarin, which has beta-blocker activity, was reported to lower IOP at 1% topical preparation.[3] Because of its possible effect on IOP, several groups have looked into systemic delivery, contact lens delivery, and topical permeability of puerarin.[4-7]

Puerarin also has vascular effects. It is anti-vasoconstrictive in rat aorta via endothelial nitric oxide production.[8] Puerarin analogues increase chroidal blood flow.[9] Puerarin also inhibits vascular endothelial growth factor and hypoxia inducible factor 1 alpha in an experimental rat model of diabetic retinopathy.[10] In patients with diabetic retinopathy, puerarin reportedly caused a lower blood viscosity and improvement in several aspects of retinal circulation.[11]

In summary, red clover contains several different bioactive isoflavones. Puerarin has the most bioactivity related to eye disease. Its principal mechanism of action is IOP lowering, likely through a beta-blocker effect. There is also evidence that puerarin improves ocular blood flow.

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Bear bile

Douglas Rhee

Introduction

Bear bile is produced in the liver, stored in the gall bladder, and extracted from Asian black bears, otherwise known as “moon bears” because of a characteristic white-colored crescent-shaped fur on their chests. The harvest of bear bile is extremely controversial. The active ingredients of bile are ursodeoxycholic acid (UDCA) and tauroursodeoxycholic acid (TUDCA), which can be collected from slaughterhouses and purified.

Bear bile has been prescribed in traditional Chinese medicine for thousands of years for improving vision and other purported benefits.[1,2] As of March 2010, there are no references in pubmed (www.ncbi.nlm.nih.gov; search terms 'glaucoma', 'tauroursodeoxycholic acid', and 'ursodeoxycholic acid'). 'Bear bile' reveals approximately 100 articles. One study has examined the potential therapeutic benefit of TUDCA in a mouse model of retinal degeneration.[3]

Possible beneficial mechanisms of action

Anti-apoptosis

In a recent study by Boatright *et al.* TUDCA was given subcutaneously (two doses separated by 16 hours) to two mouse models of retinal degeneration, the $Pde6b^{rd10}$ (rd10) and light-induced retinal degeneration (LIRD) mice. Both strains have mutations in the beta subunit of rod photoreceptor cGMP phosphodiesterase causing a loss of photoreceptors through apoptosis. In the TUDCA treated rd10 and LIRD mice, there was a significant decrease in apoptotic markers, using TUNEL and anti-active casepase-3 immunostaining. The preservation of photoreceptors resulted in preserved functioning on electroretinograms. It is noteworthy that RGC are not affected in the rd10 and LIRD mice, nor did treatment affect RGC.[3] Thus, generalizing these findings to glaucoma without further study would not be warranted. In non-ocular tissue, TUDCA has also been shown to decrease the rate of rat cardiac cells undergoing apoptosis following an experimental model of acute myocardial infarction.[4]

Summary

TUDCA has some demonstrated anti-apoptotic effects. It remains unclear if TUDCA acts only through caspase dependent pathways and at what step the cascade is blocked. As the pathogenesis of glaucoma likely involves apoptotic RGC death, TUDCA merits further study in relevant glaucoma models and cell types.

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Ginseng

Kwok-Fai So and Raymond Chuen-Chung Chang

This discussion will focus on the series Panax ginsengs, including *Panax ginseng* and *Panax quinquefolius*. Ginsenosides are considered the active components of ginseng. The roots of American ginseng (*P. quinquefolius*) and Asian ginseng (*P. ginseng*) are taken orally. According to the Chinese medicine literature, ginseng powerfully augments genuine Qi, fortifies the spleen and lung, calms the mind and enhances mental function. The medical concept of Qi is related to it being the basic substance that makes up the human body.

The root of North American ginseng exerts immunostimulatory effects on the CNS.[1] The saponin fraction of ginseng, ginsenosides, protects ischemic hippocampal neurons[2] and cortical neurons[3,4] from glutamate-induced neurotoxicity. In addition, saponins of *Panax quinquefolius* L. delay neuronal death during ischemia[5,6] and glutamate-induced excitotoxicity.[3]

Using a mixture of American ginseng extract, *Ginkgo biloba* extract and St John's Wort (*Hypericum perforatum*) extract, in combination or alone, we have investigated the survival and regeneration of axotomized RGC in an optic nerve transaction model in adult hamsters.[7] Effects of herbal extracts on axonal regeneration were studied by attaching a peripheral nerve graft onto the transected ocular stump to induce regeneration. Operated animals received daily oral administration of vehicle or herbal extracts, alone or in combination, for seven and 21 days, respectively, in the survival and regeneration experiments. Surviving and regenerating RGC were retrogradally labeled with Fluoro-Gold. The eyes were enucleated and the retinas were flat-mounted for the counting of the labeled RGCs. Treatment with ginseng, *Ginkgo biloba* and St. John's Wort alone failed to offer neuroprotection to injured RGC. However, treatment using the mixture with the three extracts significantly augmented RGC survival seven days post-axotomy. Treatment with the same mixture also induced a significant (87%) increase in the number of regenerating RGC 21 days after optic nerve transaction. It also suggests that the therapeutic value of herbal remedies can be maximized by the use of mixtures of appropriate herbs. In an argon laser-induced glaucoma model in rats, there is a 16% RGC loss in the experimental eye with high IOP8 14 days after the laser-induced injury. Using the same mixture of the three extracts, we have shown that almost all RGC survived after the injury (unpublished observation).

The mechanism of how the herbal extracts work is still not clear. However, it may be related to enhancement of the immune system. The immune response triggered by traumatic injury plays a crucial role in neuronal degeneration in the CNS. Autoimmune T cells against myelin basic protein in the CNS significantly promote the recovery and reduce the spread of damaged area in optic nerve and spinal cord crush models.[9,10] The neuroprotective effect of autoimmune T cells may be related to the natural autoimmune T cells found in healthy individuals.[11] Enhancing the neuroprotective effect by increasing the T-cell response or modifying the T cells to an appropriate phenotype against a particular insult

may provide a novel therapy for neurodegenerative diseases.[12] *Panax ginseng* has mitogenic activity to T-lymphocytes.[13] Polysaccharides from ginseng induce the production of interferon-gamma and of TNF-alpha *in vitro*.[14] Augmentation of cell-mediated immune functions, including chemotaxis, phagocytosis, lymphocytes and natural killer cell activities, have been demonstrated in humans after treatment with *Panax ginseng*.[15] We hypothesize that herbal extracts exert their neuroprotective function on damaged RGC by enhancing the immune response after experimental glaucoma and optic nerve injury.

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Wolfberry

Kwok-Fai So and Raymond Chuen-Chung Chang

Introduction

RGC death underlies visual loss in glaucoma. Although elevated IOP is the most important known risk factor for glaucomatous damage, the pathophysiologic mechanisms may be mediated via some combination of IOP-dependent compressive effects of the cribriform plates in the lamina cribosa on the RGC axons, pressure-induced tissue ischemia, and local neuroimmune responses. To protect RGC, non-pharmaceutical medicine may play an important role either directly or by modulating glial responses. For example, involvement of microglia in glaucoma has been reported both in human and animal models. In human glaucomatous eyes, microglia in the optic nerve head and parapapillary region become activated and redistributed.[1] In animal models, the presence of microglia in retinas exposed to chronic ocular hypertension appears as early as three days and lasts for about two months.[2,3] Activation of microglia may provide neuroprotective factors. However, over-activation of these CNS macrophages can be detrimental, because they produce free radicals and pro-inflammatory cytokines. Having multiple effects on both RGC and the neighboring glial cells, wolfberry is an ideal candidate in this therapeutic and preventive pursuit.

Wolfberry (*Lycium barbarum* L., belonging to the Solanaceae family, also named *Fructus lycii*) has been regarded as an 'upper class' Chinese medicine, indicating that its fruit can be an ingredient in Chinese cuisine or formulated Chinese medicine. According to tradition, wolfberry can nourish the liver and kidney, helping the re-balance of yin and yang in the body. The biological effects of wolfberry have received increasing attention. Its value in Chinese and herbal medicine are high and significant as long as we can provide scientific evidence with modern technology.

The attractive red color of wolfberry has led us to believe that it must play a role in strengthening eyesight and protecting our eyes. According to Chinese medicine theory, nourishing the liver in turn nourishes the eyes. Chemical analysis of wolfberry shows that it contains high levels of carotene and zeaxanthin, which can provide nutrients and anti-oxidants directly to the eyes.[4-7] However, our routine diet does not rely on Wolfberry to provide carotene. Therefore, protective effects of Wolfberry to the eyes should not be limited to high carotene and zeaxanthine content. There are other protective mechanisms, both direct and indirect.

In fact, increasing lines of experimental studies have revealed that wolfberry has a wide array of functions which may be due to its high polysaccharide content instead of zeaxanthin and carotene. The polysaccharides in wolfberry can exhibit anti-aging, anti-tumor, cytoprotective, neuromodulation and immune modulation effects. To elicit anti-aging effects, polysaccharides from wolfberry modulate other organs or systems. We name this type of modulation 'indirect effects'. Alternatively, polysaccharides can directly act on cells antagonizing toxins.

Evidence for the neuroprotective effects of wolfberry

Early reports from our laboratory demonstrated the neuroprotective effects of wolfberry in a laser-induced photocoagulation of ocular hypertension model.[8] Survival of RGC was nearly 100% back to normal. Indeed, wolfberry has long been known to improve eyesight.[9-13] Recently, it has also been shown that wolfberry can restore visual function in experimental light-induced phototoxicity and macular degeneration.[11-13] Wolfberry also protects RGCs from glutamate- and nitric oxide (NO)-induced neuronal apoptosis in the retina.[11,12] Indeed, by using primary neuronal cell cultures as an experimental model, we have recently shown that wolfberry can antagonize glutamate excitotoxicity.[14]

While attenuation of glutamate and NO neurotoxicity by a natural herb is not surprising, the re-adjustment of body immunity in aging by this natural herb is novel. Polysaccharide isolated from natural herbs serving as biological response modifiers can effectively modulate immunity. For example, the polysaccharide extract of wolfberry enhances phagocytic activity in macrophages, stimulates proliferation of splenocytes and lymphocytes, activates nuclear factor κB (NF-κB) in B-lymphocytes, up-regulates mRNA expression for interleukin-2 (IL-2) and TNFα in human peripheral blood mononuclear cells, stimulates cytotoxic T lymphocyte (CTL) toxicity, and enhances the production of antibody in experimental rats and even in aged patients.[15-18] As wolfberry elicits mild but not potent stimulation of immunity, all the above immune stimulatory findings prompt us to hypothesize that polysaccharide extracts can be used to manifest neuroprotection by immunocompetent cells such as microglia/macrophages and lymphocytes. In fact, our results demonstrated that wolfberry modulates the activation processes of retinal microglia.[19] Further research is needed to examine the role of wolfberry in manipulating neuroimmune responses of both microglia and astrocytes to protect RGC against glaucoma.

Wolfberry can also stimulate the expression of neuroprotective and neurotrophic proteins. We have recently shown that wolfberry can induce the expression of βB2-crystallin.[20] Since βB2-crystallin is a chaperone to stabilize misfolded proteins and facilitates axon elongation in neuroregeneration,[21] expression of this kind of chaperone will help RGC survive under stress. In addition to treatment, wolfberry can reduce the risk factors leading to neurodegenerative diseases. For example, it attenuates the neurotoxicity of hyperhomocysteinemia,[22] a risk factor leading to vascular problems and possibly glaucoma.[23]

Taken together, ours and other results have shown that wolfberry may prevent glaucoma, serve as herbal medicine to treat glaucoma by attenuating pathological factors, exerting direct neuroprotection on RGC and modulate glial responses. Wolfberry has great potential to be developed into a disease-modifying drug for the treatment of glaucoma.

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Bilberry

Kwok-Fai So and Raymond Chuen-Chung Chang

The name bilberry, sometimes known as blueberry, whortleberry or hurts, is given to several species of low-growing shrubs in the genus Vaccinium. The one species it refers to most is *Vaccinium myrtillus*, which bears edible fruits. It is a potential source of natural anthocyanin antioxidants.

It has been claimed that bilberries may improve night vision, but a study on the effect of bilberry on night visual acuity and contrast sensitivity did not support this claim.[1] The authors conducted a double-blind, placebo-controlled, crossover design trial using young men with good vision, comparing the effect of 160 mg of bilberry extract (25% anthocyanosides) and placebo.

In a study using streptozotocin-induced diabetic rats treated with antioxidants including troxerutin, bilberry and calcium dobesilate, the development and progression of retinopathy was followed using fundus photography.[2] The VEGF-mRNA density showed an increasing tendency by 20% in the diabetic rats compared with the non-diabetic controls, and this increase was corrected by 10 mg/kg troxerutin, 50 mg/kg troxerutin and bilberry. Thus, bilberry containing high levels of anthocyanin pigments has been linked to attenuation of diabetic retinopathy.

In another study, accelerated OXYS rats with early senile cataract and macular degeneration were given control diets or diet supplemented with 25% bilberry extract (20 mg per kg of body weight including 4.5mg of antocianidin).[3] At three months, > 70% of control OXYS rats exhibited cataract and macular degeneration, whereas the supplementation of bilberry extract completely prevented damage in the lenses and retinas.

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Acupuncture and glaucoma
Simon Law

Introduction

Acupuncture, a branch of Chinese traditional medicine, has been used for over 2000 years in the treatment of various illnesses. In the past two decades, it has grown in popularity in Western countries. In Chinese traditional medicine, the body is seen as a delicate balance of two opposing and inseparable forces: yin and yang. Yin represents the cold, slow, or passive principle, while yang represents the hot, excited, or active principle. An imbalance of these two forces is associated with blockage in the flow of Qi (vital force or energy) and leads to various illnesses. Qi flows along pathways known as meridians with acupuncture points on the human body that connect with them (NCCAM 2009). The underlying philosophy of acupuncture is that disorders related to the flow of Qi can be prevented or treated by stimulating the relevant acupuncture points on the body surface. The points are stimulated typically by inserting needles; however, related techniques such as manual (acupressure), electrical or laser stimulation of acupuncture points are also often included under this term.[1]

Mechanisms of action

The exact mechanism or physiologic process of the effects of acupuncture is far from clearly delineated. Research efforts have focused on explaining how it works within the framework of Western medicine. Different mechanisms of action have been proposed.[2,3] The most commonly cited mechanism is that it stimulates the release of neurochemicals (usually endogenous opioids or serotonin). 'Gate theory' or segmental effects is another proposed mechanism specifically for analgesia. In the gate theory, sensory input from acupuncture is thought to block or interfere with nociceptive pain signals at the spinal level. A number of studies also report a possibility of altered physiologic functions that are regulated by the autonomic nervous system, such as heart rate, blood pressure, post-menopausal vasomotor symptoms, and respiration. By incorporating the results from studies on different systems, a model termed the broad sense hypothalamus-pituitary-adrenal (BS-HPA) axis has been proposed.[2] The model hypothesizes that the central nervous system is essential for processing the effect of acupuncture by modulating the autonomic nervous system, neuroimmune system and hormonal regulation.[4,5] It seems likely that different mechanisms proposed are part of an elaborate interaction of different body systems. Acupuncture may simply stimulate self-regulatory processes and this would account for reported benefits in many pathologic conditions.[3]

Potential effects on glaucoma

Ocular effects associated with acupuncture have been studied in animal models and small samples of subjects. Some studies report potentially beneficial effects

of IOP reduction, improvement of central visual acuity, alteration of visual field, increase of ocular blood flow, preservation of normal waveform characteristics of multifocal electroretinogram (mfERG), alteration of visual function tested by visual evoked potential (VEP), and increase of retinal nerve growth factor.

Intraocular pressure and central vision

Most clinical studies of the effect of acupuncture on IOP and vision are case series and results are conflicting. Dabov *et al*.[6] reported that treatment resulted in IOP reduction measured by Maklakoff tonometry in three of eight patients with glaucoma. In this study, 50 patients of a variety of eye diseases were enrolled, and all reported a subjective improvement of vision. Uhrig *et al*.[7] reported a significant IOP decrease 15 minutes and 24 hours after acupuncture treatment in three patients with glaucoma and 15 patients with ocular hypertension. Liu *et al*.[8] measured IOP before and five minutes after single point acupuncture in 79 eyes of 40 normal subjects. IOP was lowered in 49 eyes, increased in eight, and there was no change in 22. Mean IOP was significantly lowered by 1.61 mmHg. Wu *et al*.[9] measured IOP after acupuncture (24.9 ± 0.9 mmHg) in 120 patients with primary open-angle glaucoma and found it significantly lower than baseline (33.7 ± 1.1 mmHg). Kurusu *et al*.,[10] in 22 eyes of 11 patients with glaucoma, found IOP significantly reduced and visual acuity significantly improved 15 minutes after acupuncture. However, the effect weakened with time following each treatment, with subjects returning nearly to baseline levels by three to four days following a treatment. In 21 patients with POAG and 13 with OHT, Ewert and Schwanitz[11] found acupuncture to lower IOP significantly. Patients also reported subjective improvement of quality of life and better compliance with medications. Wong *et al*.[12] observed increased visual acuity but no significant change of IOP in glaucoma patients. Sold-Darseff and Leydhecker[13] treated 18 patients with glaucoma and found no significant alterations of IOP.

Most, if not all, of the studies included no control group nor compared acupuncture with application of sham needles. In addition, different types of glaucoma were usually enrolled and patients were frequently on medical therapy with multiple topical drops or systemic carbonic anhydrase inhibitors.

Research conducted on animals to investigate the effects of acupuncture on IOP has been more consistent. In a rabbit model of glaucoma evaluating the effects of electroacupuncture using two acupuncture needles placed in close proximity to the sciatic nerve, Chu *et al*.[14] noted a reduction of IOP up to nine hours after the stimulation. A simultaneous reduction of blood pressure, aqueous flow rate, and aqueous catecholamine levels (norepinephrine and dopamine) were recorded during the early time period of electroacupuncture induced hypotension, but sustained IOP reduction seems to be associated with increased aqueous humor endorphin levels. In addition, the opioid receptor antagonist, naloxone, inhibited the IOP reduction associated with electroacupuncture. The electroacupuncture-induced ocular hypotension was reduced markedly in sympathetically denervated eyes.[14] IOP in dogs receiving treatment at three

acupuncture points was approximately 10% lower than in control dogs receiving no acupuncture.[15] Ralston *et al*.[16] observed a decrease in IOP following acupuncture in experimentally induced glaucoma in dogs.

Visual field

In a study to ascertain the effects of contralateral acupuncture on brain function using blind-spot mapping, 40 healthy volunteers in whom the right-side blind spot was larger than that on the left were randomly assigned a single point electroacupuncture treatment applied to a point on either the right or the left side of the body. Electroacupuncture to the contralateral side decreased the blind-spot size on perimetry, whereas that to the ipsilateral side increased the blind-spot size. The authors suggested that contralateral side electroacupuncture treatment has a better effect on brain function.[17]

Blood flow

Chorioretinal blood flow measured with the Heidelberg Retinal Flowmeter showed a significant increase during single point acupuncture between the thumb and forefinger in healthy young volunteers.[18] Experienced subjects showed greater changes than unexperienced ones. Stimulation of specific acupuncture points produced specific effects on blood flow in arteries to the brain and eye. Blood flow velocity in the supratrochlear artery in patients with eye diseases was increased by acupuncture treatment to eye-specific acupuncture points, while no significant increase of blood flow velocity was measured in the middle cerebral artery. On the other hand, stimulation of acupuncture points believed to increase cranial circulation increased blood flow velocity in the middle cerebral artery significantly, but left the supratrochlear artery unaffected.[19] In another study, blood flow velocity of the ophthalmic artery in healthy volunteers increased during acupuncture.[20] Increase of blood flow volume of the central retinal artery (CRA) was associated with treatment with only one of the three acupuncture points studied along the GB meridian as measured by Color Doppler imaging and acupuncture treatment of a non-meridian acupuncture point was not associated with change of retinal blood flow.[21]

Multifocal ERG (mfERG)

In a rat glaucoma model, Chan *et al*.[22] found that 2-Hz but not 100-Hz electroacupuncture treatment preserved mfERG waveform characteristics in terms of the N/P ratio. The same group had previously shown that 2-Hz electroacupuncture treatment inhibit the expression of nitric oxide synthase-2 (NOS-2), which may have a role in glaucoma damage.[23]

Visual evoked potential (VEP)

Sagara *et al*.[24] analyzed 19 healthy subjects (38 eyes) and found that in those with delayed P100 latencies of ≥ 101.7 msec (total average of the group), acupuncture stimulation contributed to a pattern reversal of the VEP by shortening the P100 latency to closer to the average.

Retinal growth factor

Applying low-frequency electroacupuncture treatment to Royal College of Surgeons (RCS) rats (an inherited retinitis pigmentosa rat model) during a critical developmental stage of retinal cell degeneration was associated with an increase of retinal nerve growth factor (NGF) protein and brain derived nerve factor (BDNF) protein and NGF high-affinity receptor (TrkA) expression, when compared with controls.[25] The treatment was also associated with an increase of outer nuclear layer (ONL) thickness and enhanced vascularization.

Retinal ganglion cells (RGCs)

In rabbits subjected to high-pressure perfusion of the anterior chamber by increasing IOP to 30 mmHg and 50 mmHg, those receiving electroacupuncture treatments had more relatively intact RGC remaining compared to those without treatment.[26]

Limitations of study

The term acupuncture embraces a variety of stimulation techniques, including different types of acupuncture needles used, electric or laser stimulation with or without needle acupuncture, application of moxibustion with acupuncture, and acupressure without needling. In addition, different acupuncture points or groups of points, different intensity, duration, and frequency or repetition rate of stimulation were studied under the same category of acupuncture.

The acupuncture points chosen for studying the effect on glaucoma were usually based on clinical experience and traditional theory of Chinese medicine. It is important to remember that Chinese traditional medicine views diseases as an imbalance of two opposing forces, yin and yang. Therefore, the selection of points was based on the traditional way of using points for symptoms and applied to a new disease.[27] Clinically, the number of main points or supplemental points to be used for treating a particular disease or symptom is not fixed and may vary during the course of acupuncture treatment based on the patient's response. For instance, it is customary to use the traditional eye specific main points initially and judging from the response, resort to supplemental points when necessary. This clinical heterogeneity makes comparisons or analyses on studies on acupuncture difficult. For instance, the number of acupuncture points studied may vary from one to more than 20 among different studies.

Most of the studies of the effects of acupuncture on glaucoma are case series with no comparison group or control group included. A comparison group on another treatment may provide a valid differentiation of the exposure to acupuncture treatment, but possible placebo effects associated with acupuncture treatment cannot be controlled for. Some acupuncture studies on other illnesses include a control group using sham acupuncture. However, sham acupuncture may not be considered as a non-inert placebo and may elicit a physiological response. One may argue that the effects of acupuncture may not depend on specific points, location or techniques.[28]

Complications and safety

Relatively few complications from the use of acupuncture have been reported to the Food and Drug Administration (NCCAM 2009).

Implications

Because of ethical considerations, randomized clinical trials comparing acupuncture alone with standard glaucoma treatment or placebo are unlikely to be justified in the near future in countries where standards of care have already been established. However, trials in which acupuncture in combination with another glaucoma treatment is compared with the other glaucoma treatment alone will be of interest. It would be valuable for experienced researchers and clinicians to agree on certain basic standards in administration of acupuncture in clinical trials. Adequate data on IOP, central visual acuity, contrast sensitivity, visual field changes, optic nerve and retinal nerve fiber layer analysis, ocular blood flow, pattern electroretinography (PERG), multifocal ERG, visual evoked potential (VEP), multifocal visual evoked potential (mfVEP), potential harms, visual-related quality of life and economic outcomes will help in evaluating effectiveness and safety of acupuncture appropriately.[29]

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Exercise

Clement C.Y. Tham

Introduction

Glaucoma is a disease of the optic nerve, with progressive and irreversible loss of optic nerve fibers. Risk factors for glaucoma include intraocular pressure (IOP), age, race, family history, refractive error, and vascular factors. Exercise has both short- and long-term effects on IOP and vascular factors, such as ocular blood flow (OBF). Exercise may, therefore, influence the pathogenesis and / or progression of glaucoma.

Potentially beneficial effects of exercise in glaucoma patients

Intraocular pressure-lowering effects

Isometric exercise is defined as work performed by a muscle with no change in the length of that muscle. In general, acute isometric exercise results in acute but transient IOP reduction,[1,2] which correlates with hyperventilation and hypocapnia.[2-5]

Dynamic (isokinetic) exercise is defined as work performed by a muscle with change in length of that muscle. Walking and swimming are examples of dynamic exercise. Acute dynamic exercise results in acute but transient IOP lowering in the post-exercise period.[6-11] The magnitude of IOP lowering can be up to 12.86 mmHg in glaucoma patients. IOP lowering induced by dynamic exercise appears to correlate with the intensity of the exertion,[11-14] and is more pronounced in glaucoma patients than in normals.[11] It has no significant correlation with blood pressure,[13,15] heart rate,[16] or hypocapnia.[17] The IOP-lowering effect appears to be addictive to the effect of glaucoma drugs.[18] There is no significant difference in IOP lowering between aerobic and anaerobic exercises.[19] Dynamic exercise results in greater IOP reduction than isometric exercise, but of shorter duration.[20]

The mechanisms underlying exercise-induced IOP reduction are not well delineated. Three mechanisms have been proposed: osmotic dehydration of the globe, reduced aqueous production due to reduced ultrafiltration, and a hypothalamic reflex.[21-23]

The above exercise-induced IOP reductions were all short-lived and their relevance in the long-term management of chronic glaucoma is uncertain. Long-term regular exercise is associated with overall improvement in physical fitness. Physical fitness appears to be associated with lower baseline IOP [24-27,

but diminished acute IOP-lowering response to exercise.[9,24,27] On termination of the exercise regimen, values return to pre-training levels within 3 weeks.[26] Such sustained reduction of IOP associated with regular exercise and improved physical fitness may be more relevant to the halting of glaucoma progression, but controlled studies are needed to confirm such potential therapeutic benefits.

Effect of exercise on ocular blood flow

Reduced ocular blood flow (OBF) is a potential risk factor for glaucoma.[28] In healthy subjects, OBF is unchanged during exercise due to vascular autoregulation.[29,30] This autoregulation fails at ocular perfusion pressures greater than 67% above baseline.[29,30] The relevance of these findings to the pathogenesis and progression of glaucoma is uncertain. The effect of exercise on OBF in glaucoma patients has not been studied.

Potential deleterious effects of exercise in glaucoma patients

Certain isometric exercises, such as weightlifting and exercise at maximal exertion, may paradoxically increase IOP,[31-36] and the increase may be even more significant when the subjects are holding their breath.[35] Raised intracranial pressure may contribute to the IOP increase.[34]

Exercise may also provoke increased IOP in patients with pigmentary glaucoma.[37] In these patients, the potentially harmful effect of exercise on IOP should be carefully weighed against the beneficial effects of exercise on general health.

Young adults with advanced glaucoma may sometimes experience a temporary loss of vision during vigorous exercise. This was attributed to a 'vascular steal' phenomenon.[38] The relevance of this phenomenon to glaucoma progression is uncertain.

Conclusions

In general, acute exercise results in an acute but transient IOP reduction in the post-exercise period. Physical fitness secondary to a long-term regular exercise regimen is associated with lower long-term baseline IOP. Certain types of exercise, e.g. weight lifting, may increase IOP. Certain subtypes of glaucoma, e.g. pigmentary glaucoma, may have IOP increase after exercise. However, it remains uncertain whether such exercise-induced IOP changes correlate with glaucoma pathogenesis and / or progression. Taking also into consideration the beneficial effects of exercise on general health and well being, the author believes glaucoma patients should be encouraged to perform regular aerobic exercise.

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Stress in glaucoma

Lori Ventura

The effects of psychological stress on ocular illness in general and on glaucoma in particular are given little to no consideration in the pathogenesis or treatment of disease. It is clear from a plethora of articles in all fields of medicine that no organ system is protected from the effects of negative emotional states.[1] As a part of the central nervous system, and privy to the alarmed cross-talk of local hormones and neurotransmitters, one would surmise that the eye and its projections would be particularly vulnerable to the effects of psychological stress.

The stress response

Sympathetic activation

The complexities of stressor-induced activation of SAM (sympathetic adrenomedullary) and the HPA (hypothalamic pituitary axis) and has been

comprehensively reviewed in other publications.[2-4] An abbreviated summary of the neural pathways provoked by stressors is provided here. Stressful stimuli may first be perceived visually or auditorily, or may be triggered by emotional signaling or imagery at the right pre-frontal cortex. Whatever the origin of the stressor, there is signaling to the hippocampus for an interpretation of the event based on memory. From the hippocampus, stimuli that evoke a fear response will synapse with neurons in the amygdala sending efferent projections to the paraventricular nucleus (PVN) of the hypothalamus, which secretes corticotropin releasing hormone (CRH) and arginine vasopressin (AVP).[5] In addition to an antidiuretic effect, AVP increases peripheral vascular resistance to increase arterial blood pressure. Corticotropin releasing hormone (CRH) travels in the hypothalamo-*hypophyseal portal* circulation to the pituitary (perhaps within ten seconds) to stimulate the release of ACTH, enkephalins and endorphins.[5,6] In addition to regulation of ACTH release (and later cortisol production), CRH flows diffusely throughout the brain, and serves as a neurotransmitter that mediates acute as well as chronic sympathetic arousal, providing an important link between the autonomic and adrenocortical branches of the stress response.[6] Noradrenergic centers in the brainstem (locus coeruleus) and spinal cord activate the sympathetic adrenomedullary (SAM) release of epinephrine from the adrenal medulla and norepinephrine from the peripheral autonomic nervous system. CRH and noradrenergic neurons in the CNS innervate and stimulate each other.[5]

Activation of the hypothalamic pituitary axis (HPA)

Acutely stressful stimuli activate SAM within seconds as well as neurons of the hypothalamus to produce cortisol release hormone (CRH). CRH-containing neurons stimulate the pituitary to release ACTH, endorphins and enkephalins into the bloodstream.[5] ACTH then stimulates the release of cortisol from the adrenal cortex. The hypothalamic pituitary axis (HPA) response to stress is not as immediate as SAM, but occurs within minutes.[6] Under normal non-stressed conditions, cortisol levels peak in the early morning hours, fall over the course of the day, in a fairly steep slope, to reach a low around 4PM and remain low throughout the night only to peak again in the morning, and this is known as the diurnal fluctuation. Under conditions of chronic stress, the feedback inhibition of cortisol at the hypothalamus is dysregulated to result in a flattening of the normally steep slope whereby serum cortisol levels should significantly fall over the course of the day. With chronic stress and a flattened cortisol slope the levels of serum cortisol remain elevated throughout the afternoon and night, never falling to the lowest levels of the normal diurnal curve. How this dysregulation occurs is complex. It is due, in part, to CNS noradrenergic stimulation of CRH which overrides feedback inhibition at the hypothalamus.[6] Cortisol receptors at the hypothalamus may become less sensitive under chronically stressful conditions.

Chronic psychological stress

Conditions that produce the chronic elevation of cortisol, are life altering events which are associated with sleeplessness. The conditions which are most likely to induce chronic debilitating stress are the emotional adjustments of retirement, reduction in income, chronic illness, loss of mobility or function, isolation from or loss of loved ones, marital discord, divorce, chronic strain such as caregiver's stress, problems with children, re-location, problems with school performance, work dissatisfaction, and many others.

Vasospasm

The first mechanism by which stress may cause injury to the eye is through diminished microvascular perfusion through sympathetic nervous system overdrive. Acutely, the immediate response to psychological stress is activation of sympathetic adrenomedullary axis or SAM with vasoconstriction of blood vessels, which may be narrowed to varying degrees from years of arteriolosclerosis. Stress-induced vasospasm may compromise perfusion of the microvascular beds of the circulatory system of the optic nerve, thereby inducing hypoxia, which may acutely exacerbate glaucoma. Initial ischemic insult with a sudden vaso-occlusive event, or subsequent reperfusion injury may induce damage. Chronic psychological stress, with ongoing activation of SAM, results in vasoconstriction that may be prolonged, and may lead to hypertension and accelerated progression of arteriolosclerosis. Ocular conditions that may theoretically be exacerbated by acute or chronic psychological stress would be any of the microangiopathic diseases such as hypertensive retinopathy and/or diabetic retinopathy, etc.

Endogenous cortisol elevation

The second potential mechanism of how stress may exacerbate ocular disease is through the overdrive of the hypothalamic pituitary axis (HPA). As mentioned, chronic psychological stress has been shown to elevate cortisol levels to induce a flattening of the daytime cortisol slope.[7] Such chronic cortisol elevation, and flattening of the slope, is associated with worsening outcomes in breast cancer,[7] and may have deleterious effects on ocular diseases. There is an implied association between chronic stress and central serous chorioretinopathy(CSR), since CSR is known to occur in Cushing's Disease with endogenous cortisol excess[8] Ocular hypertension and glaucoma also occur in endogenous Cushing's Disease[9]

Psychological stress and vasospasm in glaucoma

Retinal ganglion cells (RGCs) as one of the most metabolically active cells of the body have high numbers of mitochondria. Mitochondria play an important role in energy (ATP) production through the oxidative phosphorylation pathway and the regulation of cell death by apoptosis.[10] Mitochondria are particularly

abundant along the unmyelinated intraretinal axons of the RGCs to supply energy in high demand for electrical conduction and axonal transport[11] A steady supply of oxygen is necessary for oxidative phosphorylation to generate ATP. The microvascular supply of oxygen to RGC axons may deteriorate with aging as progressive arteriolosclerosis may result in vascular compromise of the inner retinal circulation. There is a natural loss of RGCs with aging in the normal population.[12] Several risk factors for glaucoma have been identified, some of which are strong including high intraocular pressure, increasing age, family history of glaucoma, Black race, and other possible risk factors including high myopia, hypertension, diabetes, migraine headache and vasospasm. These latter four implicate further vascular insult to an already compromised microvascular supply of oxygen secondary to the arteriolosclerotic changes of aging. Psychological stress-induced vasospasm of the supply to the optic nerve may further reduce perfusion in these diseased conditions, and theoretically worsen axonal function which may lead to premature apoptosis. Whether the ischemia itself and/or reperfusion injury damages these structures is under investigation.[10]

Stress and endogenous cortisol elevation in glaucoma

Endogenous elevation of cortisol levels secondary to chronic psychological stress may be damaging to the trabecular outflow apparatus depending on the concentration and duration of this elevation. Human trabecular meshwork cells contain glucocorticoid receptors,[13,14] and would therefore be expected to respond to glucocorticoid administration. The exogenous administration of glucocorticoids in man can generate a progressively elevated intraocular pressure (IOP) which is dependent on glucocorticoid potency, pharmacokinetics, duration of treatment, route of administration, as well as differences in individual responsiveness.[15] Glucocorticoid-induced ocular hypertension is due to increased aqueous humor outflow resistance.[15,16] Morphological examination of the trabecular meshwork of patients with glucocorticoid-induced glaucoma has shown an increased deposition of extracellular material in the trabecular beams and in the juxtacanalicular tissue, and a decrease in intratrabecular spaces.[15,17] With topical, periocular, intravitreal or oral administration of steroids for ocular inflammatory conditions, patients may suffer from a steroid-induced intraocular pressure elevation which may be severe and prolonged enough to require filtering surgery of the eye to lower the IOP. Jaffe *et al*.[18] studied the effects of intravitreal fluocinolone acetonide implants (Retisert) for treatment of uveitis. By week 34 following implantation, 51.1% of implanted eyes required ocular antihypertensive drops, and 5.8% underwent glaucoma filtering surgery. During this same period, the IOP of the fellow eyes did not rise significantly. I*n August of 2008,* s*afety labeling changes were approved by FDA's Center for Drug Evaluation and Research (CDER). B*ased on clinical trials with Retisert, CDER warned that approximately 77% of patients will require IOP lowering medications to control intraocular pressure and 37% of patients will require filtering procedures to control intraocular pressure within three years post-implantation. Endogenous cortisol elevation

of Cushing's Disease is known to be associated with ocular hypertension.[9] At the Bascom Palmer Eye Institute, an anecdotal case of an intraocular pressure spike in a previously controlled glaucoma patient stricken by a severe chronic psychological stressor has been observed. Pressure elevation lasted for several weeks, and then returned to baseline levels as the patient coped with and adjusted to the stressor. The relationship between endogenous cortisol elevation and intraocular pressure responses requires further study.

Immune balance in glaucoma

Inflammatory mechanisms of glaucoma are being studied by different investigators. Michal Schwartz has pioneered the concept of harnessing the immune system to combat neurodegenerative diseases including glaucoma.[19] Her group has shown that immune deficiency or suppression impair the recovery process after optic nerve crush, whereas boosting a self-specific immune response, by both passive and active immunization, promotes recovery. Those same T cells that can lead to the development of autoimmune disease can protect neurons under neurodegenerative conditions, and it is a sub-population of regulatory T cells which regulates the autoimmune response to promote protection over injury. Dr. Schwartz' team introduced the concept of a therapeutic T-cell mediated vaccination to boost the immune response to facilitate neuroprotection in glaucoma.[19] This immune defense involves lymphocytes, resident and infiltrating innate immune cells, the microglia, and macrophages. The antigens of choice are synthetic antigens, such as glatiramer acetate, that weakly cross-react with self-antigens in the retina and optic nerves. The vaccine induces a beneficial immune response that recruits immune effector cells to counteract or neutralize many of the compounds and factors that contribute to ongoing destruction, and in addition supports cell renewal and repair.[20]

Immune balance and psychological stress in glaucoma

Working with Cohen *et al*.,[21] Dr. Schwartz has also published that maladaptation to mental stress in mice was mitigated by the adaptive immune system via depletion of naturally occurring regulatory CD4+CD25+ cells. This begs the question of how maladaptation to psychological stress may affect immune balance in patients with glaucoma. Furthermore, a different team lead by Wax and Tezel has proposed that the inflammatory cytokine TNF-α may be harmful to retinal ganglion cells thereby having an etiologic role in glaucoma.[22,23] While ischemic insults are implicated as the trigger for TNF-α mediated damage to the RGC, it is not known what effect psychological stress may have as an inciting factor in RGC damage in glaucoma. It is known that psychosocial stress may alter TNF-α production in other diseases such as cancer, Crohn's disease, and other autoimmune conditions.

Conclusion

When IOP is markedly elevated, clinicians often inquire about the recent use of oral, topical or injected steroids, but fail to ask about emotional stressors. There is an implication that since exogenous steroid use may lead to increased intraocular pressure and glaucoma, a prolonged stress-induced increase in endogenous cortisol and catacholamines, with subsequent alterations of the immune response, may also be at play. Clinicians may consider inquiry regarding potential psychosocial or environmental stressors in the context of a previously well-controlled glaucoma patient who develops a dramatic IOP increase or sudden deterioration of function. Finally, the effects of meditation[24] and acupuncture[25] which are thought to act on enhanced parasympathetic tone and the release of endorphins,[26] may be helpful in mitigating the stress response in glaucoma.

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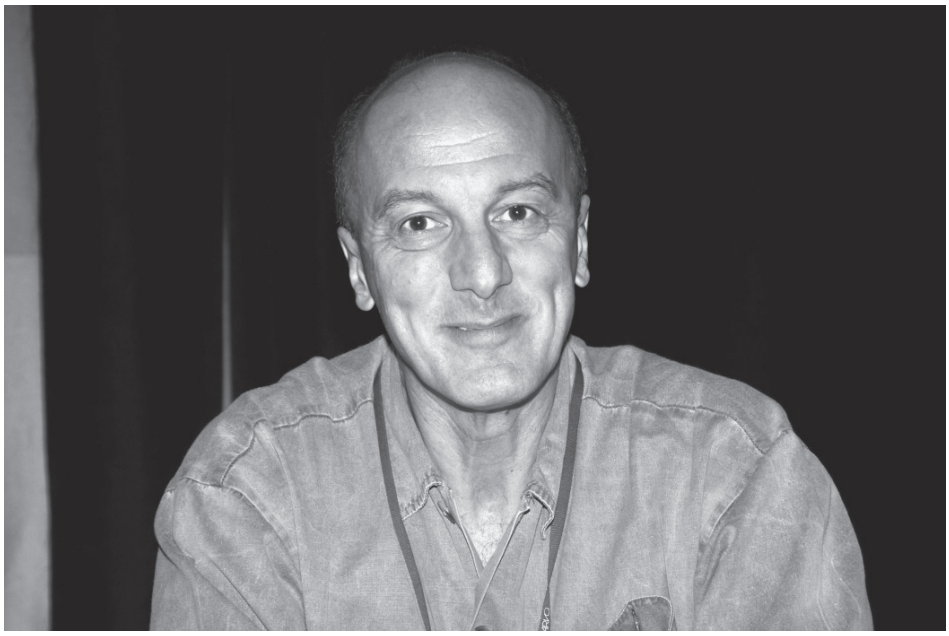

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Makoto Araie and Jeffrey Liebmannn.

Arthur Sit and Jonathan Crowston.

Tina Wong and Remo Susanna.

9. NEUROPROTECTION

Tina Wong, Jonathan Crowston, Ingeborg Stalmans, Francesca Cordeiro, Clive Migdal

Section leader: Clive Migdal
Co-leaders: Jonathan Crowston, Tina Wong
Participants: Robert Casson, Francesca Cordeiro, Helen Danesh-Meyer, Stefano Gandolfi, Jonathan Kipnis, Ted Krupin, Len Levin, Stuart Lipton, Keith Martin, Carlo Nucci, Neville Osborne, Leopold Schmetterer, Michal Schwartz, Ingeborg Stalmans, Ian Trounce, Manuel Vidal-Sanz

Consensus statements

1. A neuroprotective strategy for glaucoma is defined as a therapy that prevents the occurrence or progression of optic neuropathy and preserves visual function by mechanisms other than IOP lowering.
2. Agents that lower IOP have been shown to protect the optic nerve from glaucoma progression.
   Comment: Some agents that lower IOP might additionally confer protection to the optic nerve through mechanisms that are independent of IOP lowering, but there is insufficient evidence for this dual effect with any agent at the present time.
3. Therapeutic approaches for preventing RGC death may aim to prevent primary or secondary degeneration of retinal ganglion cells.
4. Evidence from experimental models suggests that neuroprotection could be conferred by:
   a. Inhibiting the pathogenic mechanisms that injure or kill RGCs.
   b. Rendering the optic nerve more resistant to injury.
5. Numerous studies have demonstrated neuroprotection in experimental models of glaucoma or optic nerve injury, but good evidence demonstrating neuroprotection in clinical studies is lacking.
6. Challenges in translating experimental evidence of neuroprotection into clinical proof may be due to:
   a. The therapy may not be effective in humans.
   b. The lack of sufficiently robust tools to assess clinically the state of optic nerve health.

Medical Treatment of Glaucoma, pp. 261-266
Edited by Robert N. Weinreb and Jeffrey Liebmann

c. The lack of animal models that are good representatives of human glaucoma.
d. The lack of well-designed and well-conducted clinical studies.

7. Current testing paradigms are insufficiently sensitive and specific to detect change in a logistically feasible time frame. The development of accurate, sensitive, specific and reproducible clinical tests that provide information on the current state of health of the optic nerve are required to increase the feasibility of clinical development of neuroprotective agents. *Comment:* A desired embodiment of such clinical testing would allow detection of progression before the damage is irreversible.

What is neuroprotection (NP)?

A neuroprotective agent in glaucoma can be defined as a therapy that prevents the occurrence or progression of optic neuropathy and preserves visual function by primary mechanisms other than lowering intraocular pressure (IOP).

- Although agents that lower IOP are neuroprotective, for the purpose of this consensus report, we will focus on non-IOP mechanisms for NP.
- Neuroprotectants may have a direct action on the optic nerve RGCs or an indirect action via other associated cell populations.[1]
- Neuroprotectants may protect visual function (by primary mechanisms) that target the visual system beyond the ON.
- NP may include neuroregeneration (lost neurons restored) and neurorecovery (sick neuron retored to normal functionality).

Mechanisms of optic nerve damage

Axonopathy

- Biomechanical forces, stress and strain[2]
- Blockade of axonal transport[3]
- Ischaemia/hypoperfusion of RGC axons[4,5]

Primary somopathy

Secondary damage from adjacent reactive glia[6]

- Glial activation may also be beneficial to RGCs through IL-2 expression – thereby activating a protective autoimmune phenomena

Additional damage may be derived from:

- inner retinal ischaemia
- deafferentation from other retinal neurons

Therapeutic targets for neuroprotection

Neuroprotection can be achieved by three fundamental approaches:

- Inhibition of mechanisms of primary injury that contribute to the pathogenesis of glaucomatous optic neuropathy. (*e.g.*, NMDA receptor antagonists, bax knock-out mice, exogenous neurotrophic growth factors)[7,8]
- Rendering the optic nerve more resistant to injury (*e.g.,* calorie restriction[9]). Evidence for the validity of both of these approaches has been generated in experimental models.
- Inhibiting the effects of secondary degeneration[10,11]

Specific therapeutic approaches can be categorized as:

Mechanical

- Reduced mechanical stress on RGC axons at the lamina cribrosa
- Alteration of biomechanical/material properties of the optic nerve head
- Alteration of the material properties of the RGC axons

Neuronal

- Axoprotection for the RGC axon
- Somaprotection for the RGC cell body
- Dendroprotection for the RGC afferent network
- Thermoprotection (target protection) for the RGC efferent network

Glial

- Decrease glial activation[12,13]
- Inhibit effects of glial-derived toxic/activating factors
- Increase pro-survival and/or pro-regenerative effects of glial activation

Immunological

- Experimental evidence also supports a protective role for T-cells
- Copolymer-1 a glatiramer acetate (Cop-1) has been shown to be protective against neurodegeneration in several animal models[14]
- T-cell involvement – loss results in impaired neuronal survival has been reported in Alzheimer's and Parkinson's diseases.

Evidence for NP in glaucoma – experimental and clinical studies

Neuroprotection has been demonstrated in several experiemental glaucoma/optic nerve injury models using a wide range of therapeutic agents. A recent review of NP for the treatment of glaucoma in adults[15] concluded that: 'Although neuroprotective agents are intended to act as pharmacological antagonists to prevent cell death, the evidence that they are effective in preventing retinal ganglion cell death, and thus preserving vision in patients with OAG, has not

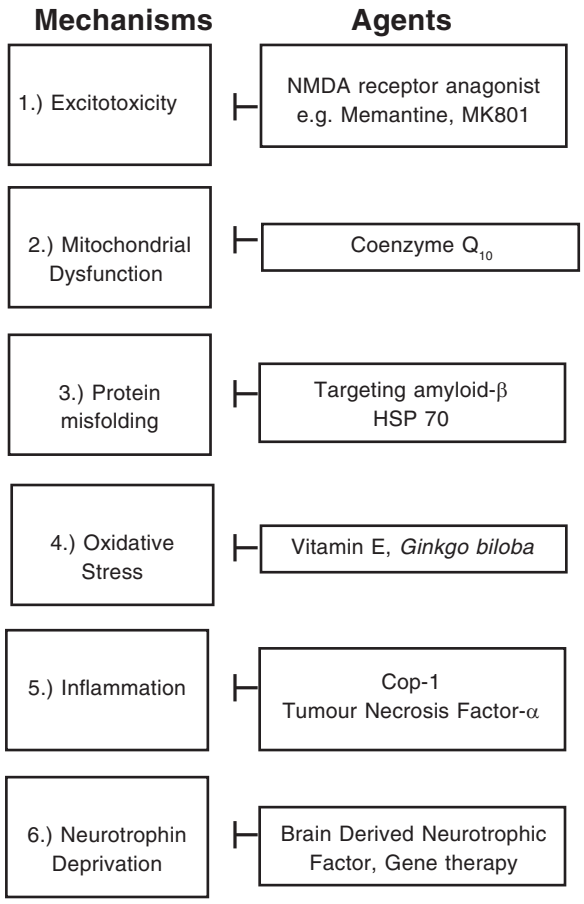

Fig. 1. Mechanisms for neuroprotection with candidate agents

been demonstrated. Longterm RCTs are needed to determine whether or not neuroprotective agents may be beneficial for individuals with OAG.'

The lack of robust evidence demonstrating NP in clinical practice may be consequent to the lack of appropriate tests for evaluating optic nerve health in glaucoma or a general resistance of the human glaucomatous optic nerve to protection by mechanisms other than IOP lowering.

Assessing neuroprotection in experimental and clinical studies

Animal studies

A number of acute and chronic models for optic nerve damage have been developed prinicipally in rodents and non-human primtes. These include short

(cannulation) and longer-term (laser, microbeads, immunological and transgenic models) IOP elevation and direct trauma (cut, compression) to the optic nerve.[16-18]

A number of structural and functional endpoints have been used in experimental models including:

Structural endpoints

- Optic disc photos/Imaging (OCT/HRT/GDx)
- RGC imaging techniques

Functional endpoints

- Visual field
- Contrast sensitivity?
- Dark adaptation?
- PERG?

The lack of robust clinical tests that provide information on the current state of health of the optic nerve is a major impediment to the assessment of, and clinical development of neuroprotective agents. Gold standard evidence still needs to come from randomized, ideally double-masked, trials with reasonable power. New imaging techniques that evaluate the state of optic nerve/retinal ganglion cell health or death and are sufficiently sensitive and specific to assess treatment reponse are needed to further develop NP.

Challenges in translating NP into clinical practice – is it relevant to glaucoma?

- defining the major molecular pathways involved in RGC death in glaucoma
- proof that delivery of such therapies can consistently protect the nerve from damage with
- appropriate animal models that reflects the human disease process (regardless of glaucoma type)
- development of robust endpoints that measure similar structural and functional outcomes and clinical endpoints of neuroprotective effects of the drug for both animal models and human disease
- absolute confirmation of neuroprotective effect would be the maintenance of functional RGCs even after the treatment is withdrawn and assist in excluding a temporary effect of the drug. However, is this really important? Since glaucoma is a lifelong progressive disease, it would appear necessary to remain on treatment for life to maintain the neuroprotective effects
- combination therapy with IOP lowering would seem to be the role for neuroprotective agents

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10. MEDICAL MANAGEMENT OF GLAUCOMA IN INFANTS AND CHILDREN

James D. Brandt, M.D. and Elizabeth Hodapp, M.D.

Participants: Ivan Goldberg, Jeffrey Liebmann and Robert N. Weinreb

Consensus Statements

1. The primary treatment of glaucoma in infants and young children is surgery.
   Comment: In many situations, however, the clinician must treat elevated IOP medically while awaiting surgery or after a partially-successful procedure.
   Comment: Only rarely should medical therapy be the primary treatment of glaucoma in infants and young children.
   Comment: A young child is not a small adult: systemic adverse reactions rarely seen in adults can occur in young children.
2. Outflow medications (pilocarpine and prostaglandin analogues) are variably effective in pediatric glaucomas, whereas aqueous suppressants lower IOP more consistently.
   Comment: Systemic and topical carbonic anhydrase inhibitors can be safe and effective. If possible, systemic use should be monitored by a pediatrician.
   Comment: Topical beta-blockers are effective; systemic safety is the major concern. Betaxolol is safer than timolol.
   Comment: Topical brimonidine is absolutely contraindicated in children under two years, and must be used with great caution in older children. Apraclonidine may be safer, for short-term use, but clinical data is lacking.
   Comment: Prostaglandin agonists are less effective in children than in adults, and are more likely to be effective in older children.
   Comment: Miotics are rarely used in phakic children.

The primary treatment of glaucoma in infants and young children is surgery. Angle surgery (*e.g.*, goniotomy *ab interno* or trabeculotomy *ab externo*) alone or combined with trabeculectomy has a high rate of success and often provides years or decades of IOP control. Glaucoma drainage devices can also be useful in patients with congenital aphakia or complex anterior segment syndromes. In many situations, however, the clinician must treat elevated IOP medically while awaiting surgery or after a partially-successful procedure. Medical therapy only rarely should be the primary treatment of glaucoma in infants and young children.

Medical Treatment of Glaucoma, pp. 267-271
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Because pediatric glaucomas are a heterogeneous and rare group of disorders, the safety and efficacy of currently-available glaucoma medications have not been tested in children with the rigor of adult regulatory trials and with one exception the pharmacokinetics of glaucoma drugs in infants has not been formally studied. Nonetheless the literature does provide useful information and the clinician managing pediatric glaucoma should consider two major issues:

- **A young child is not a small adult.** Topical medications are designed to reach a concentration in the tear film sufficient to drive drug into an adult-sized eye. The majority of a 50-µl eye drop is absorbed systemically but is usually of little consequence in a 70-kg adult. On the other hand, although a full-term 3.5-kg neonate still requires an adult-size eye drop to achieve adequate intraocular drug concentrations, the systemic absorption can be significant. In the only prospective study of the systemic pharmacokinetics of a topical glaucoma medication in children performed to date, systemic exposure to latanoprost acid was six-fold higher in younger children (0 to < 3 years of age) compared with adults.[1] Although this was not of any safety consequence, this pharmacokinetic study demonstrated that the lower body weight, lower blood volume and possibly lower hepatic blood flow and drug clearance leads to much higher systemic concentrations of topically-applied medications in a young child. Systemic adverse reactions rarely seen in adults can occur in young children. In systemically ill children the treating ophthalmologist should advise the pediatric team of the potential systemic effects of all topical agents
- **Pathophysiology and pharmacologic responsiveness may be different in children.** Though all the classical glaucoma mechanisms (*e.g.*, angle closure, uveitis, steroid-induced, 'open-angle') are seen in the pediatric population, the majority of glaucomas presenting in the first year of life occur as the result of a major developmental abnormality in the outflow tract of the eye. Eyes with newly-diagnosed infantile glaucoma have not been studied using modern histopathology, but these eyes usually have a visibly abnormal trabecular meshwork and at surgery, the canal of Schlemm is sometimes absent. The usual mechanisms of drug action may therefore be irrelevant in such an aberrant outflow tract. This may explain why outflow medications (pilocarpine and prostaglandin analogues) have been found variably effective in pediatric glaucomas,[2] whereas aqueous suppressants generally are more consistent at lowering IOP.

Glaucoma medications by class – considerations in children

Carbonic anhydrase inhibitors

Carbonic anhydrase inhibitors (CAIs) are effective suppressants of aqueous production and can lower IOP well. Acetazolamide tablets may be pulverized

and delivered as a suspension or acetazolamide powder for IV use can be compounded in an oral elixir. A convenient final concentration is 50 mg/ml and the usual dose is five to ten mg/kg every six to eight hours. Systemic use results in metabolic acidosis that may correlate with poor weight gain;[3] it should be used chronically in young children only rarely.

Topical CAIs (dorzolamide and brinzolamide) are somewhat less effective at lowering IOP than systemic acetazolamide[4] but both commercially-available drops appear to be quite safe.[5,6] Modest additivity of the topical and systemic administration of CAIs has been reported.[7] The systemic pharmacokinetics of topical CAIs and their effects on systemic acid-base parameters have not been studied.

Beta-adrenergic antagonists (beta-blockers)

Topical beta-blockers are potent aqueous suppressants and can effectively lower IOP in young children. This class of medications can have potent systemic side-effects including bradycardia, central nervous system depression and bronchospasm and for this reason the major issue in their use is safety. Passo and colleagues measured random plasma timolol levels and found a hundred-fold higher level of the drug in a three-week old infant (34 ng/ml) compared with the average blood level among ten adult patients (0.34 ng/ml).[8] Clinicians should inform pediatricians when topical beta-blockers are used in young glaucoma patients, as many pediatricians are not aware of the potential for systemic effects. Because betaxolol is more protein-bound and has a larger volume of distribution than other beta-blockers, it has a better safety profile in infants and young children than timolol.

Alpha-adrenergic agonists

Topical alpha-adrenergic agonists (apraclonidine and brimonidine) are effective at lowering IOP through a combination of aqueous suppression and enhancement of uveo-scleral outflow. Brimonidine crosses the blood-brain barrier and has been associated with profound central nervous system depression in children younger than two years of age. [9-13] **Topical brimonidine should not be used in children less than two years of age and should be used with great caution in older children.** In contrast, apraclonidine does not cross the blood-brain barrier and may be safer for short-term use.[14]

Prostaglandin analogues

Topical prostaglandin analogues are less effective in children than in adults and are more likely to be effective in older children and in children with juvenile-onset glaucoma.[2] They are not effective in the early-onset form of Sturge-Weber Syndrome with glaucoma but may be useful in some children with the later-onset form.[15] Despite variable efficacy in children, the primary advantage of

prostaglandin analogues is systemic safety and the convenience of once-daily administration.

Miotics

Topical miotics are rarely used in phakic children. With frequent dosing, rising systemic levels of these cholinergic agonists in small children can result in classical cholinergic effects such as diaphoresis and diarrhea. Miotics should be avoided in uveitic glaucoma. Echothiopate iodide 1/8%, a topical cholinesterase inhibitor, is commercially available and may be useful for the treatment of glaucoma in aphakic children.

Recommendations

Neonates

Consult with a pediatrician. A CAI, either acetazolamide, five mg/kg three times a day or a topical CAI three times a day is generally the first choice. Alpha-adrenergics are absolutely contraindicated. At this age, the patient is extremely likely to be a surgical candidate.

Infants and toddlers, up to about three years

Consult with the pediatrician. Oral or topical CAI as above is the first choice. If there is no systemic contraindication, a beta-blocker is the second choice, usually betaxolol. Avoid alpha-adrenergics. Prostaglandins are not likely to work.

Young children, about three years to about nine or so

Consult with the pediatrician if considering an adrenergic or oral medication. If the child can have accurate tonometry performed in the office, try the drug in one eye first. This gives some information about efficacy, and it also delivers half the systemic dose of binocular treatment so any side effects will be milder. The first choice remains a topical CAI. If insufficient and if the child has no contraindications a fixed combination CAI + beta-blocker is reasonable and more convenient to administer. If insufficient, an alpha-adrenergic agent may be considered in the older end of this age group. Prostaglandin analogues can be used in this age group, but are not likely to be effective.

Older children

Consult with the pediatrician if considering an adrenergic or oral medication. By this age, it is likely that the pressure can be tested in the office. Although prostaglandins may not work well, it is reasonable to try them because of their

low incidence of systemic effects and their long duration of action. Unless contraindicated, a once-daily beta-blocker should be used before a topical CAI because of the frequency of dosing. Fixed-dose CAI + beta-blocker is generally the next choice followed by an alpha-adrenergic agent. It is best to avoid medications that must be dosed during the school day.

Children with uveitis

These patients should be cared for by someone who specializes in ocular inflammation if possible. Treatment of the inflammatory disease, which includes both suppression of cell and flare and prevention of synechia formation, is essential. It is not appropriate, for example, to under-treat the inflammation to avoid elevated pressure which may result from steroid use or from increased aqueous humor formation. Aqueous suppressants (beta-blockers and CAIs) are the primary glaucoma medications used in pediatric uveitis.

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11. TREATMENT OF GLAUCOMA IN PREGNANCY

Elizabeth Hodapp

Participants: Ivan Goldberg, Jeffrey Liebmann and Robert N. Weinreb

Consensus statements

1. Appropriate management of the pregnant/lactating glaucoma patient requires balancing the risk to the fetus of treatment against the risk to the mother if treatment is reduced or suspended.
   Comment: While a complete lack of prospective human data complicates this decision-making process, publications provide a guide.
2. Like all systemically-absorbed medications that are used during pregnancy and lactation, the maternal use of topical anti-glaucoma medications carries risks of teratogenicity, of interference with establishment or maintenance of pregnancy, or of side effects in the neonate.
   Comment: Prostaglandin analogues may be associated with uterine contraction.
   Comment: Beta-blockers and alpha agonists can cause serious toxicity (respiratory and central nervous system depression) When possible, these agents should be withdrawn during the last few weeks of pregnancy.
   Comment: Topical CAIs are generally well tolerated.
3. Laser trabeculoplasty can be a reasonable initial or adjunctive intervention in pregnant and nursing women
4. Filtering surgery, preferably without anti-fibrosis chemotherapy, can be considered in certain cases.

Since the thalidomide experience of the 1960's, both patients and doctors have avoided medication use during pregnancy. However most women with glaucoma use daily medication to prevent progressive glaucomatous damage and most ophthalmologists are uncertain as to what course to recommend to their pregnant patients.[1] Appropriate management of the pregnant glaucoma patient requires balancing the risk to the fetus of treatment against the risk to the mother if treatment is reduced or suspended. A complete lack of prospective human data complicates this balancing act. A typical package insert for a glaucoma medication states that there are 'no adequate and well-controlled studies in pregnant

Medical Treatment of Glaucoma, pp. 273-278
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women' and cautions that the drug should be used 'only if the potential benefit justifies the potential risk to the fetus.'[2]

Despite the lack of prospective studies, the literature does provide some help, and it is possible to recommend a reasonable course based on available information. As with glaucoma in general, the treatment options include medical therapy, laser treatment, and incisional surgery.

Treatment options: Medical therapy

Sources of information

Human experience

Glaucoma is uncommon in women of child-bearing age, and anecdotal data regarding the effects of glaucoma medications in humans is minimal. However many pregnant women use systemic drugs which are similar or identical to glaucoma medications. There is extensive uncontrolled experience on the use of beta-adrenergic blockers and alpha-adrenergic agonists in patients with hypertension. Parasympathomimetics and carbonic anhydrase inhibitors have also been used systemically. In addition, side effects noted in newborns treated with glaucoma medications provide help in choosing treatment in late stages of pregnancy.[3,4]

Animal experience

Animal reproduction studies are performed for all new medications, but their relevance to humans is unclear. Known human teratogens may have no noticeable effect in laboratory animals, and animal teratogens may cause no abnormalities in humans. Moreover, these studies generally employ doses that are much higher than those achieved with clinical use.[3-5] The available animal data do not provide sufficient information to guide medication choices.

Pharmacology

All topical glaucoma medications are absorbed to some degree systemically, and basic pharmacology implies that glaucoma medications will enter the fetal circulation. Transplacental diffusion correlates with low molecular weight, lipid, solubility, lack of protein-binding, and non-ionized status.[3] All glaucoma drugs are of low molecular weight and are to some degree lipid soluble, unbound, and not ionized; thus they cross the placenta.[2] The same logic implies that maternal glaucoma medications are present in breast milk, although only timolol has been reported to be present.[6,7]

Risks of medical therapy

In addition to the major concern of teratogenicity, medications may interfere with the establishment or maintenance of pregnancy and may cause complications in the newborn.

Teratogenicity

Birth defects occur commonly; by chance alone, approximately 3% of women who use glaucoma medications during pregnancy will bear children with a major or minor abnormality.[3] Because the major organ systems develop early – the heart, for example, is completely formed by the eighth week – the embryo of a woman on chronic therapy will be exposed to medication during the critical stages of development before the patient is aware that she is pregnant. No glaucoma medication, ophthalmic anesthetic, or diagnostic drop is known to be a human teratogen. However none has been proven to be risk-free.[4] Patients should be informed that medical treatment carries some risk, but they may be reassured that the available data suggest that such risk is very low.

Risk to the pregnancy

The effect of glaucoma medications on the maintenance of an established pregnancy is not known. All ophthalmic prostaglandin analogs can cause contraction the uterine smooth muscle. It is not known if the very low systemic levels achieved with topical use are of realistic risk, but in the absence of better data, it seems reasonable to avoid prostaglandin analogs in women who are or desire to become pregnant.

Risk to the fetus and newborn

A comparison of 244 pregnant women using topical glaucoma medications to a control group of 1952 well-matched pregnant determined that use of drugs other than beta-blockers was associated with low birth weight.[8] Both beta-adrenergic blockers and brimonidine have been reported to cause serious toxicity, including respiratory and central nervous system depression, in neonates treated for glaucoma. These drugs will be present in the newborn if used close to delivery. Carbonic anhydrase inhibitors, including oral acetazolamide, have been used for decades in infants with congenital glaucoma and are generally well-tolerated. However a case of transient renal tubular acidosis with a measurable serum acetazolamide level in a preterm infant whose mother used the medication has been reported.[9]

Treatment options

Laser therapy

Laser trabeculoplasty lowers pressure in most treated individuals with primary open angle glaucoma, pigmentary glaucoma, and exfoliative glaucoma. It is a reasonable initial treatment for any patient with these conditions, but it is particularly attractive for the patient who is pregnant or is attempting to conceive. Laser treatment carries a small risk of transient or prolonged elevation in IOP, but as initial treatment in appropriate cases the risk is very small.

Incisional surgery

Incisional surgery during pregnancy is reserved for patients with uncontrolled, severe disease. Only a handful of reports deal with eye surgery during pregnancy, but there is extensive reported experience on non-ocular surgeries employing general and local anesthesia during all stages of pregnancy. Uncomplicated surgery is not felt to be associated with congenital anomalies or other poor outcomes. If surgery is necessary, topical or local anesthesia should be used; supplemental antifibrotic agents should not be used. Post-operative steroid and cycloplegic treatment is probably safe, as are ophthalmic antibiotics excluding tetracyclines.[3]

Management: The currently-pregnancy or lactating patient

Fortunately, glaucoma is generally a slow moving condition – in the early Manifest Glaucoma Trial only about 2/3 of individuals with glaucoma who were untreated showed progression over six years.[10] When determining how aggressively to treat an individual patient, her degree of damage is usually more important than her IOP because the more advanced the disease, the greater is the chance that a small degree of worsening will cause symptomatic damage.

The general steps in glaucoma management apply to pregnant patients: establish a baseline/stage the disease; set a goal; treat to achieve the goal; and monitor for progression

Pressure goals

Pressure goals during pregnancy are usually relaxed upward. Most patients and doctors will accept some risk to the mother, particularly early in pregnancy, as a cost of minimizing risk to the fetus, but few are willing to unconditionally suspend treatment. A reasonable set of goals for the first 20 weeks is 35 mmHg for mild damage, 30 mmHg for moderate damage, and 25 mmHg for advanced damage. From month four through the end of lactation, the goals of 30 mHg,

25 mmHg, and 20 mmHg are reasonable. If worsening occurs, and additional 30% lowering is indicated.

Treatment algorithm

For all patients, the treatment sequence is identical – observation, then laser if appropriate to the diagnosis, then medical treatment, and finally incisional surgery.

Medication principles

When topical therapy is used, three principles should always be followed:

- Use the minimum medication sufficient to achieve the goal
- Employ nasolacrimal obstruction to decrease systemic absorption
- Discuss treatment with the obstetrician and pediatrician

Drug choice

Months 1 through 8

Beta-blockers, alpha-agonists, and/or topical carbonic anhydrase inhibitors are probably safe. Prostaglandin analogs are not recommended, and, if used, should be immediately stopped if any uterine contractions are noted. Pilocarpine is probably safe, but it is poorly tolerated in most young patients.

Month 9

Beta-blockers and alpha-agonists should generally be stopped to avoid complications in the neonate. If they are continued, the pediatrician should be consulted and the patient should be advised to stop her medication at the onset of labor. Topical carbonic anhydrase inhibitors may be continued.

Lactation

Topical carbonic anhydrase inhibitors and prostaglandin analogs are reasonable choices. If beta-blockers and/or alpha-adrenergic agents are used, the infant should be monitored closely for evidence of systemic toxicity.

Follow-up frequency

If a patient's IOP is approximately the same as prior to pregnancy, no change in follow-up is indicated, If the IOP is higher than usual, she should have more frequent visual fields and optic nerve examinations. For mild to moderate disease, a field exam every four to six months seems reasonable. For severe disease, a field every two to three months may be appropriate.

The patient who is considering becoming pregnant

It is best to discuss reproductive plans with patients of child bearing potential prior to pregnancy. Appropriate treatment depends on the degree of a patient's glaucoma damage, the height of her pressure, her personal preferences, and the number of pregnancies that she plans.

Patients with glaucoma which is amenable to laser therapy should be offered such treatment. Those whose disease requires medical treatment should be advised that their medication will reach the baby and that early pregnancy is the period of greatest teratogenic risk. A woman who is attempting to conceive should consider avoiding prostaglandin analog use. Women who have advanced disease and are in marginal pressure control may benefit from surgical intervention prior to conception. All patients should contact their eye doctor as soon as they become pregnant.

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12. UNMET NEEDS

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Consensus statements

1. Identification of biomarkers of retinal ganglion cell dysfunction:
   - A more reliable tool for measuring the health of retinal ganglion cells is needed for more effective evaluation of treatment outcome.
   - There is a need to identify new models to test drugs.
2. Identification of novel targets for glaucoma treatments that lower IOP and preserve retinal ganglion cell function should be sought.
   Comment: Structural changes in the optic disc or retinal nerve fiber layer often precede functional changes and could be useful for primary endpoints in clinical trials.
3. New agents need not necessarily have enhanced pressure-lowering efficacy compared with prostaglandin analogues, particularly if they have an additive effect when used with existing medications.
4. Continuous IOP monitoring and home tonometry: There are currently no commercially available devices that allow continuous monitoring of IOP in humans.
   Comment: There is insufficient evidence at this time to show that home tonometry with any device provides accurate and reliable IOP measurement.
   Comment: Drugs that provide sustained lowering of IOP throughout the 24-hour day may be advantageous.
   Comment: However, it still is uncertain if additional IOP data from continuous IOP monitoring or home tonometry provides additional clinical information to the current measures of IOP peak, mean and fluctuation.
5. Objective measurement of patient adherence to glaucoma medication: Nonadherence to treatment regimens is common in glaucoma patients. Addressing the risk factors for poor adherence and developing new methods to improve adherence are pivotal to effective delivery of glaucoma treatment.
6. There is insufficient information regarding current treatment practices and the most appropriate glaucoma treatment strategies for developing countries.
7. Regulatory agencies should develop uniform standards for preservatives and unpreserved medications that could be applied worldwide.
8. A worldwide color-coding scheme for caps of classes and fixed combination of glaucoma medications is recommended.

Medical Treatment of Glaucoma, pp. 279-285
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9. Additional studies of the effects of different treatments on ocular blood flow and its relationship to glaucoma are needed.
10. Biomarkers for glaucoma diagnosis and progression are needed.
11. Improved delivery methods for drug therapies are needed.
12. A medical treatment is needed to restore retinal ganglion cell function or regenerate the optic nerve.

Detecting and following changes of the optic disc, retinal nerve fiber layer (RNFL) and visual field is the standard of practice to diagnose glaucoma and monitor its progression. The optic disc and the RNFL are often evaluated with fundus photography or digital imaging technology including optical coherence tomography, scanning laser polarimetry and confocal scanning laser ophthalmoscopy. For measurement of visual field, automated white-on-white perimetry is the current standard although frequency doubling technology (FDT) and short wavelength automated perimetry (SWAP) may detect visual field changes earlier than standard automated perimetry.[1-5] Yet, optic disc, RNFL and visual field measurements may fall short of directly indicating the integrity of retinal ganglion cells (RGCs). In early glaucoma, functional damage is often undetectable until there is substantial loss of RGCs and RNFL.[6,7] When the disease is advanced, it may be difficult to measure further reduction in neuroretinal rim and RNFL thicknesses. There is a need for more reliable biomarkers to monitor the health of RGCs at different stages of glaucoma and evaluate treatment outcome in clinical and experimental settings.

A biomarker is generally considered to be an indicator of a biological state that can be measured physically or biochemically. Measuring progressive loss of RGCs is a direct indicator of glaucomatous damage. A number of experimental studies have investigated the possibility of imaging RGCs *in vivo*. With intravitreal injection of Alexa Fluor 488-labeled annexin 5, Cordeiro *et al*. demonstrated that apoptotic retinal cells could be visualized *in vivo* with a confocal laser scanning ophthalmoscope in an experimental model of glaucoma.[8] Using this technology, they investigated the potential of targeting amyloid-β formation and aggregation pathway in the management of glaucoma.[9] Leung *et al*. described a non-invasive approach to image RGC damage in transgenic mice that express enhanced cyan fluorescent protein (CFP) driven by Thy-1 promoter using a modified confocal scanning laser ophthalmoscope.[10,11] Thy-1 is a cell-surface glycoprotein expressed by projection neurons in many parts of the nervous system.[12] In the retina, it is largely expressed in the RGCs.[13] The loss of Thy-1 expression was proposed to be related to a reduction in transcription as a result of shutting down of non-essential metabolic function either prior to or during programmed cell death.[14] Reduction of Thy-1 expression could thus serve as a sensitive indicator of RGC stress. Further characterization of these models is needed to determine their usefulness in assessing potential new treatment for glaucoma.

There are many molecules involved in the pathways of RGC degeneration that may serve as active biomarkers for glaucomatous damage. Increased markers of

oxidative stress,[15,16] mitochrondrial DNA damage[17-19] and increased expression of matrix metalloproteinases[20,21] are all implicated in the pathological process of glaucoma. Current investigations aim to identify novel biomarkers for glaucoma diagnosis and progression and investigate the utility of molecular diagnostic tests.

Continuous IOP monitoring

While higher mean intraocular pressure (IOP) is a well-recognized risk factor for development and progression of glaucoma, less is known about the importance of continuous IOP monitoring for management of glaucoma. The 24h-hour IOP variation has been attributed to changes in aqueous humor dynamics (production and drainage pathways), body positions (sitting and supine), as well as other physiological and environmental factors. With IOP measurements taken in the physiologic positions (sitting in the diurnal period and supine during the nocturnal period), Liu *et al*. showed that IOP was higher during the nocturnal period for both normal individuals and glaucoma patients.[22-24] In glaucoma patients, IOP fluctuates more during the diurnal period and two-thirds of subjects had IOP peaks during the nocturnal period.[25] Although these observations suggest that continuous IOP monitoring may have potential benefits in guiding treatment, the link between 24-hour IOP fluctuations and glaucoma progression is weak. Asrani *et al*. showed that diurnal IOP variation measured by self-tonometry (five times a day for five days) was a significant risk factor of visual field progression in glaucoma patients over a mean follow-up of five years.[26] In contrast, Liu *et al*. demonstrated that the amplitude of the 24-hour IOP variation in untreated patients with early glaucomatous changes was actually less than that in normal controls.[27] Their results do not support an association between a large 24-hour IOP variation and early glaucomatous damage. Data from major clinical trials investigating the relationship between long-term IOP variation and glaucoma progression are equally conflicting. In the Advanced Glaucoma Intervention Study (AGIS), inter-visit IOP fluctuations (defined as the standard deviation of all available IOP measurements) were associated with an increased risk of visual field progression.[28] In contrast, in the Early Manifest Glaucoma Trial (EMGT), inter-visit IOP fluctuations were not associated with visual field or optic disc progression.[29] It is plausible that the disparity in conclusion could be attributed to differences in study design and outcome measures. The role of continuous IOP monitoring and the association between IOP fluctuations and glaucoma progression require further investigation.

There are currently no commercially available devices for continuous IOP monitoring although a number of portable tools have been tested for home tonometry.[30-33] Home tonometry increases the number of IOP measurements but does not provide ambulatory 24-hour measurements. High variability of IOP measurements would be expected as the accuracy of IOP measurements would be patient dependent. The development of IOP sensing contact lenses may be promising for continuous IOP monitoring.[34,35] Nevertheless, there are techni-

cal challenges including motion artifacts and circadian variations in corneal thickness and curvature that need to be overcome before such clinical testing becomes routine.

Adherence to medical therapy

Poor adherence to medical therapy is a common, well-recognized problem in management of glaucoma. In the Glaucoma Adherence and Persistency Study (GAPS), data from administrative claims of 13,956 subjects receiving an initial glaucoma medication revealed that the mean medication possession ratio (defined as the days of prescription supply dispensed divided by the number of days between the first and last prescription refill) was 0.64 and the median was 0.57.[36] 90% of subjects failed to refill medications continuously over the 12-month study period. Patients with poor adherence to medication are at risk of disease progression and associated with visual loss in advanced glaucoma.[37] Detecting and identifying barriers of non-adherence, and improving adherence and persistence are major challenges in medical therapy of glaucoma.

Detecting and measuring adherence in a brief office encounter is difficult. Clinician's prediction of adherence correlated weakly with the actual dosage taken by patients.[38,39] An objective measure is therefore needed to monitor adherence. One example is the use of a dosing aid, which has been shown acceptable for recording the dates, times and number of drops administered.[40] In a prospective study evaluating adherence on 196 subjects using the Travatan Dosing Aid, Okeke *et al*. reported a mean adherence rate of 0.71 with a range between 0.02 and 0.97.[41] The agreement between clinician assessment and dosing aid recorded adherence rate was poor. Non-adherence is more often found in patients taking multiple medications. The development and application of dosing aid for other classes of glaucoma medication would facilitate clinicians to detect non-adherence and evaluate treatment outcome.

Objectively and accurately measuring adherence is elemental to identifying barriers to non-adherence. In the analysis of 196 glaucoma patients taking travoprost and using a dosing aid, risk factors for poor adherence were extremes of age, African American ethnicity, and less than excellent heath after adjusting for education and income.[42] Understanding how the number of medications, cost, tolerability, difficulty administrating drops, and doctor-patient communication influence the behavior of individual patients is also important to improve adherence. In a randomized controlled trial, Okeke *et al*. showed that intervention programs including watching an educational video, reviewing current barriers to drop-taking, receiving regular phone call reminders, and having audible and visible reminders activated on drop application devices can improve adherence with glaucoma medications.[43] Although it is still uncertain what specific type of intervention is most beneficial, future research in devising cost-effective intervention program targeting specific barriers of individual patients is warranted.

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Jeffrey Liebmann, Anne Coleman and Ivan Goldberg.

SUMMARY CONSENSUS POINTS

Section 1 – Who should be treated?

1. In general, treatment is indicated for patients with glaucoma or glaucoma suspects who are at risk for developing functional impairment or decrease in vision-related quality of life from the disease.
   Comment: Treatment is generally indicated when the risks of progressive disease outweigh the risks and potential side effects of treatment.
2. All treatment decisions should take into account the presence of coexisting ocular conditions, the patient's life expectancy and general health status, as well as his/her perceptions and expectations about treatment.
3. The rate of disease progression is of fundamental importance in considerations of treatment for glaucoma patients. Treatment is indicated for patients whose rates of progression will most likely result in loss in vision-related quality of life over the projected remaining years of life.
4. Treatment is generally indicated for patients with definitive glaucomatous visual field loss, particularly in circumstances when such loss has been determined to be progressive at a measurable rate.
5. Changes of the optic nerve and/or retinal nerve fiber layer (RNFL) characteristic of glaucoma predict functional vision loss in glaucoma and thus patients with such documented structural evidence of progressive damage should generally be treated with intraocular pressure lowering therapy.
6. The decision regarding whether or not to treat glaucoma suspects should involve a consideration of risk factors for disease development, including age, family history of glaucoma, intraocular pressure, central corneal thickness, presence of pseudoexfoliation, disc hemorrhages and measures of structural and functional integrity of the optic nerve head and retinal nerve fiber layer.
   Comment: While it is clear that progress has been made in establishing risk factors for glaucoma progression, much work remains to be done to better refine risk models. Nonetheless, the factors that affect the risk of progression help decide the expected prognosis of the individual's untreated disease and thereby the frequency of follow-up and aggressiveness of the therapy to be undertaken.
7. Imaging of the optic nerve head and retinal nerve fiber layer can provide useful predictive information about the risk of developing functional loss from glaucoma and thus can serve as a surrogate predictor of such vision loss.
8. Selective visual function tests may be predictive of functional loss in glaucoma patients and thus may be used as complementary tests to assist in treatment decisions.
9. Predictive models or risk calculators may assist clinicians in providing more objective estimates of the risk of glaucoma development for individual patients.

Comment: Predictive models are based on restricted populations of patients that were selected based on strict inclusion and exclusion criteria and that may not be representative of all patients seen in everyday clinical settings. Use of these models should be restricted to those patients who are similar to the ones included in the studies used to develop and validate such models and calculators.

Section 2 – Treatment goals

1. The target IOP is the IOP range at which the clinician judges that the estimated rate of progression is unlikely to affect the patient's quality of life.
   Comment: Although recommended by most experts, there is insufficient evidence that using target IOP is associated with better clinical outcomes.
2. The determination of a target IOP is based upon consideration of the amount of glaucoma damage, the rate of progression, the IOP at which the damage has occurred, the life expectancy of the patient, and other factors including status of the fellow eye and family history of severe glaucoma.
3. The use of a target IOP in glaucoma requires ongoing re-evaluation and adjustment.
4. The benefits and risks of escalating treatment to reach a target IOP must be balanced.
   Comment: Uncertainties regarding the short- and long-term variations of IOP, accuracy of tonometer readings, patient's life expectancy, adherence to therapy and estimated progression rates remain unresolved.
5. Treatment goals include IOP, visual function and structural (optic disc, RNFL) outcomes and QOL.
   Comment: It is uncertain whether patient reported outcomes of glaucoma can be applied in clinical practice, and whether they capture clinically meaningful progressive changes.

Section 3 – Drugs

1. All eye drops have the potential for systemic effects, which may be decreased with a lower concentration, reduced frequency of administration and using nasolacrimal occlusion or gentle eyelid closure.
   Comment: During pregnancy and lactation, the risks and benefits of these medications should be evaluated for each patient.
2. Topical cholinergic agents can effectively reduce intraocular pressure.
   Comment: In open-angle glaucoma, cholinergics enhance aqueous outflow through the trabecular meshwork by means of ciliary muscle contraction.
   Comment: Cholinergics may open the drainage angle in certain instances of angle closure by stimulating the iris sphincter muscle.

Comment: The effects of pilocarpine are representative of this class. Pilocarpine has an additive hypotensive effect to β-blockers, alpha-2 adrenergic agonists, and carbonic anhydrase inhibitors. It can be additive to prostaglandin analogues in some patients.
Comment: Common ocular side effects of pilocarpine, which limit its use, include brow-ache, induced myopia, and dimness of vision.
Comment: TID or QID dosing is associated with poor adherence.

3. Indirect cholinergic agents are reserved for open-angle glaucomas in aphakic or pseudophakic eyes.
   Comment: Indirect cholinergic agents are cataractogenic and also may cause adverse systemic effects.
4. Topical β-blockers are effective IOP-lowering agents.
   Comment: Topical β-blockers decrease IOP by reducing aqueous humor formation. All non-selective β-blockers have comparable IOP-lowering efficacy. *Comment:* Topical and systemic β-blockers are poorly additive with respect to lowering IOP.
   Comment: Although some β-blockers have intrinsic sympathomimetic activity (ISA) or α-blocking properties, their clinical properties are similar to those of other non-selective β-antagonists. However, ISA may reduce respiratory and cardiovascular side-effects related to β-blockade.
5. Timolol, and possibly all other β-blockers, have minimal IOP-lowering efficacy during sleep.
   Comment: Non-selective topical β-blockers are contraindicated in patients with asthma, chronic obstructive pulmonary disease (emphysema and bronchitis) some cases of congestive heart failure, bradycardia, and heart block.
6. The IOP-lowering efficacy of betaxolol, a relatively selective β-1-blocker, is less than that of non-selective β-blockers.
   Comment: Betaxolol is relatively safer than a non-selective β-blocker in patients with known reactive airway disease.
7. Carbonic anhydrase inhibitors (CAIs) are effective IOP-lowering agents.
   Comment: CAIs reduce IOP by suppressing aqueous humor production through inhibition of the isoenzyme carbonic anhydrase II.
   Comment: CAIs are the only category of drugs available commercially in both topical and systemic formulations to lower IOP.
   Comment: For systemic CAIs, major side effects include paresthesia, malaise, gastrointestinal disturbances, renal disorder, blood dyscrasia, and metabolic acidosis.
   Comment: For topical CAIs, side effects include ocular burning, stinging, bitter taste, superficial punctuate keratopathy, blurred vision, tearing, headache, and transient myopia.
   Comment: CAIs may increase ocular blood velocity; however, there is insufficient evidence for any clinical benefit of this effect for glaucoma patients.
   Comment: Topical CAIs and systemic CAIs are poorly additive with respect to lowering IOP.

8. Systemic CAIs are contraindicated with sulfonamide allergy, with depressed sodium and/or potassium blood levels, and in metabolic acidosis.
9. The non-selective adrenergic agonists, epinephrine and its pro-drug (dipivefrin) are effective IOP-lowering agents.
   Comment: Adrenergic agonists reduce IOP by decreasing aqueous formation and increasing outflow.
   Comment: Adrenergic agonists are contraindicated in infants and children because of systemic side effects.
   Comment: IOP-lowering efficacy of adrenergic agonists is less than that with timolol. This class is often additive to prostaglandin analogues but not to non-selective β-blockers.
   Comment: Local side effects include hyperemia and blepharoconjunctivitis. Systemic circulatory effects include hypertension and tachyarrhythmias.
10. Selective alpha-2 adrenergic agonists reduce IOP by suppressing aqueous inflow and increasing outflow. They also may affect episcleral venous pressure.
    Comment: Systemic side effects with selective alpha-2 adrenergic agonists include dry mouth, drowsiness and hypotension.
11. There is insufficient evidence for neuroprotection by selective alpha-2 adrenergic agonists in humans.
12. Bunazosin, a selective α1A antagonist, increases uveoscleral outflow.
    Comment: Although it is well-tolerated, the hypotensive effect of topical bunazosin is weaker than that of topical timolol.
13. Prostaglandin analogues (PGAs) are the most effective IOP-lowering agents of all topical glaucoma medications, and generally are first line therapy.
    Comment: PGAs lower IOP by increasing uveoscleral aqueous humor outflow, and may also have an effect on outflow facility.
    Comment: Common side effects of prostaglandin analogue drops include conjunctival hyperemia, reversible increase of eyelash length, thickness and pigmentation, irreversible increase of iris pigmentation, and increase of eyelid skin pigmentation. Rare side effects include uveitis, reactivation of herpetic keratitis and cystoid macula edema.
    Comment: PGAs are systemically safe, but are relatively contraindicated in pregnancy, as are all glaucoma medications.
14. Preservatives used for multi-dose topical ophthalmic medications can cause ocular surface changes.
    Comment: Benzalkonium chloride (BAK), in particular, has been associated with ocular surface changes in chronic use. Alternative preservative systems are increasingly used in multi-dose bottles in an effort to decrease the potential for deleterious effects on ocular surface. However, direct comparisons between these agents are lacking.
    Comment: Preservative free systems, in the form of unit dose packages, are a viable alternative to traditional multi-dose bottles. In theory, they may have fewer ocular surface effects, however, direct comparisons with preserved agents are lacking.

Section 4 – Selection of drugs

1. Only the IOP lowering effect should be considered to define the comparative efficacy of an ocular hypotensive agent.
2. Initiation of therapy: prostaglandin analogues (PGA) are recommended as first choice agents for most eyes with glaucoma.
3. IOP reduction with initial monotherapy should be at least 20% from baseline.
   Comment: IOP reduction of less than 10% should be considered as non-response.
   Comment: Switching drugs within the PGA class may, upon occasion, provide greater IOP lowering.
4. Adjunctive therapy is indicated when existing therapy fails to reach the target IOP.
   Comment: Adjunctive therapy should be limited to one drug from each class.
   Comment: The efficacy of a drug when used as monotherapy is usually less when used as an adjunctive agent.
5. Provided the use of the combination product is as efficacious as the two components administered independently, fixed-combinations are preferred when possible over the use of two separate bottles due to convenience, reduced amount of preservative instillation and possible improved adherence.
   Comment: Evidence is lacking that fixed combination products provide better outcomes than the individual components delivered separately.
6. Surgery is indicated when medical therapy fails to adequately lower the intraocular pressure or prevent progression, the risk of progression remains too high despite the use of medical therapy, or is not possible due to allergy, intolerance, poor adherence or lack of availability.

Section 5 – Medical treatments of other types of open-angle glaucomas

1. PG analogs are first choices for monotherapy in pseudoexfoliative glaucoma and pseudoexfoliation syndrome with ocular hypertension when treatment is required.
   Comment: Pilocarpine can reduce iris movements in eyes with pseudoexfoliation and, therefore, may reduce deposition of exfoliation material or pigment in the trabecular meshwork.
2. PGAs are first choices for monotherapy in pigmentary glaucoma.
   Comment: Pilocarpine can be effective in pigmentary glaucoma in reducing reverse pupillary block and diminishing iris movements.
3. Medical treatment of inflammation is first line treatment for uveitic glaucoma.

Section 6 – Drug delivery

1. Poor adherence / perseverance / dyscompliance are major problems in glaucoma. Patients taking fewer doses than prescribed are at risk of having worse outcomes than those taking a higher proportion.
   Comment: On average, most studies of glaucoma patients estimate that about 70% of doses are taken. This may vary depending on duration of treatment, number of medications taken and severity of the disease.
2. Patient self-report of adherence is often overestimated.
   Comment: Physicians do not accurately predict which patients are poorly compliant.
   Comment: While not readily available, better systems to reliably and easily monitor patient drop taking behavior are desirable since they would provide feedback for physicians to better identify patients with difficulty adhering to drop regimens.
3. Risk factors for lower adherence rates have been identified and include younger and older age, race/ethnicity, and depression.
   Comment: While poor adherence can occur in all patients, additional efforts may be required in patients with these risk factors.
4. Patients often have difficulty properly administering drops to their eyes.
   Comment: Efforts to improve adherence should address physical barriers.
   Comment: Observation of patient eye drop administration can detect patients that are unable to instill them.
5. For at least the next several years, topical IOP-lowering medication will remain the mainstay for glaucoma treatment.
   Comment: Despite limitations (inconvenience, dependence on the compliance of the patients and well-described adverse events in particular on the conjunctiva), topical anti-glaucomatous medication is (relatively) cheap, easily available, and generally safe, and it is reversible, should side effects arise.
6. A change in the preservatives of eye drops to a less toxic and more tissue-friendly formulation, and/or the development of preservative free drug delivery systems is needed to reduce the preservative related side-effects and tissue toxicity while delivering enough drug to control the intraocular pressure.
7. Non-IOP dependent therapy for glaucoma and also new drug delivery systems remain a high priority unmet medical need in glaucoma management.

Section 7 – Health economics

1. There are wide variations in reported costs of glaucoma therapy across nations.
   Comment: There is little information from developing countries.

Comment: With the exception of the US, the differences in costs of therapy are largely related to the level of economic development in various regions of the world.

2. Cost of one time surgery is substantially greater than medication in the short term, but lower in the long term.
   Comment: Changes in medication costs may alter this.
   Comment: Surgical failure may alter this because of the need for additional medication and/or surgery.
3. Generic drugs potentially can reduce direct treatment costs.
   Comment: More studies are needed comparing generic and branded drugs.
4. Side effects of glaucoma medications have minimal economic impact.
5. There do not appear to be significant differences in the cost of fixed combination products compared with individual components.
6. Failed medical therapy is defined differently in each country and depends on the cost and availability of medical therapy and surgical alternatives in that country.
   Comment: Pricing of glaucoma medications is not transparent.

Section 8 – Non-pharmaceutical medications and approaches

1. There is a paucity of clinical trial information examining neuroprotective effects of non-pharmaceutical compounds (alternative or complementary therapies) for glaucoma.
   Comment: Bio-availability of these natural compounds has not been well studied, and clinical studies of their efficacy and safety are needed.
2. Exercise reduces IOP, but the extent, duration and clinical significance are unclear.
   Comment: Exercise also can increase ocular blood flow, but the significance of this is unknown.
3. Acupuncture has been reported to lower IOP and increase ocular blood flow.
   Comment: The reported results are inconsistent and additional studies are needed before it is employed in clinical practice.

Section 9 – Neuroprotective therapies

1. A neuroprotective strategy for glaucoma is defined as a therapy that prevents the occurrence or progression of optic neuropathy and preserves visual function by mechanisms other than IOP lowering.
2. Agents that lower IOP have been shown to protect the optic nerve from glaucoma progression.
   Comment: Some agents that lower IOP might additionally confer protection to the optic nerve through mechanisms that are independent of IOP lower-

ing, but there is insufficient evidence for this dual effect with any agent at the present time.
3. Therapeutic approaches for preventing RGC death may aim to prevent primary or secondary degeneration of retinal ganglion cells.
4. Evidence from experimental models suggests that neuroprotection could be conferred by:
    a. Inhibiting the pathogenic mechanisms that injure or kill RGCs.
    b. Rendering the optic nerve more resistant to injury.
5. Numerous studies have demonstrated neuroprotection in experimental models of glaucoma or optic nerve injury, but good evidence demonstrating neuroprotection in clinical studies is lacking.
6. Challenges in translating experimental evidence of neuroprotection into clinical proof may be due to:
    a. The therapy may not be effective in humans.
    b. The lack of sufficiently robust tools to assess clinically the state of optic nerve health.
    c. The lack of animal models that are good representatives of human glaucoma.
    d. The lack of well-designed and well-conducted clinical studies.
7. Current testing paradigms are insufficiently sensitive and specific to detect change in a logistically feasible time frame. The development of accurate, sensitive, specific and reproducible clinical tests that provide information on the current state of health of the optic nerve are required to increase the feasibility of clinical development of neuroprotective agents.
   Comment: A desired embodiment of such clinical testing would allow detection of progression before the damage is irreversible.

Section 10 – Medical management of glaucoma in infants and children

1. The primary treatment of glaucoma in infants and young children is surgery.
   Comment: In many situations, however, the clinician must treat elevated IOP medically while awaiting surgery or after a partially-successful procedure.
   Comment: Only rarely should medical therapy be the primary treatment of glaucoma in infants and young children.
   Comment: A young child is not a small adult: systemic adverse reactions rarely seen in adults can occur in young children.
2. Outflow medications (pilocarpine and prostaglandin analogues) are variably effective in pediatric glaucomas, whereas aqueous suppressants lower IOP more consistently.
   Comment: Systemic and topical carbonic anhydrase inhibitors can be safe and effective. If possible, systemic use should be monitored by a pediatrician.
   Comment: Topical beta-blockers are effective; systemic safety is the major concern. Betaxolol is safer than timolol.

Comment: Topical brimonidine is absolutely contraindicated in children under two years, and must be used with great caution in older children. Apraclonidine may be safer, for short-term use, but clinical data is lacking.
Comment: Prostaglandin agonists are less effective in children than in adults, and are more likely to be effective in older children.
Comment: Miotics are rarely used in phakic children.

Section 11 – Treatment of glaucoma in pregnancy

1. Appropriate management of the pregnant/lactating glaucoma patient requires balancing the risk to the fetus of treatment against the risk to the mother if treatment is reduced or suspended.
   Comment: While a complete lack of prospective human data complicates this decision-making process, publications provide a guide.
2. Like all systemically-absorbed medications that are used during pregnancy and lactation, the maternal use of topical anti-glaucoma medications carries risks of teratogenicity, of interference with establishment or maintenance of pregnancy, or of side effects in the neonate.
   Comment: Prostaglandin analogues may be associated with uterine contraction.
   Comment: Beta-blockers and alpha agonists can cause serious toxicity (re spiratory and CNS depression) When possible, these agents should be withdrawn during the last few weeks of pregnancy.
   Comment: Topical CAIs are generally well tolerated.
3. Laser trabeculoplasty can be a reasonable initial or adjunctive intervention in pregnant and nursing women
4. Filtering surgery, preferably without anti-fibrosis chemotherapy, can be considered in certain cases.

Section 12 – Unmet needs

1. Identification of biomarkers of retinal ganglion cell dysfunction:
   - A more reliable tool for measuring the health of retinal ganglion cells is needed for more effective evaluation of treatment outcome.
   - There is a need to identify new models to test drugs.
2. Identification of novel targets for glaucoma treatments that lower IOP and preserve retinal ganglion cell function should be sought.
   Comment: Structural changes in the optic disc or retinal nerve fiber layer often precede functional changes and could be useful for primary endpoints in clinical trials.
3. New agents need not necessarily have enhanced pressure-lowering efficacy compared with prostaglandin analogues, particularly if they have an additive effect when used with existing medications.

4. Continuous IOP monitoring and home tonometry: There are currently no commercially available devices that allow continuous monitoring of IOP in humans.
   Comment: There is insufficient evidence at this time to show that home tonometry with any device provides accurate and reliable IOP measurement.
   Comment: Drugs that provide sustained lowering of IOP throughout the 24-hour day may be advantageous.
   Comment: However, it still is uncertain if additional IOP data from continuous IOP monitoring or home tonometry provides additional clinical information to the current measures of IOP peak, mean and fluctuation.
5. Objective measurement of patient adherence to glaucoma medication: Nonadherence to treatment regimens is common in glaucoma patients. Addressing the risk factors for poor adherence and developing new methods to improve adherence are pivotal to effective delivery of glaucoma treatment.
6. There is insufficient information regarding current treatment practices and the most appropriate glaucoma treatment strategies for developing countries.
7. Regulatory agencies should develop uniform standards for preservatives and unpreserved medications that could be applied worldwide.
8. A worldwide color-coding scheme for caps of classes and fixed combination of glaucoma medications is recommended.
9. Additional studies of the effects of different treatments on ocular blood flow and its relationship to glaucoma are needed.
10. Biomarkers for glaucoma diagnosis and progression are needed.
11. Improved delivery methods for drug therapies are needed.
12. A medical treatment is needed to restore retinal ganglion cell function or regenerate the optic nerve.

DISCLOSURE CODES DEFINITIONS – CATEGORY CODE SPECIFIC FINANCIAL INTERESTS:

N (No Commercial Relationship) Indicates there is no commercial relationship relevant to the related to the Consensus on Medical Therapy.

F (Financial Support) Indicates if you have received through your employing institution or personal support from a for-profit company, or competing company, in the form of research funding or research materials or services at no cost, such support being the subject of the Consensus on Medical Therapy.

I (Personal Financial Interest) Indicates if you are an investor in a company or competing company, other than through a mutual or retirement fund, which provides a product, service, process or equipment that is related to the Consensus on Medical Therapy.

E Indicates if you are an employee of a company or competing company with a business interest that is related to the Consensus on Medical Therapy.

C Indicates if you are, or have been within the last three years, a consultant for a company or competing company with a business interest that is related to the Consensus on Medical Therapy.

P Indicates if you are an inventor/developer designated on a patent, patent application, copyright, or trade secret, whether or not the patent, copyright, etc. is presently licensed or otherwise commercialized, which is related to the Consensus on Medical Therapy.

R Indicates if you have received gifts in kind, honoraria or travel reimbursement valued in any amount in the last twelve months from a company or competing company which provides a product, service, process or equipment that is related to the Consensus on Medical Therapy.

Name	Y/N	F	I	E	C	P	R
Aihara, Makoto	N						
Albis, Oscar	N						
Alencar, Luciana	N						
Alm, Albert	Y	Two year research support for an investigator-initiated study on follow-up of glaucoma with imaging			Attended a Glaucoma Advisory Panel arranged by Allergan in 2009. A fee and travel from the company		
Anton, Alfonso	Y	Pfizer, Merck, Allergan, Zeiss, Heidelberg			Merck, Santen, Zeiss		Alcon, Allergan, Merck, Santen, Pfizer
Aquino, Norman	Y						Alcon, Pfizer, MSD
Araie, Makoto	Y	Pfizer, Alcon, Santen, Kowa, Otsuka, Senju, Banyu, Wakamoto Competing consultant			Pfizer, Alcon, Allergan, Kowa, Senju, Banyu Designated on patent	Asteras	Pfizer, Alcon, Santen, Kowa, Otsuka, Senju, Banyu
Asrani, Sanjay	Y						Honoraria from Merck and Alcon Labs
Aung, Tin	Y	Alcon, Allergan, Ellex, Clarity, Carl Zeiss Meditec					Alcon, Santen, Pfizer, Clarity
Ayyala, Ramesh	Y	Educational grant from Alcon,TX. Educational grant from Allergan, CA. Research support from New World Medical, CA Consultant, iSciences Interventional,CA					
Azuaro-Blanco, Augusto	Y						Allergan
Barton, Keith	Y	AMO, Alcon, New World Medical, Merck, Santen					Alcon, Allergan, Merck.
Blumenthal, Eytan	N						
Boland, Michael	N						
Bourne, Rupert	Y	Allergan					Allergan

Name	Y/N	F	I	E	C	P	R
Brandt, James	Y				Alcon Laboratories; Allergan; Pfizer		Alcon Laboratories; Allergan; Pfizer
Broadway, David	N						
Bron, Alain	Y	Allergan, Alcon, MSD, Pfizer, Théa			Allergan, Alcon, MSD, Pfizer, Théa		Allergan, Alcon, MSD, Pfizer, Théa
Casson, Robert	Y						Travel expenses to national meeting supported by Ellex Lasers
Chandra Sekhar, Garudadri	Y						Allergan
Clark, Abbott	Y	Alcon Laboratories, Inc.			Alcon Laboratories, Inc.		
Coleman, Anne	Y				Alcon, Allergan, and Pfizer		
Cordeiro, Francesca	Y	Allergan				Imaging technology	Allergan Visufarma
Covar, Ranier	N						
Crowston, Jonathan	Y	Advisory Board for Alcon, Allergan, Pfizer Research funcing from Allegan, Alcon			Allergan, Alcon, Pfizer		Allergan, Alcon, Pfizer
Dada, Tanuj	N						
Damji, Karim	N						
Danesh-Meyer, Helen	Y	Allergan, Alcon-unrestricted research funds Allergan/Alcon/ Pfizer- support for Glaucoma NZ					
de Moreas, Gustavo	N						
de Natale, Renato	N						
Denis, Philippe	Y						Pfizer, Allergan, Alcon, MSD
Deokule, Sunil	N						

Name	Y/N	F	I	E	C	P	R
Fang, Seng Kheong	Y						Alcon, Allergan
Fechtner, Robert	Y	Allergan			Alcon, Allergan		
Feijoo, Julio Garcia	Y	Alcon. MSD. Pfizer. Allergan			Alcon. MSD, Pfizer.		
Feldman, Robert	Y	Alcon, Allergan, Pfizer, Novartis, Regeneron			Alcon, Pfizer, Allergan		
Fernando, Sandra	N						
Fingeret, Murray	Y	Carl Zeiss Meditec, Heidelberg Eng, Optovue			Allergan, Alcon		
Flammer, Josef	N						
Friedman, David	Y	Pfizer, Alcon, Zeiss-Meditec			Bausch and Lomb, NicOx, Allergan, Pfizer, Novartis		
Gandolfi, Stefano	Y	Allergan, Alcon, SIFI, Bausch&Lomb, Novartis					Allergan, Alcon, MSD, Pfizer
Ge, Jian	N						
George, Ronnie	Y				MSD		Allergan, Pfizer
Girkin, Chris	Y	Merck, Pfizer, Alcon, Allergan			Pfizer, Alcon, Allergan		
Goldberg, Ivan	Y	Alcon, Allergan, Pfizer			Alcon, Allergan, Merck, Pfizer		Alcon, Allergan, Ellex Lasers, Merck, Pfizer
Greenfield, David	Y	Pfizer, Allergan			Pfizer, Alcon, Allergan		Pfizer, Alcon, Allergan
Grehn, Franz	Y	Merck			Allergan		
Grierson, Ian	Y	From Alcon an Unrestricted Grant for the study of the trabecular meshwork $30,000.					Lecturing fees from MSD and also from Allergan.
Grigera, Daniel	Y						Allergan, Merck
Grus, Franz	N						

Name	Y/N	F	I	E	C	P	R
Gupta, Neeru	Y	Alcon Laboratories Inc., Allergan Inc., Pfizer Ophthalmics, Merck & Co., Inc.			Allergan Inc., Pfizer Ophthalmics, Merck & Co., Inc.		Santen Pharmaceutical Co., Ltd
Hangai, Masanori	N						
Harris, Alon	Y	Study sponsorship from Merck, Allergan, Pfizer			Merck, Pfizer, Allergan		
He, Mingguang	N						
Healey, Paul	Y						Alcon, Allergan, Pfizer
Higashide, Tomomi	N						
Ho, Ching Lin	N						
Hoh, Sek-Tien	N						
Holló, Gábor	Y				Alcon, Allergan, MSD, Pfizer, Santen		Alcon, Allergan, MSD, Pfizer, Santen
Hommer, Anton	Y				Allergan,Alcon, Merck, Pfizer, Santen		
Honjo, Megumi	N						
Iester, Michel	Y	A grant from SIFI, Merck					
Inatani, Masaru	N						
Iwase, Aiko	N						
Jampel, Henry	N						
Jonas, Jost	Y				Allergan Co.; MSD; Pfizer; CellMed AG, Alzenau; Morphosys AG, Munich; SOOFT SpA Montegiorgio, Italy		
Kahook, Malik	Y	Alcon, Merck, Actelion, Genentech			Alcon, Merck, Allergan, Genentech		
Kashiwagi, Kenji	N						
Kass, Michael	N						

Name	Y/N	F	I	E	C	P	R
Katz, L. Jay	Y				Glaukos Corporation		Alcon, Allergan, Pfizer, Lumenis
Kaufman, Paul	Y	Inspire, Santen, Danube Pharmaceuticals, Cara Therapeutics, Nu-Lens, Lens AR, Inc			Inspire, Alcon, Santen, Allergan, Bausch & Lomb, Cytokinetics, QLT, Danube Pharmaceuticals, Cara Therapeutics, Cascade		Inspire, Pfizer, Alcon, Santen, Allergan, Bausch & Lomb, Cytokinetics, QLT, Danube, Cascade
Kee, Changwon	N						
Khaw, Peng	Y	Pfizer, AstraZeneca, Promedior, Summit, GSK Personal	Lumemed		Pfizer, Allergan, Bausch & Lomb, GSK, AstraZeneca, Merk, Alcon		Pfizer, Bausch & Lomb
King, Anthony	Y	Allergan, Alcon					
Kipnis, Jonathan	N						
Konstas, Ansatasios	Y	Alcon, Allergan, MSD, Pfizer			Alcon, Allergan, MSD		Alcon, Allergan, MSD, Pfizer
Kook, Michael	N						
Krupin, Ted	Y				Alcon, Allergan, Ovation Pharm. Merck, Pfizer		Alcon, Allergan, Merck, Pfizer
Kymes, Steven	Y	Pfizer, Allergan			Pfizer, Allergan, Genentech		
Lai, Jimmy	Y	Equipment and clerical support form Pfizer for "Glaucoma risk factor screening project" to be held in March 2010					
Lam, Dennis	N						
Law, Simon	Y	Allergan, Merck			Allergan, Alcon		
Lee, Paul	Y	Duke University, Alcon, Pfizer, National Institute of Helath Personal	Pfizer, Merck		Alcon, Allergan, Pfizer	Duke Eye Center	
Lerner, Fabian	Y				Alcon, Sidus		Alcon, Allergan, Merck, Pfizer

Name	Y/N	F	I	E	C	P	R
Leung, Chris	Y	Carl Zeiss Meditec, Optovue, Luminus			Merck, Pfizer		Carl Zeiss Meditec, Merck
Leung, Dexter	N						
Levin, Len	Y				Alcon, Allergan, Biogen, Inspire, Merck, Serono	Assigned to Wisconsin Alumni Research Foundation	
Levkovitch-Verbin, Hani	N						
Lewis, Richard	Y				Allergan, Alcon, Pfizer, Vistakon, iScience, Aquesys, Ivantis, QLT		
Liebmann, Jeffrey	Y	Heidelberg Eng, Carl Zeiss Meditech, Topcon, Optovue, Diopsys					
Lin, Shan	Y						Allergan, Alcon & Pfizer
Lipton, Stuart	Y	Allergan, Inc.			Allergan, Adamas Pharm, Vertex Pharm, Orphagen, Forest Labs	Allergan, Forest Labs, Adamas Pharm	Allergan, Forest Labs, Vertex Pharm
Liu, John	Y	Alcon, Allergan, Pfizer					
Martin, Keith	Y				Alcon, Allergan, MSD, Pfizer		Alcon, Allergan, MSD, Pfizer
Maul, Eugenio	N						
McCluskey, Peter	N						
McKinnon, Stuart	Y	Pfizer, Inc.			Allergan, Inc.		Allergan, Inc.
McLaren, Grant	N						
Medeiros, Felipe	Y	Alcon, Allergan, Pfizer, Merck			Alcon, Allergan, Pfizer		
Melamed, Shlomo	Y				Solx		Allergan, Ellex, MSD, Alcon, Teva, IOPtima

Name	Y/N	F	I	E	C	P	R
Migdal, Clive	Y	Alcon, Allergan			Alcon, Allergan, Merck, Pfizer, Santen		Alcon, Allergan, Merck, Pfizer, Santen
Miglior, Stefano	Y						Merck, Pfizer, Alcon
Moroi, Sayoko	Y	Clinical research grant from Merck to compare positional IOP variation in patients with Glaucoma					Royalties from Lippincott for glaucoma textbook
Mosaed, Sameh	Y						Allergan
Mozaffaraieh, Maneli	N						
Nesher, Ronit	N						
Nouri-Mahdavi, Kouros	Y				Allergan		
Nucci, C.	Y	SIFI, Catania, Italy					Congress participation expenses fromAlcon, MSD, Thea, Visufarma (Italy) Medivis (Italy)
Nussenblatt, Robert	N						
Osborne, Neville	N						
Paranhos, Augusto	Y	Allergan			Allergan, Alcon		Allergan, Alcon
Parikh, Rajul	Y				MSD Pharmaceuticals Private Limited		
Parisi, Vincenzo	N						
Park, Ki Ho	Y						Alcon, Allergan, Pfizer
Park, Sung Chul	N						
Perez Grossmann, Rodolfo	N						
Pfeiffer, Norbert	Y	Alcon, Allergan, MSD, Chibret, Pfizer, Santen, Bausch & Lomb					Alcon, Allergan, MSD, Chibret, Pfizer, Santen, Bausch & Lomb

Name	Y/N	F	I	E	C	P	R
Prum, Bruce	Y	Alcon			Allergan		
Quigley, Harry	N						
Radcliffe, Nathan	Y				Allergan		Allergan
Rai, Sushma	Y				Have been on the CORE Speakers' Bureau for Allergan since 2009		
Realini, Anthony	Y				Alcon		
Rhee, Douglas	Y				Santen, Johnson and Johnson		Alcon, Allergan, Pfizer
Ritch, Robert	N						
RojanaPongpun, Prin	N						
Rosetti, Lucca	Y						Alcon, Allergan, MSD, Pfizer
Sakata, Lisandro	N						
Schlottmann, Patricio	N						
Schmetterer, Leopold	Y	Croma, Pharmaselect, Astra Zeneca, Baxter, Ursa Pharm, Allergan, Farmak, Merck			Merck, Bausch and Lomb, Croma		Merck, Bausch and Lomb. Croma, Alcon, Novartis
Schuman, Joel	Y	EyeIC, Inc.			Pfizer, Inc.	Bioptigen, Inc., Carl Zeiss Meditec, Inc.	Pfizer, Inc.
Schwartz, Gail	Y				Pfizer, Allergan		Pfizer, Allergan
Schwartz, Stephen	Y		Pfizer			University of Miami	
Schwartz, Michal	Y	I have received a research funding but not relevant to the subject of the Concensus on Medical Therapy			I have been a consultant for a company but on a subject that is not related to the Consensus subject of Medical Therapy		
See, Jovina	N						

Name	Y/N	F	I	E	C	P	R
Serle, Janet	Y	Novartis, Novagali, Acorn, Speedel, Aerie Competing consultant			Merck, Alcon, Allergan		
Shaarawy, Tarek	Y						Alcon, Allergan, Merck, Santen
Shah, Peter	Y	Research grant from Pfizer UK					Received travel grant to AAO from Allergan UK
Shrivastava, Anurag	N						
Singh, Kuldev	Y				Alcon, Allergan, Pfizer, Santen, Novartis,		Honoraria or travel reimbursement: Alcon, Allergan, Merck, Pfizer, Santen, Merck
Sit, Arthur	Y				Alcon, Allergan, Pfizer		
So, Kwok-Fai	N						
Spaeth, George	N						
Stalmans, Ingeborg	Y				Allergan, Alcon, MSD		Allergan, Alcon, MSD, Pfizer
Sugiyama, Kazuhisa	N						
Susanna, Remo	Y	Pfizer, Merck, Alcon, Allergan			Pfizer, Merck, Alcon, Allergan		
Tanihara, Hidenobu	Y				Senju, Santen, Alcon, Pfizer, Banyu		
Tavares, Ivan	Y	Alcon Labs, Allergan		Allergan			Alcon Labs, Allergan, Merck & Co, Pfizer Ophthalmics
Tham, Clement	Y	Alcon			Alcon, Pfizer, Allergan		Alcon, Pfizer, Allergan
Thieme, Hagen	N						
Thomas, Ravi	Y						Allergan
Thygesen, John	Y	Research funding: Alcon, Allergan, Merck, Pfizer, Santen, Merck			Alcon, Allergan, Merck, Pfizer, Santen, Merck		Honoraria or travel reimbursement: Alcon, Allergan, Merck, Pfizer, Santen, Merck

Name	Y/N	F	I	E	C	P	R
Tomidokoro, Atsuo	N						
Topouzis, Fotis	Y	Heidelberg Engineering, Inc, Pfizer, Inc, Alcon, Inc,			Pfizer, Inc, Merck and CO, Inc		Pfizer, Inc, Alcon, Inc, Merck and CO, Inc
Toris, Carol	Y	I have receive support from Alcon, Allergan and Pfizer to study the efficacy and mechanism of actio of glaucoma drugs under development.					
Traverso, Carlo	Y	Allergan, MSD, Optonol, Glaukos, Pfizer, Santen					Allergan, MSD, Optonol, Glaukos, Pfizer, Santen
Trounce, Ian	N						
Tsai, James	Y	Merck, Pfizer			Alcon, Allergan, Inspire, Merck, Pfizer		
Tuulonen, Anja	Y						Pfizer, Merck & co, Santen, Alcon
Varma, Rohit	Y	Pfizer, Allergan	Aquesys, Replenish		Alcon, Allergan, Pfizer, Bausch & Lomb, Merck, Laboratorias Sophia, Replenish		Alcon, Allergan, Pfizer, Merck, Replenish
Ventura, Lori	N						
Vidal-Sanz, Manuel	Y	Allergan					
Viswanathan, Ananth	Y				Allergan, Pfizer		Alcon, Allergan, MSD, Pfizer
Vizzeri, Marco	N						
Wang, Ningli	N						
Wei, He	N						
Weinreb, Robert	Y	Lumenis, Novartis			Aciex, Alcon, Allergan, Bausch & Lomb, Glaxo, Merck, Novartis, Othera, Pfizer		Alcon, Allergan, Merck, Pfizer

Name	Y/N	F	I	E	C	P	R
Wells, Tony	Y				Allergan, Alcon		Allergan, Alcon
Wong, Tina	N						
Wu, Lingling	N	Santen, Pfizer Japan, Alcon Japan			Alcon Japan, Pfizer, Pfizer Japan, Otsuka, Kowa, Banyu		Santen, Alcon Japan, Pfizer Japan, Otsuka, Banyu, Senju
Yamamoto, Tetsuya	Y	Santen, Pfizer Japan, Alcon Japan			Alcon Japan, Pfizer, Pfizer Japan, Otsuka, Kowa, Banyu		Santen, Alcon Japan, Pfizer Japan, Otsuka, Banyu, Senju
Yoshitomi, Takeshi	Y	Santen Alcon Pfizer Senju Kaken					
Yücel, Yeni	Y	Allergan					
Zeyen, Thierry	Y						Alcon, Allergan, Merck Sharp & Dohme, Pfizer

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