When and How to Incorporate Steroids for Persistent Diabetic Macular Edema: A Discussion of Real-World Treatment Optimization Strategies

ABSTRACT: In the United States, diabetic macular edema (DME) is the leading cause of vision loss among people with diabetic retinopathy. Despite the availability of different therapies for DME, up to half of patients with DME show some persistent edema after anti-vascular endothelial growth factor (VEGF) treatment alone, leaving these patients at high risk for vision loss. However, dosing in a similar fashion to that of pivotal anti-VEGF trials is difficult because of real-life challenges faced in clinical practice. This is particularly true for DME, in that the frequency and burden of anti-VEGF injections are a major challenge to patient care. Research evaluating anti-VEGF therapies has shaped the treatment paradigms for patients with DME, and similar benefits have also been noted in clinical trials evaluating the use of intravitreal steroids. Treatment with a long-term intravitreal corticosteroid, which requires fewer injections than treatment with most short-acting therapies, has been found to reduce inflammation and improve vision in a percentage of patients. This roundtable discussion, which took place during the 2018 annual meeting of the Vit-Buckle Society, reviews the current treatment paradigms for DME and evaluates how to customize and optimize treatment strategies geared toward individualized patient care.

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ophthalmologists without a diagnosis of diabetes yet have findings of DR. Prevention and screening are paramount, as patients with undiagnosed diabetes can present with complications later that have gone unrecognized for years. Persistent DME is an example of a complication that unfortunately can be unforgiving over the long term. We have seen the impact of persistent DME on final visual potential in several studies. In the RISE/RIDE twin trials, patients in the sham group who could crossover to ranibizumab (Lucentis; Genentech, South San Francisco, CA) at 24 months had only modest visual gains despite reasonable anatomic improvements (Figure 1). Similarly, in a post hoc analysis of the Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol I study, those eyes with persistent macular edema being treated with ranibizumab had less visual acuity gains than eyes with the least macular edema. Both studies highlight the importance of eliminating visually significant DME in a timely fashion for best visual acuity results.

Carlos Buznego, MD: Diabetes and cataracts are common conditions in elderly adults. Approximately 25% of patients undergoing cataract surgery have coexistent diabetes mellitus. Fortunately, only about 14% of these patients have evidence of DR, and even fewer of those are diagnosed with DME.

Eichenbaum: Of those patients with DR, 7% have severe enough disease to develop DME, which is a considerable number of people and a potential health care burden for those patients. Patients with diabetes are more complex from a retinal perspective—they have angiogenic components, inflammatory components, vascular components with ischemia, and mechanical components with retinal traction or vitreous hemorrhage. My patients with DME tend to be a little older and have many comorbidities, including problems related to peripheral vascular disease, kidney disease, and neuropathy. How does your typical patient with DME present?

Dhoot: My typical patient with DME has had diabetes for several years, usually accompanied by various comorbidities. They also have a lot of time, mobility, and transportation issues, which can make it difficult for them to make routine retina appointments, as well as appointments for the numerous other physicians they need to see.

Weng: I encounter a wide variation in age and disease duration among my patient population, but I generally see DME more frequently in patients with a longer duration of diabetes. I also find that the disease tends to affect a younger, working population, which plays a key role when considering treatment burden.

Wykoff: I see patients across the full spectrum of DR, from no manifestations of the disease to blindness, and everything in between. Compliance and early intervention are key. If these patients present late in the disease process, are mismanaged or simply have an aggressive disease course despite adequate therapy, they can be at risk for going blind. These patients and their caregivers should be aware that complete loss of vision is a potentially very real outcome in the absence of appropriate treatment.
Sheth: My patient population is a mixed bag. The degree of retinopathy often dictates whether they have DME.

**A SHIFT IN RESEARCH: THE ROLE OF INFLAMMATION**

Eichenbaum: For more than 10 years, the treatment of DME with intravitreal injections with anti-vascular endothelial growth factor (VEGF) agents has been studied, and today, there is a wealth of research in the treatment of patients with DME. A significant proportion—between 30% and 50%, depending on age—of patients in the more modern frequent-injection studies, such as the DRCR.net Protocol T trial, have detectable post-treatment edema. The presence of this residual edema leads clinicians to look for more modalities or agents to control anatomy, while reducing the burden of care. How has research impacted the way studies are designed and how data are presented?

Wykoff: Many trials—including Protocol T, RISE/RIDE, and VISTA/VIVID—have demonstrated that regular anti-VEGF injections can improve visual acuity across a population. However, all the patients in these phase 3 trials had central-involved DME with associated visual loss. The optimal management of distinct DME populations is still being determined, including patients with non–central-involved DME and patients with central-involved DME with preserved visual acuity. Ongoing trials such as the DRCR.net Protocol V will hopefully inform the management of such patient groups in the anti-VEGF monotherapy pharmaceutical era. Nevertheless, although results of these trials showed robust visual acuity gains with anti-VEGF dosing through 2 to 3 years of management, a substantial portion of patients did not achieve 20/40 or better visual acuity. In other words, even under ideal conditions with regular anti-VEGF dosing, many patients still do not achieve optimal visual outcomes, indicating that new approaches to this disease are needed.

Sheth: When evaluating research, such as the DRCR.net Protocol T or the RISE/RIDE trials, one notices that frequency of treatments differs between trial participants and patients in a clinical practice (Figure 2). For example, in RISE/RIDE, patients were injected monthly and gained an average of 10.2 letters. Surgeons use that information to guide how they treat their patients, but it is not the reality of clinical practice. Surgeons need to determine the right approach for clinical patients. Multiple studies have demonstrated real-world treatments of three anti-VEGF injections per year, and no clinical trial has demonstrated superior results with less frequent dosing of these agents.

**Dhoot:** Research efforts are shifting toward achieving maximal visual acuity and anatomic results while maximizing durability. As discussed above, the ability of patients to adhere to fixed monthly dosing is difficult, and real-world DME studies are proof of this finding. Therefore, treatment options that can have sustained effects would be greatly beneficial, and many of the upcoming DME trials address this notion.

Weng: Interestingly, ophthalmologists use optimal coherence tomography (OCT) scans and observe the size and/or distribution of cysts to guide disease management in DME, yet it is known that there can be discordance between anatomic and visual acuity results. What is important to remember is that VEGF does not act alone in this disease; inflammation plays a key role in the development of DME. Thus, it is important to consider other classes of therapy when managing DME, especially if anti-VEGF monotherapy is not producing the desired results.

Eichenbaum: Evidence that DME pathology extends beyond VEGF to other etiologies, specifically inflammation, is accumulating. Some aqueous and vitreous studies suggest the longer a patient has diabetes, the more proinflammatory cytokines and intercellular adhesion molecules are present. When I encounter patients who have persistent DME despite antiangiogenics, my first line of therapy, I then explore inflammatory and less vasogenic causes for that patient. What is the role of inflammation in DME, and what inflammatory features do you look for in patients with diabetes?

Sheth: I try to determine the cause of the DME with OCT and fluorescein angiography findings. To start, I begin...
treatment with anti-VEGF therapy, which is a good test because patients will either improve or not improve with it. If a patient has DME that persists or recurs on anti-VEGF therapy, then logic dictates something else needs to be addressed—likely inflammation—so then I treat the patient with a steroid and he or she often improves.

**Dhoot:** Interesting data exist regarding measured levels of aqueous VEGF and other cytokines at varying levels of the Early Treatment Diabetic Retinopathy Study severity scale. While there is a small rise in VEGF levels as DR severity increases, inflammatory cytokines are expressed at much greater levels with increasing DR severity. Clinically, a lack of anatomic response to VEGF suppression is suggestive of the greater role of inflammatory cytokines.

**Wykoff:** Fortunately, anti-VEGF injections work for both the neovascular and DME components of DR. Typically, the neovascular component is acutely responsive to anti-VEGF injections, at least transiently. In comparison, the reduction in DME volume after an anti-VEGF injection can be highly variable. I find a general rule is that the greater volume of DME a patient has, the less acutely responsive the eyes will be to anti-VEGF monotherapy. I use this rule for prognostication, for educating my patients, and also for consideration of using a corticosteroid. In general, thick, boggy retinas take longer to dry out with anti-VEGF injections than eyes with less fluid.

**FIRST-LINE TREATMENT OF DME**

**Eichenbaum:** What is your first line of treatment for the typical patient with DME—a patient who presents with central-involved DME, without neovascularization, and with some ischemia, significant edema, and vision loss?

**Weng:** I typically start with anti-VEGF therapy as many studies have shown that anti-VEGF therapy is effective for many patients. I usually start off with a series of at least three, monthly treatments, and then I will gauge how they are responding based on visual acuity and OCT findings.

**Wykoff:** I too start with anti-VEGF therapy in most treatment-naïve cases. In the frequent clinical situation in which a patient is asymptomatic yet has DME without proliferative DR, which I prefer to treat with anti-VEGF injections, I often do not treat patients on the first visit. I perform widefield fluorescein angiography and spend time reviewing the imaging with patients and their caregivers. I discuss the importance of optimal cardiovascular risk factor control in collaboration with their primary care team. I also educate patients on how to monitor their visual acuity in a monocular fashion. I would like patients to recognize their symptoms before I start treatment and, therefore, will initiate therapy at the next visit when they have had time to realize their visual symptoms.

**Eichenbaum:** I typically do that too. DME is not an emergency care situation that requires same-day treatment. If an asymptomatic patient with DME presents with good vision in both eyes, then I often talk to the patient about DME, and I obtain imaging for patient-teaching purposes.

**Dhoot:** For patients with DME, I usually treat the same day, starting with anti-VEGF therapy. Patients are often willing to begin treatment immediately when it comes to DME. The retinal images are a powerful teaching tool, and at the initial visit, I always review both the fluorescein angiography and OCT scans with patients. At subsequent visits, I make a point of reviewing OCT findings and changes so that patients have objective feedback. I also take that opportunity to educate patients about microvascular and macrovascular complications of diabetes at the initial visit, emphasizing compliance with medications and glycemic control.

**Sheth:** My first line of anti-VEGF treatment for a typical patient with DME is on-label use of ranibizumab or aflibercept (Eylea; Regeneron, Tarrytown, NY). I find educating the patient up front leads to more patient compliance, because I find when patients are informed, they are more likely to buy in to the treatment plan. I also think it saves time in the long run because fewer conversations are required later as patients trust the physician and understand the plan.

**INDIVIDUALIZING TREATMENT: STEROIDS AND COMBINATION THERAPY**

**Eichenbaum:** Randomized, controlled trial data demonstrate the efficiency of fixed combinations of steroid with antiangiogenics and show a clear, anatomic benefit has been established. In DRCR.net Protocol U, patients received at least three, monthly protocol ranibizumab injections, so they had some level of uniform, frequent antiangiogenic treatment before randomization into the trial. If edema persisted, patients were then randomly assigned to two study arms. Patients in one arm received a combination treatment of dexamethasone and ranibizumab, while patients in the other arm were treated with ranibizumab monotherapy. After 24 weeks, both groups in aggregate had similar improvements in visual acuity, but the combination arm had better reduction in retinal thickness. The results of the DRCR.net Protocol U trial, albeit a short study, also suggested that pseudophakic patients performed better both anatomically and visually when given combination therapy.

Consider the patient with DME who comes back after 2 to 6 weeks on anti-VEGF therapy with minimal response.
I consider switching to or adding on a steroid between the third and sixth injection, erring slightly earlier than I had in the past. I discuss with patients how steroid use may reduce their requirement for injection treatment, and more importantly, how the addition of this therapy will probably improve their macular anatomy. Currently, two corticosteroids are approved by the U.S. Food and Drug Administration for treating DME—0.7 mg dexamethasone implant (Ozurdex; Allergan, Irvine, CA) and 0.19 mg fluocinolone acetonide (FAc) sustained-release intravitreal implant (Iluvien; Alimera Sciences, Alpharetta, GA).

In my practice, I switch to a 0.7 mg dexamethasone implant as my first-line intravitreal steroid. When and how do you switch from anti-VEGF therapy to intravitreal steroid therapy and/or combination therapy?

**Wykoff:** My interpretation of the Protocol U data is that adding an intravitreal steroid to the enrolled population was advantageous from an anatomic perspective. Protocol U utilized a 24-week study period, a relatively short-term duration of treatment in the context of DME management, and therefore, I interpret the anatomic outcomes as more meaningful than the visual outcomes. My goal for patients with DME is to dry the retina, so adding a steroid in patients who have persistent DME despite multiple anti-VEGF injections as defined in Protocol U, may be clinically valuable.

**Dhoot:** The number of sequential anti-VEGF treatments I administer without positive anatomic gains has decreased over the years. If I do not see a response or forward progress after three or four injections, then I begin to consider whether inflammation may be playing a larger role and typically switch to a steroid. When I switch, I typically treat with a 0.7 mg dexamethasone intravitreal implant.

**Sheth:** Introducing the idea of switching to steroid therapy or combination therapy early in the process is important because it may take months for a patient to be ready for treatment with intravitreal steroids. For example, I have a patient who is a 55-year-old man receiving bilateral anti-VEGF injections for DME, and his vision was not improving. He had significant persistent edema requiring anti-VEGF injections every 4 weeks, and he was beginning to get frustrated. I started the steroid conversation approximately 3 months after his third anti-VEGF injection—a little later than was typical for me—but it took that long for him to accept the fact that his vision was not improving. In his case, I discussed using the 0.7 mg dexamethasone intravitreal implant with him, with the goal of drying the retina, in combination with anti-VEGF therapy.

**Weng:** Data from trials such as RISE/RIDE demonstrate that monthly anti-VEGF injections improve vision and lead to continued improvement for many patients. Like most retina specialists, I almost always initiate DME treatment with anti-VEGF injections. However, the proportion of patients receiving anti-VEGF monotherapy who have persistent DME is not insignificant, and when considering the challenges of adhering to strict monthly therapy in real-world settings, I am inclined to integrate steroid therapy if I feel that patients have no response or a suboptimal response to anti-VEGF. Previously, I would switch to a different anti-VEGF agent before doing so, but I was not impressed by the results. In these cases, I find that it is beneficial to try a different agent and see if that will yield a better response.

I approach DME as the multifactorial disease it is; selecting a treatment is not an either/or choice. In my experience, many patients achieve good outcomes on steroid therapies with boosters of anti-VEGF; the retina specialist is not limited to choosing just one treatment.

**TREATMENT CHOICES BASED ON REAL-WORLD DATA**

**Eichenbaum:** Clinical research provides surgeons with valuable data for treatment; however, the research treatment protocols are not often indicative of daily clinical practice and treating everyday patients. Real-world data from the USER and PALADIN trials support the concept of combination therapy. This includes the use of the 0.19 mg FAc intravitreal implant. Although they are not randomized, controlled trials, these real-world studies provide good data surgeons can apply. The USER trial, a four-center trial, looked back on patients who had received the FAc intravitreal implantation, and the PALADIN trial, a 41-center prospective trial without a protocol-mandated treatment, collected data regarding real-world use of the FAc intravitreal implant. Patients entering these two trials received more treatments and had less stable anatomy before receiving the FAc intravitreal implant than after receiving the FAc intravitreal implant. Both trials showed similar reduction in treatment burden, stabilization of OCT, and visual acuity. How do these data impact your plan for patients with persistent edema while on antiangiogenic monotherapy?

**Wykoff:** The timing of when I might consider a 0.19 mg FAc intravitreal implant for DME management is highly individualized. For example, a patient with a post-vitrectomy eye can be an ideal candidate for the FAc implant early in the treatment process as, in my experience, anti-VEGF agents do not have the same durability of biological activity after vitrectomy.

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Dhoot: I begin to consider the 0.19 mg FAc intravitreal implant early in the treatment process. Typically, when I first discuss with patients the 0.7 mg dexamethasone intravitreal implant—which lasts about 3 months—I also mention there is a steroid that lasts up to 3 years. Often, physicians will observe a good anatomic response in patients with the 0.7 mg dexamethasone intravitreal implant, but then the fluid returns. At this point, I consider treating with the 0.19 mg FAc intravitreal implant.

Weng: I typically begin with the 0.7 mg dexamethasone intravitreal implant because it is helpful to determine whether a patient has a beneficial response to steroids and also to confirm the patient did not experience a significant increase in IOP. Depending on individual circumstances, I may switch patients to a 0.19 mg FAc intravitreal implant even after a single 0.7 mg dexamethasone injection. I agree with Dr. Dhoot in his observations; some patients respond well to the 0.7 mg dexamethasone intravitreal implant but then experience recurrence of DME several months later. When another 0.7 mg dexamethasone implant is injected, they often demonstrate the same fluctuating pattern again. I consider these patients good candidates for the 0.19 mg FAc intravitreal implant because the cyclic nature of DME resolution and recurrence—which may possibly be damaging to the retina in the long term—is mitigated by the pharmacokinetic properties of the implant’s 3-year microdose delivery system (Figure 3).

Sheth: Six weeks after I inject the first 0.7 mg dexamethasone intravitreal implant, I check the patient’s IOP results. If the medication appears to be working, then we conduct a benefits investigation for the 0.19 mg FAc intravitreal implant. Alimera has worked with our billers and staff to streamline the process for insurance approvals so that our patients do not experience any surprises.

Wykoff: Patients generally like the idea of fewer injections and the concept of a therapeutic option that can last 3 years. I emphasize that the expectation is not to be free of injections but rather to reduce treatment burden with fewer injections. If patients want to stretch out their treatment intervals but are unable to do so with anti-VEGF dosing, then I consider steroid therapy as an option.

Eichenbaum: Patience is key because the process moves more slowly with the low-dose, stable release of steroid in the 0.19 mg FAc intravitreal implant in patients with DME. I give the 0.19 mg FAc intravitreal implant to patients who have previously received regular steroid treatment and are doing well. I want patients to continue to do well but receive treatment less often. USER and PALADIN data support this decision to use the 0.19 mg FAc intravitreal implant in a patient who comes in with good vision and retains it but who may be able to receive treatment much less often with foundation therapy. Do you inject the 0.19 mg FAc intravitreal implant into a patient whose retina appears edematous, or do you prefer to dry the retina first?

Sheth: I would inject the 0.19 mg FAc intravitreal implant into patients who had significant edema, and the initial effect

**EVALUATING STEROID OPTIONS**

**Eichenbaum:** In my experience, steroid therapy will dry the retina in most patients with persistent fluid in DME. With a duration of therapy up to 36 months, the 0.19 mg FAc intravitreal implant is a reasonable choice for foundation therapy. When do you consider a foundation therapy with the 0.19 mg FAc intravitreal implant?

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**“Real-world data support that greater than 50% of patients do not require any further treatment in the follow-up period after receiving the 0.19 mg FAc intravitreal implant.”—DILSHER S. DHOOT, MD**
is different from that of anti-VEGFs. A surgeon can wait until the edema has lessened, supplementing with another steroid agent or an anti-VEGF, or a surgeon can inject with the 0.19 mg FAc intravitreal implant.

**Weng:** Regardless of whether the surgeon injects earlier or later, treatment with the 0.19 mg FAc intravitreal implant is often beneficial, even if the retina is boggier. The response may be less pronounced initially in these patients, and the patient may require a few booster injections, but I find that over time, patients achieve similar visual gains, often with a significantly lower injection burden.

**Wykoff:** It is common and expected to see an immediate and substantial drying in the context of DME after an anti-VEGF injection or delivery of a 0.7 mg dexamethasone intravitreal implant because a high concentration of pharmaceutical is delivered in a bolus fashion. The impact of the 0.19 mg FAc intravitreal implant on retinal edema is less pronounced initially but can build over time and be sustained for many months. After an 0.19 mg FAc intravitreal implant injection, I typically will see patients in 6 to 8 weeks; at that time, if I see improvement, which I define as at least a 10% reduction in fluid, then I will often continue to observe without additional treatment. In comparison, if I see no change in fluid status, I may consider administering an anti-VEGF or dexamethasone injection.

**Dhoot:** I agree. Ideally, I inject at the end of a 0.7 mg dexamethasone intravitreal implant’s effect, so patients’ retinas are usually drier. I think that in the real world, regarding steroids, surgeons have a bias toward injecting in patients with boggier eyes, and only recently are data, such as those from USER and PALADIN, being collected on injecting steroids in patients with better visual acuity. It turns out patients presenting with better visual acuity can achieve even better outcomes compared to patients with chronic DME, especially in terms of durability.

**Eichenbaum:** Do you challenge patients with an intravitreal corticosteroid or with a topical corticosteroid before FAc implant injection?

**Wykoff:** I have used both intravitreal as well as topical steroids to determine if a patient is not a steroid responder. I often perform my steroid challenge with topical prednisolone. If a patient is treated reliably with prednisolone or 0.05% difluprednate ophthalmic emulsion (Durezol; Alcon Laboratories, Fort Worth, TX) for 1 to 2 months, and he or she has not shown a significant increase in IOP, then I am comfortable using the 0.19 mg FAc intravitreal implant at that point.

**Sheth:** I prefer to perform a steroid challenge with a 0.7 mg dexamethasone intravitreal implant, but I am exploring the addition of a topical challenge. In one satellite clinic in which I practice, it is logistically difficult for me to perform a challenge with a dexamethasone implant because of how infrequently I attend the clinic. In this scenario, we have discussed having the general eye care providers challenge the patients with topical steroid drops for 4 to 6 weeks before using the 0.19 mg FAc intravitreal implant.

**Eichenbaum:** The topical steroid challenge is good for IOP, but the 0.19 mg FAc intravitreal implant is a corticosteroid with a drying effect, and I want it to be a success when I decide to use it. Topical steroids will not dramatically improve vision or substantially dry the retina in most patients with DME. Data suggest that the patients who achieved the best outcomes with the 0.19 mg FAc intravitreal implant were the ones who began that treatment with a good level of visual acuity, and that usually correlates with a drier retina. Therefore, I will forgo a topical challenge and remain most comfortable performing an intravitreal challenge before the 0.19 mg FAc intravitreal implant.

**Navigating the Adverse Effects of Intravitreal Steroids: Cataract Formation**

**Eichenbaum:** The average patient with DME is 55 to 60 years of age and may have a cataract. In your practice, do you treat phakic and pseudophakic patients differently?

**Wykoff:** I am hesitant to use intravitreal steroids in the setting of an eye with a relatively clear lens. In my view, even a single intravitreal steroid injection permanently changes the trajectory of cataract development in that eye. That said, I do not want a cataract to get in the way of what I think is the best option to achieve a dry retina. I mention early in my discussions with patients that they have some degree of cataract at baseline. That way, if I want to employ a steroid agent at some later point, I can reflect with patients on the fact that they already have a cataract and that although the medication may accelerate the time frame of when they will need intervention for the cataract, it is not per se causing the cataract.

**Buznego:** Steroid injections are known to accelerate cataract formation. Still, steroids in the eye are beneficial, but they have limited penetration ability in the vitreous when delivered topically. Direct delivery into the vitreous with an injection of either steroid monotherapy or combination therapy may be preferable. In addition, from a cataract surgeon’s perspective, steroid injection reduces the cost and compliance issues associated with frequent drop administration for patients.

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“Patients generally like the idea of fewer injections and the concept of a therapeutic option that can last 3 years.”

— CHARLES C. WYKOFF, MD, PhD, FACS

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**Dhoot:** I agree that bringing up cataract formation early is important, and I explain to patients the real risks of elevated IOP and cataract formation. I used to avoid treating middle-aged patients with intravitreal steroids because of a fear of cataract formation, but as my practice and my experience has evolved, I now find it is more important to dry the retina. If edema persists with anti-VEGF treatment and intravitreal steroids are necessary, then to me, the cataract status is not an issue.

**Weng:** Unless a patient has a clear lens, I introduce the term “cataract” early in his or her treatment course, and I also explain that cataracts fall on a spectrum. If I am considering intravitreal steroid therapy, I tell patients that the medication may cause their cataracts to advance on the spectrum, but I reassure them that cataracts are treatable. I emphasize to patients the importance of focusing first on addressing the DME. Data show that the patients who develop cataracts because of intravitreal steroid use and then have their cataracts removed achieve visual acuity that is just as good as, if not better than, that of patients who had cataract surgery before treatment began.

**NAVIGATING THE ADVERSE EFFECTS OF INTRAVITREAL STEROIDS: ELEVATED IOP**

**Eichenbaum:** In addition to cataract formation, another adverse effect that can occur from the use of intravitreal steroids is an elevation in IOP, or steroid-induced ocular hypertension. MEAD study data show 30% to 40% of patients injected with the 0.7 mg dexamethasone intravitreal implant experienced an increase in IOP. In the FAME trials, investigators assessed the efficacy and safety of low- and high-dose FAC intravitreal implants in patients with DME. Despite both doses (0.2 µg/day and 0.5 µg/day) being shown to significantly improve visual acuity over 2 years, some patients experienced elevated IOP.

Typically, I inject the 0.7 mg dexamethasone intravitreal implant and monitor for IOP response. If I decide to switch the patient to the 0.19 mg FAC intravitreal implant, I prefer to inject it approximately 6 weeks after the dexamethasone treatment when the retina is as dry as possible. How do you monitor IOP in patients who have received intravitreal steroids, and how do you manage that risk for elevated IOP?

**Sheth:** I inform patients that a rise in IOP is a possibility after intravitreal steroid injection, so I have patients return to see me monthly for the first 3 months. If IOP remains stable, then I will wait 2 months to see the patient, and if still stable after that, then I have the patient return quarterly. It is important for surgeons to emphasize, in a 3-year length of drug delivery with the 0.19 mg FAC intravitreal implant, the importance of returning for regular follow-up appointments.

**Weng:** I ask patients to return 6 weeks after injection. If the IOP is normal at that point, then I typically schedule patients for a return visit every 3 months. I have only had one patient experience an IOP increase; I brought him back 2 weeks later after starting an IOP-lowering drop, and his IOP has remained controlled on a single agent.

**Buznego:** Cataract surgery alone reduces IOP. Also, if patients with DME intend to undergo cataract surgery, then inflammatory responses would be monitored over their multiple office visits.

**Wykoff:** I typically see patients 4 to 6 weeks after injection of an intravitreal corticosteroid. If a patient has a significant IOP response, such as an increase of at least 10 mm Hg or an absolute IOP rise to 30 mm Hg or above, then I am hesitant to continue with steroid therapy.

**Eichenbaum:** Consider a patient injected with the 0.7 mg dexamethasone intravitreal implant who experiences an increase in IOP to 30 mm Hg. If the surgeon treats the patient with a topical antihypertensive medication and IOP decreases and remains no greater than 20 mm Hg through a second and third treatment with a 0.7 mg dexamethasone intravitreal implant on topical antihypertensive medication, then is this patient now a candidate for the 0.19 mg FAC intravitreal implant?

**Dhoot:** Several of my patients have experienced an IOP response and ocular hypertension, and I treat them with topical medications. If a patient’s IOP remains controlled with the use of one or two topical agents, then I may perform another steroid challenge with a second 0.7 mg dexamethasone intravitreal implant, but my thinking is shifting based on real-world data analysis. It is likely that these patients are candidates for the 0.19 mg FAC intravitreal implant if their IOP remains lower than 25 mm Hg and is controlled with the topical medications.

**Weng:** The 0.19 mg FAC intravitreal implant should not be excluded as a treatment option for patients who do not respond to other DME therapies and whose IOP can be controlled with topical eye drops. However, surgeons should inform patients that regular use of topical medication will likely be necessary. For these patients, I also like to involve my glaucoma colleagues early so that their relationship with the patient is already established, should their involvement become necessary.

**Eichenbaum:** If the patient’s IOP does not improve, then I work with the referring doctor and explicitly communicate the patient’s situation. The referring doctor either handles the case from that point or refers the patient to a glaucoma specialist. How do you manage a patient with an intravitreal steroid medication whose IOP remains at about 28 mm Hg to 32 mm Hg despite the use of multiple classes of antihypertensive eye drops?

**Wykoff:** I explain to patients that eye care includes many subspecialties, and I encourage early comanagement with...
other physicians. For a patient whose IOP does not rapidly normalize with initial topical agents that suppress aqueous formation, I typically refer the patient to a glaucoma specialist.

**Dhoot:** I, too, will involve a glaucoma specialist early in the process. Data support the use of selective laser trabeculectomy, which is often the next type of treatment after eye drops, to manage steroid-induced IOP response.31

**Weng:** The sooner elevated IOP is addressed, the better. There is no harm in getting a glaucoma specialist involved early.

**Buznego:** As a comprehensive ophthalmologist, my path is slightly different from that of a retina specialist, but because I work in a multispecialty practice, it is still straightforward. Typically, a retina specialist would start this patient on topical therapy and set an appointment to have the patient return to the practice to see me or one of my associates in 1 to 2 weeks. If needed, we can consult with our glaucoma specialist as well.

**Eichenbaum:** In clinical trials of the FAc implant, significantly elevated IOP occurred and some patients required glaucoma surgery.28,31 However, newer real-world data from trials such as USER and PALADIN showed no significant change in the incidence or severity of IOP response or the very low incidence of glaucoma surgery before and after 0.19 mg FAc implantation.23,24,28 and the same has been the case with my own patients. The U.S. label for the 0.19 mg FAc implant requires pretreatment with a course of ocular steroid, and the minority of participants in the registration trial had an ocular steroid challenge. The USER and PALADIN real-world studies seem to imply that retinal specialists are good at selecting appropriate patients. In your real-world clinical experience, have your patients experienced uncontrolled elevated IOP after injection of the 0.19 mg FAc intravitreal implant?

**Weng:** I have only had one patient experience an IOP elevation to the upper 20s mm Hg, and he is doing well on a single IOP-lowering drop.

**Dhoot:** Only one of my patients, out of many, experienced elevated IOP.

**Eichenbaum:** Sometimes, I find a patient may need an early “booster” for macular edema in the first 6 to 8 weeks while the 0.19 mg FAc intravitreal implant starts to take effect. Do you give patients a booster with an anti-VEGF injection or a 0.7 mg dexamethasone intravitreal implant after 0.19 mg FAc intravitreal implant injection?

**Wykoff:** I typically boost with an anti-VEGF injection when needed.

**Sheth:** Historically I have boosted with an anti-VEGF. Over the past year, however, I have had a few patients who seem to only respond to steroids, and in those cases, I have boosted with a dexamethasone implant.

**Weng:** I also boost with anti-VEGF if necessary, but only after the 6-week point.

**Dhoot:** In the past, I administered only anti-VEGF boosters. Now, if there is breakthrough of the disease, I may also boost with the 0.7 mg dexamethasone intravitreal implant and have the patient return in 4 to 6 weeks for an IOP check.

**CONSIDERATIONS FOR THE CATARACT SURGEON**

**Eichenbaum:** What impact does diabetes have on patients seen in a cataract surgeon’s practice?

**Buznego:** Many general ophthalmologists have experience treating patients with diabetes, and a cataract is commonly seen in these patients. It is logical that patients with poorly controlled diabetes would have more rapid development of cataracts, and younger patients with diabetes tend to experience a higher incidence of cataract formation.32 Communication between surgeons and their patients about how diabetes affects the entire body—including the eye—is important. It is critical that general ophthalmologists prepare their patients.

**Eichenbaum:** Should cataract surgeons obtain a formal retinal consult in patients with severe retinopathy or DME before cataract surgery?

**Buznego:** Yes, because if the patient has severe retinopathy, then the long-term problem is not the cataract. I am straightforward with my patients, emphasizing they have two problems—the cataract and a retina condition. I explain that I will address the cataract, but the long-term retina issue will be handled by the retina specialist.

**Eichenbaum:** What impact does cataract surgery have on patients with DME?

**Buznego:** Many cataract surgeons now perform OCT on most patients presenting with retinopathy. In our integrated practice, the retina specialist decides whether intravitreal therapy independent of cataract surgery or in conjunction with cataract surgery is most appropriate. Still, cataract surgeons must be aware of the retina condition that will cause issues with contrast sensitivity in the long term. Therefore, surgeons should not implant multifocal diffractive intraocular lenses (IOLs) in patients with DME. An astigmatism-correcting IOL, however, improves contrast sensitivity,33 so if a patient has more than 1 diopter of astigmatism—even with macular issues—then he or she may benefit from astigmatism correction with a monofocal toric IOL.
Eichenbaum: In patients with DME who also have a cataract, do you find a difference in outcome between those who receive intraocular anti-VEGF therapy and those who receive intraocular steroid therapy?

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— VEERAL S. SHETH, MD, MBA, FACS

Buznego: The retina specialist chooses the agent, but both help with intraocular inflammation. Although anti-VEGF agents are more helpful with controlling vascular permeability, administering steroids makes more sense because they impact higher up on the disease pathway and address multiple inflammatory pathways, rather than just those related to vascular permeability.

PREPARING FOR OPTIMAL OUTCOMES

Eichenbaum: Data in both MEAD and FAME randomized, controlled trials show that patients with DME who became pseudophakic during the trials achieved good outcomes.27,28 This is likely partly true because these patients had an intraocular anti-inflammatory agent present in the eye at the time of cataract surgery. Like any procedure, cataract surgery is inflammatory, and the procedure upregulates inflammatory mediators such as cytokines.34 If a patient with treated DME will undergo cataract surgery, then I often administer an intravitreal steroid even if the patient has been doing well with antiangiogenics. If that steroid is an 0.19 mg FAc intravitreal implant, then I prefer the patient be treated for at least a couple of weeks before the cataract surgery to give the 0.19 mg FAc intravitreal implant time to work. How do you prepare a patient who has DME for cataract surgery?

Weng: I update patients on their cataract development at each visit, noting if vision is being affected by cataract growth. Before referring them to a cataract surgeon, I prefer for these patients’ retinas to be as dry as possible, with the expectation that some edema may persist. I track patients’ OCT scans as they trend downward until a plateau is reached, and then I clear patients for surgery from a retina standpoint, reminding them that they will likely continue receiving injections throughout the perioperative course. There is evidence that after cataract surgery, upregulation of the inflammatory cytokines occurs in the eye,34 so it makes sense to have a steroid present in the eye at that time to carry patients through to a good end-result.

Buznego: I usually prescribe patients preoperative non-steroidal anti-inflammatory drugs, antibiotics, and topical steroids to administer 2 days to 1 week before surgery. Then, I instruct patients to use topical anti-inflammatory therapy for about 1 month after cataract surgery. I instruct those patients to continue this treatment until told to stop, and then the retina specialist and I consult with each other. Often, those patients receive eye drop therapy for 2 to 3 months.

Sheth: I try to time my treatment of these patients about 1 to 2 weeks before their cataract surgery, with the plan to see them about 4 weeks after their surgery. I would not necessarily change the treatment regimen because of the surgery, but for those patients who seem to have postoperative edema despite recent anti-VEGF therapy, I will add an intravitreal steroid.

Dhoot: FAME data suggest that between 6 and 12 months after injection of an 0.19 mg FAc intravitreal implant, the patient experiences a decrease in visual acuity,26 but then visual acuity improves after the cataract has been removed, and these patients who have been rendered pseudophakic do as well as patients who were originally pseudophakic.

Eichenbaum: Younger patients with DME can also be challenging to treat. Do you alter your management protocol when treating a young patient with diabetes?

Buznego: My young patients with diabetes are aware that cataracts will likely develop anyway, so they are not often surprised when a cataract develops. Young patients with hyperopia often embrace cataract surgery because the procedure can improve their uncorrected vision. However, patients who do not have presbyopia are more challenging to treat because losing accommodation is undesirable, and I do not find that these patients achieve optimal outcomes with multifocal IOLs.

PEARLS

Eichenbaum: What are your pearls for treating today’s patients who have DME?

Sheth: Surgeons should not be afraid to switch therapy to the 0.19 mg FAc intravitreal implant early in the process, but then they must be patient. The population with DME is heterogeneous, and they have heterogeneous responses to medications. I think the field of ophthalmology today is fortunate to have a relatively large toolkit that helps patients achieve optimal results in terms of anatomy and vision.

Weng: It is important to keep in mind that patients seen in clinical practice are not trial participants, and surgeons treating them should take into consideration real-world factors—such as employment, transportation challenges, and being busy with young families—and attempt to optimize their vision in the least invasive and least burdensome way.
Dhoot: I think it is important not to under-treat patients. As a group, retina specialists tend to under-treat patients, and I think a foundational treatment should be more seriously considered.

Wykoff: I recommend clinicians individualize each patient’s therapy. I tend to be straightforward, even blunt, when educating patients. One must note two significant risks of using steroids—cataract acceleration and possible IOP elevation. I communicate that although both are manageable, both are real.

Eichenbaum: Physicians should be familiar with the extensive amounts of data on DME. At the same time, however, they must be aware that the data cannot be applied uniformly and formulaically to all patients. The retina specialist must individualize treatment of patients in an evidence-based fashion.

Physicians should also keep in mind that the patients who have the best results are the patients who had the best vision early during treatment. My pearls are to work with who have the best results are the patients who had the best ever, they must be aware that the data cannot be applied tensive amounts of data on DME. At the same time, how-

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