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Clinical Considerations in LOW-TENSION GLAUCOMA

A roundtable discussion.

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This continuing medical education activity is jointly sponsored by the Dulaney Foundation and *Glaucoma Today*.

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A ROUNDTABLE DISCUSSION.

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STATEMENT OF NEED

Considered a variety of open-angle glaucoma, normal- or low-tension glaucoma is characterized by glaucomatous optic neuropathy and visual field loss as well as an IOP of less than 21 mm Hg.[1] In the Beaver Dam Eye Study, almost one-third of subjects with definite open-angle glaucoma had low tension in the involved eye.[2] The progression of glaucomatous damage to the optic nerve in the presence of what is generally considered to be a normal IOP has raised debate over the cause of glaucoma.[1] Research has demonstrated that IOP is one factor in the pathogenesis of low-tension glaucoma, which indicates that decreasing pressure should be beneficial in patients at risk of disease progression.[3] Safely reducing IOP sufficiently in eyes with low tension to prevent disease progression, however, can be challenging. That concern combined with the idea that low-tension glaucoma may also have a pressure-independent component[1] have increased clinicians' interest in neuroprotective drugs.

In order to effectively diagnose and manage low-tension glaucoma, physicians must understand the relationship of structural and functional change in glaucoma, the importance of fluctuations in IOP, the efficacy of currently available therapy, and the status of research on perfusion pressure and neuroprotective agents.

TARGET AUDIENCE

This activity is designed for ophthalmologists.

LEARNING OBJECTIVES

Upon completion of this activity, the participant should be able to

- recognize the importance of implementing structural and functional assessments in glaucoma
- identify how the treatment of glaucoma has changed during the past 10 years
- understand the significance of IOP's variability to the management of glaucoma and the potential value of continuous measurements of pressure
- assess the risks and benefits of observation versus treatment in cases of low-tension glaucoma
- discuss the available research on perfusion pressure and neuroprotective agents

METHOD OF INSTRUCTION

Participants should read the learning objectives and continuing medical education (CME) activity in their entirety. After reviewing the material, please complete the self-assessment test, which consists of a series of multiple-choice questions. To answer these questions online and receive real-time results, please visit www.dulaneyfoundation.org and click "Online Courses."

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Dr. Katz discloses that he has received grant/research support from and is on the speakers' bureaus of Alcon Laboratories, Inc.; Allergan, Inc.; Merck & Co., Inc.; and Pfizer Inc.

Dr. Krupin discloses that he has received grant/research support from and is on the speakers' bureaus of Alcon Laboratories, Inc.; Allergan, Inc.; and Pfizer Inc. He is a consultant to Alcon Laboratories, Inc.; Allergan, Inc.; Merck & Co., Inc.; Ovation Pharmaceuticals, Inc.; and Pfizer Inc.

Dr. Liebmann discloses that he has received grant support from Carl Zeiss Meditec, Inc.; Heidelberg Engineering, Inc.; and Optovue, Inc. He is a consultant/advisor to Alcon Laboratories, Inc.; Allergan, Inc.; Diopsys Corporation; Optovue, Inc.; Pfizer Inc.; and Topcon Medical Systems, Inc.

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All others involved in the planning, editing, and peer review of this educational activity have indicated that they have no financial relationships to disclose. ■

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CURRENT UNDERSTANDING OF GLAUCOMA

Weinreb: What is our current understanding of glaucoma?

Liebmann: Glaucoma is an optic neuropathy characterized by a progressive loss of retinal ganglion cells and their axons that leads to the characteristic pattern of optic nerve injury known as *cupping* and an associated loss of visual function. The pattern of anatomic damage and visual field loss respects the horizontal meridian and the anatomy of the retinal nerve fiber layer (RNFL). IOP-dependent damage is the most important risk factor for disease onset and progression.

Weinreb: How has our understanding of glaucoma changed during the past 10 years?

Katz: A large proportion of practitioners have come to accept the concept of preperimetric glaucoma in which structural change without functional change is evidence of disease. We also now place a greater emphasis on using technology to help us diagnose and monitor glaucoma.

Weinreb: What is our concept of low-tension glaucoma (LTG)? Is it really a separate disease entity?

Katz: A mix of factors influences whether someone will develop glaucoma. There may be a little bit more of one factor in the normal-pressure or low-pressure continuum than there is in the high-pressure continuum. For example, there may be more of a vascular component in addition to pressure. There appear to be more disc hemorrhages, migraines, and Raynaud's disease in the LTG group of patients.[4-7]

DIAGNOSIS

Weinreb: Which diagnostic modalities do you currently use?

Katz: I perform structural and functional assessments of all patients. The rare exceptions are patients who are totally cupped out, for whom disc photography is not going to provide much information, and patients whose visual field has been wiped out, for whom visual field testing is not going to provide much information. I perform standard achromatic perimetry to monitor patients. For select individuals, such as ocular hypertensives and the relatively young, I will also perform a type of selective functional test such as short-wavelength automated perimetry or frequency-doubling technology perimetry.

> "Reliance on visual fields to assess glaucomatous progression has been problematic in clinical practice. ... In many individuals, ... structural change precedes functional change."
>
> –Robert N. Weinreb, MD

Liebmann: As Dr. Katz mentioned, glaucoma assessment involves an evaluation of both the structure and the function of the optic nerve. For example, I obtain stereoscopic photographs of the optic nerve at the time of the initial examination and periodically thereafter. Photographs provide critical information (such as the presence of a disc hemorrhage) that cannot be obtained with any of the currently available computerized imaging devices.

I use functional testing as Dr. Katz described. If the achromatic visual field is normal, I may try selective tests of visual function to seek evidence of more subtle functional loss or more detailed structural examination with an imaging device to look at the RNFL.

Weinreb: Reliance on visual fields to assess glaucomatous progression has been problematic in clinical practice. Clinicians often do not examine and document the condition of the optic nerve while caring for patients with glaucoma.[8] In many individuals, however, structural change precedes functional change. In the Ocular Hypertension Treatment Study (OHTS), a change in the optic disc often preceded a change in the visual field in patients with ocular hypertension who were developing glaucoma.[9] Felipe Medeiros, MD, PhD, and colleagues at the Hamilton Glaucoma Center at the University of California, San Diego, recently reported that photographic changes in the optic disc also often precede visual field changes in patients with established glaucoma and that the photographic alterations were highly predictive of changes in visual function.[10] These studies highlight the essential need for examining the optic nerve structure to diagnose as well as detect glaucomatous progression.

Liebmann: In OHTS, approximately half of the endpoints were based on a change in the appearance of the optic disc without concomitant visual field change.[2]

Krupin: Getting back to the issue of functional change and early disease, in OHTS, only 8.3% of the treated group and 10.1% of the observation group had concurrent visual field and optic nerve endpoints.[5]

Liebmann: The entrance criteria for OHTS precluded patients who had overt glaucomatous optic neuropathy but did not exclude patients with suspicious discs that were compatible with early glaucoma. Some of the patients likely had early glaucomatous damage that did not trigger an exclusion criterion.

Katz: You still had to have a change over time to be diagnosed with glaucoma in OHTS, whether it was the optic nerve or visual field.

Liebmann: Since many retinal ganglion cells can be lost before the visual field changes, it is important to examine the optic disc and RNFL for progression.

Krupin: I measure the IOP and examine the optic nerve for a possible disc hemorrhage during every office visit. My approach to selective testing is a little different. For someone who has a hemifield defect on standard automated perimetry, I may use selective testing for the part of the field that does not have a white-on-white defect.

Liebmann: I usually reserve the use of selective tests of visual function for eyes with normal achromatic perimetry but will occasionally use these tests to determine if the actual functional loss exceeds the area of damage detected by achromatic perimetry.

Krupin: Glaucoma is a bilateral disease that is often asymmetric. I also use selective visual field tests and RNFL analysis in the fellow "normal" eye to detect early glaucomatous damage.

HISTORICAL PERSPECTIVE ON TREATMENT

Weinreb: How has the treatment of glaucoma changed?

Katz: Large clinical trials, most of which were funded by the National Eye Institute, have supported the setting of a target pressure or reduction in IOP for the various types of glaucoma and different stages of the disease.[5,11-13]

Weinreb: The single event in glaucoma management that has emerged in the past 10 years is the use of the target IOP concept?

> "I have generally become more aggressive in my target pressures [during the past 10 years]. ... A critical look at my records showed a lot of patients whose disease progressed while they were under my care."
>
> –L. Jay Katz, MD

Katz: Having pressure as a surrogate goal of treating glaucoma is the first step.

Weinreb: How do your target pressures today compare with those of 10 years ago?

Katz: I have generally become more aggressive in my target pressures for a variety of reasons. Like many physicians, I have been in practice for a number of years, and a critical look at my records showed a lot of patients whose disease progressed while they were under my care. That realization made me believe that, in many of these cases, I should have been more aggressive about the target pressure I had set. I have changed my approach in the hope that I will improve the outcomes for the patients I am treating now.

Weinreb: Is that change also related, at least in part, to the current availability of medications that are better tolerated and safer?

Katz: Yes, I think that, if you have less onerous treatments, you are likely to be more aggressive. Today's drugs are better tolerated and require less frequent dosing than the agents we prescribed 10 years ago. They are therefore better accepted by patients.[14-16]

Weinreb: Ten years ago, the prostaglandin analogues were introduced into glaucoma management. As safe, well-tolerated, highly effective agents, they have emerged as first-line therapy for the disease.

Katz: The availability of these agents has also changed how we approach patients with ocular hypertension and glaucoma suspects. Today, we may proceed with treatment in some of these individuals rather than observe them, as we did before we had access to this drug class.

Weinreb: For the past several years, we have also implemented risk profiling for patients with the introduction of risk calculators.[17,18] In particular, we now perform pachymetry to assess central corneal thickness[19]; this was not a recognized risk factor in the development of glaucoma or the establishment of glaucomatous progression 10 years ago.

Dr. Krupin, how would you characterize glaucoma management 25 years ago?

Krupin: We followed the rule of 21, according to which an IOP of 21 mm Hg meant that the patient had glaucoma. The appearance of the optic nerve was irrelevant.

Katz: At that time, a patient could not have glaucoma without visual field loss.

Krupin: I disagree. I think we were just treating pressure.

Weinreb: Timolol was introduced in 1978 and rapidly became the prevailing therapy for open-angle glaucoma.

Dr. Krupin, did you examine the optic disc in the 1970s?

Krupin: In St. Louis, we performed manual static perimetry, Goldmann tonometry, and disc photography. We also performed tonography.

SIGNIFICANCE OF IOP FLUCTUATIONS

Weinreb: What is the relative importance of fluctuations in mean IOP?

Liebmann: Clinicians agree that IOP plays a key role in disease pathophysiology and treatment. The most important IOP parameter to evaluate glaucoma, however, remains a subject of considerable controversy. Our understanding of the patient IOP profile is very limited. We measure IOP at certain times of the day, and information about patients' pressure outside of office hours remains limited. I think it makes the most sense to recognize that IOP is variable. If elevated IOP is damaging the eye, my opinion is that the highest pressure, or peak pressure, is likely causing the most damage. Wide fluctuations in IOP signify that control is not good and that the patient may be experiencing more peaks in IOP than are being noted during routine testing.

Given patients' longer life expectancies and an increased awareness that progression still occurs despite treatment, many physicians opt for a lower target IOP than was typical 10 or 20 years ago. Fortunately, our medicines are more potent and allow us to achieve the lower target more easily.

> "While IOP is the only glaucoma risk factor we can modify, we should be aware of the limitations of the measurement."
>
> –Theodore Krupin, MD

Katz: The peak IOP is what we are really dealing with on a patient-by-patient basis. The issue of short- or long-term IOP fluctuation is a hot topic right now. Some studies suggest that it is important,[20,21] and others do not.[22] It remains unsettled whether IOP fluctuation is an independent risk factor for glaucomatous progression.

Most of us do not have the ability to measure IOP for 24 hours or to routinely check patients while they are supine. This information may be very important. We do not know. Moreover, there may be differences in the ability of drug A versus drug B or of surgery versus medications to lower IOP through the 24-hour period or while patients are supine.

Without sufficient data to draw conclusions on these points, my day-to-day management of patients resembles Dr. Liebmann's. Patients start at a peak IOP level, and I strive to keep their pressures a certain percentage or an absolute number below that on a regular basis.

Weinreb: What IOP parameter do you think is the most relevant?

Krupin: The problem is the variability of IOP. When I am examining a patient in the office, I am looking for the peak pressure. In addition, like all clinical measurements, IOP has a variability during a given recording (eg, ±1.5 mm Hg) as well as a 24-hour fluctuation and difference with body position. While IOP is the only glaucoma risk factor we can modify, we should be aware of the limitations of the measurement.

Weinreb: The World Glaucoma Association's consensus on IOP viewed mean IOP as having the best evidence for showing glaucomatous progression. It also indicated that there was insufficient evidence to suggest

that daytime or 24-hour IOP fluctuation was a significant risk factor for glaucomatous progression.[23]

Liebmann: Although I agree that daytime mean IOP is an important IOP parameter, other parameters may also be important. In OHTS, for example, a peak IOP target pressure was set for each patient, and there was strict adherence and monitoring to keep all measured IOPs below this peak. This created a scenario in which the mean IOP was also lower, but the goal of the treatment was to keep the IOP below the target, not to achieve a specific mean IOP.[5]

Weinreb: Moreover, since they measured IOP only during the diurnal period, the peak pressures over 24 hours were not identified.

Liebmann: Do you think these issues about IOP call into question the treatment concept of target IOP?

Weinreb: I think that we will not know that answer until we can continually monitor IOP.

Liebmann: We should emphasize looking at the optic disc and the visual field as, ultimately, how to judge the effectiveness of treatment—not the amount of pressure reduction during the day. If the optic nerve and visual field remain unchanged, the treatment is probably acceptable.

Krupin: We are obtaining more measurements of diurnal IOP, but I do not think we have been doing so to determine the mean IOP value. I think most of us have been attempting to determine what the peak value is.

Weinreb: In practical terms, that is how we manage glaucoma.

CURRENT APPROACHES TO TREATMENT

Overview

Weinreb: How do you typically treat most of your glaucoma patients? Are you setting a target pressure? What are you using as first-line therapy?

Krupin: Target pressure is a guess. It is a percentage decrease based on the level of glaucomatous damage.

Weinreb: How do you establish the target pressure?

Krupin: Most of my patients are referred, so I have some history on them. If I do not, I will obtain a couple of IOP measurements while they are in the office, and I will look at a percentage decrease at which to aim. I am trying to determine the target IOP I need to stop the progression.

My first line of therapy is medical.

> "If we believe glaucoma is a pressure-related disease, then we should lower the IOP as effectively as possible while minimizing the patient's treatment burden and risk."
>
> –Jeffrey Liebmann, MD

Weinreb: Do you have a standard drug you use as first-line therapy?

Krupin: A lot of times, I will not prescribe a prostaglandin analogue. During a discussion of side effects, many of my patients will ask to try something else first. Although my bias is to use the most effective medication, which is a prostaglandin, I also have to foster my relationship with the patient. It is not uncommon that I will start with a beta-blocker, which means I am measuring the patient's blood pressure and pulse.

Liebmann: I almost always start with a prostaglandin analogue if the patient has glaucoma. All of the phase 3 clinical trials for these agents demonstrated superior IOP lowering when compared to timolol monotherapy.[24] If we believe glaucoma is a pressure-related disease, then we should lower the IOP as effectively as possible while minimizing the patient's treatment burden and risk.

Weinreb: You are not using beta-blockers as first- or second-line therapy?

Liebmann: For the most part, I tend to use beta-blockers when a prostaglandin analogue combined with a topical carbonic anhydrase inhibitor or alpha-adrenergic agonist fails to control the IOP.

Katz: Some patients are apprehensive about prostaglandin therapy, often for cosmetic reasons. For example, the irides of some patients—especially those that are hazel—may become irreversibly darker, and that may be a

deterrent to using prostaglandin analogues for certain individuals. Aside from that, I think that prostaglandins are the most dominant drug class because of their efficacy and safety systemically.[25-28] That is where beta-blockers fall short.

In select cases, patients cannot afford their drugs, so I prescribe the best drug for their economic situation. Other individuals are adamant about not wanting to be on any medication at all. To me, laser trabeculoplasty is analogous to medication,[29] so I will use this modality as first-line treatment in a small percentage of patients.

Like Dr. Liebmann, I sometimes prefer other topical agents as adjunctive medication to a beta-blocker out of concern for a patient's overall health—for example, a marathon runner.

Weinreb: When do you perform laser trabeculoplasty as a first-line treatment?

Katz: Usually, I reserve this approach for two groups of people after providing a comparative discussion about glaucoma drugs and laser trabeculoplasty. The first consists of executive decision makers (often, they are business owners, white-collar workers, attorneys, physicians) who do not want to bother with drops and prefer laser treatment initially. The second group comprises individuals who are physically incapable of instilling topical drops and those who are opposed to using medication (for health reasons, cost, etc.). Many of these individuals feel comfortable with the concept of laser therapy, but they currently represent only about 10% of the patients.

Liebmann: I use laser trabeculoplasty in much the same way that I use medications. Laser trabeculoplasty is not a panacea, however, and if a patient is suffering progressive damage to the visual field or optic nerve, the best intervention may be incisional surgery.

Krupin: If your patient is using one medication and progressing, do you go straight to surgery?

Liebmann: Most often, I will add a second medication or perform laser trabeculoplasty, provided that there is a realistic expectation of reaching the desired target IOP. Many patients whose glaucoma progresses while under our care, however, may require more IOP reduction than is typically achieved with medical therapy.

Krupin: Has that been effective? It has not been my experience.

> "My suspicion is that the vast majority of patients with progressive visual field loss end up in the OR within 10 years regardless of how you manipulate their medical therapy."
>
> –Jeffrey Liebmann, MD

Katz: I think that Dr. Liebmann may be quick to the draw, but the number of medications we try has gone down over the years. Ophthalmologists no longer try five or six different combinations of medication. We test two, maybe three, and then move away from drugs.

Krupin: Then, you are going to laser therapy.

Liebmann: In the best-case scenario, adding a second medication typically results in a decrease in IOP of less than 20%. Additional medicines often result in less of a reduction than that.

Krupin: In the Early Manifest Glaucoma Trial (EMGT), the hazard ratio for progression increased by 11% for every 1 mm Hg of higher IOP.[18] Does the reverse happen when the IOP is reduced by 1 mm Hg? What is the benefit of decreasing the IOP from 18 to 14 mm Hg, when Dr. Liebmann is saying that this patient is not going to do well anyway? My experience has been different. I cannot predict the success of treatment based on one medication. Many of my patients are stable on two medications for a long period of time.

Liebmann: My suspicion is that the vast majority of patients with progressive visual field loss end up in the OR within 10 years regardless of how you manipulate their medical therapy.

Krupin: The 10 years following a trabeculectomy can include a lot of problems, so everything is a balance. I was asked once what I would want if I had glaucoma. I would not have laser therapy or surgery first. Barring contraindications, I would choose prostaglandin therapy with a maximum tolerance for three medications, three drops a day. If I needed a second agent, I am biased on theoretical grounds in favor of an alpha2 agonist. I know it will lower the IOP. When patients do not adhere to

prescribed therapy, however, I broach surgery as an option early.

Weinreb: Do you ever use any IOP-independent therapies?

Krupin: I am not using gingko. I do not prescribe memantine, but approximately 15 subjects from my memantine trial are still using it. I do not know which of our subjects in Allergan's memantine trial (Allergan, Inc., Irvine, CA) were taking the medication. The memantine study is complete and the studied medication discontinued. I noticed glaucomatous progression in some patients whose disease had been stable during the 4 years of the trial. These individuals want to be on the "study medication."

Liebmann: Of course, that is an off-label use and an informed consent issue.

Krupin: Yes, there is a form that they sign about the drug's off-label use.

Liebmann: I do not ask patients to sign an informed consent form for the off-label use of medication, although I document the discussion and the various options and alternatives in the patient's chart. I have occasionally used memantine, a drug currently approved to treat Alzheimer's disease, in desperate patients whose glaucoma appears to be progressing despite very large amounts of IOP lowering.

Katz: I do not endorse using any "nonpressure" agents, even in desperate situations. They may hurt rather than help patients. A past example was the use of oral calcium channel blockers, theoretically, to help improve ocular blood flow by ocular vasodilation. Patients may become systemically hypotensive, however, with a resulting drop in ocular perfusion pressure that could be harmful.[30,31]

Weinreb: What is perfusion pressure?

Liebmann: Ocular perfusion pressure is determined by subtracting the IOP from the upper arm measurement of systolic blood pressure.

Weinreb: Do you prescribe memantine as an unapproved treatment to prevent glaucomatous progression?

Liebmann: I consider the use of this agent in two groups of patients. The first is individuals for whom a further reduction in IOP is possible but overly risky. Most of them have seen a neuro-ophthalmologist to rule out other unusual diseases or causes of optic nerve degeneration. These patients are few in number. The second group is patients who initiate a discussion about pressure-independent therapy, often based on their own or their children's research on the subject. I understand Dr. Katz's concerns, but I would rather guide patients through a drug's use than not. It is important to note that memantine failed to achieve its therapeutic goal in its phase 3 clinical trials.

> "I do not think there is any compelling evidence to make me treat LTG and high-tension glaucoma differently."
>
> –L. Jay Katz, MD

Katz: I suggest telling patients to lose weight and exercise.

Krupin: I also do this. Weight loss increases life spans.

Liebmann: I tell patients to exercise regularly, to lose weight if they are overweight, and to manage their overall medical health. I also ask them some general questions about their lifestyle and offer counsel on any indicated changes.

Weinreb: What are the barriers to adequately lowering IOP on a consistent basis?

Liebmann: The number-one problem is adherence.

Krupin: I agree with Dr. Liebmann. The adherence problem is my main reason for prescribing prostaglandins.

Special Considerations in LTG

Weinreb: Is there any reason to treat LTG differently than primary open-angle glaucoma?

Katz: I do not think there is any compelling evidence to make me treat LTG and high-tension glaucoma differently.

Weinreb: You lower the IOP in both cases?

Liebmann: Yes, but the difference lies in patient surveillance. I think there may be subtle differences between the pressure-dependent and pressure-independent components of visual field loss. I think they may affect the optic nerve slightly differently.

Krupin: What is the evidence?

Weinreb: A study showed that patients with LTG had more central defects.[32] There is a bias in the study, however, because the patients who were being examined had been referred for a loss of vision. If you are losing your vision, you are more likely to have an impairment of central vision.

Liebmann: It has been suggested that patients with LTG may have a greater predilection for damage in the central visual field compared to patients with primary open-angle glaucoma and higher IOPs.

Krupin: Are you finding a difference between superior and inferior field progression in high-pressure or low-pressure cases?

Liebmann: I suspect that different regions of the optic disc have varying susceptibility to elevated IOP. I do not think glaucoma is a single disease. Different patients respond differently to IOP and our interventions.

Weinreb: So you treat the LTG patient differently?

Liebmann: I reduce the IOP, but my disease surveillance is slightly different.

Krupin: During the World Glaucoma Congress, the point was made that not all practitioners treat every patient with LTG.

Liebmann: In the vast majority of patients, LTG is a very slowly progressive disease.[33] Although I treat most patients, the disease's velocity for some of our older patients may not be vision threatening.

Krupin: If I had LTG, I would want to receive medical therapy.

Weinreb: Dr. Liebmann, would you treat a patient who had moderate-to-severe disease, sometimes without waiting to observe progression?

> "In some cases, the potential risks of treatment outweigh the potential benefits, particularly if the patient has a short life expectancy."
>
> –Robert N. Weinreb, MD

Liebmann: Yes.

Weinreb: What about a highly myopic patient who exhibited minimal changes when you were uncertain about the status of the optic disc? Could you afford the luxury of waiting and retesting?

Krupin: Yes, because all LTG patients do not progress.

Weinreb: I tend to agree with you. In general, I treat if I see evidence of optic nerve damage, particularly if it is moderate to severe.

Krupin: Similarly, I will treat high myopes with low IOP when I am uncertain if the optic nerve and field loss relate to their glaucoma or their myopia.

Liebmann: Again, these decisions are driven by longevity. Today, people generally have long life expectancies, so we are inclined to treat. We should bear in mind that the median time to progression in the LTG study was over 2,000 days.[26] For most people, LTG is a slowly progressive disease. I will carefully observe a patient with LTG who has a small notch and no field loss before deciding on a treatment.

Krupin: The oldest patient on whom I have performed filtering surgery was 95. Her other eye was blind. She is now 105 years old.

Weinreb: For treatment, I factor in the stage of the disease, the patient's life expectancy, and whether there is any evidence of progression. In some cases, the potential risks of treatment outweigh the potential benefits, particularly if the patient has a short life expectancy. Most patients will have progression of their glaucoma if you observe them long enough.

Liebmann: A fair number of my patients ask if they can avoid medical treatment. I present them with all

their options, but I do not think it is that simple. Most of us treat reflexively. We diagnose, and we treat. Considering the spectrum of disease, I think the best approach is to make the diagnosis first and then decide whether to treat.

Katz: Do you believe that everybody deteriorates at a steady rate?

Weinreb: A problem with some of the visual field testing analytical methods is the assumption made about linear progression. Glaucoma progresses linearly in some cases but not all. Certain patients will exhibit stability for some time and then suddenly deteriorate before stabilizing again.

Katz: I remember a patient with stable LTG whom I elected to observe and whose IOP remained stable. Then, at one visit, her IOP was the same, but she had rapidly developed a paracentral scotoma and was deeply upset.

Krupin: Is anyone using calcium channel blockers?

Katz: For blood pressure control. There are differences in LTG populations. In Japan, the typical LTG patient at initial diagnosis seems to be a male in his 30s. In the United States, patients with LTG generally present at an older age.

Weinreb: In my opinion, the glaucoma observed in Japanese patients—often characterized by repeated and frequent disc hemorrhages—is quite different from the open-angle glaucoma that we observe in patients who are not Japanese.

Krupin: There is no way to measure ocular blood flow anyway.

Liebmann: Does the disease progress faster in Japanese patients?

Weinreb: There are no data to support that, because no high-quality comparative studies have been completed. Some studies are in progress.

PERFUSION PRESSURE

Weinreb: What do we know about perfusion pressure (defined as the difference between blood pressure and IOP) and glaucoma?

> "Low perfusion pressure has been well associated with the onset of glaucoma and perhaps disease progression."
>
> –Jeffrey Liebmann, MD

Liebmann: Low perfusion pressure has been well associated with the onset of glaucoma and perhaps disease progression.[34-36]

Although I do not monitor blood pressure in my office, I ask patients what their blood pressure is and if they have hypertension or low blood pressure. I incorporate that information into the risk assessment. I also ask patients if they are on systemic hypertension medications.

Krupin: You are taking two variables, IOP and blood pressure, and you do not know how they are related.

Liebmann: Pressure in the eye and blood pressure in the body—I am assuming that low blood pressure is not good for glaucoma patients.

Krupin: I agree with you.

Liebmann: Again, it is an issue of improved patient longevity. We have a large group of older patients now whose blood pressure is managed very tightly. It is changing the type of disease that we see.

Krupin: Why haven't ophthalmologists traditionally measured blood pressure in the office?

Liebmann: Blood pressure assessment has not been part of the traditional eye examination. We should probably improve communication with our patients' internists to better understand the role of blood pressure in individual patient management.

Weinreb: Is anyone routinely checking patients' blood pressure?

Krupin: Outside of a study, no.

Weinreb: Data on low perfusion pressure that emerged from the EMGT[37] and the Barbados Eye Study[38]

are compelling. An argument can be made that we should assess and consider patients' perfusion pressure.

Katz: There are units for measuring blood pressure at home, and occasionally, I will ask patients to do so. In rare cases, the blood pressure dips nocturnally. Aside from instructing these individuals not to use their blood pressure medication before going to bed and maybe not prescribing a topical beta-blocker, what else can I really do? I am not going to recommend the use of salt tablets or tell the internist to change his or her target for blood pressure control. That is why I do not measure blood pressure in all patients.

FUTURE DIRECTIONS

Continuous IOP Monitoring

Weinreb: Among the tools that are needed for glaucoma management is a continuous measurement of 24-hour IOP. What impact will such a tool have?

Katz: Continuous IOP measurements will indicate when patients are not using their medication as directed and reveal the occurrence of spikes in pressure. This information will hasten practitioners' movement through their treatment paradigm. We will become more aggressive sooner.

Liebmann: The 24-hour continuous monitoring of IOP will be a huge research boon to our understanding of glaucoma and the relationship between peak IOP and disease progression.

Weinreb: No single technology today has the potential for being as disruptive to glaucoma management in the next 5 years as continuous IOP monitoring. Such technology would allow enhanced individualization of our diagnosis and treatment.

Liebmann: How will it affect diagnosis?

Weinreb: We all agree that glaucoma outcomes depend significantly on IOP, but we do not really understand how. Measuring IOP continuously for 24 hours will provide evidence for or against many of our current suppositions. For example, I categorize glaucoma medications into two broad categories: those that have a 24-hour effect and those that have a fairly limited effect, largely during the diurnal period. A prostaglandin analogue lowers the IOP during the day and night, whereas a beta-blocker only lowers pressure during the day.[39] By obtaining individualized information, we should be better able to determine how we can tailor our therapy. In some patients, we may want to target their nocturnal IOP. Two-thirds of the patients studied in our sleep laboratory have their highest pressure outside of office hours.[40] If there is a relationship with peak IOP, it is conceivable that we may treat some patients only at night, others only during the day, but most during the entire 24-hour day. Risk profiling could also change and be refined with 24-hour measurements of IOP.

> "No single technology today has the potential for being as disruptive to glaucoma management in the next 5 years as continuous IOP monitoring."
> –Robert N. Weinreb, MD

Liebmann: That information is valuable, but it does not change our need to determine the rate of progression.

Weinreb: Obtaining meaningful data on progression can take several years in the current US health care system. Some insurers only permit functional testing once or twice a year, and you need several visual fields to identify a trend. With some individuals, this process can take several years or more. In contrast, if you understand at the outset that someone is at high risk to develop or progress with glaucoma, you can either initiate treatment or make a good case for better allocation of health care resources through more frequent testing in a subset of patients.

Krupin: I would bet that the IOP data are going to be noisy. It will register when the patient rubs his or her eyes, sneezes, etc.

Katz: That might be relevant to the disease process.

Weinreb: Do you think lowering IOP is sufficient in all or most of our patients?

Krupin: No.

Liebmann: I disagree somewhat. We do not fully understand IOP and the effects of our interventions. Once we

have 24-hour pressure data, however, we may find that our pressure reduction was not nearly as good as we thought and that lowering the IOP further will prevent most people from going blind from glaucoma.

Krupin: You must have some surgical patients whose pressures are 7 or 8 mm Hg.

Weinreb: All of us have patients at any level of pressure whose glaucoma continues to progress despite pressure lowering. The reality is that we do not know whether we have not lowered their IOP sufficiently or whether they have a pressure-independent disease.

Katz: I think we all agree on that. I actually read this question two ways. One is the way we are discussing it. The other is, have we lowered pressure effectively in most of our patients in the United States? I would say absolutely not.

Drug Delivery

Weinreb: Any other promising developments for glaucoma?

Katz: I think that the implantable device being used to deliver steroids certainly has potential for glaucoma therapy.[41,42] Anything that is long lasting and will eliminate the patient as the middleman delivering a drug will be beneficial.

Weinreb: Delivering drugs directly to the retina or the optic nerve would be of interest.

Neuroprotection

Weinreb: Which agents will we use in the future? Some drugs have been described as exhibiting neuroprotective effects experimentally and are being evaluated clinically.

Krupin: I hope for neuroprotective agents that prove effective for the treatment of glaucoma. While IOP reduction will always be an important part of our therapy, drugs with a mechanism of action that does not depend upon lowering IOP would have a great impact for our patients.

Weinreb: What is the status of the Low-Pressure Glaucoma Treatment Study (LoGTS)?

Krupin: LoGTS enrolled subjects with LTG who were randomized to receive either brimonidine or timolol. Their diurnal pressure on no therapy had to be less than 21 mm Hg, and in fact, only two patients developed a pressure of 21 mm Hg during the entire 4-year study. While these medications have equal IOP-lowering properties, the alpha2 agonist brimonidine in laboratory studies has exhibited neuroprotective properties.[43]

> "Drugs with a mechanism of action that does not depend upon lowering IOP would have a great impact for our patients."
>
> –Theodore Krupin, MD

Weinreb: Why did you select brimonidine and timolol?

Krupin: There is experimental evidence in a variety of animal models of elevated IOP that brimonidine possesses a neuroprotective property.[44-46] Potential mechanisms for these neuroprotective effects include the upregulation of brain-derived neurotrophic factors in the retinal ganglion cells and the retina, the activation of cell-survival signaling pathways and antiapoptotic genes, and the modulation of N-methyl-D-aspartate receptor function.[47-50] Timolol was chosen because it lowers IOP similarly to brimonidine.

Weinreb: Is LoGTS the first clinical study of the neuroprotective effects of brimonidine in human patients with glaucoma?

Krupin: It is the first published study.

Katz: We have not had a new drug class since 1996. There are some exciting agents in development, but outside pressure lowering is neuroprotection. Unfortunately, memantine did not do well in studies. Brimonidine is exciting for the reasons that Dr. Krupin mentioned, but that has not yet translated into clinical application. The area of neuroprotection is an open field. Every journal I read discusses another potential cascade to target in neuroprotection. Immunomodulation has been talked about for years. Can you actually inoculate people against glaucoma? These are all fascinating ideas.

Weinreb: I would like to thank the faculty for their contributions to this program. ■

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CME QUESTIONS

1. Structural change can often precede functional change in glaucoma.
A. True
B. False

2. Changes in the management of glaucoma during the past 10 years include
A. the setting of a target IOP
B. the use of prostaglandin analogues as first-line therapy
C. the implementation of risk profiling in the assessment of patients
D. the measurement of central corneal thickness
E. All of the above
F. A, B, and D
G. A, C, and D

3. Is 24-hour IOP fluctuation an independent risk factor for glaucomatous progression?
A. The research firmly supports that it is.
B. The evidence for this assertion is insufficient.

4. In most cases, the progression of low-tension glaucoma is slow.
A. True
B. False

5. What is the current status of memantine?
A. It is approved for the treatment of Alzheimer's disease.
B. It is the current subject of a phase 3 trial for the prevention of glaucomatous progression.
C. Its use as glaucoma therapy is off label.
D. All of the above
E. A and C

6. Which of the following statements is true?
A. Ocular perfusion pressure is calculated by subtracting the IOP from the systolic blood pressure, as measured at the upper arm.
B. Low perfusion pressure is associated with the onset of glaucoma.
C. A and B
D. None of the above

7. Prostaglandin analogues
A. are currently the dominant first line of the pharmacologic treatment of glaucoma
B. have proven safety and efficacy
C. lower IOP during the day and night, whereas beta-blockers lower IOP only during the day
D. can cause cosmetic changes that may be of concern to patients
E. All of the above
F. A, B, and D

8. Research has demonstrated that patients' peak pressure may occur outside of office hours.
A. True
B. False

9. The potential benefits of continuous measurements of IOP over a 24-hour period include
A. the recording of any IOP spikes
B. the recording of a given patient's peak IOP and when it occurs
C. information on if and when a patient is not taking his or her IOP-lowering medication as prescribed
D. All of the above
E. A and B

10. In various animal models of elevated IOP, experimental evidence has indicated that brimonidine has neuroprotective properties, potentially via
A. the upregulation of brain-derived neurotrophic factors in the retinal ganglion cells and the retina
B. the activation of cell-survival signaling pathways and antiapoptopic genes
C. the modulation of N-methyl-D aspartate receptor function
D. All of the above
E. A and B

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