Introduction

A panel of experts gathered during the 2015 annual meeting of the American Academy of Ophthalmology for a roundtable discussion on how ophthalmologists select patients who may benefit from the 0.19 mg fluocinolone acetonide intravitreal implant (Iluvien; Alimera Sciences, Alpharetta, GA), as well as how to manage the adverse events associated with its use. I would like to thank the faculty members for their participation, as well as Alimera Sciences for supporting this OSLIRetina supplement. For more information on this topic, visit www.healio.com/ophthalmology/journals/osli.

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ABSTRACT: The diabetic macular edema (DME) treatment paradigm has evolved as the understanding of the disease pathology has grown. Since 2012, four pharmacotherapies have been approved by the U.S. Food and Drug Administration for the treatment of DME. First-line treatment of DME with anti-vascular endothelial growth factor [VEGF] agents has become the gold standard; however, an appreciable percentage of patients do not respond to anti-VEGF therapies. In patients who inadequately respond to anti-VEGF therapies, the underlying disease pathology may be mediated by a multitude of growth factors and inflammatory cytokines. For these patients, corticosteroids are an attractive treatment option because they not only downregulate VEGF, but also an array of cytokines. The phase 3 MEAD and FAME trials demonstrated significant visual acuity improvements associated with dexamethasone and fluocinolone acetonide, respectively, in patients with DME; however, class-specific adverse events, including increased intraocular pressure and cataract development, must be considered before use.

A panel of experts gathered during the 2015 annual meeting of the American Academy of Ophthalmology for a roundtable discussion focused on patient selection and adverse event management associated with the use of the 0.19 mg fluocinolone acetonide intravitreal implant.

INTRODUCTION

Scott W. Cousins, MD: Diabetes represents an ongoing health issue, and the number of worldwide cases could reach 300 million by 2030.1,2 In the U.S., diabetic retinopathy (DR) is the most common cause of vision loss in the working-age population, and macular edema can occur at any stage of retinopathy.3,4 Recent developments in the treatment landscape show encouraging results in patients with diabetic macular edema (DME).

Since 2012, four pharmacotherapies have been approved by the U.S. Food and Drug Administration (FDA) for the treatment of DME.6-9 The FDA-approved anti-vascular endothelial growth factor (VEGF) agents are ranibizumab (Lucentis; Genentech, South San Francisco, CA) and aflibercept (Eylea; Regeneron Pharmaceuticals, Tarrytown, NY).5,6 The FDA-approved corticosteroids are 0.7 mg dexamethasone intravitreal implant (Ozurdex; Allergan, Irvine, CA) and 0.19 mg fluocinolone acetonide intravitreal implant (Iluvien; Alimera Sciences, Alpharetta, GA).8,9 When diagnosing DME, what is the initial examination process of patients with type 2 diabetes suspected to have DME?

Christopher D. Riemann, MD: I perform a complete clinical examination. I generally perform optical coherence tomography (OCT) and fluorescein angiography (FA), often with widefield angiography.

Pauline T. Merrill, MD: I agree; however, widefield angiography is not available in all of our offices, so my colleagues and I use Early Treatment Diabetic Retinopathy Study (ETDRS) seven-field fluorescein angiograms. Therefore, we rely on a clinical examination, OCT, and FA.

Matthew P. Ohr, MD: I agree, and for patients with diabetes, I include a blood pressure assessment, particularly for patients with uncontrolled hemoglobin A1c (HbA1c).

Cousins: What is the present consensus regarding classification of DME by OCT and FA?

Holekamp: Previously, diagnosis of clinically significant DME was based on ETDRS criteria for “clinically significant
DME.” With the advent of OCT and clinical trial inclusion criteria, the disease is classified as non–central-involved or central-involved. FA is useful in less well-defined cases.

**Ohr:** Generally, central-involved thickening is the criterion used to initiate injection therapy.

**Riemann:** Not every patient with DME needs monthly anti-VEGF therapy indefinitely. FA is still useful because if it shows evidence of microaneurysms causing leakage, focal laser is an option. However, I would not want to perform focal laser on juxtafoveal microaneurysms when there is already macular ischemia or diffuse leakage by FA.

**Cousins:** Would it be prudent to begin treatment of a patient with DME without a fluorescein analysis?

**Holekamp:** If the patient’s vision, clinical examination, and OCT analysis make sense, then treating the DME without a fluorescein analysis would be acceptable.

**Merrill:** I tend to perform FA on new patients with diabetes because it is important to know the macular perfusion status before treatment initiation.

**CONSIDERATIONS FOR WHEN TO TREAT DME**

**Cousins:** For a patient with treatable DME, should treatment be initiated immediately, or should the patient attempt to manage systemic diabetes control before beginning treatment?

**“A complex interplay between VEGF and inflammatory cytokines is believed to be important in DR development.”**

— VICTOR H. GONZALEZ, MD

**Cousins:** If a patient had non–central-involved DME but their vision was approximately 20/40, would that change the tendency to intervene?

**Ohr:** If there is clear evidence of DME outside of the fovea and there are no cysts by OCT analysis but there is evidence of possible previous ischemic fovea damage, then absolutely. If a patient had non–central-involved DME but did have extrafoveal leakage that met classic ETDRS criteria, I might consider focal/grid laser treatment rather than starting treatment with an anti-VEGF agent.

**DME PATHOPHYSIOLOGY**

**Cousins:** What are the major contributions to DME pathophysiology, and how do they influence treatment choices?

**Victor H. Gonzalez, MD:** The pathophysiology of DR, particularly DME, is complex. Hyperglycemia initiates the events that result in tissue injury, including upregulation of VEGF production and initiation of the inflammatory process.10 A complex interplay between VEGF and inflammatory cytokines is believed to be important in the development of DR. These different mechanisms can affect treatment responses to currently available therapies. A recent analysis reported that the long-term response to anti-VEGF treatment could be determined in patients with DME by week 12.11 Those patients with VEGF-driven DME demonstrated profound response to anti-VEGF therapy early in the study. Conversely, patients that had little to no response to anti-VEGF therapy by week 12 did not have a significant response to continued monthly therapy by study end. Collectively, these findings suggest the differential response to anti-VEGF therapy may be due to the inflammatory disease component.

**Holekamp:** Anti-VEGF treatment is not only used as a therapy but also as a diagnostic. If the patient responds to anti-VEGF therapy, the patient’s DME is VEGF-mediated; however, if there is an incomplete or absent response, the disease is multifactorial and there are additional cytokines contributing to the pathology.

**Cousins:** The 0.19 mg fluocinolone acetonide intravitreal implant was recently reported to significantly delay progression to proliferative DR as well as to reduce DR severity,12,13 suggesting both have an inflammatory component that would benefit from continuous steroid therapy.

**RECENT CLINICAL TRIAL DATA**

**Cousins:** What are the key points from the Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol T trial?

**Ohr:** The Protocol T trial examined visual acuity response to aflibercept, bevacizumab, (Avastin; Genetech, South San Francisco, CA) and ranibizumab in patients with DME.14 For
patients with better baseline visual acuity, there was no difference in efficacy among the three therapies. However, in patients with baseline visual acuity of 20/50 or worse, aflibercept appeared to demonstrate an improvement in visual acuity compared with bevacizumab or ranibizumab.

Cousins: Should these data be interpreted to mean that aflibercept is superior to bevacizumab and ranibizumab for treating patients with DME?

Holekamp: In patients whose visual acuity is 20/50 or worse, the data show better efficacy for aflibercept compared with ranibizumab or bevacizumab. The most compelling aspect of these results was that, among the patients with poor baseline vision, 67% and 50% of those treated with aflibercept and ranibizumab, respectively, achieved at least 15 letters of vision improvement; however, this leaves a substantial portion of patients who do not experience visual improvement to this extent. What is also important, but frequently overlooked, is that to get these results, patients needed 10 injections a year. In the real world, patients are getting fewer than four injections in a 12-month period of time.15 Therefore, drawing real-world inferences based on clinical trial data needs to be done with caution.

TREATMENT STRATEGIES FOR DME: ANTI-VEGF THERAPY

Cousins: In clinical practice, how many anti-VEGF injections are patients receiving per year?

Gonzalez: Patients who receive only anti-VEGF therapies are treated with six to eight injections per year. We give all patients a three-injection challenge. If patients do not demonstrate a significant improvement by week 12, a change in therapy is considered. Once the vision and OCT values either have remained stable for two consecutive injections or have normalized, we begin a treat-and-extend protocol. If after 12 weeks there is no significant change from baseline, we consider switching patients with 20/50 or worse visual acuity to aflibercept whereas for these patients with 20/40 or better visual acuity, we consider alternative therapy such as steroids or laser.

Cousins: For a patient with DME and 20/50 or worse visual acuity, what is the initial treatment, and when should switching agents be considered?

Riemann: The chosen drug is dependent on baseline visual acuity — those with good initial vision respond to all anti-VEGF agents. Even if their vision is 20/50 or worse, I might initiate therapy with bevacizumab and switch if they do not respond to three injections.

Merrill: If a patient has 20/50 or worse visual acuity, I would ideally start with aflibercept. If there is an insurance requirement that another option must be tried first and that option produces an insufficient response, then it is reasonable to try three aflibercept injections. However, I am thinking ahead to other therapies.

Cousins: How many anti-VEGF injections should be given before concluding that a patient does not have VEGF-mediated DME?

Holekamp: I have been using four anti-VEGF injections, but based on a recent subanalysis of the DRCR.net Protocol I trial, I think using three injections is reasonable. The key is that clinicians must be cognizant of how the patient’s vision responds to treatment so that the pathology specific to the DME can be determined.

Riemann: It is important not to group all anti-VEGF therapies together. Retina specialists know that delaying treatment by more than a year results in worse long-term outcomes.16 I switch patients to different anti-VEGF therapies if the initial anti-VEGF therapy fails to produce an efficacious response. This underscores the need to distinguish between anti-VEGF responders and nonresponders.

Holekamp: The DRCR.net Protocol T does not give information about switching anti-VEGF therapies or about patients who did not respond to therapy. A subanalysis of DRCR.net Protocol I by Susan Bressler investigated anti-VEGF nonresponders, but a similar analysis of DRCR.net Protocol T has not yet been conducted.

TREATMENT STRATEGIES FOR DME: CORTICOSTEROIDS

Cousins: What are the different corticosteroid options available for patients with DME?

Holekamp: There are two FDA-approved corticosteroid treatments for patients with DME. The first option is the 0.7 mg dexamethasone intravitreal implant. The second option is a sustained drug delivery device that is sold as the 0.19 mg fluocinolone acetonide intravitreal implant.

Cousins: Does the 0.7 mg dexamethasone intravitreal implant meet the definition of continuous therapy, or is it a pulse therapy?
Holekamp: Although the 0.7 mg dexamethasone intravitreal implant is continuous for more than a 3- to 4-month time period, in the real world, it is mostly used as a modified pulse therapy. The 0.19 mg fluocinolone acetonide intravitreal implant is continuous for 3 years.

Cousins: If the patient is an anti-VEGF nonresponder, is switching to a treatment with corticosteroid appropriate, and, if so, what would be the initial agent?

Gonzalez: Before I switch to a corticosteroid, I make sure that I have not missed a short-lived response to anti-VEGF therapy. If there is truly no response, I first treat with the 0.7 mg dexamethasone intravitreal implant.

Merrill: I anticipate needing to use a steroid injection, and therefore, I conduct a trial with a topical corticosteroid. Then if the patient is an anti-VEGF nonresponder, I already have a sense of their intraocular pressure (IOP) response to corticosteroids.

Cousins: Other than a challenge with three to six anti-VEGF treatments, are there any other clues as to who will be a candidate for corticosteroids?

Gonzalez: The ideal approach would be to perform a vitreous analysis at baseline on all of our patients with DME, which is currently impractical. I use retinopathy severity and disease chronicity to help identify patients who may be corticosteroid candidates.

Cousins: What is the time to efficacious response with the 0.19 mg fluocinolone acetonide intravitreal implant versus intravitreal triamcinolone acetonide (IVTA) treatment?

Ohr: There is typically a more rapid response with IVTA compared with the 0.19 mg fluocinolone acetonide intravitreal implant. The 0.19 mg fluocinolone acetonide intravitreal implant is a chronic, low-dose corticosteroid, so sometimes it takes several months for a response to be observed.

Holekamp: I am part of a postmarketing, prospective trial investigating safety in patients who received the 0.19 mg fluocinolone acetonide intravitreal implant. The protocol required that I follow up within 1 week after patients received the 0.19 mg fluocinolone acetonide intravitreal implant to identify immediate, very good responders. At the 1-week visit, patients are already responding to the 0.19 mg fluocinolone acetonide intravitreal implant—the macular edema has significantly improved even at this time point.

Cousins: What should a new user of this implant expect for the response time?

Ohr: I advise patients that they may need to wait for 2 to 3 months before a response is noted because the 0.19 mg fluocinolone acetonide intravitreal implant behaves differently than IVTA and the 0.7 mg dexamethasone intravitreal implant (which have more rapid onset). Patients need to be aware of that, as well (for a summary of durations of effect for different corticosteroids, see Table 1).

**REVIEW OF THE FAME DATA**

Cousins: What are the topline data from the FAME trials?

Holekamp: The primary endpoint of the FAME clinical trials was assessed at 2 years postrandomization. These clinical trials began in 2005 before the era of treating DME with anti-VEGF therapies. In the FAME trials, patients were randomized to two doses of fluocinolone acetonide; however, I will only talk about the FDA-approved 0.2 µg/day fluocinolone acetonide dose versus the sham control arm. The sham control arm was heavily treated with intravitreal anti-VEGF agents, intravitreal steroids, and laser. Nevertheless, the study met its primary endpoint (28.7% of patients treated with the 0.19 mg fluocinolone acetonide intravitreal implant gained at least 15 letters of best corrected visual acuity compared with 16.2% of those who received sham control).

Cousins: Given that these trial data are from 10 years ago and standard of care has changed, how are the FAME results interpreted in a modern practice setting? Are the results still relevant? What do the results say about the 0.19 mg fluocinolone acetonide intravitreal implant efficacy?
Ohr: The data are relevant, but have to be taken in context. A key point is the inclusion criteria specified that patients receive at least one focal/grid macular laser treatment prior to randomization. Further, even though the sham control group could receive rescue treatment, the 0.19 mg fluocinolone acetonide intravitreal implant treatment was still associated with clinically significant visual acuity improvement compared with sham control, further highlighting the fact that the implant offers visual benefit. This is important because the sham control arm was not a traditional control — patients actually received standard-of-care rescue treatments.

Riemann: Although this certainly is not a head-to-head trial comparing the 0.19 mg fluocinolone acetonide intravitreal implant with anti-VEGF therapy, it does inform the discussion somewhat of a clinically relevant and statistically significant difference supporting the benefit of corticosteroids.

Holekamp: This may be informing the discussion of a comparison between a sustained, continuous drug delivery treatment versus sporadic pulse therapy, which may imply a benefit of continuous therapy rather than pulse therapy. Hypothetically, treatment with pulse therapy may not allow patients to achieve the most optimal results.

Ohr: Patients with DME are part of the workforce, which means that getting nine anti-VEGF injections per year may not be feasible. A treatment that would offer long-term coverage has huge implications.

Cousins: What is the difference between the 0.59 mg fluocinolone acetonide intravitreal implant (Retisert; Bausch & Lomb, Bridgewater, NJ) and the 0.19 mg fluocinolone acetonide intravitreal implant?

Holekamp: The only commonality between these two implants is they both provide an extended fluocinolone acetonide release. The doses are different and the 0.59 mg fluocinolone acetonide intravitreal implant is a larger drug delivery system that is surgically implanted. The 0.19 mg fluocinolone acetonide intravitreal implant is smaller, is injected in the office, provides a smaller amount of daily drug delivery, and has a more favorable adverse event profile.

The 0.59 mg fluocinolone acetonide intravitreal implant is approved for uveitis, whereas only the 0.19 mg fluocinolone acetonide intravitreal implant is approved for DME.

**IMPLANTATION TECHNIQUE**

Cousins: Please describe the 0.19 mg fluocinolone acetonide intravitreal implant injection procedure.

Holekamp: A window on the injection device allows visualization of the implant. Initially, the injection lever is slid forward, which pushes the implant to the tip of the needle. At this point, the injection is similar to other intravitreal injections, and the button is further depressed to deliver the implant. It is important to note that inspection of the eye afterward may not permit visualization of the implant due to its small size. My process is to visualize the implant in the window, but once it is pushed to the end of the needle, I immediately inject to minimize the possibility of prematurely releasing it from the needle. Therefore, delivery of this implant requires a more organized process than an anti-VEGF injection. It is not difficult, but the first time it is performed, extra care should be taken.

Cousins: Are there any other tips for performing the injection that may be beneficial for a new user? Is a stepped injection or a direct-in approach preferable?

Ohr: I go direct in. However, it is difficult to visualize the 0.19 mg fluocinolone acetonide intravitreal implant in the eye following injection.

Riemann: I think clinicians have to be careful to avoid a beveled, stepped injection because the 0.19 mg fluocinolone acetonide intravitreal implant injector has a thin-walled needle and a biplanar insertion may bend the needle. I prefer to pierce the sclera in a straight line usually at a 45° angle to the sclera. This lengthens the scleral path and hopefully decreases the risk of leak.
Holekamp: I also give a subconjunctival lidocaine injection, whereas I typically do not do this when administering an anti-VEGF injection. I displace the conjunctiva with a cotton tip and then go straight in.

MANAGEMENT OF CORTICOSTEROID CLASS-SPECIFIC ADVERSE EVENTS: CATARACT

Cousins: When would the risk of cataract development affect the decision to move forward with a corticosteroid?

Gonzalez: Studies have indicated that failure to treat central-involved DME promptly can be detrimental to vision. If after 12 weeks I see minimal to no response with an anti-VEGF agent and, depending on the presenting visual acuity, I consider switching to another anti-VEGF therapy. With a phakic patient, I start with an anti-VEGF agent, and if there is an insufficient response after three to four injections, I switch to another anti-VEGF agent for three to four injections. However, if their edema is still significant, I consider whether the significance of treating the retina outweighs the risk of cataract development.

Riemann: The risk of cataract development is significant; however, DME control is more important. Cataract surgery is exquisitely optimized, especially for well-controlled DME.

Holekamp: The MEAD study provides reassurance for corticosteroid use in patients with DME regarding cataracts as adverse events. In that study, 68% of patients (phakic at baseline) who received the 0.7 mg dexamethasone intravitreal implant developed a cataract, and 59% underwent cataract surgery. Also, patients who underwent cataract surgery during the study did as well, if not better, than the patients who were pseudophakic at randomization.

Merrill: In the FAME trials, patients who underwent cataract surgery during the trial also did as well, or better, than those who were pseudophakic at baseline.

Cousins: Are there patients for whom steroid use would be discouraged because of the risk of cataract development?

Holekamp: I would hesitate with a monocular, younger, patient who has reasonable vision in their phakic eye. I would also hesitate with a patient with myopia and anisometropia.

Ohr: If the patient wants to avoid cataract surgery, it may be prudent to use a different therapy.

Jason Bacharach, MD: A patient with pseudoexfoliation syndrome should be considered a high risk for cataract surgery.

Cousins: Should corticosteroid use in patients with pseudoexfoliation syndrome be avoided?

Bacharach: Not necessarily.

MANAGEMENT OF CORTICOSTEROID CLASS-SPECIFIC ADVERSE EVENTS: INTRAOCULAR PRESSURE

Cousins: From the perspective of a retina specialist who is considering the use of a sustained-release corticosteroid, what is the relative frequency of steroid-induced IOP response?

Richard K. Parrish, II, MD: Data from the FAME and MEAD studies suggest that approximately 60% of patients will not have an IOP response, approximately 35% to 40% will have an IOP response that will be manageable with topical therapy, and a small percentage will have a difficult-to-control steroid response. The prior steroid challenge will likely identify the majority of patients who would have the difficult-to-treat steroid response.

Bacharach: IOP response is dependent on the route of administration—if the patient does not have a positive response to topical therapy, it does not necessarily mean that they will not have an IOP increase with intravitreal injections. A greater percentage of patients will have a rise in IOP with an intravitreal compared with topical steroid, even with potent topical steroids, such as difluprednate.

Cousins: In the FAME trials, no patients treated with the 0.19 mg fluocinolone acetonide intravitreal implant in the subgroup that received a prior steroid challenge required incisional IOP-lowering surgery, but 6.1% of the 0.19 mg fluocinolone acetonide intravitreal implant-treated patients who did not receive prior steroid did require incisional surgery (R. K. Parrish, II, MD, unpublished data, 2015). What is the interpretation of these data?

Parrish: These data have to be interpreted in view of current FDA labeling. The FDA label is specific in that it states that the 0.19 mg fluocinolone acetonide intravitreal implant is indicated for the treatment of DME in patients who have been previously treated with a course of corticosteroid and did not have a clinically significant rise in IOP. Also, to be eligible for participation in the FAME trials, patients could not have...
had a steroid-induced IOP elevation that was unresponsive to topical medication. The FDA label is designed to minimize the risk of IOP elevations by stipulating that patients receive a prior course of corticosteroid without a clinically significant rise in IOP elevation. However, a course of corticosteroids and clinically significant rise in IOP are open to interpretation and not defined by the label.

Cousins: What is a typical prior corticosteroid challenge before using the 0.19 mg fluocinolone acetonide intravitreal implant?

Ohr: My challenge is one treatment with IVTA.

Gonzalez: My challenge is with the 0.7 mg dexamethasone intravitreal implant.

Holekamp: My challenge is multiple IVTA treatments or 0.7 mg dexamethasone intravitreal implants because the patient must demonstrate the need for chronic use of a corticosteroid.

Merrill: My challenge is topical corticosteroid for 1 to 2 months typically concurrent with an anti-VEGF therapy. Then if the patient does not have a significant IOP rise with the topical corticosteroids, I will try either IVTA or the 0.7 mg dexamethasone intravitreal implant. While the patient is being treated with a corticosteroid, I pay close attention to IOP and edema resolution.

Cousins: If a retina physician is not part of a multidisciplinary practice, what is the thought process if a difficult-to-treat rise in IOP is created? Should the patient be referred back to the referring general ophthalmologist or to a glaucoma specialist?

Merrill: I call the referring ophthalmologist and discuss his or her comfort level in managing the patient versus referring to a glaucoma specialist.

Gonzalez: I inform the referring ophthalmologist that the patient will be receiving a corticosteroid, and that these therapies carry a risk of elevated IOP. If concerned about the pressure, I will refer the patient directly to a glaucoma specialist.

Cousins: Patient compliance is another important consideration. What is the follow-up process after administering the 0.19 mg fluocinolone acetonide intravitreal implant? How often should the patient be monitored for both DME and IOP?

Riemann: After treating a patient with the 0.19 mg fluocinolone acetonide intravitreal implant, I have an eye care specialist check the patient 2 weeks later, and then I examine them 6 weeks post-treatment. Then depending on how the patient is doing, I usually examine them 3 to 4 months later and then every 6 months.

Cousins: How frequently should IOP be monitored in these patients?

Ohr: Initially, I monitor IOP at 4 to 6 weeks after treating with the 0.19 mg fluocinolone acetonide intravitreal implant and then examine 2 months later. Then, as long as the patient is not showing any trend of elevated IOP, I would consider extending the time I monitor them.

Gonzalez: The first follow-up is 4 to 6 weeks after treating with the 0.19 mg fluocinolone acetonide intravitreal implant. For the first year, I examine them every 3 months, and then for the second year, I evaluate at 6 months.

Holekamp: I evaluate the patient at 1 month after treating with the 0.19 mg fluocinolone acetonide intravitreal implant and then every 3 months. I recommend examining the patient at 3 months as was done in the FAME trials.

Cousins: The FAME trials showed approximately 30% of patients developed an IOP increase in the second year. From the perspective of a glaucoma expert, what is an advisable follow-up procedure?

Bacharach: I recommend using the FAME trials as a guide for the follow-up procedure. An early visit makes sense because there is a small group of hyperresponders that experience an IOP elevation quickly. I definitely recommend a 2- to 4-week examination after treatment with a corticosteroid. Then, I would evaluate quarterly.

Cousins: Could IOP be monitored quarterly by a general eye care provider?

Holekamp: Yes, but the patient has DME, and the 3-month visit following corticosteroid treatment is not just to check IOP but also to monitor the control of DME and to ensure the patient is not developing proliferative disease or significant pre-proliferative disease. These patients are going to be involved in our practice for a significant period of time.

Cousins: In patients who are currently receiving the 0.19 mg fluocinolone acetonide intravitreal implant and are subject to satisfying the FDA indication criteria, what is the experience with steroid-induced IOP rises?

“While the patient is being treated with a corticosteroid, I pay close attention to IOP and edema resolution.”

— PAULINE T. MERRILL, MD
Holekamp: The FDA indication has mitigated the risks associated with this implant. I have used the 0.19 mg fluocinolone acetonide intravitreal implant with 10 to 15 patients, and they have not experienced any IOP increases because the high responders are ineligible for treatment.

Cousins: The 0.19 mg fluocinolone acetonide intravitreal implant European label does not require a prior course of corticosteroids; rather, it stipulates that patients must have had an insufficient response to prior therapy. Nonetheless, the European experience is comparable to Dr. Holekamp’s scenario regarding few steroid-induced IOP increases and lack of incisional surgery.

Parrish: I think the most important finding of the FAME trials was that 3-year visual acuity outcome was the same whether patients had no IOP response, an IOP response controlled with medication, or an IOP response requiring incisional surgery (R. K. Parrish, II, MD, unpublished data, 2015). In other words, intervention for elevated IOP, including incisional surgery, did not adversely affect the visual acuity outcome.

Cousins: How is IOP being measured in clinical practice?

Ohr: I use Goldmann applanation.

Merrill: I use a Tono-Pen (indentation tonometry).

“Improving vision from 20/70 to 20/30 is a big deal — it’s the difference between driving and not driving.”
— CHRISTOPHER D. RIEMANN, MD

Cousins: What feedback can be provided on the accuracy of Tono-Pen versus Goldmann applanation as a standard way of measuring pressure?

Bacharach: The Goldmann applanation tonometer has some fallacies. It is the gold standard, but there are other factors; for example, the thickness of the cornea. But in general, both of those modalities are reasonable for a retina group to use.

MANAGEMENT OF CORTICOSTEROID CLASS-SPECIFIC ADVERSE EVENTS: GLAUCOMA

Cousins: What was the incidence of glaucoma development, defined as a cup-to-disc ratio increase greater than 0.2 during the course of the study, during the FAME trials?

Parrish: Stereoscopic optic disc photographs were taken in both the treated and contralateral eyes at baseline and at scheduled visits throughout the 36-month trials. The images were evaluated by the University of Wisconsin-Madison Fundus Photograph Reading Center, a group that is recognized, validated, and trusted. The images were masked to time and randomization (R. K. Parrish, II, MD, unpublished data, 2015). The results showed that four patients treated with the 0.19 mg fluocinolone acetonide intravitreal implant had an increase in cup-to-disc ratio greater than 0.2, which was associated with an IOP elevation. However, statistically this did not meet the criteria for saying there was a difference compared with those who received sham control. The notion that there is rampant optic nerve injury is not the case. Baseline and follow-up visual field analyses were not performed because it is unlikely that meaningful visual field data could be obtained for patients with 20/80 visual acuity before and after treatment. The conclusion from the data is development of glaucomatous optic neuropathy is extremely uncommon, and when it occurs, it is associated with elevated IOP.

Bacharach: There are patients with a susceptibility to develop IOP elevations and glaucomatous change. Clinicians know that patients with antecedent glaucoma or who have primary relatives with glaucoma carry a greater risk to develop elevated IOP when treated with corticosteroids.

Riemann: It is also important to point out that diabetes is a risk factor for glaucoma, and patients with diabetes may have pale nerves. This is important because even if a patient develops glaucoma, the drug contribution versus diabetes warrants consideration. In the FAME trials, 12% of sham control-treated patients had an IOP increase, 14% needed IOP-lowering medications and less than one percent needed glaucoma surgery.

SPECIAL CONSIDERATIONS FOR THE 0.19 MG FLUOCINOLONE ACETONIDE INTRAVITREAL IMPLANT

Cousins: Consider the following patient who received a challenge with a triamcinolone injection. The initial IOP was 20 mm Hg, but after the steroid challenge, the IOP rose to 25 mm Hg. If the patient then was treated with a topical glaucoma medication and the IOP dropped to 16 mm Hg, should this patient be treated with the 0.19 mg fluocinolone acetonide intravitreal implant?

Merrill: I may discuss the 0.19 mg fluocinolone acetonide intravitreal implant as an option, but I would refer patients to their general ophthalmologist first for a complete baseline glaucoma screening, including corneal thickness and visual field examinations, to determine concern for IOP. I also would perform retinal nerve fiber layer (RNFL) OCT analysis. I would try the 0.7 mg dexamethasone intravitreal implant first to further assess IOP response and determine whether the pressure can be controlled topically before using the 0.19 mg fluocinolone acetonide intravitreal implant.
Riemann: I focus on patient compliance. If the patient is compliant and topical medication lowered the pressure, I can refer them to the glaucoma specialist if necessary. All of these things considered, I would use the 0.19 mg fluocinolone acetonide intravitreal implant. Improving from 20/70 to 20/30 is a big deal—it is the difference between driving and not driving.

Gonzalez: I would go with the 0.7 mg dexamethasone intravitreal implant first because it is an intravitreal agent, and I know the effect will last about 3 months. If the edema returns and the pressure has remained stable, then I will consider using the 0.19 mg fluocinolone acetonide intravitreal implant.

Holekamp: Any patient for whom the 0.19 mg fluocinolone acetonide intravitreal implant is not contraindicated is a candidate for this treatment if that is what is in their best, long-term interest. The label states the contraindications are ocular and periocular infections, glaucoma (defined as cup-to-disc ratio > 0.8), and hypersensitivity. I consider three criteria when deciding to treat with the 0.19 mg fluocinolone acetonide intravitreal implant. First, the macular edema must respond to corticosteroids. Second, the patient must have an IOP profile with which I feel comfortable and can control. Third, the patient must need long-term, sustained therapy. In the case Dr. Cousins just described, I would use the 0.7 mg dexamethasone intravitreal implant while monitoring the pressure. Ultimately I would go to the 0.19 mg fluocinolone acetonide intravitreal implant once the patient has satisfied the three criteria.

Merrill: I would add a fourth criteria—patient compliance.

Holekamp: I agree, but usually patients who are candidates for steroid therapy have previously received multiple anti-VEGF injections. Therefore, I have established a long-term relationship with these patients and have a good record of their compliance.

Cousins: Dr. Parrish, what is the appropriate baseline glaucoma analysis for a patient with an easy-to-control steroid response who will benefit from the 0.19 mg fluocinolone acetonide intravitreal implant?

Parrish: It really depends on visual acuity. For all patients, optic disc assessment and OCT of the RNFL should be considered. If the patient has macular edema and good (> 20/40) visual acuity, a suitable visual field analysis is likely. However, abnormally thick OCT RNFL measurements have been reported in patients with DME, and those patients with severe DME and vision loss are likely to have poor visual field due to macular disease.

Holekamp: I think retinal physicians need to perform baseline studies because, if patients need a referral to a glaucoma specialist, physicians should have that baseline information. This includes optic disc photographs, OCT of the nerve fiber layer corneal thickness, and possibly baseline visual field analysis (depending on the status of their macula to perform the test reliably).

“Any patient for whom the 0.19 mg fluocinolone acetonide implant is not contraindicated is a candidate for this treatment.” — NANCY M. HOLEKAMP, MD

Riemann: The patient should also be encouraged to have more frequent follow-up visits.

Cousins: Should these analyses be repeated 3 to 6 months later after the edema has responded to the corticosteroid?

Parrish: Yes, that is a great idea, and it would establish a new baseline. Examining the optic nerve for evidence of focal neuroretinal rim thinning, disc hemorrhage, or generalized cup expansion is also something that can be done.

Bacharach: I also like the idea of re-evaluating the eye biannually, if possible.

Cousins: Is it safe to use steroids in patients who have had a trabeculectomy (for context, the patient has an IOP of 16 mm Hg with no topical therapy)?

Bacharach: Patients who have had prior incisional glaucoma surgery can still be steroid responders.

Cousins: Are these patients likely to be steroid responders?

Parrish: It is unclear. It depends on the pressure at baseline.

Cousins: If the patients have a tube shunt in place, does that change susceptibility to a steroid response?

Parrish: No. It does not guarantee that the patient will not be a steroid responder.

Bacharach: An additional point is that the typical choice of topical medication for glaucoma is prostaglandins, and in eyes that are already in a pro-inflammatory state, it probably makes sense to consider aqueous suppressants as the first modality. These can be used either as an individual agent or as a fixed-dose combination.
Gonzalez: Is there a one-drop combination that is the best for steroid responders?

Parrish: In the FAME trials, prostaglandins, beta blockers, alpha-2 agonists, and carbonic anhydrase inhibitors were all used to lower IOP (R. K. Parrish, II, MD, unpublished data, 2015). I agree that it may be beneficial to use a treatment that would decrease aqueous production. If the trabecular meshwork is blocked because of the steroid or unusual proteoglycan metabolism, it is unlikely that this will be reversed with medication. Therefore, aqueous suppression, whether it is with beta blockers, alpha-2 agonists, or topical carbonic anhydrase inhibitors, makes a lot more sense.

Cousins: If a patient with an 0.19 mg fluocinolone acetonide intravitreal implant experiences an IOP increase, would an IOP-lowering laser procedure, rather than topical medication, be appropriate?

Bacharach: Laser procedures are effective, and selective laser trabeculoplasty (SLT) is an efficacious option. Several case series have described laser procedures to lower steroid-induced IOP escalations, which precluded the need for incisional surgery. My experience is that laser procedures are an excellent alternative for patients.

Parrish: The peer-reviewed literature is limited to individual case reports, and a few small series suggest the benefit of selective or argon laser trabeculoplasty is better than what would have been predicted based on general response (these patients tend to have high IOP levels). Also, there were patients in the FAME trials who underwent laser trabeculoplasty and did not need incisional surgery. If topical therapy fails, laser procedures are an obvious next step.

Riemann: What is the duration of effect of SLT?

Bacharach: In the literature, SLT is efficacious in approximately 80% of patients, which is similar to that of argon laser trabeculoplasty. However, this is not in steroid responders; this is a generalization in patients with open-angle glaucoma. There is approximately 80% to 90% initial responsiveness and a 10% failure rate per year, so by year 5, 50% of the patients lose the effect.

Cousins: Could the laser procedure be used instead of topical medication?

Parrish: I think it is reasonable to speculate that if a laser procedure is effective in patients who have been previously treated with topical IOP-lowering medication, it would also work in patients who have not received prior IOP-lowering therapy. I cannot provide any evidence-based literature to support this conclusion, but it is biologically plausible.

Gonzalez: For a community-based retina specialist who does not have a glaucoma specialist readily available, how long should a topical therapy be used before referring the patient to a glaucoma specialist?

Parrish: I think it depends on the pressure level and the nerve appearance. For example, if the patient has a cup-to-disc ratio of 0.3 with a healthy neuroretinal rim, and the IOP is 25 mm Hg to 27 mm Hg, the rate of glaucomatous change may take years. However, if a patient starts out with a cup-to-disc ratio of 0.7, and the IOP is in the low 30 mm Hg range with topical therapy use, they should be referred to a glaucoma specialist immediately.

Cousins: What are the thoughts regarding 0.19 mg fluocinolone acetonide intravitreal implant dislocation into the anterior chamber?

Riemann: I have not seen an 0.19 mg fluocinolone acetonide intravitreal implant in the anterior chamber; however, this has been reported with the 0.7 mg dexamethasone intravitreal implant. It is rare, and may occur if the posterior lens capsule is not intact or if the zonular complex is damaged. In this case, they can be observed, repositioned, or removed. A concern with dislocating implants in the anterior chamber is corneal edema. Device migration and corneal edema has been reported with the 0.7 mg dexamethasone intravitreal implant (but I am unaware of any cases with the 0.19 mg fluocinolone acetonide intravitreal implant). The 0.7 mg dexamethasone intravitreal implant is contraindicated in patients with a torn posterior lens capsule because of the risk of anterior chamber migration (this is also a warning in the 0.19 mg fluocinolone acetonide intravitreal implant prescribing information). It has been suggested that if the 0.7 mg dexamethasone intravitreal implant migrates into the anterior chamber, prompt removal may minimize the extent of corneal edema.

Gonzalez: Regardless of the corticosteroid, I evaluate the patient to make sure there is no obvious chamber disruption. To my knowledge, the 0.19 mg fluocinolone acetonide intravitreal implant has not been reported to migrate into the anterior segment, although the risk is always
present. If I find that the barrier between the anterior and posterior segment has been compromised, I will not offer the patient the 0.19 mg fluocinolone acetonide intravitreal implant.

**CONCLUSION**

**Cousins:** Corticosteroids represent an attractive option for patients with DME who have a suboptimal or inconsistent response to anti-VEGF therapies. The current FDA-approved corticosteroids, the 0.7 mg dexamethasone intravitreal implant and the 0.19 mg fluocinolone acetonide intravitreal implant, have demonstrated significant visual acuity improvements compared with their respective controls in phase 3 clinical trials. However, the adverse events associated with corticosteroids, particularly cataract development and glaucomatous change to the optic nerve head associated with elevated IOP, warrant consideration before treatment initiation. The current roundtable discussion provides opinions from experts as to how they select patients who are appropriate candidates for receiving an 0.19 mg fluocinolone acetonide intravitreal implant. Using the 0.19 mg fluocinolone acetonide intravitreal implant FDA indication as guidance, the panel of discussants provided their insight into how the language of the 0.19 mg fluocinolone acetonide intravitreal implant label is meant to mitigate the risk of developing elevated IOP.

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