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REVIEW[®] of Ophthalmology

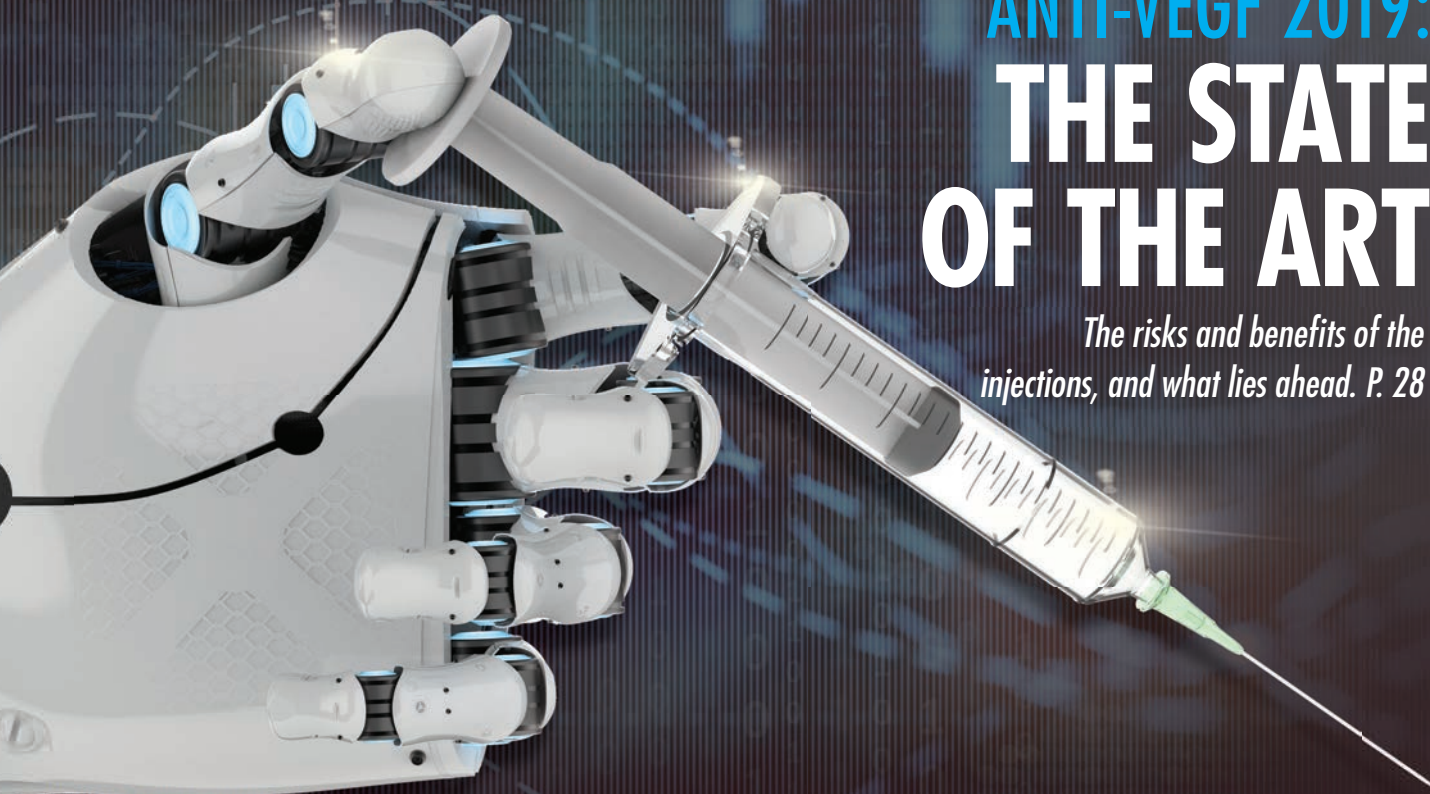
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ISSUE FOCUS: RETINA

ANTI-VEGF 2019: THE STATE OF THE ART

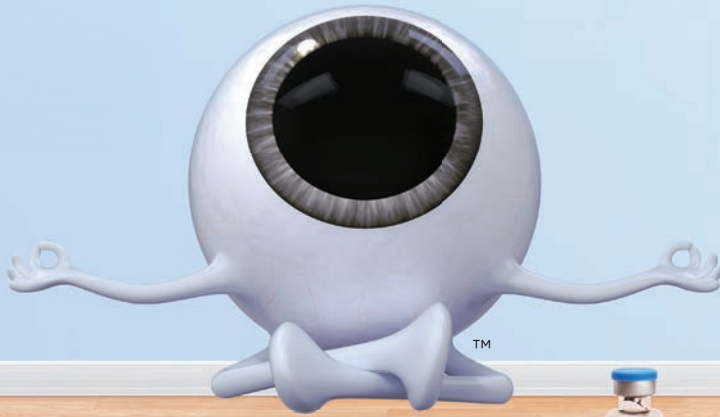
*The risks and benefits of the
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- How to Tackle Complicated Cataract Cases **P. 36**
- Expert Tips and Technology for Catching Narrow-angle Glaucoma **P. 40**

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Studies Delve into Retina And Glaucoma Drug Usage Patterns

Since the introduction of aflibercept, ranibizumab and bevacizumab, the frequency of anti-VEGF injection procedures has been increasing.

A recent study of anti-VEGF injections examined trends in distribution and usage of anti-VEGF agents, using data from the Centers for Medicare & Medicaid Services on Medicare Plan B beneficiaries from 2012 to 2015.¹ In this observational cohort study, the researchers evaluated over 2.5 million injections. Of these, 870,843 were with aflibercept; 697,412 were with ranibizumab; and 1,147,432 were with bevacizumab.

The study found that just 3 percent of ophthalmologists account for between 17 and 31 percent of the total number of injections. The researchers also saw an increase in aflibercept injections (a 69.4-percent increase) that coincided with decreases in ranibizumab (7.1 percent) and bevacizumab injections (17.1 percent).

Discussing the results, study co-author Shriji Patel, MD, Vanderbilt University School of Medicine, says, “Initially when we started this, we figured to some extent there was going to be a top-heavy distribution, just because there are practitioners that are very busy. They’re going to do a lot of injections and probably skew the trend upward.”

The variability in the cost of these therapies has garnered national attention. “The approximately 40-fold price differences between these anti-VEGF therapies, in the context of comparable proven efficacy for AMD, diabetic

macular edema and retinal vein occlusion alongside the growing economic burden of health-care costs, warrant an exploration of feasible, cost-effective stewardship,” the researchers say. Aflibercept costs \$1,850 for 2 mg and ranibizumab costs \$1,170 for 0.3 mg and \$1,950 for 0.5 mg. Both are FDA-approved. Bevacizumab, used off-label, costs \$60 for 1.25 mg, according to the researchers. The study authors note that all three agents are “equally effective with regard to visual gains” and have “relatively [equivalent] clinical outcomes and safety data.”

They speculate on what drives the choice of agent. “I think a lot of it is preference,” Dr. Patel says. “Many practitioners have a good experience with a certain type of medication: It works, it’s comfortable in their hand. It might be how they were trained. In medicine, what you’re used to and what you’re comfortable with drives a lot of practice patterns, and our suspicion is that plays a key role in some of the numbers.” In the paper, the authors also note that rebates can make a difference as well. “Rarely discussed manufacturer rebates in the form of volume discounts to certain practices further complicate decision making regarding choice of anti-VEGF agent. These financial motivations affecting [the] choice of anti-VEGF agent must not be overlooked,” the researchers write.

Ultimately, despite the high costs of these injections, Dr. Patel reminds us that “the medication cost pales in comparison to the cost of the vision saved.

Even though the Medicare costs are high, it’s much less costly than taking care of patients who have gone blind for years and years.”

In another study, a different group of researchers analyzed the usage of glaucoma medications.² They found that, despite the increase in glaucoma medication use recorded in several other developed countries, topical intraocular pressure-lowering medication use in the United States remained stable from 1999 to 2014.

Researchers conducted a series of eight surveys of U.S. residents every two years from 1999 to 2014, asking patients if they’d used or taken a prescribed medication in the past month. The team found no change in the number of Americans using topical IOP-lowering medications, with 1.4 percent of respondents on the medications between 1999 and 2000, as well as 2013 and 2014. However, there was a significant increase in the use of prostaglandin analogs and combination medications, and a decrease in the use of beta-blockers.

The authors say the steady level of drug use “is particularly remarkable, as Medicare part D was implemented in 2006 in the middle of this study period and increased the coverage for prescription drugs among Medicare beneficiaries.” **REVIEW**

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Medical Devices for the New Entrepreneur: A Primer on Digital Health and Artificial Intelligence

For some, the phrase artificial intelligence bring up visions of the rise of the machines in the movie series Terminator, computers taking over the world in the movie The Matrix, or countless other stories of computers developing consciousness and then evolving uncontrolled. The basic questions raised in all of these stories, however—including what happens when computers return an incorrect answer, what's an appropriate checkpoint, and how we should allow AI to influence human decision making—are paramount to the discussion of how we regulate the use of AI in medicine.

In this installment of our series, we'll provide some background and a few high-level developmental and regulatory insights regarding devices that incorporate AI, to provide guidance for any entrepreneur developing an AI software package.

FDA Guidance

In 2018, the first AI-based system in ophthalmology, the IDX-DR, designed for “the evaluation of ophthalmic images for diagnostic screening to identify retinal diseases or conditions” was granted clearance. To date, however, there's no specific FDA guidance document regarding AI. However, the FDA does reference other reports and standard software documentation guidance in its publications.

Let's first look at the general framework of digital health. The FDA Safety and Innovation Act (FDASIA) provides a strategic framework and recommendations regarding an appropriate risk-based method for defining the oversight of health information technology that “promotes innovation, protects patient safety, and avoids regulatory duplication.”¹ The framework consists of three health IT function categories:

- administrative (e.g., admissions, claims or billing);
- health management (e.g., data capture, medication management, order entry or electronic access to records); and
- medical device (e.g., disease-related claims, clinical decision support software or mobile medical apps).

The importance of these distinctions is in the proposed risk assessment and risk miti-

gation, with the FDA being more focused on the areas of Health IT that carry higher risk.

Evaluating Risk & Modality

AI uses techniques such as machine learning (ML) to produce intelligent behavior. A system incorporating ML has the capacity to learn, based on being trained to accomplish a specific task and tracking performance measures. Ultimately, it can design and train software algorithms to learn from data, and then act on what it's learned. AI/ML-based software, when used to treat, diagnose, cure, mitigate or prevent disease or other conditions, is considered a medical device by the FDA; it's referred to as “software as a medical device” or SaMD.²



The FDA references a risk system for SaMD that was created by the International Medical Device Regulators Forum (IMDRF), based on the risk to the patient. It asks questions such as: Is there a valid clinical association with the SaMD? Does the SaMD correctly process input data to generate output data? Does use of the SaMD output achieve the intended purpose in the target patient population, in the context of clinical care?

The IMDRF risk assessment also focuses on the activities needed to validate an SaMD. The assessment is based on two things: the state of the health-care situation or condition (i.e., critical, serious or non-serious); and the purpose of the information provided by the SaMD (to treat or diagnose, to drive clinical management, or to inform clinical management). Together, these two dimensions result in a risk score ranging from I to IV. (The IMDRF report doesn't provide specific recommendations regarding regulatory oversight, but focuses more on the level of

risk as it relates to independent review.)

In addition to being assessed on a spectrum of risk to patients, SaMD is also assessed regarding where it lies on a spectrum from “locked” to “continuous learning.” Locked programs give the same result each time the same data is input. A continuous learning program, however, changes its behavior over time based on learning, so for any given set of input data, the output may change as learning progresses. This ability to adapt over time is an advantage, but it raises the question: How should algorithm changes be reviewed at the FDA prior to marketing?

Meeting FDA Criteria

The FDA is now looking at a “total product lifecycle” (TPLC) approach for facilitating rapid cycles of product improvement. On April 29, 2019, the FDA published a discussion paper titled *Proposed Regulatory Framework for Modifications to Artificial Intelligence (AI/ML)-Based Software as a Medical Device (SaMD)* that describes this in more detail, as well as explaining the agency's thoughts on its potential approach for premarket review.³

This paper proposes that applications for approval include a predetermined change-control plan, with anticipated modifications and methodologies for implementing these changes in a controlled manner, as well as a process for ongoing evaluation and monitoring to ensure safety and quality. (Note: This proposed regulatory approach would apply to only those AI/ML-based SaMD that require premarket submission—not those that are exempt from requiring premarket review [i.e., Class I exempt and Class II exempt].)

The FDA's proposed process for a TPLC is based on two principles: 1) quality systems and good machine learning practices (GMLP) that demonstrate analytical and clinical validation; and 2) an initial premarket assurance of safety and effectiveness.

When submitting a system to the FDA, a predetermined change-control plan should be developed, including a list of the types of changes the manufacturer plans to make

(Continued on page 6)

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while the SaMD is in use (SaMD pre-specifications, or SPS). It should also specify methods for controlling the risks, described in a step-by-step algorithm-change protocol (ACP). The extent to which a pre-approval of SPS and ACP can be relied on for future changes depends on multiple factors:

- changes that involve performance (assuming that performance is improved or at least maintained over time);
- changes in intended use that increase the system's IMDRF risk level, as well as certain changes related to intended use with a specific patient population that evolve with new data;
- an approach for modification after the initial review with an established SPS and ACP. Modifications may lead to a submission of a new 510(k), or be documented for reference; and
- transparency and real-world performance monitoring of AI/ML-based SaMD. This includes transparency to the patients, users and doctors, as well as the FDA.

Another key element of the regulatory landscape the entrepreneur should continue to watch is special controls documents that may appear as the agency grants clearances in the 510(k) process under a *de novo* designation. These special controls documents may include important requirements for future products with similar indications for use.

Approaching the Agency

With this background in mind, and some of the many abbreviations defined, where should the budding entrepreneur with an idea that incorporates AI start? Let's walk through some of the steps when planning for the initial regulatory interactions.

Your pre-submission package should contain the following key elements:

- **Device description.** Be as specific as possible, including flow diagrams.
- **Indications for use.** Consider other examples, and address both the target patient population and user in your full statement. Some key words that you might consider as indications include telehealth (e.g., storing, managing, displaying and enhancing images); screening (diagnostic screening and detection); and diagnosis (identification of disease and/or severity, and/or providing treatment suggestions).

Be sure to describe the target user in your package. Possibilities might include health professionals such as primary care doctors

or endocrinologists; eye-care professionals (MD or OD); general technicians (those with limited, specialized training who work in health care); and/or trained ophthalmic technicians, such as those with specialized training in fundus imaging or fluorescein angiography.

- **Proposed performance data.** Most devices of this type are Class II. Be specific about inclusion/exclusion criteria in your protocol, planned statistical analysis and endpoints. For example, if you're looking for an indication of screening, you'll probably need an all-comers study, with the patient population not defined too narrowly.
- **Proposed device output.** Representative outputs are helpful, including any different options that are possible.

General Strategies for Success

To increase the likelihood of a successful submission:

- Start regulatory considerations early. As soon as you have a solid device description and understand who your target user is, plan for a presubmission.
- Given the complexity of this type of approval, you may need to plan on multiple interactions with FDA prior to collecting your performance data.
- Remember that study size modeling is critical.
- Beware of biases. Examine your datasets for potential biases to make sure your real-world experience will mimic your testing.


Mr. Chapin is senior vice president of Corporate Development at Ora, which offers device and drug consulting, as well as clinical R&D. Mr. Bouchard is vice president for medical devices at Ora. The authors welcome your comments or questions regarding product development. Send correspondence to mchapin@oraclinical.com or rbouchard@oraclinical.com, or visit www.oraclinical.com

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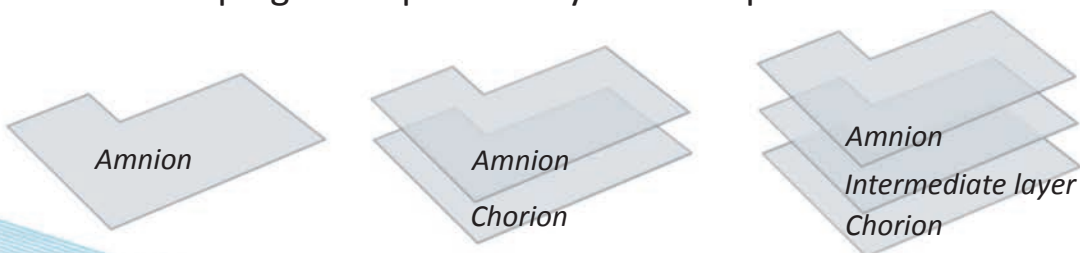


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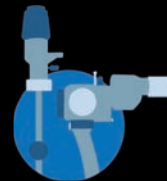
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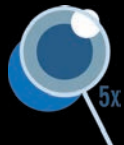
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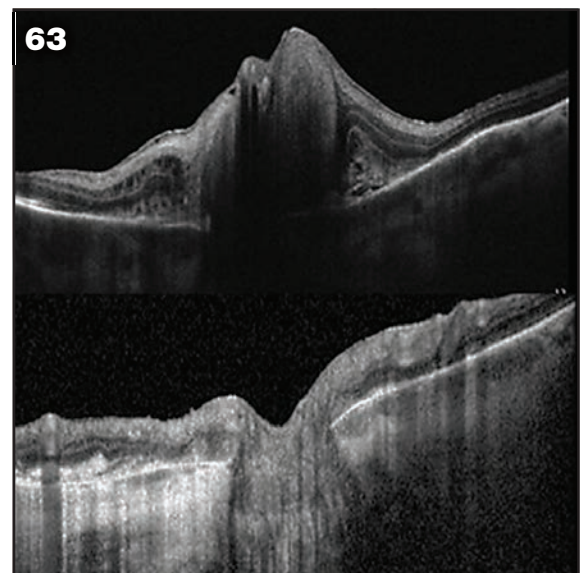
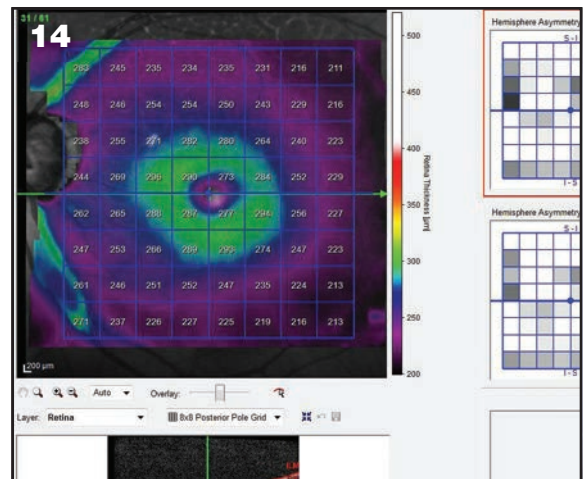
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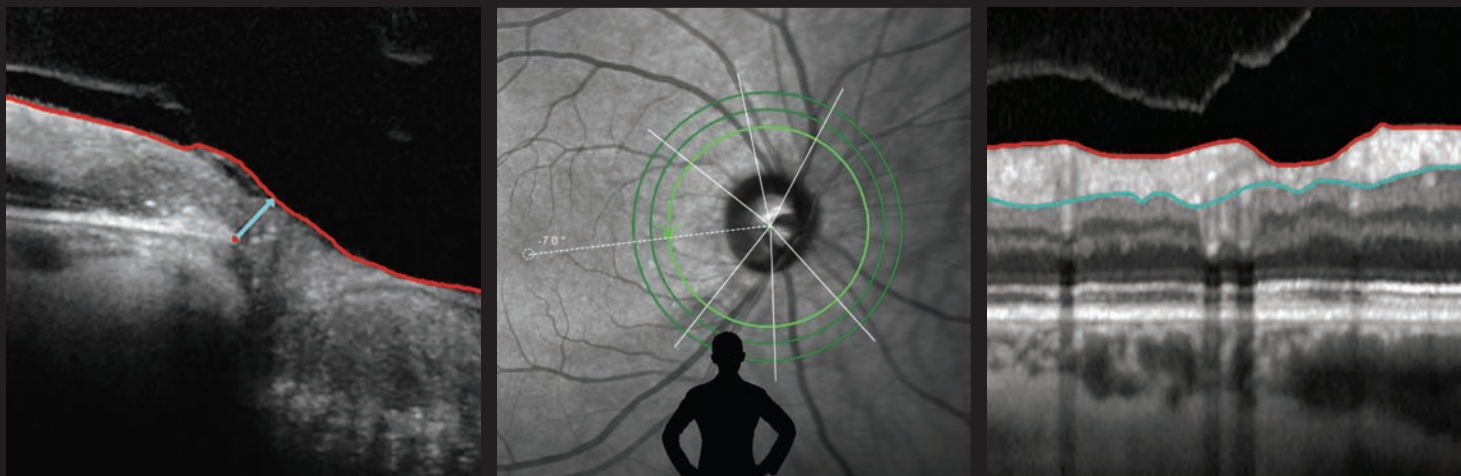
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OCT and Advanced Glaucoma: It Can Work

The popular idea that OCT isn't good for monitoring progression in advanced glaucoma may be erroneous.

Christopher Kent, Senior Editor

In recent years, along with visual fields, optical coherence tomography has become a mainstay for most practices that follow glaucoma patients. However, many ophthalmologists have come to believe that OCT is less useful for following progression when the disease is advanced. Instead, they shift their attention primarily to visual fields when patients reach that stage.

Recent studies are calling that conclusion about the usefulness of OCT into question, however, noting in particular that the fall-off in progression-monitoring capability is generally only true if you're exclusively monitoring the circumpapillary retinal nerve fiber layer. Once you broaden your scanning to include the macular region, OCT may be very useful, even in advanced disease. Furthermore, even if you only monitor the optic nerve, some surgeons are questioning whether the drop-off in measurement capability is clinically significant for more than a few patients.

Here, surgeons with expertise in this area share their experience and offer advice on how to best use OCT when monitoring patients who have

advanced glaucomatous disease.

Measuring the RNFL

Alexander T. Nguyen, MD, in private practice in Waterbury, Connecticut, and a clinical instructor at the Yale University School of Medicine, notes that the idea that OCT isn't helpful for monitoring advanced glaucoma is a commonly held belief.

"I think this idea arose from a couple of studies, especially some spearheaded by the San Diego group and Felipe Medeiros, MD," he says. "He and his group studied the relationship between visual field function, estimated ganglion cell counts and average retinal nerve fiber layer thickness. They noted that early in the disease OCT is very good at detecting changes that occur, while visual fields are not as helpful. From this they constructed what glaucoma specialists recognize as the expected structure-function curve. This model predicts that in advanced disease, the relationship reverses. Visual field testing becomes very sensitive to detecting changes in retinal ganglion cell loss, while change becomes more difficult

to detect with OCT."

Dr. Nguyen acknowledges that there's some truth to this, explaining that the increasing measurement difficulty clinicians may encounter using OCT to monitor advanced disease can be understood in mathematical terms. "Imagine you have a million retinal ganglion cells," he says. "If you lose 10 percent early on, that's 100,000 ganglion cells lost. That's going to look like a big change on OCT, while a visual field might not pick up any functional loss. But in advanced disease, you might only have 100,000 retinal ganglion cells left. Losing 10 percent would be a loss of only 10,000 cells—a small loss that OCT might not be able to pick up. On the other hand, functional loss at this point might be more readily detected by visual field assessment."

Sanjay Asrani, MD, professor of ophthalmology at Duke University School of Medicine, director of the Duke Eye Center of Cary and head of the Duke Glaucoma OCT Reading Center in Durham, North Carolina, agrees that the problem isn't a lack of change; it's the amount of change. "The problem is that the scale

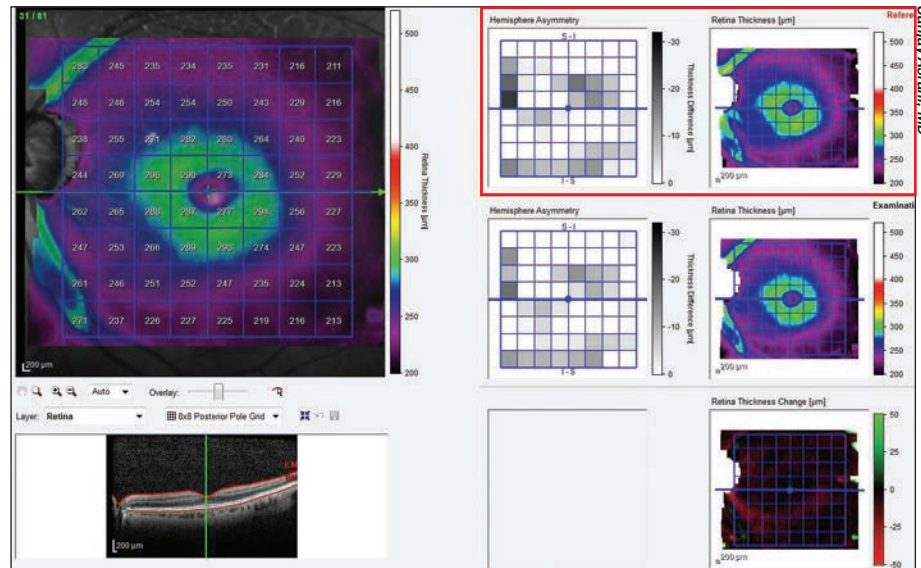
at which it's happening at that point in the disease isn't properly represented on the OCT displays of most manufacturers," he says. "That makes it extremely difficult for us to identify and measure the change once the nerve fiber layer reaches the floor effect level, which is about 35 to 40 μm ."

Dr. Nguyen points out, however, that it's easy to overestimate the difficulty of following progression in advanced disease using OCT—even if you're only monitoring the retinal nerve fiber layer. "Yes, OCT can become less sensitive at detecting changes as we approach the measurement floor for these instruments, but most patients with advanced disease are not yet at that level," he says. "Most of our patients haven't reached the point of having no-light-perception vision, where their nerve fiber layer is on its last fibers. That means that OCT can still detect changes in the majority of advanced patients."

"It also matters whether you're looking at specific parts of the retinal nerve fiber layer," he continues. "For example, Jonathan Myers, MD, at Wills Eye Hospital, presented a paper at the 2018 meeting of the American Glaucoma Society that showed that if you look at specific sectors of the circumpapillary retinal nerve fiber layer, you'll find that some of them are still preserved, even in advanced disease. In other words, you can still detect changes in certain sectors. And that's just one example. The point is, not everyone with advanced disease has reached the measurement floor, so clinicians shouldn't arbitrarily abandon OCT because a patient's disease is advanced."

Monitoring the Macula

It's also become clear that changes



An example of using OCT to monitor progression at the macula in advanced glaucoma. The top right hand scan (in the red rectangle) is the baseline scan. Scan data from a subsequent visit (middle right) is subtracted from it, leaving the bottom right image, which shows the difference between the two. The red areas show the loss of tissue between the two visits. The arcuate shape of the change is a classic sign of glaucomatous damage.

in the macula caused by glaucoma progression are different from the changes around the optic nerve, opening up another avenue for keeping OCT in the game. "Doctors have been primarily looking at the nerve fiber layer," Dr. Asrani points out. "When that reaches the floor effect, it's extremely difficult to identify small changes anymore. But at that point, the *macular* thickness and/or ganglion cell thickness can assist in monitoring even advanced glaucoma. In other words, if you know where to look, you can still use OCT to follow patients with advanced glaucoma."

Dr. Asrani explains that in advanced glaucoma, the macular region still has residual thickness. "That's partly because in normal eyes, the ganglion cells are stacked up about six layers deep at the macula," he says. "As a result, the volume occupied by the ganglion cell layer and nerve fiber layer is considerable at that location. That's what makes it possible to continue to observe changes there."

Dr. Nguyen notes that monitoring

the macula has become a hot topic. "It's been hypothesized that macular parameters in glaucoma progress more slowly," he says. "The idea is that glaucoma patients may reach the measurement floor in the macular region later than in retinal nerve fiber layer, if change is occurring at a slower rate."

"Several papers have found evidence that macular OCT parameters may be better than the circumpapillary retinal nerve fiber layer for detecting changes later in the disease," he continues. "For example, Joel Schuman, MD, recently published a paper that suggested that for patients with a retinal nerve fiber layer thickness less than 60 μm , he was still able to detect macular changes in his patients.¹ Our group conducted a study that looked at both macular parameters and nerve fiber layer parameters, and we didn't find this to be the case.² However, we used a different definition of severe disease, and it's possible that our study was too small; we may not have had enough patients for the

data to confirm this finding.”

Dr. Asrani points out that it’s possible for the macula to reach a floor effect as well. “That can happen when the patient has a very small central island,” he says. “At that point the macula becomes extremely thin and you can’t follow progression beyond that point. Then, we’re forced to rely on a 10-2 visual field or subjective interpretation by the patient.”

Regarding the patient’s subjective analysis, Dr. Asrani explains that prior to this point, a patient won’t notice changes in vision caused by the disease unless he’s extremely vigilant. “In glaucoma, loss of vision is simply absence of vision,” he points out. “It’s not like a black area appears in your visual field. Even if patients have lost half of their peripheral vision, they typically can’t discern how much change is taking place until the disease reaches end stage. At that point in the disease, the patient can tell you whether or not he’s getting worse because there’s such a small amount of vision left.”

Strategies for Success


Surgeons offer these tips to help make the most of OCT monitoring of glaucoma patients:

- **Monitor both the circumpapillary retinal nerve fiber layer data and the macular parameters, even in early disease.** Dr. Nguyen encourages doctors to do this. “The information is complementary,” he says. “Some studies have been conducted to try to figure out if one is better for monitoring glaucoma progression, and there is some data suggesting that macular parameters might be a better predictor of visual field loss. Nevertheless, I think we should just follow them both. They both provide useful information.”

Dr. Asrani agrees. “When managing a glaucoma patient you should always monitor the macular thickness as well

as the nerve fiber layer thickness,” he says. “If the change you see in the nerve fiber layer thickness is also present in the macula, that will give you more confidence that the changes in the nerve fiber layer are indeed real. So, you should do this from day one.

“Almost all machines have the capability of analyzing both the macula and retinal nerve fiber layer,” he adds. “It doesn’t add much testing time—only a few more seconds.”


“It’s possible to detect changes in severe disease using OCT, but we shouldn’t be falsely reassured if we don’t find evidence of change using OCT. It doesn’t mean that no loss is happening.”
 — A.T. Nguyen, MD

- **Establish a baseline; then look for macular changes in the shape of an arc.** Dr. Asrani explains that the parameter you should monitor depends on the software of the OCT machine you use. “The software might give you the ganglion cell layer thickness or the thickness of the ganglion cell complex, which includes the nerve fiber layer thickness,” he says. “Some machines may give you the full thickness of the retina. Whichever hardware and software you’re using, establish a baseline and then see if change is happening in the macula.

“The macular changes are classically in an arc-like shape,” he notes. “That’s the typical hallmark of glaucoma. If it’s in the same region as where

the nerve fiber layer has changed, it confirms that the change was caused by glaucoma.”

- **Be alert for false positives caused by other macular problems.** Dr. Nguyen points out that macular damage can also be caused by comorbid conditions, leading clinicians to erroneously believe that a patient’s glaucoma has gotten worse.

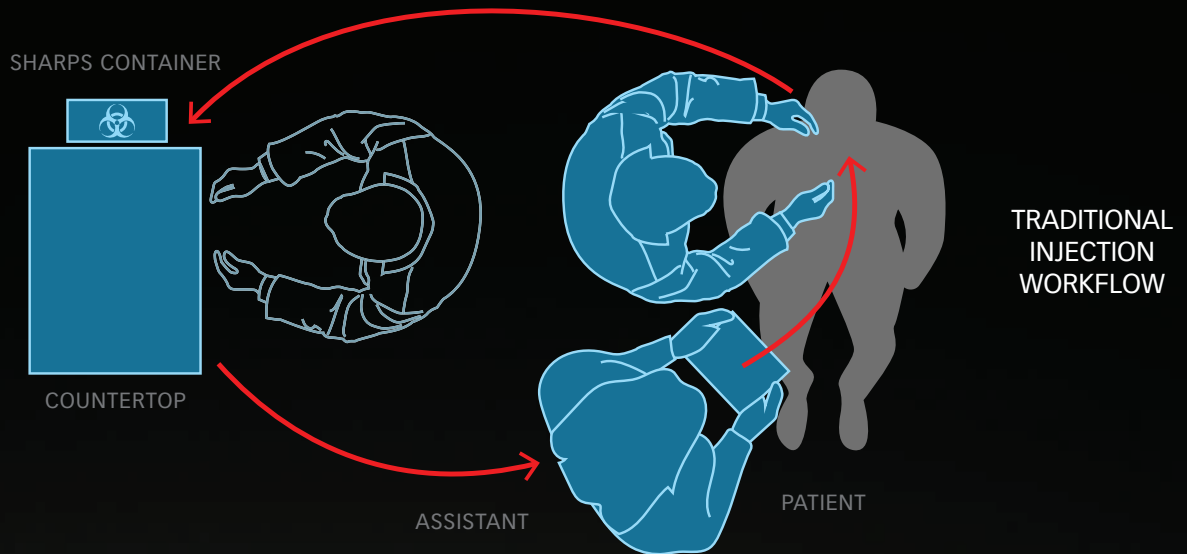
“When monitoring the macula for glaucoma, I’ve found that we have a lot of false positive readings because of the high incidence of other ocular conditions,” he says. “We’ve had quite a few patients with both glaucoma and macular degeneration or cystoid macular edema, whose macular parameters made them look like their glaucoma was getting worse. In reality, another problem such as macular degeneration was driving the change. So you have to remember that any macular damage you find could have been caused by another ocular disease.”

Dr. Nguyen says he hasn’t seen many papers addressing this potential source of confusion. “The problem is, when we do clinical studies, we want very clean data,” he explains. “For example, when we conducted our recent study, we excluded patients with macular degeneration, despite the fact that in our clinics many of our glaucoma patients have coincident macular pathology. There’s a paucity of data about how macular disease might result in false positives when monitoring the macula for glaucoma progression.

“I think this is a valid concern—especially if you’re seeing 100 patients a day and depending on an OCT algorithm to tell you who’s worsening,” he adds. “When you’re that busy, you may not have the time to review all the data yourself. You may falsely conclude that a patient’s glaucoma is getting worse, when the reality is that it’s

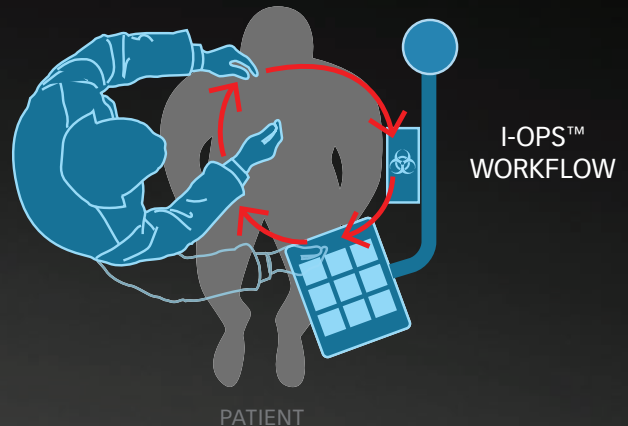
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Astigmatism: Find a Happy Medium

A surgeon answers the question: How much astigmatism do surgeons have to correct?

Christine Leonard, Associate Editor

Cataract surgeons will often do whatever it takes to eliminate patients' astigmatism and bring them as close to emmetropia as possible. They sometimes run into limits in terms of how much astigmatism they can effectively correct, however—though they say that patients can sometimes tolerate low levels of cylinder without much complaint. Following is some expert advice for managing astigmatism in your next case.

The Impact of Astigmatism

Mitchell P. Weikert, MD, MS, associate professor at the Cullen Eye Institute, Baylor College of Medicine, says the impact of astigmatism depends on multiple factors, such as visual task, interaction with other aberrations, pupil size, accommodative state, neuroadaptation and subjective blur threshold. "In all cases," he says, "it leads to meridional variation in retinal image blur and a reduction in distance, near, stereo and contrast visual acuity."

Dr. Weikert cites a 2013 study on the relation between uncorrected astigmatism and visual acuity in pseudophakia that shows that as hyperopic and myopic astigmatism increases, distance

visual acuity decreases, independent of the axis.¹ "But one interesting finding," Dr. Weikert notes, is that "as higher-order aberrations increase, the image quality improves for near objects." Likewise, a 2014 study on image quality analysis of pseudophakic eyes with uncorrected astigmatism found that distance visual acuity decreases with higher order aberrations, while near image quality increases.² Dr. Weikert explains this, saying, "when you have myopic astigmatism, as objects come closer, the conoid of Sturm gets pushed closer to the retina.

"The astigmatism threshold at which the average person notices a decrease in vision is about 0.25 D," says Dr. Weikert. "Studies have shown that in young phakic patients, visual acuity decreases as astigmatism increases. At around 0.37 D people can still see 20/20, but at 0.75 D, this drops to 20/25 and at 1.5 D to 20/40."

Dr. Weikert notes that pupil size also makes a difference when it comes to astigmatism levels. "The smaller the pupil, the better the acuity—it's intuitive," he says. "As pupil size gets smaller, you get more of a pinhole effect, so the effect of the astigmatism

decreases. Astigmatism effects are not as great for smaller pupils."

Treating the Astigmatism

Like many surgeons, Dr. Weikert prefers a toric IOL to corneal relaxing incisions for correcting astigmatism.

"The Barrett formula is good across the board," he says, "but formula choice these days is dictated by length of the eye rather than toric versus non-toric." Dr. Weikert says he doesn't hang his hat on just one formula. He likes to have at least three measurements to compare. "My go-to formula is the Barrett, along with the Holladay 1 and the Hill RBF."

In addition to the three formulas, Dr. Weikert employs biometers like the IOLMaster 700 or LenSTAR, topography and tomography to measure the front and back of the cornea, and Pentacam to measure posterior corneal astigmatism. "It's nice when you see agreement among multiple measurements of magnitude and axis of astigmatism," he says.

Dr. Weikert prefers to take measurements of both the front and back of the cornea. "Most formulas just measure the anterior surface to predict the back of the cornea," he notes. "Now though,

people are trying to measure the front and the back to get accurate measures of true corneal astigmatism.” In a well-known 2012 study on the contribution of posterior corneal astigmatism to total corneal astigmatism, in which he participated, he and his co-authors found that taking posterior corneal measurements instead of relying only on anterior corneal measurements can help avoid “overcorrection in eyes that have with-the-rule astigmatism and undercorrection in eyes that have against-the-rule astigmatism”³ when selecting IOLs.

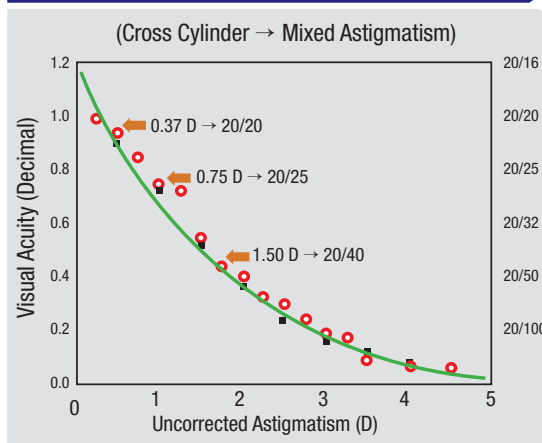
Dr. Weikert says measuring many patients over the years has taught him a lot about the best way to approach astigmatism correction. “Since individual measurement on a person-to-person basis doesn’t seem to explain the whole picture, most surgeons use population norms to try to figure out how much astigmatism to target in patients,” he says. “You need to be meticulous in your preop planning and measurements. You want to make sure you have good-quality measurements.”

If toric IOLs aren’t within a patient’s means, Dr. Weikert’s second choice for correcting astigmatism is incisions, which are effective for low amounts of astigmatism. “You don’t have as great a range of correction as IOLs and can’t treat as high levels of astigmatism, and you have more variability of what you achieve versus what you can target, however,” he explains. “If a patient presents with lower levels of astigmatism but has variable measurements, I might defer astigmatism correction until after cataract surgery, especially if the patient doesn’t have enough astigmatism for a toric IOL.”

Accounting for SIA

Dr. Weikert says surgically induced astigmatism may not be that big of a

Distance Visual Acuity vs. Astigmatism



Graph quantifying the visual acuity decrease as the level of astigmatism increases in young phakic patients.⁴

factor in the final outcome.

“It may be helpful to look at your own SIA data, if you have time,” he says, “[but] the data for SIA is very noisy. You have to compare measurements preop and postop, and the data tends to be all over the map. Measuring only the cornea is noisy, for example. You can have variations up to 0.5 D of astigmatism in the same person from week to week.”

Surgically induced astigmatism accounts for only very small changes, Dr. Weikert avers. “The overall spherical power of the lens and the overall refractive power of the cornea don’t change too much,” he says. “Maybe a tiny bit in a hyperopic direction, but not much.”

Some toric calculators, such as the Barrett calculator, factor in SIA. Dr. Weikert also finds the Baylor nomogram useful for determining the level of astigmatism your surgery might produce. When gauging this, you have to calculate the SIA yourself. “It’s small,” he says.

Acceptable Astigmatism

Low levels of astigmatism still warrant correctional surgery, but at a certain point, changes in visual

acuity become less significant, Dr. Weikert says. “Looking solely at image quality, when you remove higher order aberrations, image quality improves as astigmatism decreases,” he notes. “Going from 0.5 D to 0.3 D will offer some improvement in acuity, but it doesn’t make a huge difference. From 0 to 0.5 D astigmatism, image quality doesn’t really change much.”

In the case of high-contrast vision, Dr. Weikert says that acuity improves slightly with decreasing levels of astigmatism. But “once you get below 0.3 D, it doesn’t matter—there’s no improvement. And low-contrast acuity is pretty much independent of astigmatism.”

Dr. Weikert points out that there are some cases where a small amount of astigmatism is desirable. “You want to shoot for a little residual with-the-rule astigmatism,” he advises. “As people age, they shift from with-the-rule to against-the-rule astigmatism by about 0.38 D over a decade.” Dr. Weikert recommends leaving about 0.25 D of WTR astigmatism as a cushion for this transition.

When further correction won’t significantly improve visual acuity, it’s time to stop. Ultimately, Dr. Weikert says surgeons should aim for no more than 0.5 D of postop astigmatism. “Or 0.3 D or less if you really want to get it down,” he adds. [REVIEW](#)

Dr. Weikert is a consultant to Alcon Laboratories and Ziemer Ophthalmic Systems.

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Managing Noninfectious Posterior Uveitis

Sean McKinney, Senior Editor

New approaches and strategies for treating noninfectious uveitis involving the posterior segment.

Only 10 in 100,000 adults and three in 100,000 children are diagnosed with noninfectious posterior uveitis.¹ But interest in this often intractable, sight-threatening condition has never been greater. With FDA approval of two new therapeutic agents—the biologic adalimumab (Humira, AbbVie) in June of 2016 and a 0.18-mg fluocinolone acetonide intravitreal insert (Yutiq, EyePoint Pharmaceuticals) in October of 2018—specialists and general ophthalmologists are evaluating new data and continuing to explore best approaches to treatment.

In this report, experts offer guidance on advances in therapies, complications and optimized inflammation control, which is critical to saving vision and improving quality of life.² Cost, insurance coverage, efficacy and patient preferences need to be considered for this critical condition, which accounts for 5 percent to 20 percent of legal blindness.³

Initial Presentation

Recall that noninfectious posterior uveitis, associated with complex comorbidities, typically results from a T-cell-mediated autoimmune process that involves proinflammatory cytokines.⁴ The condition encom-

passes diverse and often difficult-to-control inflammatory disorders, including spondyloarthropathies, Behçet's disease, sarcoidosis, juvenile chronic arthritis, Vogt-Koyanagi-Harada syndrome, immune recovery syndrome, uveitis with tubulointerstitial disease and others.⁵ When you see a patient with suspected posterior uveitis, experts urge you to combine a complete medical and social history with a comprehensive dilated eye examination and, as needed, ancillary studies, including optical coherence tomography and fluorescein angiography, to help confirm and classify the primary site of inflammation. Conduct laboratory workups of possible systemic inflammatory, infectious and malignant etiologies.

Akshay Thomas, MD, MS, a retina and uveitis specialist at Tennessee Retina, also applies the following approach to therapy. His advice:

1. Rule out any infectious cause.
2. Rule out syphilis, via laboratory evaluation.
3. Test for tuberculosis and Lyme disease in patients with risk factors for exposure.
4. Rule out a herpetic cause or toxoplasma in patients with retinitis.
5. Withhold heavy oral corticosteroids—certainly injection—until you've ruled out an infectious etiol-

ogy of the inflammation.

6. Consider topical steroids, pending laboratory results.

If your patient has infectious uveitis, appropriate antimicrobial, antiviral or antiparasitic therapy needs to be initiated. For infectious retinitis, oral steroids may be added once the retinitis appears to be consolidating. (Dr. Thomas says he almost never uses local steroid injections in a patient with infectious uveitis.)

After Infection's Ruled Out

After confirming a diagnosis of noninfectious posterior uveitis, Dr. Thomas says that the degree of inflammation informs treatment.

"If the predominant sites of inflammation are in the anterior chamber—with or without cystoid macular edema—use of topical steroids, either prednisolone acetate or difluprednate acetate emulsion (Durezol), may be appropriate initially," he notes.⁶ "For significant vitritis, retinal vasculitis, significant CME, choroiditis or chorioretinitis, topical therapy alone may be insufficient. In such eyes with either unilateral disease or very asymmetric disease, local steroid injections, implants and inserts can be quite effective.⁷ This therapy provides a rapid response and avoids the side effects of systemic medications. In eyes with significant bilateral disease, I usually enlist systemic therapy, if the patient can tolerate it. This typically involves a course of oral steroids with a taper; if inflammation flares during the taper, the patient may need to be started on immunomodulatory therapy. The only such agent FDA-approved for non-infectious uveitis is Humira. However, many other systemic agents can be employed."

If a patient with chronic bilateral disease can't tolerate systemic therapy, a long-acting local steroid implant (0.59 mg fluocinolone acetonide im-



Figure 1. In noninfectious uveitis, physicians usually quell anterior inflammation first before moving on to a therapy for the posterior segment.

plant, Retisert, Bausch + Lomb) or insert (Yutiq) may be needed.

"If you have a uveitis patient whom you treat episodically, only when he or she flares, you need to know when to switch to long-term inflammatory control," he says. "With each flare, the patient's visual potential may decline. If your approach to a chronic recurrent panuveitis is reactive—only treating during flares—your patient may experience a saw-tooth pattern of visual decline, including progressive retinal/optic atrophy, a compromised angle with secondary glaucoma or ultimately hypotony from fibrosis along the ciliary processes."

Finding Your Way

The initial treatment path isn't always clear. "Determining how traditional local treatments should fit into your armamentarium is a challenge because comparative trial data don't exist," says uveitis specialist Thomas A. Albini, MD, a professor of clinical ophthalmology who specializes in medical retina and vitreoretinal surgery at Bascom Palmer Eye Institute

at the University of Miami. "We don't have head-to-head comparisons of these treatments. Choosing the right therapy often depends on anecdotal experience—and the related experiences from other practitioners."

Corticosteroid drops provide limited efficacy in the posterior segment. "Some data support using Durezol, which can provide limited efficacy, helping control CME. Otherwise, topicals have limited effect deeper than anterior uveitis."⁶

Dr. Albini notes that, in the recent POINT study,⁷ Ozurdex and intravitreal triamcinolone demonstrated a greater and faster therapeutic effect on uveitic macular edema than periocular Kenalog. No significant differences between Ozurdex and intravitreal triamcinolone were found.

Despite these findings, Sam Dahr, MD, clinical professor at the Dean McGee Eye Institute and University of Oklahoma College of Medicine in Oklahoma City, utilizes both Ozurdex and intravitreal triamcinolone. "Intravitreal steroids can rapidly quiet a 'hot eye' and buy time for steroid-sparing therapy to take effect," he

says. “It’s often effective for anatomic and angiographic macular edema, as well as angiographic vasculitis. If a prospective cataract surgery patient with uveitis can’t take perioperative oral prednisone, intravitreal steroids one to two weeks before surgery is an effective perioperative regimen.”

When monitoring patients who have received the Ozurdex implant, Dr. Dahr finds IOP predictably peaks “in the mid 20s” at 45 to 60 days. “I often see

a cumulative and additive IOP effect after repeated sub-Tenon’s injections or intravitreal triamcinolone, but less often when using sequential Ozurdex,” he says. “I try to minimize sequential local steroid injections by utilizing steroid-sparing therapy, but sometimes I give a patient three to four injections in the first 12 to 18 months of fine-tuning a steroid-sparing regimen.”

Dr. Albini acknowledges that Ozurdex may have a better side-effect profile than triamcinolone acetonide because of a gentler effect on IOP. It also lasts up to six months, compared to triamcinolone acetonide’s three-month duration of action.

“The dexamethasone in Ozurdex doesn’t disperse and block vision, or spread into the anterior segment and cause a pseudo-hypopyon, blocking the trabecular meshwork, as triamcinolone does, increasing IOP,” he explains. Despite Ozurdex’s advantages, however, Dr. Albini remains mindful of the POINT study results, which showed a small statistically insignificant difference in outcome when comparing Ozurdex to two consecutive triamcinolone acetonide treatments. “It’s difficult to de-

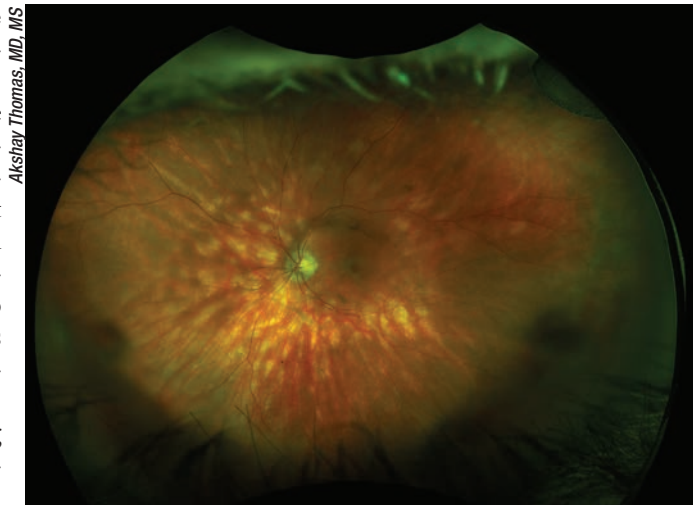


Figure 2. Conditions such as birdshot chorioretinopathy will likely need long-term therapy with either a long-acting steroid implant or an insert of a steroid-sparing systemic therapy.

cide between these treatments,” he admits. “Ozurdex has subtle advantages, but it’s also eight times more expensive than intravitreal triamcinolone, an important consideration if Ozurdex is not fully reimbursed by insurance. Also, we employ intravitreals for more difficult posterior disease involving macular edema or vascular leakage. Intravitreals are much better than systemic medications in these cases, in my view. The problem with the intravitreals is their limited course and ocular side effects, such as glaucoma and cataracts.”

Although the POINT study found intravitreal treatments reduced uveitis macular edema more effectively than periocular Kenalog, Dr. Albini says he continues to rely on Kenalog as well. “I don’t believe there is clear evidence that periocular Kenalog should be removed from our armamentarium, or that the intravitreal injections always provide greater effects. However, I do think we need to consider the risk of endophthalmitis or patient discomfort associated with an Ozurdex implant injection. In general, however, treatment choices also vary from patient to patient and among physicians. A lot of what we

do is based on personal experiences and preferences.”

Sustained-release Fluocinolone

Retisert, the long-acting intravitreal implant, and the recently approved Yutiq provide compelling alternative treatments for appropriate patients. Here’s a look at their benefits and risks.

• **Retisert.** “The two-year data from the Multicenter Uveitis Steroid Treatment (MUST) trial favored the Retisert im-

plant over traditional systemic immunomodulatory therapy for the management of non-infectious intermediate, posterior and panuveitis,” says Dr. Thomas.⁸ “The five-year MUST data showed similar outcomes between the groups. However, the seven-year MUST data favored systemic, steroid-sparing therapy. Remember that the MUST study was only designed to be a two-year study and that the five-year and seven-year data were only observational. A Retisert implant is only expected to provide inflammatory control for up to three years, after which a Retisert exchange may be needed.”⁹

Dr. Albini says a fluocinolone acetonide implant is very effective for bad cases “if you want to avoid immunosuppressant therapy, such as for a pregnant patient, who would not be a candidate for immunosuppression therapy.” He adds: “Retisert also seems to be a very viable alternative to systemic therapy. It works well over the life of the implant.”

In terms of uveitis recurrences, in the clinical trial data submitted for FDA approval, in two randomized, double-masked, multicenter controlled clinical trials, 227 patients with



YUTIQ™
(fluocinolone acetonide
intravitreal implant) 0.18 mg



Discover continuous calm in uveitis

YUTIQ™ (fluocinolone acetonide intravitreal implant) 0.18 mg

Designed to deliver a sustained release of fluocinolone for up to 36 months for patients with chronic noninfectious uveitis affecting the posterior segment of the eye¹

- **Proven to reduce uveitis recurrence at 6 and 12 months^{1*}**
[At 6 months—18% for YUTIQ and 79% for sham for study 1 and 22% for YUTIQ and 54% for sham for study 2 ($P < .01$). At 12 months—28% for YUTIQ and 86% for sham for study 1 and 33% for YUTIQ and 60% for sham for study 2.]
- **Extended median time to first recurrence of uveitis^{1,2}**
[At 12 months—NE[†] for YUTIQ/92 days for sham in study 1; NE for YUTIQ/187 days for sham in study 2.]
- **Mean intraocular pressure (IOP) increase was comparable to sham^{1,2}**
Study was not sized to detect statistically significant differences in mean IOP.

For more
information, visit
YUTIQ.com

***Study design:** The efficacy of YUTIQ was assessed in 2 randomized, multicenter, sham-controlled, double-masked, Phase 3 studies in adult patients (N=282) with noninfectious uveitis affecting the posterior segment of the eye. The primary endpoint in both studies was the proportion of patients who experienced recurrence of uveitis in the study eye within 6 months of follow-up; recurrence was also assessed at 12 months. Recurrence was defined as either deterioration in visual acuity, vitreous haze attributable to noninfectious uveitis, or the need for rescue medications.

[†]NE=non-evaluable due to the low number of recurrences in the YUTIQ group.

INDICATIONS AND USAGE

YUTIQ™ (fluocinolone acetonide intravitreal implant) 0.18 mg is indicated for the treatment of chronic noninfectious uveitis affecting the posterior segment of the eye.

IMPORTANT SAFETY INFORMATION

Contraindications

Ocular or Periocular Infections: YUTIQ is contraindicated in patients with active or suspected ocular or periocular infections including most viral disease of the cornea and conjunctiva including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections and fungal diseases.

Hypersensitivity: YUTIQ is contraindicated in patients with known hypersensitivity to any components of this product.

Warnings and Precautions

Intravitreal Injection-related Effects: Intravitreal injections, including those with YUTIQ, have been associated with endophthalmitis, eye inflammation, increased or decreased intraocular pressure, and choroidal or retinal detachments. Hypotony has been observed within 24 hours of injection and has resolved within 2 weeks. Patients should be monitored following the intravitreal injection.

Steroid-related Effects: Use of corticosteroids including YUTIQ may produce posterior subcapsular cataracts, increased intraocular pressure and glaucoma. Use of corticosteroids may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. Corticosteroids are not recommended to be used in patients with a history of ocular herpes simplex because of the potential for reactivation of the viral infection.

Risk of Implant Migration: Patients in whom the posterior capsule of the lens is absent or has a tear are at risk of implant migration into the anterior chamber.

Adverse Reactions

In controlled studies, the most common adverse reactions reported were cataract development and increases in intraocular pressure.

References: 1. YUTIQ™ (fluocinolone acetonide intravitreal implant) 0.18 mg full U.S. Prescribing Information. EyePoint Pharmaceuticals, Inc. October 2018. 2. Data on file.

Please see next page for Brief Summary of full Prescribing Information.



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5/2019
US-YUT-1900057

YUTIQ™ (fluocinolone acetonide intravitreal implant) 0.18 mg, for intravitreal injection
Initial U.S. Approval: 1963

BRIEF SUMMARY: Please see package insert for full prescribing information.

1. INDICATIONS AND USAGE. YUTIQ™ (fluocinolone acetonide intravitreal implant) 0.18 mg is indicated for the treatment of chronic non-infectious uveitis affecting the posterior segment of the eye.

4. CONTRAINDICATIONS. 4.1. Ocular or Periocular Infections. YUTIQ is contraindicated in patients with active or suspected ocular or periocular infections including most viral disease of the cornea and conjunctiva including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections and fungal diseases. **4.2. Hypersensitivity.** YUTIQ is contraindicated in patients with known hypersensitivity to any components of this product.

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6. ADVERSE REACTIONS. 6.1. Clinical Studies Experience. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. Adverse reactions associated with ophthalmic steroids including YUTIQ include cataract formation and subsequent cataract surgery, elevated intraocular pressure, which may be associated with optic nerve damage, visual acuity and field defects, secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera. Studies 1 and 2 were multicenter, randomized, sham injection-controlled, masked trials in which patients with non-infectious uveitis affecting the posterior segment of the eye were treated once with either YUTIQ or sham injection, and then received standard care for the duration of the study. Study 3 was a multicenter, randomized, masked trial in which patients with non-infectious uveitis affecting the posterior segment of the eye were all treated once with YUTIQ, administered by one of two different applicators, and then received standard care for the duration of the study. Table 1 summarizes data available from studies 1, 2 and 3 through 12 months for study eyes treated with YUTIQ (n=226) or sham injection (n=94). The most common ocular (study eye) and non-ocular adverse reactions are shown in Table 1 and Table 2.

Table 1: Ocular Adverse Reactions Reported in ≥ 1% of Subject Eyes and Non-Ocular Adverse Reactions Reported in ≥ 2% of Patients

ADVERSE REACTIONS	Ocular	
	YUTIQ (N=226 Eyes) n (%)	Sham Injection (N=94 Eyes) n (%)
Cataract ¹	63/113 (56%)	13/56 (23%)
Visual Acuity Reduced	33 (15%)	11 (12%)
Macular Edema	25 (11%)	33 (35%)
Uveitis	22 (10%)	33 (35%)
Conjunctival Hemorrhage	17 (8%)	5 (5%)
Eye Pain	17 (8%)	12 (13%)
Hypotony Of Eye	16 (7%)	1 (1%)
Anterior Chamber Inflammation	12 (5%)	6 (6%)
Dry Eye	10 (4%)	3 (3%)
Vitreous Opacities	9 (4%)	8 (9%)
Conjunctivitis	9 (4%)	5 (5%)
Posterior Capsule Opacification	8 (4%)	3 (3%)
Ocular Hyperemia	8 (4%)	7 (7%)
Vitreous Haze	7 (3%)	4 (4%)
Foreign Body Sensation In Eyes	7 (3%)	2 (2%)
Vitritis	6 (3%)	8 (9%)
Vitreous Floaters	6 (3%)	5 (5%)
Eye Pruritus	6 (3%)	5 (5%)
Conjunctival Hyperemia	5 (2%)	2 (2%)
Ocular Discomfort	5 (2%)	1 (1%)
Macular Fibrosis	5 (2%)	2 (2%)
Glaucoma	4 (2%)	1 (1%)
Photopsia	4 (2%)	2 (2%)

(continued)

Table 1: Ocular Adverse Reactions Reported in ≥ 1% of Subject Eyes and Non-Ocular Adverse Reactions Reported in ≥ 2% of Patients

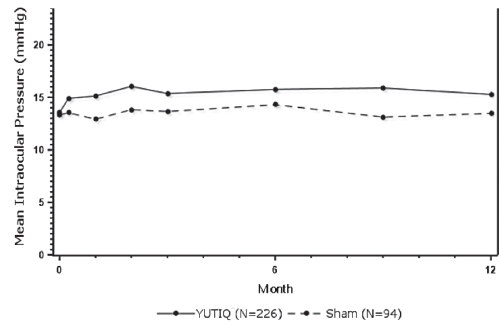
ADVERSE REACTIONS	Ocular	
	YUTIQ (N=226 Eyes) n (%)	Sham Injection (N=94 Eyes) n (%)
Vitreous Hemorrhage	4 (2%)	0
Iridocyclitis	3 (1%)	7 (7%)
Eye Inflammation	3 (1%)	2 (2%)
Choroiditis	3 (1%)	1 (1%)
Eye Irritation	3 (1%)	1 (1%)
Visual Field Defect	3 (1%)	0
Lacrimation Increased	3 (1%)	0
ADVERSE REACTIONS	Non-ocular	
	YUTIQ (N=214 Patients) n (%)	Sham Injection (N=94 Patients) n (%)
Nasopharyngitis	10 (5%)	5 (5%)
Hypertension	6 (3%)	1 (1%)
Arthralgia	5 (2%)	1 (1%)

1. Includes cataract, cataract subcapsular and lenticular opacities in study eyes that were phakic at baseline. 113 of the 226 YUTIQ study eyes were phakic at baseline; 56 of 94 sham-controlled study eyes were phakic at baseline.

Table 2: Summary of Elevated IOP Related Adverse Reactions

ADVERSE REACTIONS	YUTIQ (N=226 Eyes) n (%)	Sham (N=94 Eyes) n (%)
IOP elevation ≥ 10 mmHg from Baseline	50 (22%)	11 (12%)
IOP elevation > 30 mmHg	28 (12%)	3 (3%)
Any IOP-lowering medication	98 (43%)	39 (41%)
Any surgical intervention for elevated IOP	5 (2%)	2 (2%)

Figure 1: Mean IOP During the Studies



8. USE IN SPECIFIC POPULATIONS. 8.1 Pregnancy. Risk Summary. Adequate and well-controlled studies with YUTIQ have not been conducted in pregnant women to inform drug associated risk. Animal reproduction studies have not been conducted with YUTIQ. It is not known whether YUTIQ can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. YUTIQ should be given to a pregnant woman only if the potential benefit justifies the potential risk to the fetus. All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the United States general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. **8.2 Lactation.** Risk Summary. Systemically administered corticosteroids are present in human milk and can suppress growth, interfere with endogenous corticosteroid production. Clinical or nonclinical lactation studies have not been conducted with YUTIQ. It is not known whether intravitreal treatment with YUTIQ could result in sufficient systemic absorption to produce detectable quantities of fluocinolone acetonide in human milk, or affect breastfed infants or milk production. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for YUTIQ and any potential adverse effects on the breastfed child from YUTIQ. **8.4 Pediatric Use.** Safety and effectiveness of YUTIQ in pediatric patients have not been established. **8.5 Geriatric Use.** No overall differences in safety or effectiveness have been observed between elderly and younger patients.

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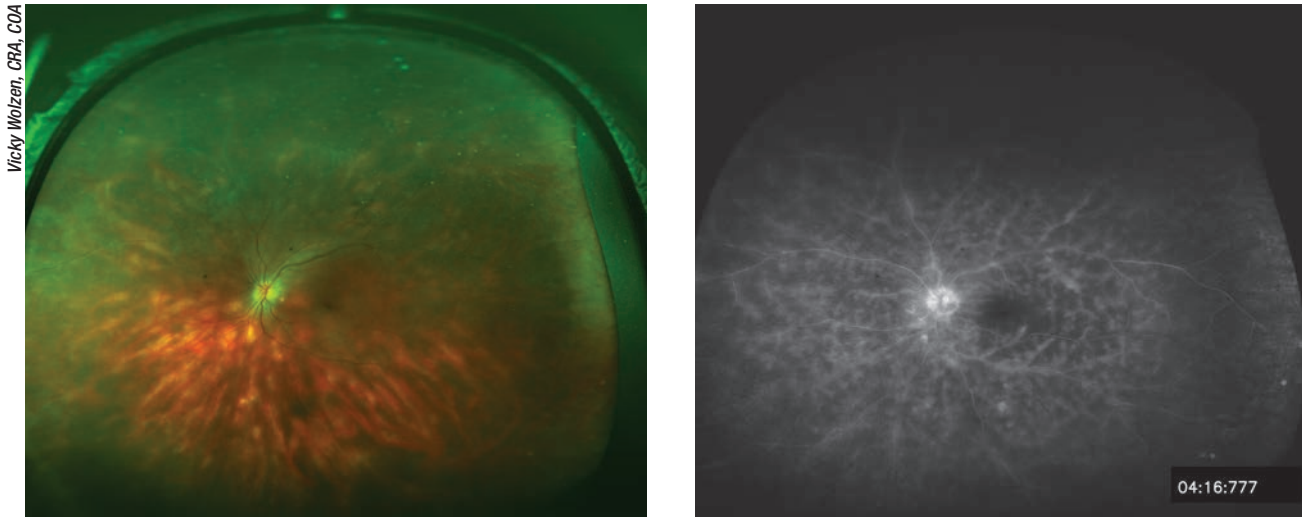


Figure 3. Color fundus photograph of birdshot retinochoroiditis in a 62-year-old woman (A) and a late-phase fluorescein angiogram of the same eye (B).

chronic non-infectious uveitis (a one-year or greater history) affecting the posterior segment of one or both eyes received a 0.59-mg Retisert. In terms of the primary endpoint, recurrence, the rates of recurrence ranged from approximately 7 percent (7/108) to 14 percent (16/116) for the 34-week post-implantation period as compared to approximately 40 percent (46/116) to 54 percent (58/108) for the 34-week pre-implantation period.¹⁰

According to the labeling, within 34 weeks post-implantation, approximately 60 percent of patients will require IOP-lowering medications to control intraocular pressure. Within an average post-implantation period of about two years, approximately 32 percent of patients are expected to require filtering procedures to control intraocular pressure. Also, within approximately two years post-implantation, “nearly all phakic eyes are expected to develop cataracts and require cataract surgery.”¹⁰

When considering the Retisert implant, Dr. Thomas determines if the patient has demonstrated a good response to local steroids. “I also make sure the patient understands the effects of long-term local steroid

therapy,” he continues. “The MUST data showed that essentially all patients with a Retisert developed a cataract, up to 77 percent of patients needed IOP-lowering drops and 37 percent of patients required filtering surgery within three years of Retisert implantation.”¹¹

Dr. Thomas notes that surgically implanting Retisert is a simple procedure. “Exchanging the old implant for a new one every three years can be more challenging and may need to be done by a vitreoretinal specialist,” he adds.^{12,13} “Some physicians may put a second implant into the eye without replacing the old one. This might not be an ideal practice as it uses up valuable real estate and the older Retiserts may be at risk of dissociation or dislocation.”¹²

In his practice, Dr. Albin has a straightforward message for patients who are considering Retisert: “You are buying three surgeries (surgical implantation and possible glaucoma and cataract procedures),” he says. “If you’re lucky, maybe two surgeries. But you’re saving yourself from being on a systemic medication. Most patients do well with systemic immunosuppression, but some avoid it be-

cause of possible side effects, such as nausea, fatigue, bone marrow suppressions or liver changes.”

For most of these patients, Dr. Albin says a second implant is put in place when the inflammation of their uveitis recurs five years after placement of the first implant. “Waiting for recurrence of inflammation might not be the best approach,” he says. “It might be best to put in another implant after the implant’s three-year release of the steroid. But that involves surgery and more accompanying risks.”

• **Yutiq.** The FDA approved the Yutiq insert after a multicenter, randomized, prospective, double-masked, sham-controlled, three-year Phase III clinical trial found the insert’s uveitis recurrence rates at 36 months to be 56.3 percent for Yutiq, which was significantly lower than that of sham-treated eyes (92.9 percent).¹⁴ Intraocular pressure-lowering drops were used in 42 percent of Yutiq-treated eyes and a third of sham-treated eyes. IOP-lowering surgery was performed in 6 percent of Yutiq-treated eyes and 12 percent of sham-treated eyes. Seventy-four percent of Yutiq patients required cataract surgery vs. 24 percent of

Role of the General Ophthalmologist in Chronic Care

If you're a general ophthalmologist who's caring for a patient with noninfectious posterior uveitis, consider serving as the quarterback of an all-star extended care team.

"Very early in the patient's course of care, I recommend that the general ophthalmologist send the patient to—or at least arrange for a telephone consult with—a uveitis specialist or a retina specialist who is comfortable with uveitis," says Sam Dahr, MD, clinical professor at the Dean McGee Eye Institute and University of Oklahoma College of Medicine in Oklahoma City. "Enlist the help of a rheumatologist as well, but understand that the ophthalmologist remains the 'quarterback.'" Dr. Dahr says the rheumatologist can help with dosing and with systemic monitoring of immunosuppression therapy. "But it's the general ophthalmologist who sets the direction for therapy and monitors disease response," says Dr. Dahr. "Rheumatologists should not be asked to 'work up' initial uveitis patients. The general ophthalmologist has the benefit of the ophthalmic exam and should select the initial workup and maintain control and management of the case."

—S.M.

sham patients.¹⁴

"In one study, 12-month data showed a reduction in inflammation and uveitis flares in eyes randomized to receive the insert over sham," says Dr. Thomas.¹⁵ "Of note, the rate of use of IOP-lowering medications over the study was similar between the groups. However, how this compares to steroid-sparing systemic therapy or the Retisert implant remains to be seen."

Yutiq is injected in the clinic, allowing it to float freely in the cavity, instead of being sutured into the eye. Unlike the dissolvable dexamethasone implant Ozurdex, however, Yutiq is packaged with polyethylene and therefore isn't degradable.

"After a patient potentially undergoes Yutiq injections every three years during a 10-year span, the question will be: How and when are we going to remove the leftover inserts from the eye?" asks Dr. Albin. "This is an issue that has to be addressed."

Yutiq became available in March of 2019. Dr. Dahr is performing initial Yutiq injections in patients who need continued intravitreal steroid therapy despite his best efforts at utilizing steroid-sparing therapy.

Often, Dr. Dahr says, noninfectious

posterior uveitis patients have recurrent macular edema, despite steroid-sparing therapy and a clinically controlled eye. Those patients' edema will often respond to an intravitreal steroid, he says. "Yutiq is an option for patients who can't tolerate or who are ineligible for steroid-

sparing therapy," he says. "I may also eventually use Yutiq when a patient has improved but is not fully controlled on traditional steroid-sparing treatment. For tough patients who can't be fully controlled on monotherapy with a traditional agent, choices for combination therapy may include the traditional agent plus Yutiq or the traditional agent plus Humira. Here, a discussion with the patient regarding individual preferences is critical."

Sustained Immunosuppression

Dr. Albin points out that many patients with noninfectious posterior uveitis may have chronic diseases, such as birdshot chorioretinopathy, Behçet's syndrome, sympathetic ophthalmia, Vogt-Koyanagi-Harada syndrome, serpiginous choroidopathy and multifocal choroiditis with panuveitis.

"A more chronic course is indicated in these cases," Dr. Albin says. "If these conditions aren't treated

Systemic Corticosteroid for Chronic Therapy?

Akshay Thomas, MD, MS, a retina specialist at Tennessee Retina, says he will be the first to use immunosuppression therapy for patients with chronic noninfectious posterior uveitis. But only when it's necessary.

"I don't rule out the use of oral prednisone in chronic patients if they have bilateral disease, which is what we find in most chronic patients," he says. "Depending on their age and other factors, to ensure they're good candidates for systemic therapy, prednisone therapy might be worth trying. A 60-mg prednisone tablet is a fairly sizeable starting dose for significant inflammation. I administer it for two to four weeks, then taper the drug slowly. I want to get most patients down to 7.5 mg or less of prednisone per day, watching for flares that might require temporary dosage increases. The quick onset of action I can achieve with a follow-up dose is like putting a bucket of water on a fire. Then I watch to see if that takes care of the inflammation, or if the inflammation comes back. Taking this approach, I may be able to spare the patient immunosuppression therapy and even birdshot chorioretinopathy."

If inflammation keeps recurring, Dr. Thomas transitions to immunosuppression therapy. But he doesn't give up on systemic doses right away.

"Remember that you need to administer immunosuppression for two to three months before it achieves a significant therapeutic effect," he says. "If appropriate for the patient, I can keep him or her on systemic steroids to bridge the gap while the immunosuppression treatment builds to therapeutic levels."

—S.M.

properly, the affected patients will most often lose their vision.”

For this reason, he and other specialists urge providers to involve specialists in these cases. “Sustained immunosuppression is what is needed,” Dr. Albini says.¹⁶ “A retina specialist or uveitis specialist will need to provide this type of chronic care. Sustained immunosuppression is beyond a general ophthalmologist’s typical purview. Most general ophthalmologists would only treat anterior uveitis.” (See “Role of the General Ophthalmologist in Chronic Care” on page 26.)

Dr. Dahr warns against waiting too long to initiate a patient on some form of steroid-sparing therapy. “The key in these cases is to commit patients with significant disease to steroid-sparing therapy early in their course rather than to wait one to two years, when a breakdown of the blood-ocular barrier makes achieving long-term control and possible remission much harder.”

Maximizing Your Options

In June 2016, Humira, an inhibitor of tumor necrosis factor-alpha (TNF α), became the only systemic non-corticosteroid agent approved by the FDA for the treatment of non-infectious uveitis.¹⁷ Infliximab is the other agent from this drug class that has been used effectively to quiet the symptoms of Behçet’s syndrome, which, as mentioned previously, is one of many inflammatory conditions associated with posterior noninfectious uveitis.¹⁸

Several off-label immunosuppressive antimetabolites have also become important in the treatment of chronic or recurrent noninfectious posterior uveitis—and will continue to play a role, experts say. These agents include methotrexate, mycophenolate mofetil (CellCept) and azathioprine (Imuran). “Specialists have

been treating with methotrexate and CellCept for a decade or more,” says Dr. Albini. “At this point, it’s not definitively clear which one is better.”¹⁹ More comparative trial data is coming in the literature.” Other off-label steroid-sparing treatments include such T-cell inhibitors as cyclosporine and tacrolimus (Prograf).

Antimetabolites With Humira

For Dr. Dahr, antimetabolite therapy remains a mainstay that has only been enhanced by the recent availability of Humira.²⁰ “Antimetabolite monotherapy will achieve long-term control in approximately one-third of cases,” he says. “Now, the combination of an antimetabolite (methotrexate, mycophenolate or azathioprine) with Humira has become very popular. Antimetabolites have 30 years of literature supporting their use for uveitis. Community rheumatologists are very comfortable with the methotrexate/Humira combination, and they can help the ophthalmologist.”

According to Dr. Dahr, in addition to its intrinsic immunomodulatory effect, methotrexate may enhance the effect of Humira by slowing the clearance of Humira and reducing the development of neutralizing antibodies to Humira. “Some patients read the Humira label and wish to avoid the drug but are willing and able to take the antimetabolite, so the antimetabolite can be used with local steroid options,” says Dr. Dahr. “Some patients may not tolerate antimetabolites but do well with Humira monotherapy, or Humira monotherapy plus an intravitreal steroid. The physician and patient must discuss combination approaches.”

Managing Costs

When considering monotherapy in the clinic, Dr. Albini says a potentially complicated choice sometimes

(Continued on page 55)

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Anti-VEGF 2019: The State of the Art

Christopher Kent, Senior Editor

Surgeons share the latest thinking about the benefits and risks of anti-VEGF therapy, and what lies ahead.

There's no question that anti-VEGF drugs have caused a sea-change in the treatment of several retinal diseases. Conditions that were basically untreatable have now become manageable, preventing what was once almost inevitable blindness. Yet there's still plenty of room for improvement; results vary, and not all patients avoid vision loss.

"When I started my career, neovascular age-related macular degeneration was a horrible disease," recalls K. Bailey Freund, MD, a retina specialist and a clinical professor of ophthalmology at the New York University School of Medicine. (Dr. Freund has been a principal investigator in several pivotal trials of novel treatments for retinal diseases.) "Nothing we could do would really help our patients. Today, certain patients do extremely well—particularly the ones that have Type 1 (subretinal pigment epithelium) neovascularization under the fovea. Others do well initially, but eventually the non-neovascular aspect of the disease kicks in and they ultimately end up losing vision, more from macular atrophy than exudative complications."

Here, retina specialists answer key questions about the current state of anti-VEGF drug treatments

for macular degeneration and other retinal diseases; share the latest insights, which suggest that neovascularization and subretinal fluid are not always a bad thing; and discuss what the upcoming years may hold.

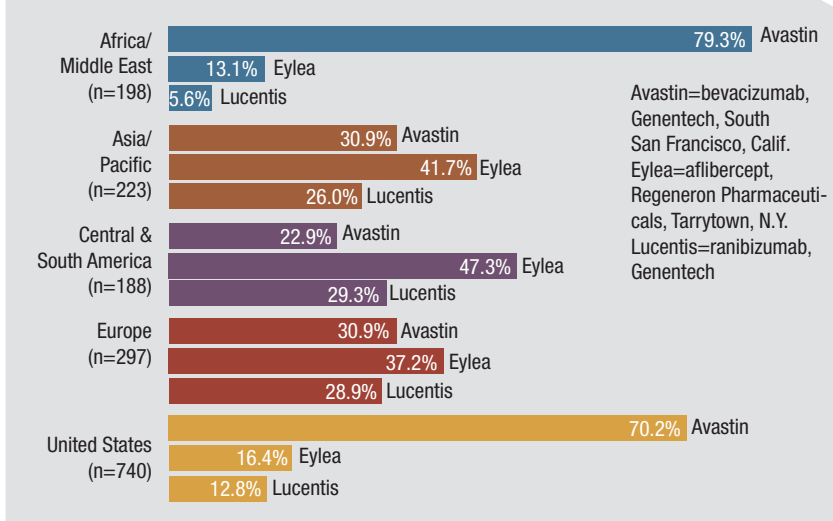
Anti-VEGF Drug Choice

"Each anti-VEGF option has an advantage that certain people prefer," notes Philip Rosenfeld, MD, PhD, professor of ophthalmology at the Bascom Palmer Eye Institute at the University of Miami Miller School of Medicine. "For example, bevacizumab is cheap. In certain countries surgeons can get a rebate for using ranibizumab, so some doctors use it because it's financially rewarding for the practice. Aflibercept is the preferred drug for certain neovascular types of disease; for example, I think it works best in fibrovascular retinal pigment epithelial detachments with a significant serous component.

"Personally, I treat with bevacizumab and aflibercept," he says. "In my non-hospital-based setting, I always start with bevacizumab and try to get a durability that exceeds six, eight or 10 weeks. If I can't get beyond that six-to-eight week interval, then I switch to aflibercept.

FULL POWERED EXAMINATION CHAIR

What is your first-line anti-VEGF agent for wet AMD?



Data from the Global Trends in Retina Survey, conducted by the American Society of Retina Specialists, in conjunction with the 20th Annual ASRS Preferences and Trends (PAT) Survey.³ Members of 42 retina societies around the world participated in the 2018 Global Trends in Retina Survey. (Reprinted with permission.)

Some surgeons prefer ranibizumab, and others prefer to use aflibercept exclusively. However, many times when patients are in Medicare Advantage plans, the choice of drug is decided by the provider.”

Dr. Rosenfeld notes that The American Society of Retina Specialists runs an annual Patterns and Trends survey, in which they ask about anti-VEGF drug choices every year. “We don’t have the results for 2019 as we speak,” he says, “but the replies for 2018 indicated that in the U.S., bevacizumab is the first-line choice for treating wet AMD for about 70 percent of retina specialists. Ranibizumab is first-line for 12 percent, and aflibercept is first-line for 16 percent. Outside the U.S.—except in Africa and the Middle East—it looks like aflibercept wins. However, treating physicians are litigating for access to bevacizumab in the U.K. In France, it’s still very hard to get.” (He notes that at a recent retina meeting in Italy, most treating physicians said that they’ve used all three drug op-

tions—ranibizumab, bevacizumab and aflibercept.)

Dr. Freund says he finds the current anti-VEGF agents to be fairly similar in terms of efficacy and safety, so he chooses his drug regimen based on the individual patient’s presentation. “I might choose one drug over another when a patient is somewhat refractory to treatment,” he says. “This is particularly true for eyes that have what I currently refer to as aneurysmal Type 1 neovascularization, more commonly known as polypoidal choroidal vasculopathy. I see many patients with this lesion growth pattern because it was first described in our practice, and I’ve published on it extensively.

“Eyes with this lesion growth pattern may have a more robust response to aflibercept,” he continues. “Clinical trial evidence from the PLANET study showed that many of these eyes respond well to aflibercept monotherapy, while data from the EVEREST II trial indicates that eyes with aneurysmal Type 1 neovascularization receiving ranibi-

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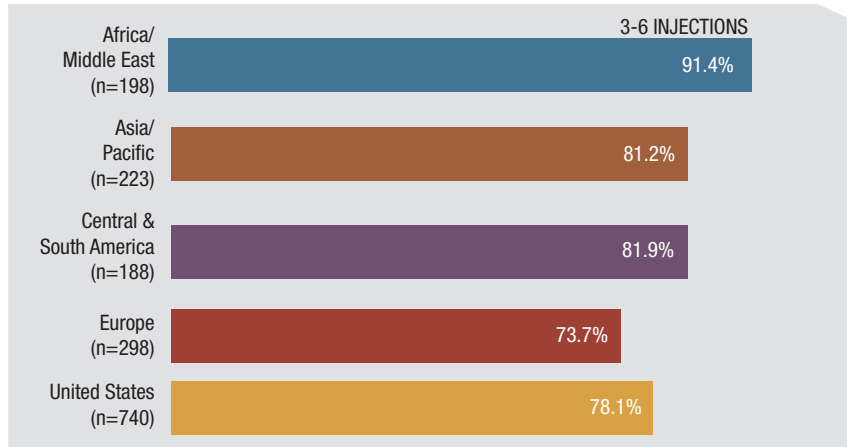
zumab may require the addition of photodynamic therapy in order to optimize visual outcomes.

“There’s another form of neovascular AMD that I call pachychoroid neovascularopathy,” he notes. “These eyes have choroidal findings that are similar to those seen in eyes with central serous chorioretinopathy. Also, they lack some of the characteristic clinical findings we associate with typical macular degeneration in elderly Caucasian patients, such as soft drusen. Those eyes may benefit from aflibercept, since aflibercept has been shown to decrease choroidal thickness more than the other agents. I find that eyes which are somewhat refractory to anti-VEGF therapy may not respond as well to bevacizumab, compared to the other agents.

“In the final analysis, a typical patient responds well to all of these agents,” he says. “Numerous studies show that bevacizumab is noninferior to the alternative FDA-approved options. However, for patients managed on a treat-and-extend regimen, I’m less comfortable extending my dosing interval beyond eight weeks with bevacizumab. So, for patients with no out-of-pocket drug expense, we may choose a different agent that could require fewer injections, particularly when frequent office visits would be very difficult.”

Of course, some patients don’t respond to the first drug the treating physician tries, but Dr. Freund points out that switching refractory patients to an alternative anti-VEGF is not a cure-all. “When aflibercept was approved, many practices did what we then called ‘switcher’ studies,” notes Dr. Freund. “We took patients who were poorly controlled with monthly bevacizumab or ranibizumab and switched them to aflibercept, expecting that because most eyes in the aflibercept trials could be maintained on injections every eight weeks, the

Physicians who consider switching anti-VEGF agents due to inadequate response after three to six injections



More data from the 2018 Global Trends in Retina Survey, conducted by the American Society of Retina Specialists.³ (For more information, see the caption for the chart on page 27.)

same might happen with these refractory cases. But the eyes we were switching were very different from the type of newly-diagnosed cases enrolled in clinical trials. All we typically found was that aflibercept might get rid of more fluid for a little longer than the prior agents. We did not find that eyes showing persistent fluid with monthly ranibizumab were fluid-free for eight weeks with aflibercept.”

Regarding the treatment protocol, Dr. Rosenfeld says he believes that most clinicians treat their patients using a treat-and-extend or modified treat-and-extend regimen. “This usually means performing monthly dosing until the macular fluid is resolved, and then extending the interval until macular fluid recurs,” he explains. “At that point the interval is shortened, and eventually a treatment interval is defined for that particular patient. When I attended the FLORetina meeting in Florence, Italy recently, this protocol seemed to be the general consensus among the attendees.”

Is Neovascularization Bad?

Clearly, neovascularization can be part of the problem in retinal dis-

eases such as macular degeneration. However, many researchers note that anti-VEGF drugs aren’t really treating the neovascularization—and they’re beginning to suspect that neovascularization may actually be a good thing in some patients.

“There are three types of macular neovascularization,” Dr. Rosenfeld explains. “The major type is what’s called Type 1, which occurs under the retinal pigment epithelium. Today, with OCTA, particularly swept-source OCTA, we can identify Type 1 neovascularization long before exudation occurs. For that reason there’s been some debate about whether we should treat Type 1 lesions with anti-VEGF therapy before exudation starts.

“I think the consensus is that we should not,” he says. “Instead, we should watch the lesions and treat when symptomatic exudation develops. The reason is that those lesions don’t go away because of treatment. What we’re doing is training them not to leak. We calm the lesion down, but we don’t make it go away.

“In fact, we’re starting to believe that when the Type 1 lesions go away, you’re left with macular at-

Do Anti-VEGF Drugs Cause Atrophy?

Philip Rosenfeld, MD, PhD, professor of ophthalmology at the Bascom Palmer Eye Institute at the University of Miami Miller School of Medicine, believes the concern about anti-VEGF therapy possibly promoting the formation of macular atrophy is still present, but receding. “There’s still some debate about whether the drugs themselves are influencing the formation of macular atrophy,” he notes, “or whether it’s just normal disease progression, or whether it’s a characteristic of certain lesion types, such as Type 3 macular neovascularization, also known as retinal angiomatous proliferation, which tends to form atrophy.”

K. Bailey Freund, MD, a retina specialist and a clinical professor of ophthalmology at the New York University School of Medicine, admits that a connection between anti-VEGF treatment and atrophy is biologically plausible. “Continuous VEGF suppression could do that, but we’re not actually providing continuous suppression,” he points out. “We give a large bolus of the drug, and over time the concentration drops to a very low level. Then we give another bolus. This may be one reason that the studies suggesting a possible link between anti-VEGF therapy and atrophy have really only shown this association when patients were treated continuously every month. Even these studies haven’t really proven that the

anti-VEGF treatment is causing the atrophy.”

Dr. Freund advises clinicians to use their judgment. “Look at the data and use common sense,” he says. “It might be reasonable to reduce injection frequency for eyes with Type 3 lesions, but not in eyes with large vascularized pigment epithelial detachments, particularly those with aneurysms—more commonly known as polyps—as these eyes appear resistant to macular atrophy, but are at risk for catastrophic hemorrhages if undertreated. So, look closely at the type of eye you’re treating and adjust your protocol accordingly.

“The data indicate that more patients in the United States and around the world lose vision to undertreatment than to overtreatment,” he adds. “So, while I think retina specialists should be concerned about causing atrophy, they should also be concerned about the disease itself, and make sure it’s kept under control.”

Dr. Rosenfeld agrees. “When patients come to us with exudative disease, not treating them isn’t an option,” he says. “So they get the injections, and we try to balance the need for reinjection and eliminating macular fluid against our concern about the possibility that overtreatment may exacerbate atrophy.”

—CK

rophy,” he says. “Many of my colleagues believe that you need to manage the neovascularization, but you don’t want to overtreat it. You want the neovascularization to stay there and just stop leaking. To put it another way, the field has evolved to believe that neovascularization is not the enemy; exudation and hemorrhage are the enemy. The neovascularization may actually be serving a very important function—providing nutritional support for the retinal pigment epithelium. Its appearance may be a normal physiologic response to a pathological condition in which you’re losing the choriocapillaris and there’s low-grade inflammation in the back of the eye. You need this neovascular complex. You just don’t want the exudation.”

“We know that patients that look clinically dry can harbor ‘non-exudative’ Type 1 neovascular tissue, which proliferates beneath the RPE with little clinical or optical coherence tomography evidence of its

presence,” says Dr. Freund. “There’s no fluid and no hemorrhage. Today, however, we have tools like OCTA that let us detect these vessels. The most notable fact is that some of these patients never develop pathologic exudation. The challenge is that we don’t know exactly what percentage of those patients will eventually develop vision-threatening fluid and hemorrhage.”

Dr. Freund frequently collaborates with Christine A. Curcio, PhD, a professor of ophthalmology at the University of Alabama at Birmingham, who is an expert in the histology of macular degeneration. “We’ve been performing clinicopathologic correlations for AMD for close to a decade,” he says. “If patients from my practice consent, we enroll them in our donor program, and the eye bank recovers the whole globe following their death. Our mission is to correlate the histology with the retinal imaging done in the clinic.

“We’re currently studying the

eyes of a patient followed for 10 years,” he says. “When she first presented, she was in her late 70s, and she’d already lost central vision in one eye from scarring due to neovascular AMD. Surprisingly, even though fluorescein angiography and OCT documented Type 1 neovascularization in her other eye, this eye never developed sight-threatening exudation, and retained excellent visual acuity for more than a decade. This unusual disease course was documented with multimodal retinal imaging, which we’re now correlating with high-resolution histology. Unexpectedly, it turns out that more than half of her macula was sitting on top of neovascular tissue, and the overlying photoreceptors maintained a healthy structure. The neovascular tissue appears to have maintained nutritional support to the fovea as the patient’s native choriocapillaris failed due to aging. So, by the time she died, the health of her outer retina appears to have

been maintained by the very same tissue that we all fear is going to cause patients to lose vision—tissue that we often do everything in our power to suppress with our anti-VEGF agents.”

Dr. Freund notes that the idea that Type 1 neovascularization could be beneficial isn't new. “This idea was first proposed by Hans E. Grossniklaus, MD and Richard Green, MD,” says Dr. Freund. “They hypothesized that Type 1 neovascularization had the potential to recapitulate the normal choriocapillaris, and this concept appears to be supported by the findings in our current donor. In some patients, these non-exudative vessels may actually be helping to preserve the overlying retina. So, the goal may not be to destroy or completely inhibit their growth but to carefully monitor eyes with these vessels so that pathologic exudation can be caught and treated early.

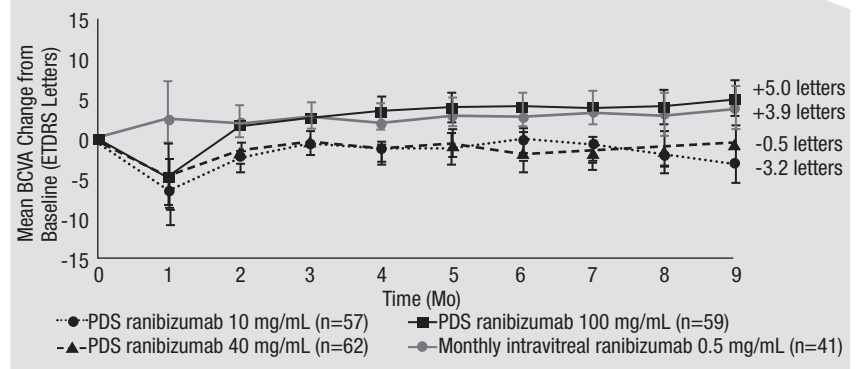
“That means we need to have the right balance,” he concludes. “We shouldn't be so aggressive that we destroy a potentially protective mechanism that could benefit our patients in future, but we also shouldn't let it get out of control and damage vision quickly with catastrophic bleeding.”

Is Fluid Always a Bad Thing?

“Studies have shown that eyes treated with intravitreal anti-VEGF therapy which continue to manifest subretinal fluid—eyes that don't go completely dry—may do as well, or even better, than eyes which dry up completely,” notes Dr. Freund. “So, a little bit of fluid may not be such a bad thing.”

Dr. Freund refers to the three main types of neovascularization occurring in exudative AMD, and says evidence is mounting that they may warrant different treat-

Port Delivery System with Ranibizumab vs. Monthly Injections



Data from the Phase II LADDER clinical trial. All patients were previously treated with and were responsive to anti-VEGF therapy. (Vertical bars=95% confidence intervals.)⁴

ment regimens. “I believe retinal specialists should look at the eye's presenting imaging characteristics, which define a lesion's subtype,” he says. “Different subtypes seem to respond differently to treatment and call for different levels of monitoring. For example, it's my strong belief that eyes presenting with Type 1 neovascularization beneath the fovea that continue to show a small amount of subretinal fluid, despite frequent dosing, are more resistant to geographic atrophy than eyes with other neovascular lesion patterns. In these eyes, a little bit of fluid is probably not such a bad thing. The main threat to vision in eyes like this appears to be the occurrence of subretinal hemorrhage if treatment is discontinued.

“In contrast, atrophy is a greater concern in eyes that have intraretinal neovascularization known as a Type 3 neovascularization or RAP (retinal angiomatous proliferation) pattern,” he continues. “Greater susceptibility to macular atrophy in eyes with Type 3 lesions has been observed in several large clinical trials. Patients presenting with Type 3 neovascularization are often older individuals with thin choroids and focal areas of macular hyperpigmentation, both of which increase sus-

ceptibility to macular atrophy. For eyes presenting with Type 3 neovascularization, I'll often first try PRN dosing, for three reasons: lesion quiescence may be long-lasting; recurrences predictably occur at the initial site of activity; and recurrent exudation with Type 3 lesions is rarely accompanied by large hemorrhages.”

Dr. Freund notes that Type 1 and Type 3 are the two most common variants of neovascular AMD. “Type 2 and mixed lesions with a component of Type 2 are less common, but the vessels in these eyes have broken through the RPE to proliferate in the subretinal space,” he says. “You have to be careful with these cases, since recurrent exudation from Type 2 lesions is in direct contact with the vulnerable photoreceptors. In that situation irreversible vision loss can occur quickly.”

Dr. Freund points out that the implication is that different types of lesions should be treated differently. “Don't simply assume that all neovascular AMD is the same and should be treated with the same regimen,” he says. “Over the short term, these slight variations in regimen may not seem to make a difference, but we often treat patients for the rest of their lives. Little dif-

ferences in how a patient does on one regimen versus another end up making a big difference over five, 10 or 15 years of treatment.”

Dr. Freund says that OCT may provide clues to the best treatment protocol. “If you see a shallow, irregular PED with heterogeneous internal contents in a patient with other findings of AMD, there’s a high probability that this finding represents neovascular tissue,” he says. “If there’s no exudation, eyes with this finding should be monitored closely, and the patient should be instructed to use an Amsler grid to monitor for conversion to active wet disease.

“When this type of vascularized pigment epithelial detachment, or Type 1 pattern, is subfoveal and associated with exudation, I use a treat-and-extend regimen of anti-VEGF therapy to control exudation,” he continues. “However, my goal is not to flatten the PED itself. I believe that intense treatment has the potential to convert a vascularized PED into avascular fibrotic tissue—tissue that will no longer be able to support the overlying retina. If there’s no hemorrhage, I’m not concerned about a little bit of persistent subretinal fluid, as long as it’s not increasing over time.”

Dr. Freund says that many of his patients have demonstrated the wisdom of this approach. “I have many patients I’ve been treating with anti-VEGF therapy for 10 or more years, some of whom have had as many as 100 injections,” he says. “Many eyes still have close to 20/20 vision.”

How Important is OCTA?

“Right now we treat based on exudation—the fluid that’s visible on structural OCT,” notes Dr. Rosenfeld. “However, people are working hard to see if the information we pick up with OCTA may be able

to influence how we treat. Many papers have been published about using OCTA to look at different types of neovascular structures that exist in these eyes with wet AMD, hoping that some of what they find would be predictive of how often we need to treat, and/or the outcome of treatment. The results have been underwhelming, which is probably because the anti-VEGF drugs treat the exudation, not the neovascularization. Thus, changes in the vasculature revealed by OCTA may be less important than the presence of exudation on structural OCT.

“However, OCTA does have a role,” he says. “It’s a very powerful way to identify eyes with dry macular degeneration that are at higher risk of exudation, so we can follow them differently. With OCTA—in particular SS-OCTA—you can see the neovascularization many months before patients actually develop exudation. It’s growing silently. This has been known since the 1970s, when autopsy eyes with dry macular degeneration were shown to harbor neovascularization; it just wasn’t leaking or bleeding. Using ICG angiography in the 1990s, retina specialists also showed that this neovascularization existed in their living patients. However, we couldn’t routinely screen patients with ICG angiography, so this discovery was largely forgotten until OCTA came along.

“Knowing that this neovascularization is present, via OCTA, is valuable information,” he says. “We recently conducted a two-year study involving 227 patients, which is currently in press. We compared eyes with and without this nonexudative neovascularization and found that there’s a 14-fold increased risk of exudation over a period of two years when neovascularization is present. So OCTA serves a purpose—just not for monitoring lesions once you

start treating. Instead, it can help to identify these lesions before exudation develops.

“For this reason, I use OCTA to check all of my dry AMD patients to see if they have these lesions,” he says. “It changes how I manage my patients. If they have the lesions, I usually follow them every two months. If they don’t have the lesions, I usually follow them every six months. It also helps me educate patients so they understand what’s going on and become partners in their own management.”

Dr. Freund says he uses OCTA frequently, but doesn’t believe it’s essential for diagnosing or treating AMD. “Often, OCT alone is sufficient to diagnose neovascular AMD or to arouse high suspicion that there’s a problem,” he notes. “In some cases, when there’s a characteristic OCT pattern of specific neovascular features, dye angiography may not be needed, especially if there’s a hemorrhage. I think OCTA is helpful if, like myself, you’re interested in identifying the neovascular lesion type to help individualize your treatment algorithm.

“Does individualizing the treatment regimen necessarily lead to better outcomes?” he adds. “I think so, but this remains to be proven. For now, I’d say that OCTA is a valuable research tool. In the future, it may become essential for a clinician managing macular degeneration.”

Dr. Rosenfeld believes clinicians will benefit from using OCTA. “I think everyone who practices retinal care needs access to OCTA, whether it’s for diabetes or AMD or vein occlusions,” he says. “It’s a remarkable tool that allows us to see the full extent of the underlying disease, and in certain situations helps us manage it better. OCTA is now our number one tool for diagnosing proliferative diabetic retinopathy. It helps us determine the

The Syringe Factor

K. Bailey Freund, MD, a retina specialist and a clinical professor of ophthalmology at the New York University School of Medicine, notes that the type of syringe used to deliver the anti-VEGF medication has become a point of consideration. “Unless a syringe is silicone-free, droplets of silicone can end up in the medication,” he explains. “Then, if you use syringes that don’t have reservoir at the tip, which can trap the silicone as it’s pushed down by the plunger, you’re more likely to inject some of that silicone into the eye. Compounding pharmacies often use fixed-needle insulin syringes which lack a reservoir at the tip. As a result, some silicone oil often gets into the vitreous.

“Lucentis now offers a pre-filled syringe that’s been designed, in part, to minimize this problem,” he continues. “Also, with aflibercept, or ranibizumab dispensed in a vial, most retinal specialists use syringes with either a Luer-Lock or Luer-Slip design. These syringes have a dead space at the tip, so when the plunger is pushed all the way down, not all of the fluid in the syringe is in-

jected into the vitreous. However, that type of syringe is frequently not used for bevacizumab, in part because the presence of a dead space requires that more drug be added, which increases the cost.

“The SCORE trial investigators reported this issue with fixed-needle syringes when they were looking at a syringe pre-filled with an Allergan steroid,” he says. “Furthermore, a study published in 2017 compared the amount of silicone expressed from syringes of different types.¹ It showed quite convincingly that when you use syringes with fixed needles, you’re more likely to see silicone droplets expressed from the needle tip. I’m also a co-author of a recently published editorial in *Retina* which discusses this topic.²”

Dr. Freund admits that the number of incidents related to this problem and compounded bevacizumab is very small. “Nevertheless, there are potential issues with a compounded drug,” he says. “All of those factors weigh into which drug you choose, even if you think there’s not much of a difference between the drugs.”

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extent of vascular nonperfusion in diabetics and vein occlusion, and it’s particularly useful for identifying the subclinical, nonexudative lesions in dry AMD. Furthermore, patients love it compared with dye-based angiograms. Meanwhile, of course, structural OCT is very useful for managing all of these conditions as well. But with OCTA scans, you get both the structural OCT and the angiographic OCT.”

Dr. Rosenfeld points out one big problem with OCTA, however, at least in the United States. “We don’t have a unique billing code for OCTA,” he explains. “The scan time is about the same as routine OCT, but the time it takes for the physician to interact with the instrument, look at the scans and extract the information by manipulating the segmentation boundaries to get the best possible image isn’t currently reimbursed. So, while the equipment is more expensive and it takes more time to evaluate the scans, the reimbursement is the same as for the more typical OCT. Outside the U.S., OCTA has a higher reimbursement, so the technology has become

very popular. But in the U.S., it’s a difficult product to sell, because doctors want the revenue from dye-based angiography.

“Despite that concern, I believe it’s worth using OCTA,” he concludes. “With it, you achieve increased patient satisfaction and patient wait time is decreased. You can see more patients, because dye-based angiography takes a long time to perform—and it’s risky. So from an economic standpoint I think OCTA wins, even without the unique billing code.”

What’s Next?

As effective as the current options are, new drugs and technology in the pipeline have surgeons hoping for even better outcomes—and a reduced injection burden.

• **Brolucizumab.** This is an investigational anti-VEGF drug from Novartis. “We hope it will provide a greater duration of action,” Dr. Rosenfeld explains.

Dr. Freund notes that brolucizumab was compared head to head with aflibercept in a trial. “The

trial compared the labeled dosing of Eylea—every four weeks times three, extended to once every eight weeks—to brolucizumab, which is given every four weeks for three injections and then extended to every 12 weeks,” he explains. “With brolucizumab, a little more than half of the eyes could be maintained on the 12-week dosing to the final 48-week endpoint. Unfortunately, the trial design makes it hard to do a direct comparison between the drugs because patients treated with aflibercept were never extended beyond eight weeks. However, during the first three months, all the eyes were dosed every four weeks. During that period, there was more improvement in OCT thickness with brolucizumab than with aflibercept. “Part of the reason for this finding is that brolucizumab is a smaller molecule in a more concentrated formulation,” he points out. “When you inject the same volume of both drugs, the molar concentration of brolucizumab is approximately 10 times that of aflibercept. That means you’re getting a lot more drug in the eye with each injection

of brolocizumab.”

One reason surgeons look forward to new options is the possibility that they'll help to treat refractory patients. However, Dr. Freund points out that it could be problematic to use brolocizumab for this purpose, at least at the outset, because of the trial design. “Let's say you have a patient that doesn't dry up as much as you hope using one of the other agents,” he says. “In the trials of the other drugs there were arms in which patients were treated monthly to the endpoint. Brolocizumab didn't have that, so it seems unlikely that the initial approval will include long-term monthly dosing. The reality is, if a refractory patient can't go for four or five weeks on the other agents, they'll probably have trouble going for eight or 12 weeks with brolocizumab. That may limit how much you can use that drug for these difficult, refractory patients.

“I believe the company is doing other studies that may eventually get a label allowing monthly treatment,” he adds, “but at the launch that could be a bit of an issue.”

• **Abicipar pegol.** Another drug being tested is Allergan's abicipar pegol. “The trial design was basically 12-month dosing head-to-head between abicipar pegol and monthly ranibizumab,” Dr. Freund explains. “The new drug met its noninferiority endpoint, which is fairly impressive. Patients went to 12 weeks and seemed to do just as well as patients getting ranibizumab every month.

“The issue is that there's been some inflammation with abicipar pegol,” he continues. “Initially about 15 percent of patients had inflammation. However, the company subsequently released data from a trial called MAPLE, where a change in the manufacturing of the drug reduced the inflammation rate to 8 or 9 percent, and so far, there's no evidence that the inflammation

caused in any of these patients was of much concern. So, you could decide to try abicipar pegol on your patient once. If the patient develops inflammation, you could stop. The risk/benefit ratio would be pretty good: There may be only a 9-percent chance that the patient will have inflammation, but there's close to a 90-percent chance that the patient will be able to be dosed once every 12 weeks. With brolocizumab you'd only have a 50-50 chance of reaching every 12 weeks. That's one way to look at the data.”

• **Sustained delivery.** A key way to reduce the injection burden, of course, is via sustained delivery. “No one likes injections,” notes Dr. Freund. “But now Genentech has an implantable port that's a refillable reservoir. Theoretically, you'd only have to do two refills a year.”

Dr. Rosenfeld says that data from the LADDER study, involving Genentech's Port Delivery System with ranibizumab, was presented at the FLORetina meeting. “It appears to provide some extended benefit for patients,” he says. “Less-frequent dosing was needed. In addition, there's a sustained-release tyrosine kinase inhibitor from Graybug Vision (Redwood City, California) that may or may not prove to be a long-term solution for this problem.”

• **Home monitoring.** “The key to monitoring those lesions is going to be some kind of home monitoring that's reliable,” notes Dr. Rosenfeld. “Our dream device would be an OCT that a patient could use every day, or every other day. That would allow us to identify exudation as soon as it develops. Home OCT monitoring would be useful for following patients who have non-exudative, neovascular lesions that we can identify with OCT angiography, who are at high risk for exudation, as well as patients on a treat-and-extend regimen. If they were testing

themselves with home OCT monitoring, we'd know as soon as the fluid develops or recurs.

“Notal Vision has a prototype that's being tested that uses an AI algorithm capable of picking up exudation,” he continues. “There are other strategies being developed as well, but the Notal Vision device may become available within a year or two. Patients wouldn't buy the instrument; it would be more of a lease situation. Medicare currently covers the cost of home monitoring, so for a nominal fee, perhaps in addition to Medicare coverage, you'd be able to have your patients monitored at home.”

• **Gene therapy.** “Two companies have gene therapies that involve injecting a viral vector into the eye,” says Dr. Freund. “Adverum Biotechnologies is in a Phase I trial with an intravitreal injection, and Regenxbio will soon be conducting a Phase II trial involving subretinal delivery of gene therapy. The viral vector inserts DNA into cells in the eye, so they start to produce either ranibizumab or aflibercept on their own. Theoretically, you could inject it once and you'd be done. To me that's very exciting.” **REVIEW**

Dr. Freund is a consultant for Allergan, Novartis, Zeiss, OptoVue and Heidelberg Engineering, and receives research support from Genentech Roche. Dr. Rosenfeld has received research funding from and is a consultant for Carl Zeiss Meditec.

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Back to Basics: Complicated Cataracts

Sean McKinney, Senior Editor

Leading surgeons
share their best
tips for residents
faced with
complex cataract
cases.

Refined techniques and instruments, both large and small, have made cataract surgery as safe and effective as it's ever been. But cases complicated by brunescient lenses, pseudoexfoliation, cloudy corneas or inflammation can still occur.

"The only way to avoid the complications of cataract surgery is to not do surgery," says Alan S. Crandall, MD, senior vice-chair, Department of Ophthalmology & Visual Sciences, Moran Eye Center, University of Utah. "The more surgery you do, the more significantly complications decrease. But they never go down to zero. If you tell me you're experiencing no surgical complications, then you either have no idea what's truly going on, or you're not telling the truth."

Highly experienced cataract surgeons say, fortunately, time-tested preventive measures and intraoperative solutions can help you avoid or get out of just about every jam.

In this report, these experts explain how to succeed when managing a multitude of challenging cataract cases.

Dense Cataracts

Most surgeons have come to expect an occasional brunescient lens

that seems to defy all attempts at simple extraction.

"When you have a patient with a dense cataract, you often also have a small, wobbly lens, miotic pupil and weak zonules as well," says Kevin M. Miller, MD, Kolokotronis Chair in Ophthalmology at the University of California, Los Angeles. "Such patients are usually very elderly, with deep-set orbits, small pupils and narrow lid fissures. The density of the nucleus makes it hard enough. But you also have to contend with these other factors."

In some cases, Dr. Miller resorts to an extracapsular cataract extraction. "But I believe we should approach every patient as a phaco candidate," he says. "In most cases, I proceed with phaco, knowing that I can always switch to a small-incision procedure, if necessary, after I start." Dr. Miller uses a mydriatic agent to expand the patient's pupil. "If that doesn't work, a ring can be inserted to expand the pupil from 3 or 3.5 mm to 6.25 or 7 mm," he says. "A ring is less traumatic than hooks. If the zonules are really loose, I can put in as many as five capsule retractors around the eye to stabilize the lens."

Dr. Miller reduces the duty cycle of his phaco unit by as much as 50 percent to reduce the odds of ther-

mal injury, using 100-Hz, on-and-off power switching to create a pulse train that helps break up the lens without disrupting the fragile internal architecture of the patient's eye.

"We can usually make progress on the lens, but it takes time," he notes.

Kathryn M. Hatch, MD, Refractive Surgery Service Site Director at Massachusetts Eye and Ear in Waltham, Massachusetts, says she likes to use the femtosecond laser to soften the cataract. "I can get to the leathery plate of the cataract and it makes the surgery for dense cataracts seem more routine," she notes.

Dr. Hatch says the MiLoop can also be a useful technology for breaking up dense cataracts because it can "cheesewire" through the lens, segmenting it. "One possible severe complication with the MiLoop can develop when the instrument isn't brought under the anterior capsule," she says. "You don't want to MiLoop the capsule. Let the instrument guide you around to the back of the lens where you can achieve a good hydrodissection, encircle the dense nucleus in the sagittal plane and safely fragment the lens."

Dr. Crandall urges surgeons to use the MiLoop if they have any doubts about achieving a good outcome with phaco.

"The MiLoop might be your best choice for a black lens that's as hard as a rock," he says. "Other factors to consider are how close the lens is to the cornea, and whether the lens is cloudy, not just dense. You might have a lens with very loose zonules that's floating around. A careful evaluation will tell you what to do. You may be pushed into doing an ECCE or a small-incision procedure, if you've been trained to do it."

Before even starting her surgeries, Jill Rodila, MD, a surgeon at Aker Kasten Eye Center in Boca Raton, Florida, peers through her slit lamp and grades the appearance of all lens-

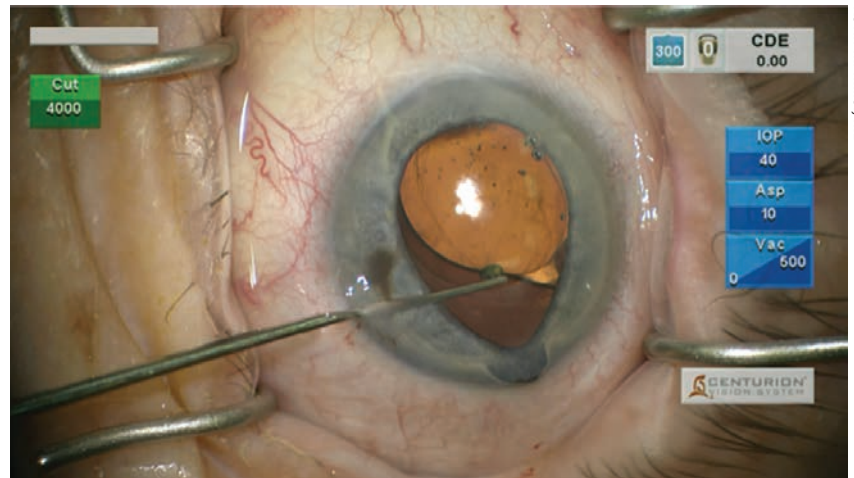


Figure 1. The iris prolapsed through the primary incision during this multifocal intraocular lens exchange.

es. "If I see a cataract with a high degree of brunescence, I prepare to use more phaco power," she says. "I use extra viscoelastic, and I prefer EndoCoat for protecting the corneal endothelium if there's a densely brunescence lens or a low endothelial cell count." For extremely dense lenses, Dr. Rodila turns to sutureless extracapsular cataract surgery (manual small incision cataract surgery or MSICS). "I can get the lens out without being harsh on the cornea," she notes. "It can be difficult to crack a very hard lens all the way when you're using phaco."

One of her biggest concerns arises when a leathery posterior cortex seems impossible to break through or mobilize. "It's very important to get a deep enough groove in the lens right from the start," she says. "I want to split the lens completely in half, if possible. In situations like this, you might need an additional chopping instrument that's smooth enough to avoid breaking the posterior capsule but also has a sharp edge that you can safely slice through the lens with."

"Here's another important point," Dr. Rodila adds. "At the end of a case, you may see a remaining piece of dense nuclear material that takes a lot of phaco power to remove. Some-

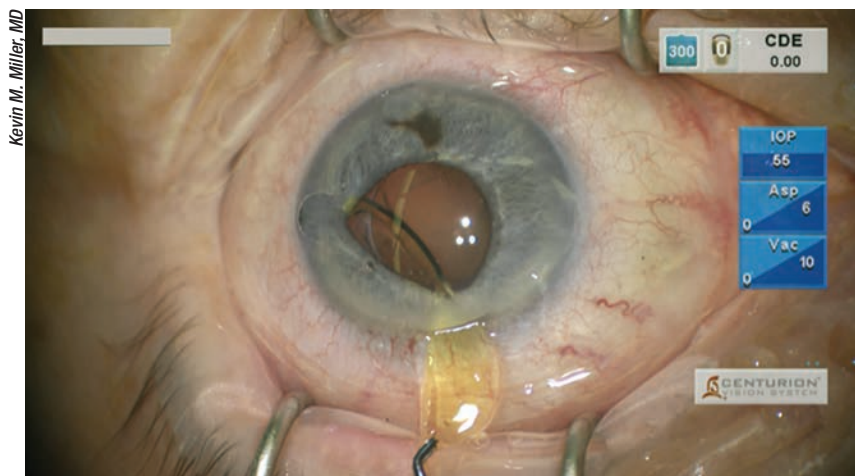
times, you may be dealing with a fragile cornea, and you have to keep the tip more posterior. When doing so, remember that the posterior capsule can be right behind the phaco tip. The rush of fluid into the phaco tip can cause the capsule to rush to the tip as well. It's wise to use a second instrument posterior to the phaco tip to protect the capsule in case it wants to bounce up into the tip."

Managing Surgical Risks

Experts say the best weapon to use against a dense lens or many other challenges that may await you inside an eye is proactive preparation.

"Look for signs and symptoms that the cataract is likely to be difficult," says Dr. Crandall. "Look for issues such as pseudoexfoliation on the capsule or a history of trauma, whether the patient remembers it or not. Look carefully for asymmetry in the depth of the chamber. Look at the patient's IOP. If it's low, that could be because of serious retinal problems, including a detachment. You may need to turn this case over to a retina specialist to avoid massive problems if the patient has a retinal detachment."

Dr. Miller says it's critical to assess the whole patient preop.



Kevin M. Miller, MD

Figure 2. Rather than push this prolapsed iris from Figure 1 back into eye during cataract surgery, the surgeon left it in the prolapsed state and opened a new incision. After removing the intraocular lens, performing an anterior vitrectomy and implanting the replacement lens, the surgeon corrected the iris prolapse with virtually no trauma or pigment release.

“It’s all about the comorbidities of the patient,” he says. “They have a cataract and they typically have all sorts of other problems. We had a deaf and blind patient recently who required the use of general anesthesia. We had to tape the forehead of a patient with chronic obstructive pulmonary disease to the gurney so that his persistent coughing would not disrupt surgery. We operate on patients with diabetes first thing in the morning so they don’t have to fast all day, risking hypoglycemia. We use lots of pillows and towels to maintain comfort and proper surgical position for patients with bad backs or other orthopedic issues. Some patients have conditions—such as juvenile rheumatoid arthritis, a history of vitritis, extensive uveitis and cystoid macular edema—that tell us they will experience intense inflammation after surgery. So we have to plan for that.”

Pupil, Iris and Zonule Issues

Dr. Hatch says one of her biggest challenges is often a small pupil. “You can pretreat patients with cyclopentolate 1% or atropine for a few days before the surgery,” she notes. “Dur-

ing surgery, you can add phenylephrine and ketorolac intraocular solution 1%/ 0.3% (Omidria, Omeros), if it’s not contraindicated.”

Dr. Rodila watches for pseudoexfoliation and history of trauma that may be associated with a case of loose zonules in a particular patient. “You can tap the slit lamp to see if the lens moves a little,” she says. “If the lens is loose when you examine it, you know there will be a risk. Look also for dislocation of the lens.”

Dr. Rodila confirms loose zonules when doing an anterior capsulotomy she typically encounters less tension when piercing the anterior capsule. When she makes her anterior capsulorhexis, she may discover striae in the capsule. “You know then that you’re definitely dealing with loose zonules,” she notes. “I proceed with the case very gently. And I try to get a good hydrodissection.”

Dr. Miller says seemingly minor techniques can have disastrous effects. “One of the worst complications is damaging a prolapsed iris,” he explains. “It’s pretty easy to do, yet damaged irises are unforgiving.” The damage can occur after the pupil gets stretched from the use of

hooks to keep it open, or when the pupil sphincter is torn by any means. “The prolapse can develop during hydrodissection,” he says. “[When this problem occurs], most often, it occurs when the phaco incision is made 1 mm long instead of 1.75 or 2 mm, and an excessive amount of viscoelastic is injected. The pressure of the visco will cause the iris to knuckle up and prolapse through the incision.

“Once the iris is outside of the eye, you have a small knuckle of visco trapped inside of it, so it’s hard to get it back in,” he says. “You’ll shred the iris if you try to poke it back inside the eye, causing significant cosmetic and functional damage that will affect appearance in light-colored eyes and vision postoperatively. In such a case, you need to evacuate the viscoelastic beneath the iris and the iris will go back in. You can continue the hydrodissection after it’s inside. If it doesn’t go in, just leave the iris outside of the eye until you’ve completed surgery through a separate incision. You can reduce the prolapse by lowering IOP later on and injecting a miotic.”

To avoid this problem? “Make sure your incision is long enough so the iris doesn’t jump out,” Dr. Miller says.

Surgeons also recommend that you avoid making your incision too posterior, which can incise the conjunctiva, causing it to billow and possibly hinder visualization of the case.

Maintaining Visualization

Vision of the inside of the eye during surgery is often taken for granted—until you start to lose it.

“We may encounter this if the cornea becomes hydrated or cloudy during surgery,” Dr. Miller says. “We can stain the capsule with some trypan blue solution to help with this situation. Keeping the cornea clear is always critical.”

Positioning of the patient is also

critical. “We had one patient who suffered a neck fracture, and his chin was stuck down,” he recalls. “We had to prop him up just about 90 degrees, almost hanging him by his feet, so that we could get the correct view, using a lid speculum to maximize exposure.”

Sometimes, Dr. Miller adds, he will get a patient with deep-set eyes that will pool up with fluid. “We do our best to dry out the eye with wicks, but to some extent, you find yourself operating underwater.”

Corneal Scars and Abrasions

Scars on the cornea can also create a problem. “When we see a scar,” says Dr. Miller, “we’ll roll the eye around to see where it’s clear, and then move the eye to that area so that we can do the surgery through a relatively clear window.”

Dr. Rodila says there are no easy answers when confronting this issue. “I rely on past experience in the presence of a cloudy or scarred cornea,” she explains. “You have to stay calm and confident when working under scarred areas. You need to trust your sense of feel, knowing where your hands are, trusting your proprioception.” She recommends using trypan blue solution to stain the anterior capsule to get the best visualization possible, especially if you can’t get a good red reflex.

Dr. Hatch, a corneal specialist, says she’s grown accustomed to scars and corneal opacities that can challenge you during surgery. “These include a variety of problems, ranging from corneal dystrophy opacities to scars resulting from prior refractive procedures, such as LASIK or RK,” she says.

“If I find corneal issues, specifically anterior basement membrane dystrophy, within the central 4 mm area and these issues are affecting biometry measurements, I may conclude

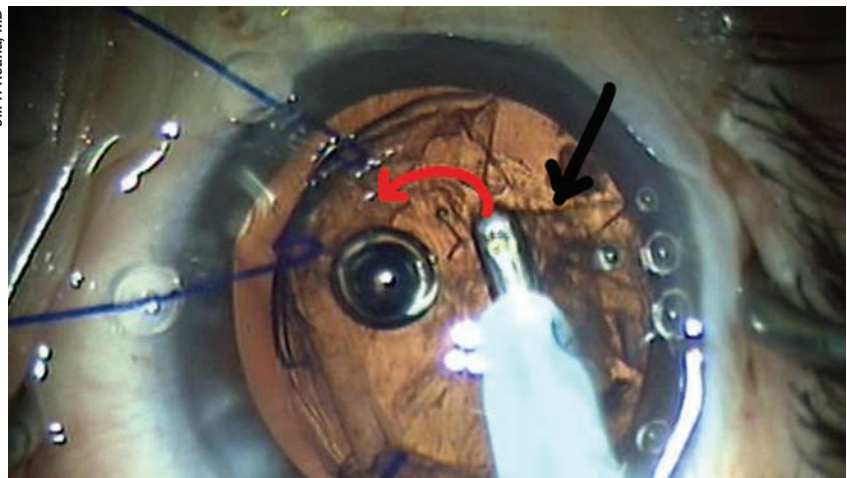


Figure 3. In a patient with a history of Marfan’s syndrome and a dislocated cataract because of sectoral absent/weak zonules, iris hooks are used to support the capsule. Without these hooks, the capsule would collapse and be easily aspirated during phacoemulsification or irrigation/aspiration. Use caution to ensure the tips of the hooks are blunt and will not puncture the capsule. When removing the cortex in the setting of loose zonules, aspirate in a tangential direction, rather than radial. This may put less tension on the zonules. The black arrow points out the cortex that is being aspirated; the red arrow indicates the direction of movement of the aspiration tip in a tangential fashion.

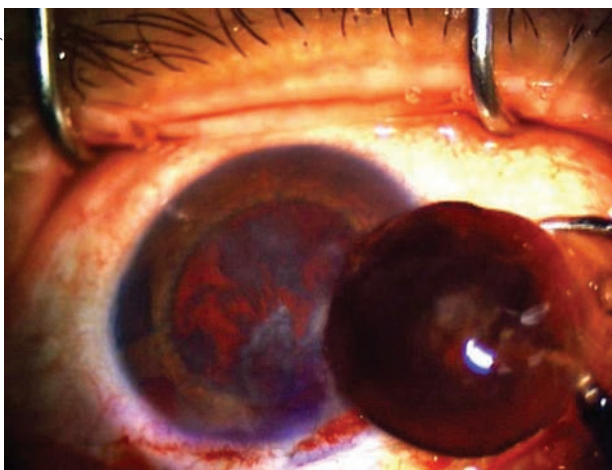


Figure 4. A brunescient lens is shown right after delivery from the eye using a lens loop during manual small incision cataract surgery (MSICS). The few remaining cortical fragments can be seen against the red reflex.

that a superficial keratectomy is warranted,” she continues. “Afterward, patients heal for four to six weeks, and repeat biometry measurements are taken prior to cataract surgery.”

Abrasions can also be caused by draping the eye too tightly before surgery, when the plastic drape abrades the cornea.

“You may need to re-drape, making sure the cut ends of the drape are away from the limbus and cornea,” says Dr. Miller. “Another common

cause of abrasions during surgery is when a surgeon pokes around to find the paracentesis.”

The preventive measure? “Put in a dye when making the paracentesis so that you can see it,” says Dr. Miller. “Some people will enter the cornea through a peripheral blood vessel to mark the incision site with a minor bleed.”

(Continued on page 48)

How to Catch Narrow-Angle Glaucoma

Michelle Stephenson, Contributing Editor

Physicians provide diagnostic tips for getting the most from gonioscopy and imaging.

Narrow-angle glaucoma is a frequently missed diagnosis because patients don't experience acute pain or vision loss. "Chronic angle-closure glaucoma is one of the most frequently missed glaucoma diagnoses I see in glaucoma referral because the angle anatomy wasn't appreciated or wasn't being treated," says Louis B. Cantor, MD, professor at the Indiana University Department of Ophthalmology. "The referral may say the patient has primary open-angle glaucoma, when in fact he or she has slowly progressive chronic angle closure and he or she just wasn't diagnosed properly initially. Chronic angle closure often clinically behaves like primary open-angle glaucoma."

In this article, glaucoma experts share their tips for catching this unique variety of the disease.

The Importance of Technicians

The first line of defense in catching narrow-angle glaucoma is the ophthalmic technician. "Technicians are the first people in the practice to see patients, so I think it's very important for technicians in the offices of comprehensive ophthalmologists, anterior segment surgeons and retinal specialists to be able to recognize what a narrow angle looks like," says Valerie

Trubnik, MD, who is in practice in Mineola, New York. "All too often, it's missed. Patients are often dilated by the technician at the beginning of their visit, and I've seen a couple of patients who have returned post-dilation from other offices in acute angle closure. It doesn't happen very often, but it can. So, it's very important to educate the technical staff about what a narrow angle looks like at the slit lamp via the Van Herick technique. If there is any question, the physician can do a gonioscopy before the dilation."

She also recommends that technicians look at the patient's refraction when considering her risk. "If someone is hyperopic or phakic, there is the possibility of narrow angles," Dr. Trubnik says. "If someone is pseudophakic, then they probably don't have narrow angles."

Michael Stiles, MD, from Overland Park, Kansas, agrees and says that all of his technicians are trained to screen for narrow-angle closure, particularly in patients who are hyperopic. "If a patient is more than +3 D hyperopic, our technicians will ask me to perform gonioscopy before we consider dilating the patient," he says. "I'll certainly check with the pen light from the side to try to gauge the gross depth of the chamber before

considering dilation, and then do gonioscopy if it looks suspicious.”

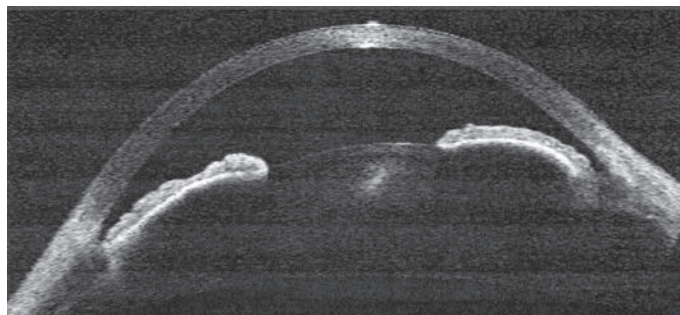
Gonioscopy

Gonioscopy remains the gold standard for assessing narrow angles and angle closure, whether acute or chronic, and glaucoma experts agree that all patients should undergo it. “The best tip for not missing [narrow-angle glaucoma] is gonioscopy, gonioscopy, gonioscopy,” Dr. Cantor says. “It’s quick, and it’s worth the time for every new patient to have gonioscopy and have the angle assessed. If there are any questions about what is seen on gonioscopy, that can be supplemented with imaging to help clinch that diagnosis or try to determine how at-risk a patient may be.”

Physicians say it’s critical to have a high index of suspicion and look at the angle in all new patients, particularly new glaucoma patients. “I’ve seen cases of narrow and potentially critical angles in myopes, so I think every new patient should undergo gonioscopy, whether or not they’re at risk for angle closure,” Dr. Stiles says. “But, certainly concentrate on the patients most at risk: hyperopes; women; the elderly; and patients with a family history of glaucoma, particularly angle-closure glaucoma.”

Dr. Stiles adds that it’s important to assess both eyes. “Unilateral narrow angles could potentially be a sign of some other type of posterior segment pathology. It’s particularly important to perform gonioscopy on the contralateral eye in a patient who has angle closure or a steamy cornea and high intraocular pressure. These patients could have neovascular glaucoma or something else,” he says.

According to Nathaniel Radcliffe, MD, who is in practice in New York City, it’s important to understand that some people will have open angles



A narrow angle in a nanophthalmic eye.

Peter Nethand, MD, PhD

glaucoma surgery have never been billed for gonioscopy. It’s surprising that so many patients undergoing glaucoma surgery haven’t had their angle examined.”

Dr. Stiles notes that some ophthalmologists use prone testing and dilation as provocative tests. “Some people use

prone testing, where patients sit in a dark room in the prone position, as a provocative test to induce elevated pressure if they’re angle-closure suspects,” he says. “I don’t find that very practical, and I don’t know if the sensitivity is strong enough to justify that in a busy clinical practice. Additionally, I don’t dilate patients as a provocative test. Many times, they’ll develop elevated pressures hours later, not immediately. Diagnosis really comes down to gonioscopy.”

in bright light conditions and closed angles in the dark. “So, when you assess the angles in your office, it’s of critical importance to do a pitch black gonioscopy with all lights in the room off, including all computer monitors and phones,” Dr. Radcliffe says. “This is called dark-room gonioscopy. Of course, a dark room setting can be used with our other two angle-detection techniques, which are anterior-segment OCT and ultrasound biomicroscopy. I use all three of those in my patients with glaucoma.”

Dr. Radcliffe also recommends performing gonioscopy at more than one visit. “Repeating gonioscopy on a different day yields slightly different results with surprising frequency,” he says. “I have patients who looked open one year and were closed the next. I don’t think that they changed in one year; I think they fluctuate from visit to visit. Gonioscopy is incredibly valuable, so, repeat it. Do it often. I do it at least annually in patients with glaucoma. And if there’s a question in my mind, I repeat it. It’s not an expensive test, so we should do as much as we need to make sure we never miss angle closure.”

Dr. Cantor also sees value in periodic gonioscopy exams. “We tend to think once we’ve done it, we never need to do it again,” Dr. Cantor says. “Gonioscopy and looking at the angle are very underutilized. Studies have shown that many patients in a Medicare database who are undergoing

prone testing, where patients sit in a dark room in the prone position, as a provocative test to induce elevated pressure if they’re angle-closure suspects,” he says. “I don’t find that very practical, and I don’t know if the sensitivity is strong enough to justify that in a busy clinical practice. Additionally, I don’t dilate patients as a provocative test. Many times, they’ll develop elevated pressures hours later, not immediately. Diagnosis really comes down to gonioscopy.”

Anterior-segment OCT

While a comprehensive clinical exam and gonioscopy are good first steps when examining a patient’s iridocorneal angle, a few supplemental technologies are now available to help ophthalmologists better understand the angle anatomy.

Probably the most commonly used adjunct to supplement gonioscopy is anterior segment optical coherence tomography. “Anterior-segment OCT is limited in that you can’t see anything posterior to the iris plane because of shadowing and loss of signal,” explains Dr. Cantor. “But one of the advantages of an anterior-segment OCT over an ultrasound, which can look posterior to the iris, is that OCT is generally a non-contact exam. Additionally, the patient can be imaged in the seated position with OCT, so that you can see what happens with the lens and you can look at multiple quadrants all at once. This

is difficult to do with ultrasound biomicroscopy, where the patient often has to be in the supine position, and you can only image certain areas of the angle at a time. And, of course, when a patient is lying down, the lens may displace posteriorly and change the angle anatomy.”

Dr. Radcliffe says you can multi-task when doing an OCT exam, since most modern OCT machines allow the capacity for anterior-segment OCT, as well as posterior-segment imaging. “If you are managing glaucoma, you should definitely invest in anterior-segment OCT capability,” he says. “Many ophthalmologists have anterior-segment OCT capability, but they don’t use it. The reimbursement hasn’t been perfect, and you can’t bill for an anterior-segment OCT done at the same visit at which you bill for an optic nerve OCT. However, it’s important to focus on the care you want to provide and not on reimbursement. So, every time I have a patient in my office and we’re scanning the optic nerve, I ask the technician to scan the angles as well—and you get surprises now and again. The key, though, is that it only takes your tech a few moments to scan the angles when he or she is already scanning either the macula or the nerve.”

Dr. Trubnik says she’s using anterior-segment OCT more often. “It depends on how the imaging is done,” she explains. “For example, it depends on how much light is in the room during imaging. Even if the angle looks open on anterior-segment OCT but appears closed to me on exam, I will, of course, still recommend a laser peripheral iridotomy.

“I also find anterior-segment OCT very useful when I’m talking to patients,” she adds. “So, for instance, if I’m consenting someone for a laser iridotomy, just doing a gonioscopy isn’t sufficient evidence for patients. Even though they trust me, it really helps if they see the anterior-segment OCT in order to visualize what

I’m talking about.”

Patients may not believe that they have narrow-angle glaucoma because they have no pain and no visual symptoms. “It’s a silent condition that they’re unaware of,” Dr. Trubnik says. “So, it can be helpful to actually show them an image of a normal anterior-segment OCT and then their narrow-angle image.”

Dr. Trubnik also uses imaging to follow glaucoma progression. “In some patients, I’ll do it every six months to show them how things are changing,” she explains. “However, I don’t by any means use it as a substitute for my exam. Just looking at the anterior segment OCT can’t diagnose someone with narrow angles or rule it out. It’s just something I use as confirmation.”

Dr. Stiles also uses imaging to follow progression. “This is particularly true if I have a patient who is at risk, but he or she isn’t convinced. ‘I’ll follow that patient for serial analysis. The other instance would be following a patient who has a fairly narrow angle even after iridotomy.’”

Ultrasound Biomicroscopy

Less often, Dr. Trubnik will perform ultrasound. “I find that it’s more helpful in patients in whom I’m suspecting plateau iris,” she says. “It shows me the ciliary body. I don’t use it on a regular basis with just a standard narrow-angle patient.”

Dr. Radcliffe agrees. “For the most part, ophthalmologists and glaucoma specialists can get along fine without using ultrasound biomicroscopy,” he avers. “There are lots of platforms available, so it’s possible to have one in your office. But you don’t need to test every day, and it is a little bit more nuanced, so, it’s nice if you have a colleague you can refer to for the occasions you need it. Everyone doesn’t need UBM in their practice. Having said that, if you do have UBM, it’s very useful. It’s particularly useful for look-

ing at the ciliary body and detecting plateau iris, which occurs in patients who’ve had an iridotomy but still have a narrow angle after the iridotomy has been performed. UBM is also useful for some of the oddball cases of angle closure that don’t make sense and don’t seem to be following the normal patterns.

“If you are performing UBM, performing it in the dark will provide the best yield in terms of detecting people with closed angles, because the pupil dilates in the dark,” Dr. Radcliffe continues. “Of course, we spend one-third of our lives with our eyes closed and our pupils dilated in sleep, so there are many glaucoma patients who look like they have open angles during the day in a lit room, but in the dark with their eyes closed is when the trabecular meshwork is getting damaged and the pressure is probably high.”

The Future

According to Dr. Cantor, the major advantage of anterior-segment OCT is that you can get quantitative assessment. “Gonioscopy is very subjective,” he notes. “With OCT, we can begin to put numbers to things and quantify the angle anatomy in ways that we couldn’t previously. In the future, I think we’ll have Fourier-Domain OCT to get more three-dimensional imaging. This may allow us to better predict those patients who are at risk for angle closure than perhaps we are able to do today. And I think the use of it will grow, but it still won’t replace gonioscopy. Rather, it will supplement our gonioscopy findings to help us better understand the angle anatomy and which patients may be at risk for developing angle-closure glaucoma.” **REVIEW**

Dr. Cantor is a consultant for Zeiss. Dr. Radcliffe is a consultant for Zeiss and Reichert. Drs. Trubnik and Stiles have no financial interests to disclose.

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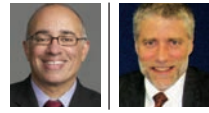
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Glaucoma Severity: Individualizing Surgery

Surgical intervention to relieve high intraocular pressure is not a “one-size-fits-all” proposition. A surgeon shares his experience.

Brian Francis, MD, MS, Los Angeles

As glaucoma specialists, we manage patients with all levels of disease, from ocular hypertensives on no medications to patients with advanced disease and limited vision. In many cases, medications aren’t sufficient to keep a patient’s intraocular pressure under control, so surgical intervention becomes necessary.

Fortunately, we have many more surgical options today than we did 10 or 20 years ago. That’s a good thing, in part because it allows us to take the severity of the patient’s disease into account when choosing a procedure. Each surgical option has different benefits and risks, so this is definitely not a case of “one size fits all.”

Unfortunately, many patients are still treated with less than ideal surgeries. We’ve seen patients in our clinic with mild, non-progressing glaucoma who had undergone a trabeculectomy. On the other hand, we’ve seen patients with advanced glaucoma who really did need a trabeculectomy but came to us having undergone a MIGS procedure.

The point is that it’s crucial to pick the right procedure for the right patient—and one of the most

important determinants of the right procedure is the stage of the disease. (Note: The treatment algorithm described in this article is my own, based on my experience, so it’s only a guideline. Surgeons should use their experience and available technology to construct their own algorithm.)

Risk Matters

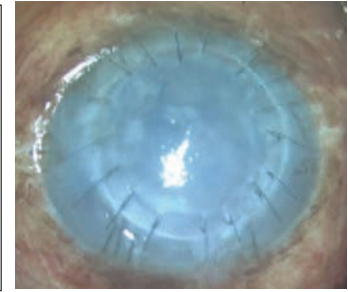
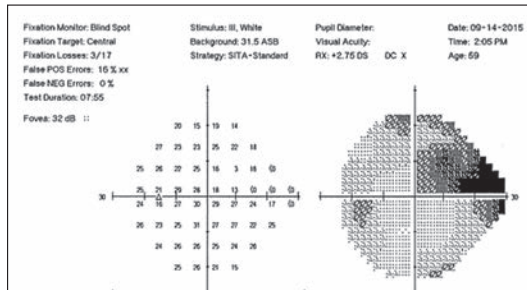
The dangers of using a procedure that’s more impactful than the patient needs are illustrated by a case we managed 15 years ago, when our surgical choices were far more limited. The patient was a 78-year-old female with primary open-angle glaucoma. Her pressure was 28 mmHg on three medications; her vision was 20/30, with a cup-to-disc ratio of 0.8. Her visual field revealed a superior arcuate scotoma and an inferior nasal step. (See illustration, facing page.) Her visual field damage was significant, but not advanced. She had what many doctors would consider moderate glaucoma.

At that time we felt that the best option for her was a tube shunt, so we implanted a Baerveldt Glaucoma

Implant (Johnson & Johnson Vision, Santa Ana, California). As expected, her IOP was high during the first six weeks before the tube opened. Once it opened, the pressure decreased significantly, to 4 mmHg. Unfortunately, at that point she developed a flat anterior chamber with a choroidal hemorrhage and effusion, requiring surgery to drain the choroidal and re-form the anterior chamber.

She ended up with a pressure of 12 mmHg, which is very good; but because of the choroidal hemorrhage, effusion and flat chamber, she developed corneal failure and required a penetrating keratoplasty. Then, the graft failed and she declined further surgery. So she went from having 20/30 vision and a pressure of 28 mmHg to a pressure of 12 mmHg with only hand-motion vision. The aggressiveness of the surgery resulted in a poor outcome.

Surgeries such as tube shunts and trabeculectomies carry significant risks. In 2011 we published a study in which we looked at a large number of our own patients that had undergone trabeculectomy, to find out how they fared in terms of vision loss



When fewer surgical options were available, riskier surgeries were often used for patients with moderate disease. In this case from 15 years ago, a 78-year-old female with moderate open-angle glaucoma received a tube shunt. Complications led to the need for a penetrating keratoplasty, but the graft failed. She ended up with only hand-motion vision.

and recovery.¹ Close to 65 percent of these patients experienced some vision loss during the postoperative period; fortunately, that loss was only permanent in 8 percent of them, so the majority recovered. (However, in some cases that recovery didn't happen until one or two years after the surgery.) Meanwhile, severe, permanent vision loss occurred in about 4 percent of the patients; and of those, about half were unexplained. The causes we could explain included hypotony maculopathy, corneal opacification and retinal hemorrhage. The 2 percent that were unexplained had no complication or identifiable cause that we could find. (See table, p. 46.)

Along similar lines, a 2017 study examined the course of vision loss after Baerveldt aqueous tube shunt placement.² The authors retrospectively reviewed 247 eyes of 222 patients who underwent Baerveldt implantations. Six months after surgery, 63 of the 247 eyes (25.5 percent) suffered long-term loss of three or more lines of Snellen visual acuity; in 24 of them, the visual loss was severe. In 18 cases, there was no identifiable cause of vision loss. Additionally, transient vision loss occurred in 76 of 242 eyes (30.8 percent). The authors concluded that a decrease in vision is not uncommon after Baerveldt surgery.

Today, of course, minimally invasive glaucoma surgeries, or MIGS, are an option. Still, we're frequent-

ly asked why we don't just do trabeculectomy in most patients; after all, the reasoning goes, it lowers pressure much more effectively than MIGS, and it's considered the "gold standard."

Yes, trabeculectomy is the gold standard when it comes to IOP lowering. But as these studies and the sample case demonstrate, there are serious risks associated with trabeculectomy and tube shunts, and those risks aren't associated with MIGS. So, in our practice we now choose the surgery we're going to perform based on a patient's disease state—how severe the existing damage is, and the patient's prognosis. That allows us to balance the patient's need for pressure reduction with the risks of the surgery in question.

Surgically Decreasing IOP

Currently, we have four different means to lower IOP surgically:

- **Create transconjunctival filtration.** We can do this via trabeculectomy or tube shunts, as well as newer options such as Xen, with the InnFocus/Santen Microshunt coming soon.

- **Decrease aqueous production.** These procedures alter the ciliary processes. The current alternatives include endoscopic cyclophotocoagulation; transscleral cyclophotocoagulation; and micropulse cyclophotocoagulation.

- **Increase trabecular outflow.**

This can be done via an internal or external approach. The former group includes *ab interno* canaloplasty; excimer laser trabeculotomy; implanting a trabecular micro-bypass stent such as iStent or Hydrus; and trabeculotomy or goniotomy using an internal approach with a tool such as the Trabectome, Kahook Dual Blade or Goniotome.

- **Increase suprachoroidal outflow.** Devices to accomplish this include the CyPass (Alcon, currently unavailable) and the iStent Supra (Glaukos) and MINiject (Staar) that are not cleared by the U.S. Food and Drug Administration. Given this list of options, the key issue becomes choosing the best alternative for the patient in front of you—in other words, individualizing the surgery for that particular patient, so that the procedure you perform isn't more—or less—than what the patient needs.

To choose the ideal surgery, you need to weigh a list of factors. Probably the most important factor is target IOP. This should be based on the patient's baseline IOP; the amount of glaucomatous damage already in evidence; and the rate at which the disease appears to be progressing. Beyond the target IOP, your choice should take into account:

- the anatomy of the eye;
- the health of the conjunctiva and sclera;
- the condition of the angle (in-

cluding how closed or open the angle is, which will affect your ability to do angle-based surgery)

- whether the patient has had prior glaucoma surgeries;
- the risk of long-term infection;
- the risk of hypotony;
- the patient's age and life expectancy;
- the patient's ability to use glaucoma medications postoperatively; and
- the patient's lifestyle and preferences.

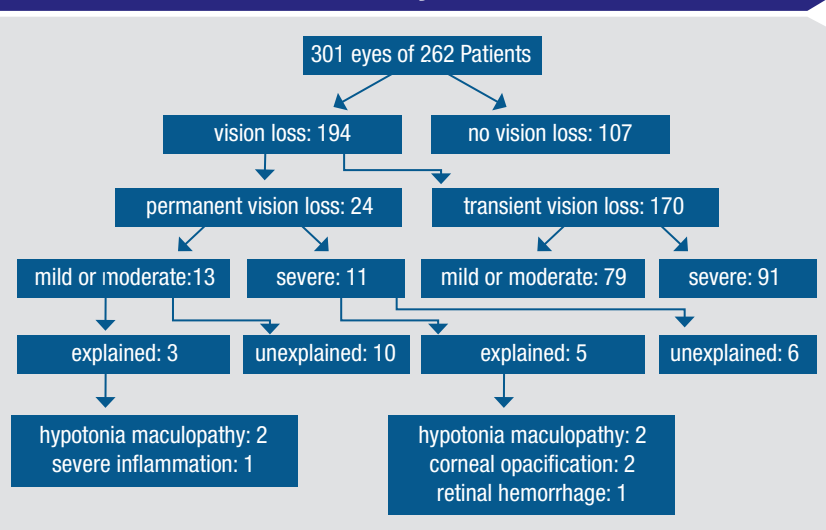
The MIGS Myth

The key to getting the best outcomes is knowing when to do which type of glaucoma surgery. Solving that dilemma has become less straightforward with the advent of MIGS. Since MIGS is relatively new, we're still trying to figure out how it fits in with the standard trabeculectomy and tube shunt options.

Many surgeons hesitate to resort to a MIGS procedure when a patient's pressure is relatively high—for example, greater than 30 mmHg. Surgeons have heard that MIGS procedures generally produce a pressure drop of about 25 percent, so they calculate that they'll only get a drop of 7 or 8 mmHg if the baseline pressure is 30 mmHg. Then, they may conclude that such a patient needs an aggressive form of surgery to achieve an acceptable pressure.

Actually, this 25-percent drop with MIGS is a myth; regardless of the starting pressure, many MIGS procedures will leave your patient in the mid-teens. Thus, the higher the starting pressure, the more pressure drop you're going to get. In fact, many MIGS procedures consistently produce pressures in the 15- to 16-mmHg range, and sometimes lower, regardless of the baseline pressure. For example, many patients starting with a pressure of 35 mmHg will end up at 16 mmHg following a

Vision Loss after Trabeculectomy with MM-C¹



A 2011 study conducted by the author illustrates why trabeculectomy should be reserved for patients with advanced disease.¹

MIGS procedure. That's more than a 50-percent pressure reduction. So when deciding whether a MIGS procedure is appropriate, it's not so much the amount of pressure lowering you should consider; it's the target pressure you hope to achieve. This means that patients with very high baseline IOPs are often excellent candidates for MIGS, and a more aggressive form of surgery isn't required.

Why isn't this more widely known? For one thing, not too many patients start with pressure that high, so there's not a lot of data about what happens following MIGS in these patients. However, we recently published a study demonstrating this pressure drop in 49 patients who began with a medicated IOP of 30 mmHg or higher.³ Twenty-eight of the patients were treated with Trabectome alone; 21 underwent Trabectome combined with phacoemulsification. Mean IOP was reduced from 35.6 ± 6.3 mmHg to 16.8 ± 3.8 mmHg at one year ($p < 0.01$), and the number of medications dropped from 3.1 ± 1.3 to 1.8 ± 1.4 ($p < 0.01$). (Nine patients required secondary glaucoma surgery

and one patient had hypotony on day one, which resolved within a week.) So despite what you may have heard, MIGS procedures can be very effective in patients with high IOPs.

Of course, some patients need to reach a pressure lower than the mid-teens. In that situation, MIGS may not be appropriate, because while it can lower pressure more than many surgeons realize, it rarely will take it below the mid-teens. If you have a patient with advanced glaucoma with a pressure of 16 who is progressing, for example, that patient wouldn't be a good MIGS candidate; that person needs a trabeculectomy to get down to a pressure of 10 mmHg or lower.

The point is that whether MIGS is appropriate depends less on the patient's starting pressure, and more on whether you need to reach a very low target IOP with that patient. (The first patient we discussed, who had a pressure of 32 mmHg and a cup-to-disc ratio of 0.8, had moderate glaucoma. She would probably have done very well with Trabectome, Kahook Dual Blade or GATT, because she didn't need to achieve a pressure of 10 or 11 mmHg.)

Individualizing Surgery

I think of glaucoma surgery options as a hierarchy. The first group of options would be those that use a laser to treat the trabecular meshwork (for example, SLT). The next group involves trabecular meshwork surgery, which can mean Schlemm's canal dilation, trabecular stenting, trabecular removal by unroofing, or trabecular meshwork rupture with a procedure like GATT. The third group is suprachoroidal stents. (As everyone knows, this option is not available right now because of the recall of CyPass. However, I believe that CyPass will eventually be approved again for some treatments, and other suprachoroidal stents are in the pipeline.) The final group in my hierarchy is conjunctival filtration. The remaining type of surgery, aqueous suppression treatments, is a kind of wild card, because those procedures can be done at any disease stage. You can use them in early glaucoma combined with cataract surgery, as many surgeons do with ECP; and you can do them in advanced glaucoma patients who have failed multiple glaucoma surgeries.

Let's consider these options in the context of patients at each level of disease severity:

- **Ocular hypertension on no medications.** For these patients I'd recommend doing SLT or cataract extraction by itself. (There's good evidence from the OHTS study that cataract surgery in ocular hypertensives does help to lower IOP.)⁴

- **Ocular hypertension on medical treatment.** A patient in this situation would be thought of as a high-risk ocular hypertensive. If the patient has a cataract, you can still just remove the cataract, or you can do a minimally invasive procedure such as *ab interno* canaloplasty, or a trabecular stent. If the patient doesn't have a cataract, you can still

do SLT, an *ab interno* canaloplasty or a trabecular meshwork removal procedure such as Trabectome or Kahook Dual Blade.

- **Mild open-angle glaucoma.** If the patient has a cataract, you should consider trabecular removal, a trabecular bypass stent or performing ECP in addition to cataract surgery. If the patient doesn't have a cataract, I'd suggest trabecular removal as a primary option, whether the patient is phakic or pseudophakic.

If a mild-glaucoma patient has already had one of these procedures and it failed to achieve the goal, we can do Trab360, or GATT, which basically opens the trabecular meshwork 360 degrees. These patients might also benefit from a suprachoroidal stent, if they're available. You can also consider adding an MPCPC or ECP procedure to suppress aqueous production.

- **Moderate glaucoma.** This group is more complicated, but can be treated with a wide range of options. If the patient has a cataract, your options are similar to the previous group: trabecular removal, a trabecular bypass stent, a suprachoroidal stent (if available), and also ECP combined with cataract surgery. If the patient doesn't have a cataract, trabecular removal would be your primary choice, but you could also consider implanting a suprachoroidal stent (if available), and the Xen gel stent—using either the *ab externo* transconjunctival approach (XTC) or an internal approach. I find this way of implanting the Xen a bit easier than the internal approach, and there are two variations on it. For more moderate glaucoma, I recommend the *ab externo* transconjunctival approach. For more advanced glaucoma, I use the *ab externo* open conjunctival approach, which I call XEO.

If the moderate glaucoma patient has already failed one of these procedures, others can be performed as a

secondary procedure.

- **Severe open-angle glaucoma.** The best option here depends a lot on the patient's specific condition. If the patient has a cataract, you can do trabecular removal (or a suprachoroidal stent if available)—but only if the patient doesn't need a pressure in the 10 to 12 mmHg range. You might also consider these options if the patient is at high risk for problems associated with filtration surgery.

If the patient doesn't have a cataract, your options would include trabeculectomy, a tube shunt, and implanting a Xen, *ab externo*, open conjunctival technique. If you proceed with a tube shunt, my recommendation would be to use a non-valved shunt. These tend to achieve lower pressures, which we saw in the Ahmed vs. Baerveldt studies—although they're also associated with a higher rate of complications.^{5,6}

Incidentally, I've had many patients who clearly needed a trabeculectomy but specifically stated that they didn't want one. They'd read about them online and were apprehensive about the risks. In those cases, if the patient needs a lower IOP, sometimes we combine MIGS procedures that work in different ways. If you combine an aqueous inflow procedure with a trabecular outflow procedure, for example, you may be able to get lower pressures than you would with just one of the MIGS procedures.

If a procedure has already failed, which option comes next depends in part on which one failed. Possible choices would include XEO or XTC; trabeculectomy; a tube shunt (I recommend Baerveldt); a tube-shunt exchange (Baerveldt to Ahmed) if an Ahmed failed to achieve low-enough pressures; CPC or ECP; and a second tube (superior vs. inferior).

Ready for Anything

The bottom line is that your

choice of surgery should be based on disease severity, and it should be patient-specific. Trying to use one surgical approach for every patient is a mistake. So, if you're a glaucoma specialist, you should have several options in your armamentarium; that will allow you to appropriately manage the variety of patients and disease states you encounter.

I recommend that you be able to perform:

- a trabecular stent procedure, or an *ab interno* canaloplasty;
- a trabeculotomy or goniotomy procedure that can remove the trabecular meshwork—e.g., KDB, Trabectome, or possibly a trabeculotomy 360 or GATT procedure;
- an aqueous inflow procedure, whether it's MPCPC, ECP or TSCPC;
- a conjunctival filtration device (right now that means Xen, with the InnFocus MicroShunt hopefully

becoming an option soon);

• trabeculectomy and tube shunts. (For tube shunts, I recommend that you be familiar with both valved and non-valved options.)

Note that these recommendations are for glaucoma specialists. If you're a general ophthalmologist, you don't need to be able to offer all of these options, but you should be aware that they're available. With that knowledge, if you realize that a particular procedure would be ideal for a patient, and it's something you don't offer, you can refer the patient for that procedure. **REVIEW**

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Neomedix, Glaukos, BVI, NeOptix, Diopsys, Allergan and New World Medical; received grant support from Allergan, InnFocus, Santen, Alcon, Diopsys and Iridex; and has lectured for Bausch+Lomb and Aerie.

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(Continued from page 39)

Dealing with Inflammation

Dr. Hatch notes that she would never perform cataract surgery in the presence of inflammation. "If the patient has chronic uveitis and needs cataract surgery, I wait until the patient's eye isn't actively inflamed," she says. "Such a patient will have synechiae and small pupils.

"I give a subconjunctival dexamethasone injection or may rely on the dissolvable implant, Ozurdex (Allergan)," she adds. "Some surgeons will do intracameral injections in conjunction with a steroid and subcameral antibiotic injections along with a steroid and nonsteroidal drop. Taper over four weeks."

Wound Burns

Dr. Crandall says wound burns are rare but very serious. "One should be aware that different viscoelastics can

increase the risk for wound burns," he says. "It is critical to understand dispersive versus cohesive viscoelastics and to clear space so that there is flow in and flow out of the eye. The tip should not be clogged, because the temperature will immediately cause a burn."

"Phaco burns are very bad," adds Dr. Miller. "The cornea coagulates quickly and becomes like hard plastic. You end up needing five to seven sutures to close a 2.2-to-3-mm opening."

Dr. Miller says phaco burns frequently happen in tight incisions. "Besides developing when the tip has been occluded, a burn can occur when a tight incision crimps the sleeve of the phaco tip and that squeezes against the tip, cutting off fluid flow and causing frictional heat to generate," he says. "The phaco tip continues to vibrate, generating extreme heat."

Surgeons can easily avoid this

problem, however. "The bottom line is that phaco burns occur in tight incisions," says Dr. Miller. "The most important thing you can do is ensure that you're not making incisions that are too tight. Make the incision wide enough to avoid this problem."

Meeting Expectations

Recognizing that a variety of different challenges can arise during cataract surgery, these surgeons recommend keeping all of the strategies they discussed in mind.

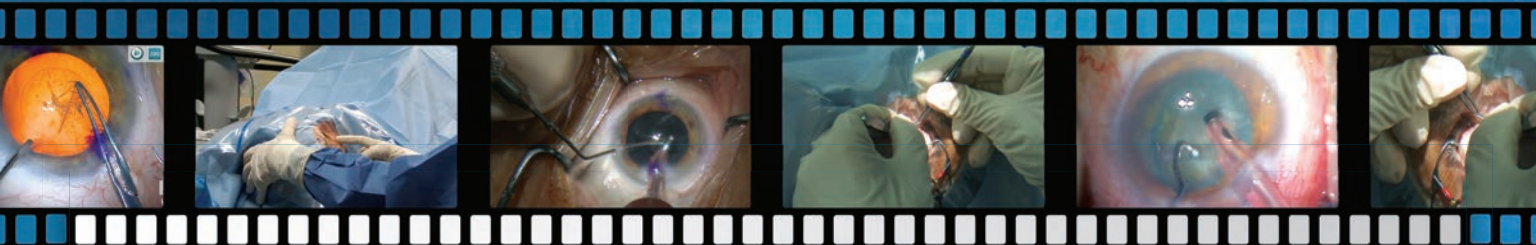
"Above all other things, I would say it's important to know what you're getting into and to communicate this honestly to your patient," says Dr. Crandall. "When it's not going to be easy, tell the patient it is not going to be easy. You need to be practical—not only in meeting surgical challenges, but also in making sure the patient knows what both of you are up against." **REVIEW**



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Satisfactory Completion - Learners must pass a post-test and complete an evaluation form to receive a certificate of completion. You must listen to/view the entire video as partial credit is not available. If you are seeking continuing education credit for a specialty not listed below, it is your responsibility to contact your licensing/certification board to determine course eligibility for your licensing/certification requirement.



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Gene Therapies for Inherited Diseases

A review of the many treatments in the research pipeline for retinal diseases that have continuously resisted treatment.

*Cristina Bostan, MD, MSc, and Cynthia X. Qian, MD, FRCSC, DABO
Montreal, Quebec*

Inherited retinal diseases resulting from genetic mutations lead to progressive retinal degeneration and loss of visual function. Until recently, clinical characterization was the mainstay of diagnosis and classification of IRDs, but genetic characterization has been gaining increasing importance. Over the past three to four decades, more than 260 genes associated with IRDs have been identified, and another 37 mapped to chromosomes.¹ This progress has led the way to the development of gene therapies to address disorders which were previously considered incurable.

This article will provide an overview of the principles of gene therapy and an update on the current active trials for the treatment of IRDs at the clinical stage of development.

Gene Therapy: Major Concepts

Genetic therapies address DNA mutations in several ways. First, the gene can be “augmented” by delivering correct copies of the genes to the affected cells, which will lead to synthesis of functional proteins. Gene augmentation is the most com-

monly used approach to IRDs. This approach targets autosomal recessive or X-linked mutations well, since blocked protein synthesis or production of an abnormal functionally null protein can be augmented and rescued by this technique.²

Second, the gene can be edited by “genome surgery” through delivery of “molecular scissors” called endonucleases to target cells, also known as Clustered Regularly Interspaced Short Palindromic Repeats” (CRISPR) technology. Lastly, the mRNA transcribed from the mutated DNA gene can be corrected or its translation stopped by the delivery of a binding anti-sense RNA segment, called “antisense oligonucleotide” (AON).

Except for AONs, the therapeutic genetic material must be delivered to target retinal cells using a vector. The most commonly used vectors are adeno-associated viruses (AAVs) and lentiviruses. Both are non-pathogenic and don't cause serious systemic adverse effects. AAVs infect both dividing and non-dividing cells, do not integrate into the host genome and have a carrying capacity of 4.5 to 4.9 kb, a size corresponding to that of smaller

genes.² Lentiviruses have less propensity to infect non-dividing cells, integrate into the host genome with a consequent small risk of new oncogenic or non-oncogenic mutations, and can carry larger genes of up to 8 kb.²

After integrating the genetic material into vectors, the preparation is amplified, purified of empty capsids and supplemented with surfactant material to prevent product adherence to its container.³ The final product can be delivered via subretinal or intravitreal injection. The choice of the administration route depends mainly on the location of the cells that are targeted by the treatment.

Subretinal injection is preferred when outer retinal layers, including photoreceptors and retinal pigment epithelium, are affected, as is the case in most IRDs. Since delivery with this technique is localized, there's minimal risk of extraocular dissemination and systemic immunogenicity. However, it requires pars plana vitrectomy under retrobulbar or general anesthesia, and can be subject to all vitrectomy-associated risks.³ As may be expected, subretinal injection induces a localized retinal detachment and/or thinning;

Table. Ongoing Gene Therapy Clinical Trials for Inherited Retinal Diseases

(registered on www.clinicaltrials.gov as of June 20th, 2019).

Disease	Gene/(vector) delivery	Phase	Status	Sponsor (country)	Trial number
LCA	QR-110 (AON, CEP290 gene) Intravitreal	I/II	Active, recruiting closed	ProQR (U.S., Belgium, France)	03140969
		II/III	Recruiting		03913143
	RPE65/AAV Subretinal	I/II	Recruiting	MeiraGTx U.K. II Ltd (U.K.)	02781480
X-linked RP	RPGR/(AAV2) Subretinal	I/II	Recruiting	MeiraGTx U.K. II Ltd (U.K.)	03252847
	RPGR/(AAV2) Subretinal	I/II	Recruiting	AGTC (U.S.)	03316560
	RPGR/(AAV8) Subretinal	II/III	Recruiting	Nightstar (U.S.)	03116113
Autosomal recessive RP	RLBP1/(AAV8) Subretinal	I/II	Recruiting	Novartis (Sweden)	03374657
	PDE6B/(AAV2) Subretinal	I/II	Recruiting	Horama S.A. (France)	03328130
	MERTK/(AAV2) Subretinal	I	Recruiting	Fowzan Alkuraya (Saudi Arabia)	01482195
Usher 1B	MYO7A/(EIAV) Subretinal	I/II	Recruiting	Sanofi (U.S., France)	01505062 02065011 (long-term)
Usher 2A	QR-421a (AON; USH2A gene) Intravitreal	I/II	Recruiting	ProQR (U.S., Belgium, France)	03780257
Choroideremia	REP1/(AAV2) Subretinal	I/II	Completed	Ian MacDonald (Canada)	02077361
	REP1/(AAV2) Subretinal	I/II	Completed	University of Oxford (U.K.)	01461213
	REP1/(AAV2) Subretinal	II	Completed	Byron Lam (U.S.)	02553135
	REP1/(AAV2) Subretinal	I/II	Active, recruiting closed	Spark (U.S.)	02341807
	REP1/(AAV2) Subretinal	II	Active, recruiting closed	STZ eyetrial (Germany)	02671539
	REP1/(AAV2) Subretinal	II	Recruiting	University of Oxford (U.K.)	02407678
	REP1/(AAV2) Subretinal	II	Recruiting	Nightstar (U.S., Germany)	03507686 3584165 (long-term)
	REP1/(AAV2) Subretinal	III	Recruiting	Nightstar (U.S., Canada, U.K., Finland, Germany, Netherlands)	03496012
Stargardt	ABCA4/(EIAV) Subretinal	I/II	Recruiting	Sanofi (U.S.)	01367444 01736592 (long-term)
Achromatopsia	CNGB3/(AAV2) Subretinal	I/II	Recruiting	AGTC, NEI (U.S.)	02599922
	CNGB3/(AAV2) Subretinal	I/II	Recruiting	MeiraGTx U.K. II Ltd (U.K.)	03001310 03278873 (long-term)
	CNGA3/(AAV2) Subretinal	I/II	Recruiting	AGTC (U.S., Israel)	02935517
	CNGA3/(AAV2) Subretinal	I/II	Active, recruiting closed	STZ eyetrial (Germany)	02610582
X-linked retinoschisis	RS1/(AAV8) Intravitreal	I/II	Recruiting	NEI (U.S.)	02317887
	RS1/(AAV2) Intravitreal	I/II	Closed	AGTC (U.S.)	02416622

LCA, Leber's congenital amaurosis; AON, antisense oligonucleotide; RP, retinitis pigmentosa; RPGR, retinitis pigmentosa GTPase regulator; AAV, adeno-associated virus; AGTC, Applied Genetic Technologies Corporation; PDE6B, phosphodiesterase 6B; MYO7A, myosin VIIA; EIAV, equine infectious anemia virus (lentivirus); REP1, Rab escort protein 1; ABCA4, ATP-binding cassette sub-family A; CNGA3/B3: cyclic nucleotide gated channels a3/b3; RS1, retinoschisin 1; NEI, National Eye Institute.

however, this is usually transient and clinically non-significant.^{2,5}

Intravitreal injection is chosen when internal retinal layers or wide areas of the retina must be treated, or when there are concerns of retinal fragility due to the underlying disease process that would prevent adequate and safe subretinal injection.³ Intravitreal administration is technically easier, but is associated with a higher risk of systemic shedding of the vector.³

Targeting IRDs

IRDs are ideal targets for gene therapy for several reasons:

- the relative immune privilege of the eye;
- the tight blood-retinal barrier limiting systemic dissemination of substances injected intraocularly;
- the compartmentalized structure and small size of the eye, requiring injection of only small quantities of drugs for efficacy;
- the accessibility of the eye, allowing precise retinal structure visualization, targeted localized drug delivery and non-invasive monitoring of the patient's response to therapy;
- the arrest of retinal cell proliferation after birth, resulting in indefinite expression of delivered genes after a single injection; and
- symmetric disease involvement of the contralateral eye that can be used as a control for evaluating a gene therapy's efficacy.²

Among IRDs, those most amenable to genetic therapies are monogenic and caused by autosomal-recessive or X-linked mutations. Dominant mutations are more difficult to address, due to the gain-of-function abnormal protein interfering with the action of the correct protein that's synthesized following treatment.² Furthermore, slowly progressive IRDs diagnosed early in the disease process are more favorable candidates, since they allow

for a wider window for treatment before the damage is too advanced and no viable target cells for gene therapy are left.³

Clinical Trials

The expanding knowledge of the natural history of IRDs, the identification of significant visual function parameters, the development of non-invasive measurement instruments capable of detecting change in these parameters, and extensive preclinical research on animal models have enabled several gene therapies to reach the clinical stage of development (*See Table, pg. 51*).

- **Leber congenital amaurosis (LCA).** A landmark clinical trial led to the approval of voretigene neparvovec (Luxturna; Spark Therapeutics) by the U.S. Food and Drug Administration in December 2017, making it the only approved IRD genetic therapy.

Voretigene neparvovec is the most clinically advanced among studied gene therapies. It targets retinal pigment epithelial specific protein 65 kDa (RPE65)-related dystrophies, such as LCA type 2, and 1 to 3 percent of retinitis pigmentosa cases. The RPE65 protein is responsible for converting all-trans retinoid to 11-cis retinal, and its absence or dysfunction leads to an inability to regenerate visual pigment in photoreceptors. Voretigene neparvovec delivers correct copies of the RPE65 gene using an AAV vector. It's administered as a single subretinal injection.

The Phase III trial studied 20 patients treated sequentially in both eyes with the drug, and nine control patients.⁶ At one year, treated patients met the primary endpoint of a significant improvement in performance in the multi-luminance mobility test when compared to control patients. Treated patients gained functional vision, allowing independent navigation over a wide range of luminance

conditions, while subjects in the control group remained stable. Non-treated patients that were crossed over to the treatment group after one year achieved final outcomes similar to those in the original intervention group. No harmful immune responses associated with the drug itself were observed.

More than 400 other mutations across the 14 LCA-associated genes are known,² and efforts to develop therapies targeting these other mutations continue. One of the most frequent LCA-associated mutations affects the centrosomal protein 290 (CEP290) gene, accounting for 15 percent of cases.² The gene encodes a protein crucial for photoreceptor cilia function. Significant progress has been made in developing an AON, QR-110 (sepfarsen), aimed at correcting the CEP290-derived mRNA before its translation into protein. In Phase I/II trials, the drug was found to be safe and well-tolerated, as well as effective in terms of visual acuity improvement and its scores in multi-luminance mobility and full-field stimulus tests.⁷ A Phase II/III commercial clinical trial (ILLUMINATE) sponsored by ProQR evaluating QR-110 is currently ongoing.⁷

- **Retinitis pigmentosa.** The most common IRD is RP.⁸ It's a genetically and phenotypically diverse disorder, characterized by primary rod and secondary cone photoreceptor degeneration.² More than 100 associated mutated genes have been identified,¹ and they collectively affect between 1 in 4,000 to 1 in 2,500 individuals.² The disease can be inherited in an autosomal recessive (50 to 60 percent), autosomal dominant (30 to 40 percent) or X-linked fashion (5 to 15 percent).² AAV-based gene augmentation therapies are underway for three autosomal recessive forms, currently at the Phase I/II stage of clinical development (*Table, pg. 51*). One of the more prevalent of these forms is a

mutation in the phosphodiesterase 6B (PDE6B) gene, accounting for 2 to 4 percent of RP cases.⁹ The encoded PDE6B protein is a subunit of PDE6, that plays an essential role in the rod phototransduction cascade. Retinaldehyde-binding protein 1 (RLBP1) gene mutations are much rarer⁹ and lead to abnormal rod retinoid metabolism. Diagnosis of the RLBP1-associated autosomal recessive form is made early due to specific fundus findings, leaving a wide therapeutic window for gene treatment.

Mer receptor tyrosine kinase (MERTK) gene mutations are also relatively rare.⁹ The MERTK protein is involved in outer photoreceptor segment phagocytosis by the RPE; these segments accumulate and lead to outer retinal degeneration when the protein is dysfunctional. Early findings are available for the MERTK gene therapy trial: Of the six patients included, none had any drug-related complications, and three experienced an improvement in visual acuity, although this wasn't maintained at two years.¹⁰ X-linked RP cases are at the more severe end of the spectrum of the disease, and 70 to 80 percent are caused by mutations in the retinitis pigmentosa GTPase regulator (RPGR) gene. Three independent commercial clinical trials—two Phase I/II trials and one Phase II/III trial—evaluating AAV-based RPGR gene therapy are currently underway.

• **Usher syndrome.** In Usher syndrome, RP is associated with audio-vestibular impairment; the disease accounts for approximately 20 to 40 percent of recessive RP.⁹ Genetically heterogeneous, it's associated with 11 loci and nine genes important to the function and stability of the photoreceptor cilium. Clinical classification of Usher syndrome (I, II or III) is based on the severity and timing of the sensory impairments.² The most severe type is Usher 1B, which is caused by a mutation in the

myosin VIIa (MYO7A) gene.² A commercial clinical trial using an equine lentivirus to deliver the large MYO7A gene subretinally, which includes a dose-escalation phase and a long-term follow-up phase, is currently ongoing. Early findings from four patients were presented in 2015: Besides the foveal detachment and transitory decrease in vision induced by the subretinal injection, there were no drug-related complications and no sustained surgical sequelae.⁵

Usher 2A is a less severe form of the syndrome. The causative mutation is found in the USH2A gene, which encodes usherin—an intercellular adhesion protein located at the basal aspect of the photoreceptor cilia. The STELLAR Phase I/II trial conducted by ProQR Therapeutics aims to evaluate the safety and efficacy of QR-421a, an AON administered intravitreally to correct the USH2A-derived mRNA. Three-month interim analysis results should be released in early 2020.¹¹

• **Choroideremia.** This is an X-linked genetic disorder affecting the outer retina and choroid, characterized by progressive peripheral visual field loss, nyctalopia and total blindness within the first 30 years of life. It's caused by a mutation in the choroideremia (CHM) gene encoding the Rab escort protein 1 (REP1), which is crucial to photoreceptor intracellular trafficking processes. Several groups have been working on treatments targeting this mutation. Three Phase I/II trials including a total of 26 patients at different stages of the disease, evaluating subretinal injections of AAV-based CHM gene therapies, are already completed. Results suggest relative safety with no severe systemic adverse effects,^{4,12,13} and with only two cases of localized retinal inflammation related to vector delivery.^{4,13} Formation of macular atrophic holes or severe retinal thinning are of concern in patients with choroideremia, whose degenerating

retina is already thin and can significantly stretch during drug injection. This complication has been described in three treated cases.^{4,13} Optimization of the surgical technique to incorporate intraoperative OCT, which can identify the correct injection plane and rapidly detect retinal thinning, is expected to circumvent this complication.¹³ Effectiveness results in terms of visual acuity are also promising, with a significant improvement of 4.5 letters in treated eyes compared to a loss of 1.5 letters on average in control eyes. Results were sustained at two years of follow-up.^{13,14} Based on its encouraging Phase I/II findings, the company Nightstar Therapeutics has initiated a Phase III clinical trial.¹⁵

• **Stargardt disease.** Stargardt's is an inherited macular degeneration. The most common causative mutation affects the ATP-binding cassette sub-family A (ABCA4) gene. The dysfunctional protein normally transports potentially toxic bisretinoid compounds from photoreceptors to the RPE.² The ABCA4 gene is relatively large, requiring the use of an equine lentiviral vector for gene therapy development. A Phase I/II trial is presently investigating the safety and efficacy of its subretinal delivery.

Preliminary results following completion of the dose-escalation cohorts (Phase I) including a total of 15 patients, suggest that the drug is relatively safe.¹⁶ Notable adverse effects related to surgery and/or treatment included prolonged, but mild, IOP elevation in one case, subretinal fluid along the superior vascular arcade in another case, lymphopenia in another patient and complaints of “flashes and floaters” in several subjects.¹⁶ Phase II and long-term follow-up of Phase I patients are ongoing.

• **Achromatopsia.** A rare progressive cone degeneration beginning in early childhood, achromatopsia is characterized by poor visual acuity, hemeralopia and complete colour

blindness. More than 75 percent of cases are caused by mutations in genes encoding cone-specification channels, namely cyclic nucleotide gated channel $\alpha 3$ and $\beta 3$ (CNGA3 and CNGB3, respectively).²

Several independent Phase I/II trials relying on subretinally-injected AAV vectors containing correct copies of one of these two genes have been initiated, but results are not yet available.

- **X-linked retinoschisis.** This condition causes a localized splitting of the retina in the macular area. The usual onset is early childhood, and it afflicts 1 in 25,000 to 1 in 5,000 males. The protein encoded by the mutated retinoschisin 1 (RS1) gene is likely involved in cell adhesion. AAV-based therapies supplementing this gene are currently at the Phase I/II development stage.

Concerns about the weakness of the retina and the possibility of damage from subretinal injections, as well as involvement of inner retinal layers, have justified the use of an intravitreal approach. An AGTC-sponsored Phase I/II trial, including a total of 27 X-linked retinoschisis patients, has shown general safety and tolerability of the AAV-based drug, with only mild transitory ocular inflammation. However, no clinical effectiveness over the six-month interim analysis period was seen.¹⁷ These results have led to AGTC's decision to continue monitoring of enrolled patients as per the study protocol, but not to further develop the product.¹⁷

Initial findings of the National Eye Institute's Phase I/II trial investigating intravitreal treatment with another RS1-gene product in nine patients have been more promising, confirming systemic safety and suggesting efficacy, with retinal cavities transiently closing in one patient.¹⁸ The trial continues, and additional doses are being explored to pursue evidence of efficacy.¹⁸

Genetic Testing

Given these advancements in genetic therapeutic approaches for IRDs, genetic testing of afflicted patients to identify those who could benefit from these treatments is now more relevant than ever. Furthermore, a genetic diagnosis is of importance for family planning, financial decisions and career orientation. Genotype diagnosis is now part of the official guidelines directing the assessment of IRD patients.¹⁹

Sensitive and specific genetic tests are available for multiple IRDs, and a mutation is identified in 60 to 80 percent of those tested.²⁰ Several types of tests can be ordered, including single-gene tests; gene panels, grouped by clinical diagnosis; whole exome sequencing, looking for mutations in the coding DNA; and whole genome sequencing, searching for mutations in both coding and non-coding DNA.³ The wider the search, the higher the chance of discovering IRD-causing mutations, but also other unrelated mutations or variants of unknown significance. Thus, the most specific test possible should be requested to avoid confusing results, as well as financial and emotional costs to the patient in case of unrelated abnormal findings.²¹ The patient should be offered professional genetic counseling both before and after testing.²¹ Most ophthalmologists aren't trained to choose among available genetic tests, interpret their results and counsel patients as to their significance, so it's paramount that an IRD specialist, a medical geneticist and/or a genetic counselor be involved.

In summary, Luxturna is the first FDA-approved gene therapy; it targets RPE65-related LCA. Other genetic therapies for IRDs are already on the way, with 23 of them in Phase I, II or III clinical trials. Most of them are gene-augmentation therapies that deliver correct copies of the gene to

the retina; however, two AON-based therapies, acting at the level of the incorrect mRNA transcription, are also being studied. Three gene therapies are currently in more advanced Phase III trials, namely an RPGR-gene drug for X-linked RP, an REP1-gene therapy for choroideremia and an AON—QR-110—for the treatment of LCA. Many more potential therapies are still in preclinical development.²

Although gene therapies for IRDs have come a long way, overcoming many barriers to clinical development, challenges remain related to choice and optimization of drug delivery techniques and selection of the optimal timing for treatment. With other upcoming therapeutic options for patients who have advanced stages of IRDs, such as optogenetics and stem cell therapies, exciting times lie ahead. **REVIEW**

Dr. Bostan is co-chief resident in ophthalmology, and Dr. Qian is an assistant professor of Adult and Pediatric Vitreoretinal Surgery and Diseases, at the Centre Universitaire d'Ophthalmologie (CUO) at the University of Montreal, Maisonneuve-Rosemont Hospital in Montreal and the Centre Hospitalier Universitaire (CHU) Sainte-Justine in Montreal. Dr. Qian is also the Director of the Inherited Retinal Diseases service and the Electrophysiology Laboratories at the University of Montreal. Dr. Bostan and Dr. Qian have no financial interest in any product mentioned.

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(Continued on page 60)

(Continued from page 27)

needs to be made between Humira and a traditional immunosuppressant such as methotrexate. “When making this choice, we need to consider that methotrexate costs \$50 month and Humira costs about \$6,000 a month,” says Dr. Albin. “Payers have different policies on reimbursing for Humira, so be aware of the policies that are being followed by a particular third-party payer. Some companies will pay for Humira only when the patient is at risk of liver disease or other conditions that would contraindicate treatment with methotrexate. Some payors will pay for Humira if your patient experiences a documented failure from another treatment. Some payors won’t pay at all. Others will pay as soon as they receive the diagnosis.”

Favoring First-line Treatments

Dr. Albin says most uveitis specialists are more comfortable with traditional immunosuppression as first-line therapy. “This is significant because Humira was a second-line or third-line treatment before it was approved for uveitis,” he points out. “Now that it’s approved, it’s a first-line treatment.” He now decides which treatments to choose based on the safety data of long-term use associated with the traditional agents compared to the limited amount of data associated with Humira. “Cost also is obviously a big factor to consider for many patients,” he adds.

However, some patients only want to receive the FDA-approved medication. “Some also want to avoid methotrexate’s required blood monitoring four to six times per year,” says Dr. Albin. “As a result, traditional treatments have often become more difficult to provide than Humira.”

He also notes which patients have liver toxicity or are trying to get pregnant. “I use Humira for these patients,” he says. “I prefer Humira for

a woman of child-bearing age. Methotrexate and CellCept are totally contraindicated for women who are or plan to get pregnant.”

T-Cell Inhibitors + Cyclosporine

Dr. Dahr says the combination of an antimetabolite and T-cell inhibitor such as cyclosporine or tacrolimus (Prograf) also remains an option.

“I see quite a bit of new-onset VKH disease in patients in their 20s,” he explains. “I often put them on an antimetabolite, plus the T-cell inhibitor at the initial presentation. I then taper their oral steroid to 10 mg within three months and taper the last 10 mg of steroid over 12 months or so. If the eyes are quiet, I may then taper the steroid-sparing therapy over the subsequent 12 to 24 months.” Dr. Dahr has found this “three-year plan” lets him avoid the local corticosteroids for VKH patients, who he says seem prone to corticosteroid-related IOP issues. Finally, the future may see a role for the interleukin-6 (IL-6) receptor inhibitor tocilizumab (Actemra), used to treat moderate to severe rheumatoid arthritis in children and adults. “Tocilizumab has shown encouraging initial data²¹ but doesn’t carry an FDA label for uveitis,” Dr. Dahr notes. “It will be difficult to procure in a community setting because of reimbursement issues.”

Continuing Progress

The future care of patients with this potentially blinding condition looks brighter, as researchers and clinicians continue to progress in the therapeutic arena.

“We now have a very good armamentarium that we can use to help these patients,” says Dr. Dahr. “However, it’s important to realize there will never be a ‘magic bullet’ drug for uveitis—or for autoimmune disease, in general. Still, the vast majority of

patients can be controlled with our current therapies, albeit often in combination.” **REVIEW**

Neither Dr. Dhar nor Dr. Thomas have declared a financial interest related to this article. Dr. Albin has consulted for Bausch + Lomb.

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A New Perspective On the Retina

You may be able to get a better view of retinal pathology with Zeiss' recently approved Clarus 700, High-Definition, Ultra-Widefield Imaging system.

Zeiss says that the Clarus 700 is the first high-resolution ultra-widefield imaging system with true color and a complete range of fundus imaging modalities, including fluorescein angiography. The company says that ultra-widefield fluorescein angiography can help ophthalmologists identify proliferative vitreoretinopathy earlier, as well as capture images of conditions such as uveitis, choroidal masses, retinal tears, retinal detachments and peripheral ischemia. Fluorescein angiography with the Clarus 700 can image details from the macula in the early phase of FA to the periphery in the late phase, the company adds.

Zeiss says the device is able to capture images that closely resemble the natural coloration of the fundus, through the use of a technology known as Broadline Fundus Imaging, which is based on slit-scanning ophthalmoscopy. In BLFI, during image capture, a broad line of illumination is scanned across the retina. A monochromatic camera cap-

tures the returned light in order to image the tissue. A single sweep of the illumination is used to illuminate the retina for image capture.

The Clarus 700 features several capture methods, including true color with RGB separation, autofluorescence green, autofluorescence blue, stereo image pairs, external eye photos and fluorescein angiography. No patient repositioning is required when switching between modalities, the company says. For information, visit <https://www.zeiss.com/meditec>.

Wipe Away Allergens

Allergies causing red and itchy eyes? Chances are patients' eyelids are suffering, too. Ocusoft has recently released an eyelid cleanser to

help wipe away allergy irritants. The company says its Ocusoft Lid Scrub removes contaminants and irritation-causing allergens like oil, debris and pollen that can irritate the tear film.

Ocusoft Lid Scrubs come in individually-wrapped pre-moistened pads and feature green tea extract, tea tree oil and PSG-2 (phytosphingosine) to "moisturize and calm irritated eyelids," the company says.

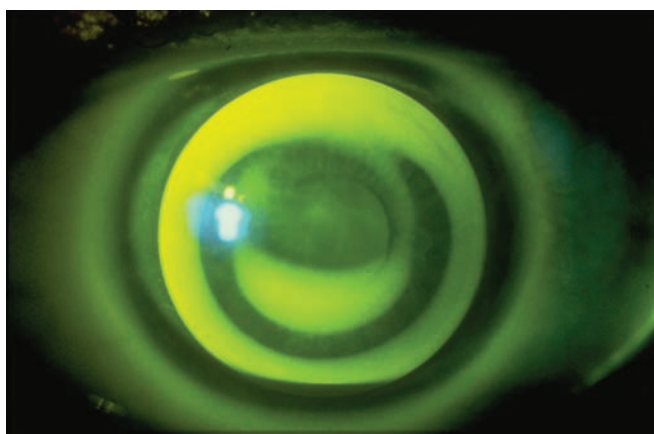
For more information, visit ocusoft.com.

New Materials for Hydra-PEG

If you're a fan of Boston Materials' XO and XO2 gas-permeable lenses for patients with such conditions as dry eye and keratoconus, then Blanchard Contact Lenses says you may be in line for an upgrade.

Blanchard recently announced that its Tangible Hydra-PEG polymer coating is now available with Bausch + Lomb's Boston XO and Boston XO2 lens materials. Tangible Hydra-PEG is a polymer coating designed to improve the wettability and lubricity of specialty lenses, as well as increase their wear time and comfort.

For more information on the lenses, visit blanchardlab.com. **REVIEW**



Bausch + Lomb's Boston GP lenses, such as this one fitted in a keratoconic eye, can now come coated with the Tangible Hydra-PEG polymer.

2ND YEAR OPHTHALMOLOGY RESIDENT WET LAB PROGRAMS

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The programs also serve as an opportunity for your residents to network with residents from other programs.

After reviewing the material, it is our hope that you will select and encourage your 2nd Year residents to attend one of these educational activities, which are CME accredited to ensure fair balance.

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Injection Frequency in CRVO Cases

In a randomized, prospective, double-masked clinical trial, researchers sought to compare the injection frequency of aflibercept and ranibizumab in the treatment of macular edema secondary to central retinal vein occlusion. According to previous *in vitro* studies, aflibercept was shown to have a significantly higher affinity to VEGF-A than ranibizumab, and mathematical models suggest aflibercept's VEGF-binding effect lasts longer. (Other studies have failed to confirm differences in binding effect between the two drugs.)

The researchers randomized 45 patients with treatment-naïve CRVO and macular edema into two groups for receiving injections of aflibercept (n=22) or ranibizumab (n=23). A treat-and-extend regimen with an 18-month follow-up period was used. Treatment intervals were extended from two to 12 weeks after three loading doses, and intervals were shortened by two weeks if macular edema recurred.

The researchers found that the mean number of injections given in the aflibercept group was significantly lower than in the ranibizumab group, with a mean of 10.9 injections of aflibercept and 14.4 of ranibizumab at study completion. Treatment intervals in the aflibercept group were significantly longer than in the ranibizumab group, with intervals of 10 and 6.6

weeks, respectively.

The study concluded that aflibercept has a longer duration of effect than ranibizumab for treating macular edema following CRVO in a treat-and-extend regimen. Aflibercept reduced the need for injections by 24.3 percent during the study period. The study also found that visual outcomes between the two groups were similar, leading the researchers to conclude that treatment burden can be reduced without negative impact on visual outcome.

Retina 2019;39:7:1370-1376
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What's in the Syringe?

Anti-VEGF injections have become the most commonly performed procedure in ophthalmology, thanks to the high volume of patients requiring intravitreal injections over long-term periods. While most studies focus on technical aspects of anti-VEGF delivery, researchers in Tel Aviv decided to look at volume output of intravitreal drug delivery, since recent studies have shown that accuracy and reproducibility with typical syringes is highly variable.

The clinical study included 669 intravitreal injections with prefilled bevacizumab (n=432, 64.6 percent), prefilled ranibizumab (n=125, 18.7 percent) and aflibercept syringes (n=112, 16.7 percent). The injections

were performed by six ophthalmologists, each doing at least 50 injections of all three drugs. Volume output was calculated as the difference in syringe weight before and after injecting the drug. Accuracy and precision were analyzed by mean absolute percentage error and coefficient of variation, respectively.

The study found that all volume outputs were significantly different from the target of 50 µL ($p < 0.0001$ for all) with mean absolute percentage errors of 12.25 ± 5.92 percent for bevacizumab, 13.6 ± 8.75 percent for ranibizumab and 24.69 ± 14.84 percent for aflibercept. Volume outputs for bevacizumab and ranibizumab were not significantly different, but both were significantly more accurate than aflibercept. The study authors note that prefilled syringes were associated with improved accuracy. They also found that overdelivery of anti-VEGF was highly common, though underdelivery occurred in 16.3 percent of injections. Overall, the authors conclude that the current practices for intravitreal injections are highly variable.

Retina 2019;39:7:1385-1391
Loewenstein I, Goldstein M, Moisseiev J, and Moisseiev E.

ELM Height for Macular Hole Prognosis

In a retrospective observational study of patients undergoing vitrec-

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tomy for macular hole surgery, researchers measured the greatest vertical height of the central external limiting membrane above the retinal pigment epithelium (ELM height) on spectral domain OCT. The goal of the study was to investigate the relationship of ELM height to pre- and postoperative variables, such as macular hole width and height and visual acuity.

Ninety-one eyes of 91 patients who had undergone surgery for idiopathic full-thickness macular hole were evaluated. ELM height ranged from 100 to 394 μm , with a mean of 220 μm . Researchers found significant correlations between ELM height and macular hole diameter and height, along with a worsening of postoperative visual acuity.

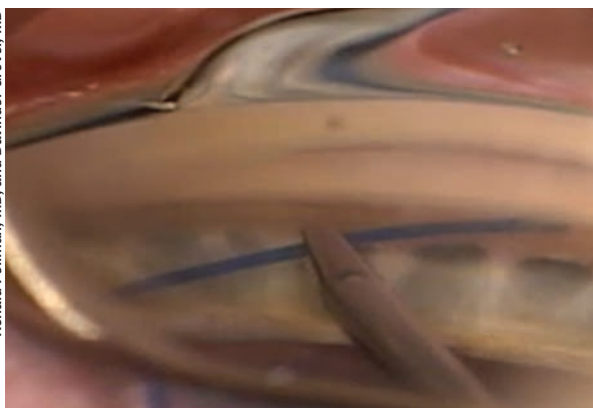
The study found that the higher the external limiting membrane height in idiopathic macular hole, the poorer the preoperative vision. A lower external limiting membrane height predicted better postoperative visual acuity for holes less than 400 μm in width. The researchers say that external limiting membrane height is a strong independent predictor of good postoperative outcomes.

Retina 2019;39:7:1392-1398
Geenen C, Murphy DC, Sandinha MT, Rees J, and Steel D.

GATT for Steroid-induced Glaucoma

Researchers evaluated the efficacy of gonioscopy-assisted transluminal trabeculotomy for lowering the intraocular pressure in steroid-induced glaucoma. They performed a retrospective chart review of all GATT procedures performed on individu-

Ronald Fellman, MD, and Davinder Grover, MD



Researchers say that gonioscopy-assisted transluminal trabeculotomy appears to be useful in cases of steroid-induced glaucoma.

als with a predominant diagnosis of steroid-induced glaucoma between March 1, 2016, and March 30, 2018, at the University of Michigan.

Primary outcome measures included IOP, the number of IOP-lowering medications prescribed and the topical steroid dosing over the duration of follow-up. A total of 13 individuals with steroid-induced glaucoma underwent the GATT procedure. Here are some of the findings:

- A significant reduction in mean IOP was found at all postoperative visits.
- The average IOP decreased by 16.4 mmHg to 19.5 mmHg between three and 24 months postoperatively.
- By 24 months, all individuals had a reduction in IOP of >20 percent.
- The number of glaucoma medications decreased significantly from an average of 3.1 medications preoperatively to an average of 0.8 medications at last follow-up.
- The majority of individuals (>67 percent) required continued use of steroids at all postoperative visits. The most common postoperative complication was a transient hyphema (38 percent).
- No individuals required a repeat glaucoma surgery or anterior chamber washout.

Researchers wrote that their small

case series suggested that GATT was an effective and safe surgical technique for decreasing IOP and decreasing medication burden in individuals with predominantly steroid-induced glaucoma. To their knowledge, this is the first study looking specifically at the efficacy of GATT for this condition.

J Glaucoma. 2019; Jun 27. [Epub ahead of print].
Boese EA, Shah M.

Late AMD in Fellow Eyes of Unilateral Cases

Investigators assessed whether the development of late age-related macular degeneration in fellow eyes with pseudodrusen was associated with the pseudodrusen pattern in individuals with unilateral exudative AMD, as part of a retrospective, ob-

servational study.

They performed a retrospective analysis on 73 individuals with unilateral exudative AMD showing pseudodrusen in their fellow eyes. Eyes were classified according to pseudodrusen pattern, which was determined based on maximum pseudodrusen ribbon length. Here are some of the study's findings:

- During the mean follow-up period of 35.5 ±18.6 months, 21 (28.8 percent) eyes developed late AMD.
- Among these eyes, 15 (71 percent) developed exudative AMD and six (29 percent) developed geographic atrophy.
- Development of late AMD in fellow eyes occurred with significantly more prevalence in individuals showing a ribbon-dominant type of pseudodrusen pattern in their fellow eye

than those showing a dot-dominant type ($p=0.0005$, log-rank test).

- Cox-regression analysis revealed that development of late AMD in fellow eyes was associated with the presence of ribbon-dominant pseudodrusen in fellow eyes (HR, 4.15; CI, 1.59 to 10.8), along with older age (HR, 1.10; CI, 1.03 to 1.17), a history of smoking (HR, 17.2; CI 1.11 to 263), presence of large soft drusen in the fellow eye (HR, 5.49; CI, 1.29 to 21.1) and retinal angiomatous proliferation (HR, 5.02; CI, 1.90 to 13.2).

Researchers determined that individuals with unilateral exudative AMD who had fellow eyes with ribbon-dominant pseudodrusen were likely to develop late AMD.

Jpn J Ophthalmol 2019; Jul 2. [Epub ahead of print].
Sakurada Y, Sugiyama A, Kikushima W, et al.

(Continued from page 16)

the macular disease that's causing the change.”

• **Don't assume a negative OCT finding is conclusive.** “It's possible to detect changes in severe disease using OCT, but we shouldn't be falsely reassured if we don't find evidence of change using OCT,” Dr. Nguyen points out. “It doesn't mean that no loss is happening, because we need a lot more change in the OCT to detect progression late in the disease. So it's possible that some of these patients are progressing, even when the OCT readings appear stable—and it's true that a visual field might be more sensitive in that situation.”

Still a Challenge

Dr. Nguyen says he's sure that Dr. Medeiros would agree that OCT remains useful in advanced glaucoma. [Note: Dr. Medeiros was not available to comment for this article.] “In

fact,” Dr. Nguyen says, “Dr. Medeiros has done some recent studies that have demonstrated this, including some interesting work that has tried to estimate where the structural measurement floor actually is.”^{3,4}

“I think the idea that OCT becomes useless in advanced glaucoma was a conclusion that became bloated and overused,” he continues. “In our work, OCT was more sensitive than visual field testing in detecting progression, even in advanced disease.” (Dr. Nguyen notes that some of the variability in reported sensitivities has to do with how different authors define advanced disease; he says his group used the clinical modification of the ICD.)

Despite acknowledging that OCT can still be useful in advanced disease, Dr. Nguyen warns clinicians not to ignore the challenges of doing so. “The basic issue is whether OCT is a good tool to monitor advanced glaucoma, and that's a valid concern,” he says. “However, we don't have a

lot of great ways to monitor patients who have very advanced disease. Visual fields aren't perfect in this situation either; field performance is highly variable. It becomes hard to tell who's getting worse, and who's just having a hard time doing the visual field test that day. Monitoring progression in advanced disease is still a challenging problem.” **REVIEW**

Dr. Asrani receives lecture honoraria from Heidelberg Engineering. Dr. Nguyen has no financial ties to any product mentioned.

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An 80-year-old woman presents to the Wills ER with gradually progressive blurred vision in her right eye.

Meera D. Sivalingam, MD, and Carol L. Shields, MD

Presentation

An 80-year-old Caucasian female with a six-week history of gradual-onset blurred vision in her right eye presented to the Wills Emergency Room for evaluation. The patient reported that over a six-week period she had noticed progressive, painless loss of the entire visual field in her right eye.

Medical History

Her past ocular history included cataract surgeries in 2000 and 2006 and a YAG capsulotomy in the right eye in 2012. Her past medical and surgical history was remarkable for type 2 diabetes, hypertension and a right total knee replacement. Her social history was significant for social alcohol consumption. Current medications included: simvastatin; metformin; pioglitazone; losartan; and liraglutide.

Examination

Ocular examination demonstrated best-corrected visual acuities of 20/40 OD and 20/25 OS. Pupils and confrontation visual fields were normal. Intraocular pressures were 14 and 13 mmHg OD and OS, respectively. Extraocular motility was full bilaterally. The anterior segment examination revealed posterior chamber intraocular lenses bilaterally with an open posterior capsule in the right eye and early posterior capsular opacification in the left eye.

Dilated fundus examination of the right eye demonstrated trace vitreous cell, disc edema with a chalky white appearance, surrounding retinal whitening, peripapillary edema and streak peripapillary retinal hemorrhages (Figure 1). The macula, vessels and periphery appeared normal. The left eye had a normal optic disc, macula, vessels and periphery.



Figure 1. Fundus photographs of the macula of the right eye on initial presentation (A) demonstrating optic disc edema, surrounding retinal whitening, streak peripapillary hemorrhages and peripapillary edema. One month post sub-Tenon's injection (B) there is resolution of optic disc edema and retinal hemorrhages. There is further improvement on follow-up three months after an intravitreal triamcinolone injection (C).

What is your diagnosis? What further workup would you pursue? The diagnosis appears on p. 64

Workup, Diagnosis and Treatment

In the emergency room, an MRI of the brain and orbits revealed focal enhancement along the right posterior globe at the right optic nerve insertion, enhancement of the superior and lateral extraconal area of the right orbit, and curvilinear enhancement of the superior extraconal left orbit. Carotid doppler ultrasound was within normal limits, while orbital doppler U/S showed increased vascularity superiorly and medially in the right orbit. Laboratory workup demonstrated a normal white blood cell count, hemoglobin, platelets, creatinine, sedimentation rate and C-reactive protein.

Ancillary imaging was obtained, including fluorescein angiography (Figure 2) and optical coherence tomography (Figure 3). FA revealed leakage from the optic disc of the right eye without macular leakage; a late frame of the left eye was normal. OCT OD demonstrated significant thickening of the optic nerve with adjacent intraretinal edema, peripapillary choroidal thickening, epiretinal membrane and disruption of the ellipsoid zone (Figure 3A). Ultrasound of the right eye showed choroidal thickening surrounding the optic disc with no evidence of extraocular extension.

The differential diagnosis of this patient, with progressive, unilateral vision loss with optic disc edema, surrounding retinal whitening and choroidal infiltration, included infectious, inflammatory and neoplastic etiologies. Possible infectious causes included bacterial (e.g., tuberculosis, syphilis, mycobacteria, Lyme disease), viral (e.g., herpes), fungal (e.g., histoplasmosis), protozoan (e.g., toxoplasmosis) and nematodal (e.g., *Toxocara*). Inflammatory etiologies

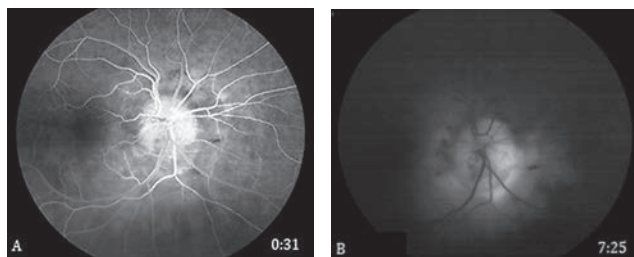


Figure 2. Fluorescein angiography reveals early (A) and sustained (B) leakage from the optic disc OD, but no macular leakage.

Discussion

Sarcoidosis is a systemic inflammatory disease that causes non-caseating granulomas throughout the body.¹ The etiology is unknown. Common systemic manifestations include bilateral hilar adenopathy, pulmonary reticular opacities, skin lesions and joint involvement. Other sites of involvement include the liver, spleen, parotid/salivary glands, heart, kidneys and muscles.¹ Although pulmonary involvement is the most common manifestation of sarcoidosis, 30 percent of patients present with extrapulmonary disease.² The inci-

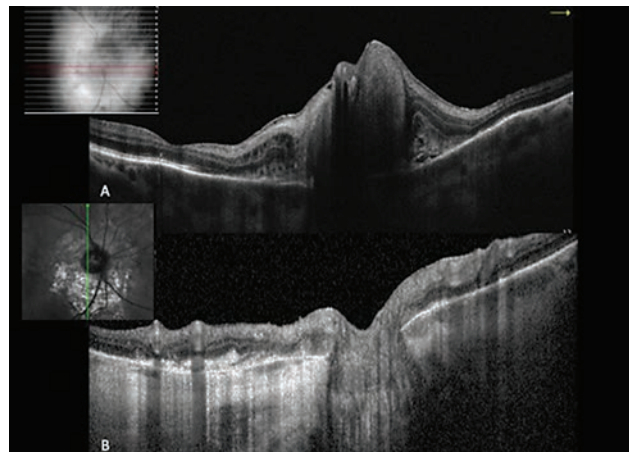


Figure 3. OCT through the macula and optic nerve of the right eye demonstrating significant thickening of the optic nerve, surrounding retinal thickening with cystoid edema, choroidal thickening and epiretinal membrane (A). Three months after sub-Tenon's and intravitreal triamcinolone (B), there is resolution of optic nerve edema, retinal edema and choroidal thickening, with residual irregularity of the retinal layers.

included sarcoidosis, giant cell arteritis, Behçets' and systemic lupus erythematosus. Neoplastic etiologies included lymphomatous or leukemic infiltration of the optic nerve, amelanotic melanoma and metastatic disease.

Angiotensin converting enzyme and a Lyme titer were within normal limits. However, given the appearance of the lesions and the clinical presentation, a preliminary diagnosis of optic nerve granuloma secondary to sarcoidosis was made. Vitreous biopsy was considered but wasn't pursued given the likely low yield, given the small amount of vitreous cell. The patient was started on oral prednisone 60 mg, which was stopped when she developed hyperglycemia, weight gain and polyuria. To avoid systemic steroids, the patient received a sub-Tenon's injection of Kenalog. One month later, fundus exam showed improved disc edema, intraretinal edema and retinal hemorrhages (Figure 1A & B and Figure 3B). The patient subsequently received an intravitreal injection of triamcinolone 2 mg. Visual acuity remained stable at 20/40. Fundus exam showed continued resolution of edema (Figure 1C).

dence ranges from 15.3 to 21.7 per 100,000.¹ The lifetime incidence is 1.3 percent in women, 1 percent in men, 2.4 percent in African Americans and 0.8 percent in Caucasians.¹

Ocular manifestations occur in 30 to 60 percent of patients and may develop in the absence of other systemic symptoms.³ Uveitis is the most common manifestation of ocular sarcoidosis. The International Workshop for Ocular Sarcoidosis developed a consensus for seven signs sugges-

tive of ocular sarcoidosis.³ They include:

- mutton fat keratic precipitates, small granulomatous keratic precipitates, and iris nodules;
- trabecular meshwork nodules or tent-shaped peripheral anterior synchiae;
- vitreous opacities displaying snowballs or “strings of pearls”;
- multiple chorioretinal peripheral lesions;
- nodular and/or segmental periphlebitis with or without candlewax dripping and/or retinal macroaneurysm;
- optic disc nodule(s), granuloma(s), and/or solitary choroidal nodules; and
- bilateral disease.³

The consensus criteria also address ancillary testing, including: negative tuberculin skin test in a BCG-vaccinated patient or in a patient who has a previously positive tuberculin skin test; elevated angiotensin converting enzyme or serum lysozyme; abnormal liver function test; chest X-ray showing bilateral hilar lymphadenopathy; and positive chest CT in patients with a negative chest X-ray.³

Additionally, IWOS proposed diagnostic criteria. Biopsy-proven disease showing non-caseating granulomas in the setting of a granulomatous uveitis is considered definite ocular sarcoidosis. In the absence of a tissue biopsy, the disease can be considered presumed, probable or possible ocular sarcoidosis depending on which of the above criteria are satisfied.³

Uveitis in sarcoidosis is generally bilateral, with anterior uveitis occurring in 22 to 70 percent of cases.⁴ Intermediate and posterior uveitis are less common, but posterior disease is still found in up to 28 percent of ocular sarcoidosis cases.¹ Ocular sarcoidosis can also involve the lids and orbits. Eyelid involvement can cause painless nodular elevations, while lacrimal gland involvement causes granulomatous inflammation within the gland, leading to disruption of proper tear production and chronic dry eye. Diffuse orbital involvement can cause

ptosis, limited extraocular movements and diplopia.⁴

Optic nerve granulomas are rare but very specific for intraocular sarcoidosis, estimated to occur in 5 percent of all sarcoid patients; one-third of these patients will have other signs of CNS involvement.^{4,5} Signs and symptoms of optic nerve involvement include rapidly decreasing visual acuity, decreased color vision and diminished contrast sensitivity.⁴ In a case series of 11 patients with sarcoidosis of the optic nerve, only two of the 11 individuals had previously known sarcoidosis.⁶ All patients had histologically confirmed non-caseating granulomatous inflammation. ACE levels were tested in three patients and elevated in only one. All patients were treated with oral corticosteroids, and seven of the 11 patients showed improvement in acuity.⁶

Corticosteroids are the main treatment for ocular sarcoidosis.¹ Treatment administration routes include topical, subconjunctival, sub-Tenon’s, peribulbar and intravitreal. Sub-conjunctival dexamethasone can have better penetration than oral steroids.¹ Typically, systemic corticosteroid use is reserved for bilateral involvement or multi-organ involvement, with initial dosing starting at 0.5-1.0 mg/kg/day.¹ Systemic, steroid-sparing agents, including methotrexate and biologics, can also be used.

In conclusion, sarcoidosis can demonstrate a wide array of intraocular manifestations. Optic nerve granulomas are a rare manifestation of ocular sarcoidosis. It’s crucial to eliminate infectious etiologies prior to initiating corticosteroid therapy. Proper ancillary testing and clinical evaluation must be applied in order to make the proper diagnosis. **REVIEW**

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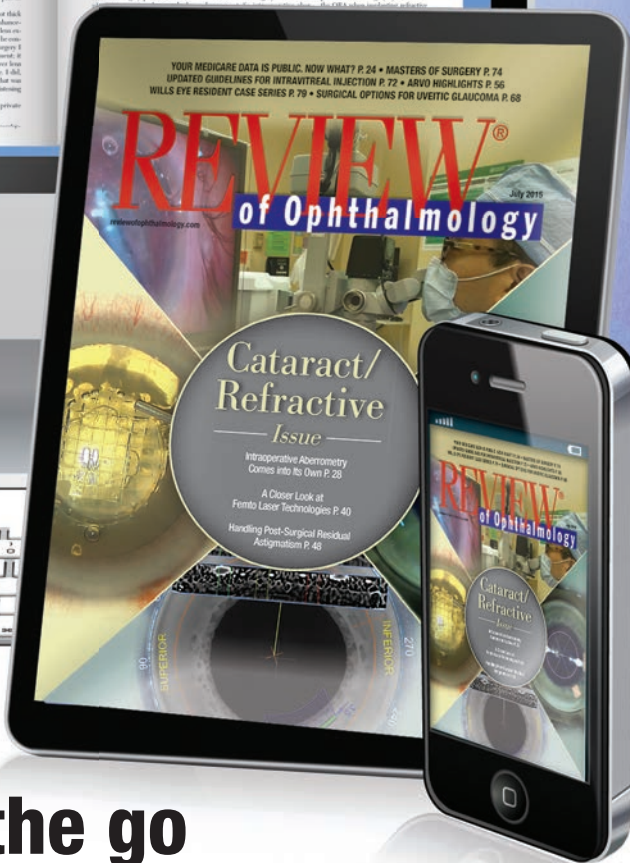
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BRIEF SUMMARY:

Consult the Full Prescribing Information for complete product information.

INDICATIONS AND USAGE

Xiidra® (lifitegrast ophthalmic solution) 5% is indicated for the treatment of the signs and symptoms of dry eye disease (DED).

DOSAGE AND ADMINISTRATION

Instill one drop of Xiidra twice daily (approximately 12 hours apart) into each eye using a single-use container. Discard the single-use container immediately after using in each eye. Contact lenses should be removed prior to the administration of Xiidra and may be reinserted 15 minutes following administration.

CONTRAINDICATIONS

Xiidra is contraindicated in patients with known hypersensitivity to lifitegrast or to any of the other ingredients in the formulation.

ADVERSE REACTIONS

Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in clinical studies of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. In five clinical studies of dry eye disease conducted with lifitegrast ophthalmic solution, 1401 patients received at least 1 dose of lifitegrast (1287 of which received lifitegrast 5%). The majority of patients (84%) had ≤ 3 months of treatment exposure. 170 patients were exposed to lifitegrast for approximately 12 months. The majority of the treated patients were female (77%). The most common adverse reactions reported in 5-25 % of patients were instillation site irritation, dysgeusia and reduced visual acuity. Other adverse reactions reported in 1% to 5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus and sinusitis.

Postmarketing Experience

The following adverse reactions have been identified during postapproval use of Xiidra. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Rare cases of hypersensitivity, including anaphylactic reaction, bronchospasm, respiratory distress, pharyngeal edema, swollen tongue, and urticaria have been reported. Eye swelling and rash have been reported.

USE IN SPECIFIC POPULATIONS

Pregnancy

There are no available data on Xiidra use in pregnant women to inform any drug associated risks. Intravenous (IV) administration of lifitegrast to pregnant rats, from pre-mating through gestation day 17, did not produce teratogenicity at clinically relevant systemic exposures. Intravenous administration of lifitegrast to pregnant rabbits during organogenesis produced an increased incidence of omphalocele at the lowest dose

tested, 3 mg/kg/day (400-fold the human plasma exposure at the recommended human ophthalmic dose [RHOD], based on the area under the curve [AUC] level). Since human systemic exposure to lifitegrast following ocular administration of Xiidra at the RHOD is low, the applicability of animal findings to the risk of Xiidra use in humans during pregnancy is unclear.

Animal Data

Lifitegrast administered daily by intravenous (IV) injection to rats, from pre-mating through gestation day 17, caused an increase in mean preimplantation loss and an increased incidence of several minor skeletal anomalies at 30 mg /kg / day, representing 5,400-fold the human plasma exposure at the RHOD of Xiidra, based on AUC. No teratogenicity was observed in the rat at 10 mg /kg /day (460-fold the human plasma exposure at the RHOD, based on AUC). In the rabbit, an increased incidence of omphalocele was observed at the lowest dose tested, 3 mg /kg /day (400-fold the human plasma exposure at the RHOD, based on AUC), when administered by IV injection daily from gestation days 7 through 19. A fetal No Observed Adverse Effect Level (NOAEL) was not identified in the rabbit.

Lactation

There are no data on the presence of lifitegrast in human milk, the effects on the breastfed infant, or the effects on milk production. However, systemic exposure to lifitegrast from ocular administration is low. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for Xiidra and any potential adverse effects on the breastfed child from Xiidra.

Pediatric Use

Safety and efficacy in pediatric patients below the age of 17 years have not been established.

Geriatric Use

No overall differences in safety or effectiveness have been observed between elderly and younger adult patients.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Animal studies have not been conducted to determine the carcinogenic potential of lifitegrast.

Mutagenesis: Lifitegrast was not mutagenic in the *in vitro* Ames assay. Lifitegrast was not clastogenic in the *in vivo* mouse micronucleus assay. In an *in vitro* chromosomal aberration assay using mammalian cells (Chinese hamster ovary cells), lifitegrast was positive at the highest concentration tested, without metabolic activation.

Impairment of fertility: Lifitegrast administered at intravenous (IV) doses of up to 30 mg/kg/day (5400-fold the human plasma exposure at the recommended human ophthalmic dose (RHOD) of lifitegrast ophthalmic solution, 5%) had no effect on fertility and reproductive performance in male and female treated rats.



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Indication

Xiidra® (lifitegrast ophthalmic solution) 5% is indicated for the treatment of signs and symptoms of dry eye disease (DED).

Important Safety Information

Xiidra is contraindicated in patients with known hypersensitivity to lifitegrast or to any of the other ingredients.

In clinical trials, the most common adverse reactions reported in 5-25% of patients were instillation site irritation, dysgeusia and reduced visual acuity. Other adverse reactions reported in 1% to 5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus and sinusitis.

To avoid the potential for eye injury or contamination of the solution, patients should not touch the tip of the single-use container to their eye or to any surface.

Contact lenses should be removed prior to the administration of Xiidra and may be reinserted 15 minutes following administration.

Safety and efficacy in pediatric patients below the age of 17 years have not been established.

For additional safety information, see accompanying Brief Summary of Safety Information on the adjacent page and Full Prescribing Information on Xiidra-ECP.com.

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