An expert panel explores evolving treatment options.

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MAXIMIZING PATIENT OUTCOMES IN DME:
A DISCUSSION OF EVOLVING, EVIDENCE-BASED OPTIONS FOR CLINICAL PRACTICE

An expert panel explores evolving treatment options.

PANELISTS:

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Retina specialists are blessed to have so many treatment options for our patients with diabetic macular edema. This is especially important in an age when the number of diabetic patients is increasing. It is expected that there will be a 59% rise in the number of diabetics internationally, according to the IDF Diabetes Atlas 2013. Therefore, finding the right treatment algorithm that maximizes patient outcomes and minimizes complications is of paramount importance currently. In this supplement, we discuss the practical issues facing most retina specialist: How often you see patients, what diagnostic tests to use, what therapeutics are initially given and how you monitor their effectiveness, and finally how you determine when to switch. Drs. Drenser, Capone, and Roth provide a real life approach to managing these complex patients with many important pearls to the process.

—Rishi P. Singh, MD
MAXIMIZING PATIENT OUTCOMES IN DME:

Patient Education and Expectations

Dr. Singh: When patients have center-involving DME, do you discuss how frequently they will need to see you and what they can expect, treatment-wise, during the first year?

Dr. Capone: Yes, but I paint the picture with broad strokes. I explain that treatment begins with regular monthly injections, and it is very likely that over 6 to 18 months, I may be able to decrease the number of injections or possibly terminate treatment. I emphasize that I cannot determine at the outset who will be able to stop and who will need to continue. That is about as specific as I get, because patients tend to cling to the good news and not hear the bad, and a small percentage of patients tend to require long-term therapy.

Dr. Singh: Dr. Roth, how do you discuss the frequency of visits?

Dr. Roth: I typically use a treat-and-extend approach for DME, so I tell patients they will receive at least three monthly injections initially, and based on their response, I will try to extend the interval between treatments. I emphasize that they will likely have approximately eight or nine injections during the first year, but the frequency is highly variable and will depend on the biology of their eyes.

I also explain to my patients that the better they modify their risk factors by losing weight and controlling their blood sugar, the more likely they will have a better visual outcome and possibly reduce the burden of treatment.

Dr. Drenser: I, too, am very vague when discussing treatment planning with patients. I tell them we will take a step-by-step approach and that they should expect a minimum of 3 to 6 months of treatment before we have the disease under control.

A second issue is that general ophthalmologists, at least in my region, often feel they can manage and treat diabetic retinopathy and DME, but are occasionally mismanaged. I cringe when I see a macula that have been lasered heavily or a retina that was undertreated with just a few spots of midperipheral panretinal photocoagulation and still have active bleeding and proliferative disease. These conditions suggest an education barrier in how to best treat patients and when it is most appropriate to refer to a retinal specialist. A third factor is limitations on treatments imposed by insurers.

Dr. Drenser: In my practice, differences in referral patterns seem to be regional. The farther away a satellite office is from easy access to care, the more the general ophthalmologists tend to manage patients. I may see patients who have persistent DME despite having undergone heavy laser treatment at those offices. Also, in some outlying areas with limited access to care, patients seem to be more willing to live with poor vision before they seek care.

In more central locations, patients come in for an appointment much earlier in the disease process. I think the general ophthalmologists in those practices see that we are achieving very successful outcomes with early aggressive treatment, and they are much more likely to send us patients who have early DME with minimal to no vision loss.

TREATMENT ALGORITHMS

Dr. Singh: Dr. Drenser, how do you decide which treatment approach might be the best for a patient with center-involving DME.

Dr. Drenser: I generally start with prescribing an anti-VEGF agent for a variety of reasons. They work well, they are well tolerated, and they have a high safety profile. Often, anti-VEGF therapy alone will control macular disease in diabetic patients. Before we start treatment, I explain to patients that we are lucky now to have multiple modes of treatment, we frequently need to implement all or some of them to get the disease under control with favorable outcomes. Typically, I do not switch therapies before administering three injections of an anti-VEGF agent, unless I am really underwhelmed by the response.
Dr. Singh: How would you define an inadequate response? Do you administer a mandatory series of three injections, or do you take a treat-and-watch approach?

Dr. Drenser: I do not do a mandatory series of three injections. I tell patients they will likely need three treatments before we can make further decisions. However, every month, at a minimum, I repeat OCT and examine the eye to make sure I am happy with the response. Three injections are not mandatory, but I do anticipate a series of three.

Dr. Capone: I also start with an anti-VEGF agent and usually administer three monthly injections, but my procedure has a subtle permutation. Admittedly, we are not treating vein occlusions, but we learned from the BRAVO and CRUISE trials that there are prompt or brisk responders, intermediate responders, and poor responders, and people tend to stay in their lane, so to speak. In other words, people who respond quickly tend to continue doing well and vice versa. Therefore, if the immediate response is poor, I switch to a steroid early—as early as 1 month for true nonresponders—rather than administer three injections of one anti-VEGF agent, then switch to another anti-VEGF agent for another three injections, and if that does not work, change to a third anti-VEGF for another three injections, before switching to a steroid. I believe many retina specialists do this “VEGF shuffle” prior to switching to a steroid.

Dr. Singh: How do you define a good response?

Dr. Capone: To me, a good response is a 50% or better reduction in edema after a single injection. I consider a reduction of 10% or less after a single injection to be a poor response, and I switch to a steroid promptly in such a case, particularly if I start with aflibercept (Eylea, Regeneron) or ranibizumab (Lucentis, Genentech) as a first-line drug. The reason I consider one of those as a first-line drug is because in Michigan, we cannot have bevacizumab available in the state or not. We also cannot order it from out-of-state providers as all pharmacies, manufacturers and wholesale distributors must have a Michigan license to do business in this state and abide by Michigan laws, whether they are physically located in the state or not.

Dr. Drenser: I completely agree with Dr. Capone. That is why I do not have a mandatory three-injection treatment routine. If I do not see at least a 40% or 50% improvement after the first injection, I have a discussion with the patient and tell him or her that we need to change the treatment regimen earlier than I anticipated. Similarly, I will switch to a steroid early in those cases rather than switch to a different anti-VEGF agent.

Dr. Drenser, when you are treating with an anti-VEGF agent, how frequently do you evaluate patients?

Dr. Capone: Sometimes, I have to make a decision if there is a biological response but edema is recurring, and the patient is living with poor vision for months. In such a case, I combine a steroid, such as the dexamethasone intravitreal implant 0.7 mg (Ozurdex, Allergan) and an anti-VEGF agent as needed.

Dr. Singh: Dr. Capone, what prompts you to switch treatments?

Dr. Capone: I agree that we sometimes see gradual incremental improvement, but if an OCT looks fundamentally unchanged, I try something different.

Dr. Singh: Dr. Drenser, when you are treating with an anti-VEGF agent, how frequently do you evaluate patients?
A different perspective can have the power to change your approach

**Indication and Usage**

**Diabetic Macular Edema**

OZURDEX® (dexamethasone intravitreal implant) is a corticosteroid indicated for the treatment of diabetic macular edema.

**Dosage and Administration**

FOR OPHTHALMIC INTRAVITREAL INJECTION.

The intravitreal injection procedure should be carried out under controlled aseptic conditions. Following the intravitreal injection, patients should be monitored for elevation in intraocular pressure and for endophthalmitis. Patients should be instructed to report any symptoms suggestive of endophthalmitis without delay.

**IMPORTANT SAFETY INFORMATION**

**Contraindications**

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

Glaucoma: OZURDEX® is contraindicated in patients with glaucoma, who have cup to disc ratios of greater than 0.8.

Torn or Ruptured Posterior Lens Capsule: OZURDEX® is contraindicated in patients whose posterior lens capsule is torn or ruptured because of the risk of migration into the anterior chamber. Laser posterior capsulotomy in pseudophakic patients is not a contraindication for OZURDEX® use.

**Hypersensitivity:** OZURDEX® 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 OZURDEX®, have been associated with endophthalmitis, eye inflammation, increased intraocular pressure, and retinal detachments. Patients should be monitored regularly following the injection.

**Steroid-related Effects:** Use of corticosteroids including OZURDEX® may produce posterior subcapsular cataracts, increased intraocular pressure, glaucoma, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses.

Corticosteroids should be used cautiously in patients with a history of ocular herpes simplex because of the potential for reactivation of the viral infection.

**Adverse Reactions**

Ocular adverse reactions reported by greater than or equal to 1% of patients in the two combined 3-year clinical trials following injection of OZURDEX® for diabetic macular edema include: cataract (68%), conjunctival hemorrhage (23%), visual acuity reduced (9%), conjunctivitis (6%), vitreous floaters (5%), conjunctival edema (5%), dry eye (5%), vitreous
The pathophysiology
— An inflammatory cascade plays a key role

The therapeutic targets
— Suppress multiple inflammatory cytokines

The clinical results
— Achieve clinically significant 3-line gains in BCVA

The #1 steroid in U.S. market share for DME

IMPORTANT SAFETY INFORMATION (continued)
Adverse Reactions (continued)
detachment (4%), vitreous opacities (3%), retinal aneurysm (3%), foreign body sensation (2%), corneal erosion (2%), keratitis (2%), anterior chamber inflammation (2%), retinal tear (2%), eyelid ptosis (2%). Non-ocular adverse reactions reported by greater than or equal to 5% of patients include: hypertension (13%) and bronchitis (5%).

Increased Intraocular Pressure: IOP elevation greater than or equal to 10 mm Hg from baseline at any visit was seen in 28% of OZURDEX® (dexamethasone intravitreal implant) patients versus 4% of sham patients. 42% of the patients who received OZURDEX® (dexamethasone intravitreal implant) were subsequently treated with IOP-lowering medications during the study versus 10% of sham patients.

The increase in mean IOP was seen with each treatment cycle, and the mean IOP generally returned to baseline between treatment cycles (at the end of the 6-month period).

Cataracts and Cataract Surgery: The incidence of cataract development in patients who had a phakic study eye was higher in the OZURDEX® group (68%) compared with Sham (21%). The median time of cataract being reported as an adverse event was approximately 15 months in the OZURDEX® (dexamethasone intravitreal implant) group and 12 months in the Sham group. Among these patients, 61% of OZURDEX® subjects versus 8% of sham-controlled subjects underwent cataract surgery, generally between Month 18 and Month 39 (Median Month 21 for OZURDEX® group and 20 for Sham) of the studies.

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

1. Based on U.S. market share of DME patients treated with intravitreal steroids: December 2014.²

Ozurdex®
(dexamethasone intravitreal implant) 0.7 mg


6. OZURDEX® Prescribing Information. 7. IMS Health Dx data through December 2014.
Brief Summary—Please see the OZURDEX® package insert for full Prescribing Information.

INDICATIONS AND USAGE
Retinal Vein Occlusion: OZURDEX® (dexamethasone intravitreal implant) is a corticosteroid indicated for the treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO).

Posterior Segment Uveitis: OZURDEX® is indicated for the treatment of non-infectious uveitis affecting the posterior segment of the eye.

Diabetic Macular Edema
OZURDEX® is indicated for the treatment of diabetic macular edema.

CONTRAINDICATIONS
Ocular or Periorcular Infections: OZURDEX® (dexamethasone intravitreal implant) is contraindicated in patients with active or suspected ocular or periorcular infections including most viral diseases of the cornea and conjunctiva, including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections, and fungal diseases.

Glaucoma: OZURDEX® is contraindicated in patients with glaucoma, who have cup to disc ratios of greater than 0.8.

Tom or Ruptured Posterior Lens Capsule: OZURDEX® is contraindicated in patients whose posterior lens capsule is torn or ruptured because of the risk of migration into the anterior chamber. Laser posterior capsulotomy in pseudophakic patients is not a contraindication for OZURDEX® use.

Hypersensitivity: OZURDEX® is contraindicated in patients with known hypersensitivity to any components of this product [see Adverse Reactions].

WARNINGS AND PRECAUTIONS
Intravitreal Injection-related Effects: Intravitreal injections, including those with OZURDEX®, have been associated with endophthalmitis, eye inflammation, increased intraocular pressure, and retinal detachments.

Patients should be monitored regularly following the injection [see Patient Counseling Information].

Steroid-related Effects: Use of corticosteroids including OZURDEX® may produce posterior subcapsular cataracts, increased intraocular pressure, glaucoma, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses [see Adverse Reactions].

Corticosteroids should be used cautiously in patients with a history of ocular herpes simplex because of the potential for reactivation of the viral infection.

ADVERSE REACTIONS
Clinical Studies Experience:

Increased IOP with OZURDEX® peaked at approximately week 8. During the initial treatment period, 1% (3/421) of the patients who received OZURDEX® required surgical procedures for management of elevated IOP.

The following information is based on the combined clinical trial results from 2 randomized, 3-year, sham-controlled studies in patients with diabetic macular edema. Discontinuation rates due to the adverse reactions listed in the table below were 3% in the OZURDEX® group and 1% in the Sham group. The most common ocular (study eye) and non-ocular adverse reactions are as follows:

Ocular Adverse Reactions Reported by ≥ 1% of Patients and Non-ocular Adverse Reactions Reported by ≥ 5% of Patients

<table>
<thead>
<tr>
<th>MedDRA Term</th>
<th>OZURDEX® N=324 (%)</th>
<th>Sham N=328 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ocular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cataract*</td>
<td>166/243* (68%)</td>
<td>49/230 (21%)</td>
</tr>
<tr>
<td>Conjunctival hemorrhage</td>
<td>73 (23%)</td>
<td>44 (13%)</td>
</tr>
<tr>
<td>Visual acuity reduced</td>
<td>28 (9%)</td>
<td>13 (4%)</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>19 (6%)</td>
<td>8 (2%)</td>
</tr>
<tr>
<td>Vitreous floaters</td>
<td>16 (5%)</td>
<td>6 (2%)</td>
</tr>
<tr>
<td>Conjunctival edema</td>
<td>15 (5%)</td>
<td>4 (1%)</td>
</tr>
<tr>
<td>Dry eye</td>
<td>15 (5%)</td>
<td>7 (2%)</td>
</tr>
<tr>
<td>Vitreous detachment</td>
<td>14 (4%)</td>
<td>8 (2%)</td>
</tr>
<tr>
<td>Retinal tear</td>
<td>5 (2%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Eyelid ptosis</td>
<td>5 (2%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Non-ocular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>41 (13%)</td>
<td>21 (6%)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>15 (5%)</td>
<td>8 (2%)</td>
</tr>
</tbody>
</table>

*Includes cataract, cataract nuclear, cataract subcapsular, lenticular opacities in patients who were phakic at baseline. Among these patients, 61% of OZURDEX® subjects vs. 8% of sham-controlled subjects underwent cataract surgery.

Increased IOP OZURDEX® vs. Sham

125 (25%) 10 (2%) 25 (50%) 10 (2%)

Increased Intraocular Pressure

Summary of Elevated IOP Related Adverse Reactions

<table>
<thead>
<tr>
<th>Treatment: N (%)</th>
<th>OZURDEX® N=324</th>
<th>Sham N=328</th>
</tr>
</thead>
<tbody>
<tr>
<td>IOP elevation ≥10 mm Hg from Baseline at any visit</td>
<td>91 (28%)</td>
<td>13 (4%)</td>
</tr>
<tr>
<td>≥30 mm Hg IOP at any visit</td>
<td>50 (15%)</td>
<td>5 (2%)</td>
</tr>
<tr>
<td>Any IOP (lowering medication)</td>
<td>136 (42%)</td>
<td>32 (10%)</td>
</tr>
<tr>
<td>Any surgical intervention for elevated IOP*</td>
<td>4 (1.2%)</td>
<td>1 (0.3%)</td>
</tr>
</tbody>
</table>

* OZURDEX®, 1 surgical trabeculectomy for steroid-induced IOP increase, 1 surgical trabeculectomy for iris neovascularization, 1 laser iridotomy, 1 surgical iridectomy

Sham: 1 laser iridotomy

Cataracts and Cataract Surgery

At baseline, 243 of the 324 OZURDEX® subjects were phakic; 230 of 328 sham-controlled subjects were phakic. The incidence of cataract development in patients who had a phakic study eye was higher in the OZURDEX® group (68%) compared with Sham (21%). The median time of cataract being reported as an adverse event was approximately 15 months in the OZURDEX® group and 12 months in the Sham group. Among these patients, 61% of OZURDEX® subjects vs. 8% of sham-controlled subjects underwent cataract surgery, generally between Month 18 and Month 39 (Median Month 21 for OZURDEX® group and 20 for Sham) of the studies.
The increase in mean IOP was seen with each treatment cycle, and the mean IOP generally returned to baseline between treatment cycles (at the end of the 6 month period).

USE IN SPECIFIC POPULATIONS

Pregnancy Category C

Risk Summary

There are no adequate and well-controlled studies with OZURDEX® in pregnant women. Animal reproduction studies using topical ocular administration of dexamethasone were conducted in mice and rabbits. Cleft palate and embryofetal death in mice and malformations of the intestines and kidneys in rabbits were observed. OZURDEX® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal Data

Topical ocular administration of 0.15% dexamethasone (0.375 mg/kg/day) on gestational days 10 to 13 produced embryofetal lethality and a high incidence of cleft palate in mice. A dose of 0.375 mg/kg/day in the mouse is approximately 4 times an OZURDEX® dose on a mg/m² basis. In rabbits, topical ocular administration of 0.1% dexamethasone throughout organogenesis (0.13 mg/kg/day, on gestational day 6 followed by 0.20 mg/kg/day on gestational days 7-18) produced intestinal anomalies, intestinal aplasia, gastrochisis and hypoplastic kidneys. A dose of 0.13 mg/kg/day in the rabbit is approximately 4 times an OZURDEX® injection in humans (0.7 mg dexamethasone) on a mg/m² basis.

Nursing Mothers:

Systemically administered corticosteroids are present in human milk and can suppress growth and interfere with endogenous corticosteroid production. The systemic concentration of dexamethasone following intravitreal treatment with OZURDEX® is low. It is not known whether intravitreal treatment with OZURDEX® could result in sufficient systemic absorption to produce detectable quantities in human milk. Exercise caution when OZURDEX® is administered to a nursing woman.

Pediatric Use:

Safety and effectiveness of OZURDEX® in pediatric patients have not been established.

Geriatric Use:

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

No adequate studies in animals have been conducted to determine whether OZURDEX® (dexamethasone intravitreal implant) has the potential for carcinogenesis. Although no adequate studies have been conducted to determine the mutagenic potential of OZURDEX®, dexamethasone has been shown to have no mutagenic effects in bacterial and mammalian cells in vitro or in vivo mouse micronucleus test. Adequate fertility studies have not been conducted in animals.

PATIENT COUNSELING INFORMATION

Steroid-related Effects

Advise patients that a cataract may occur after repeated treatment with OZURDEX®. If this occurs, advise patients that their vision will decrease, and they will need an operation to remove the cataract and restore their vision.

Advise patients that they may develop increased intraocular pressure with OZURDEX® treatment, and the increased IOP will need to be managed with eye drops, and, rarely, with surgery.

Intravitreal Injection-related Effects

Advise patients that in the days following intravitreal injection of OZURDEX® patients are at risk for potential complications including in particular, but not limited to, the development of endophthalmitis or elevated intraocular pressure.

When to Seek Physician Advice

Advise patients that if the eye becomes red, sensitive to light, painful, or develops a change in vision, they should seek immediate care from an ophthalmologist.

Driving and Using Machines

Inform patients that they may experience temporary visual blurring after receiving an intravitreal injection. Advise patients not to drive or use machines until this has been resolved.

Dr. Drenser: I see patients monthly for at least the first 3 months, until I am convinced we are on the right pathway. Once the edema is under control, I start to extend the interval between visits through a treat-and-extend approach.

Dr. Capone: I also tend to see patients monthly until the edema has resolved, and then I extend. So, I am a treat-and-extend person, not an as needed treatment person. I refer to as needed treatment as treat and skip. I have had more failures if I skip an injection. I feel I maintain better control if I extend gradually.

Dr. Roth: My approach is the same as Dr. Capone’s.

Dr. Singh: Dr. Drenser, if you treat with the dexamethasone intravitreal implant 0.7 mg because of a poor response to an anti-VEGF agent, when do you next see that patient after initiating therapy?

Dr. Drenser: I still see patients monthly to determine if the steroid is producing an adequate response. Some patients do well with anti-VEGF therapy alone, others do well with steroids alone, but at least 40% of my patients need multiple-modality treatment. So, typically, a patient receiving the dexamethasone implant 0.7 mg still requires some anti-VEGF to optimize the response. Therefore, I follow patients fairly closely until the edema is under control. I do not start extending the time between visits until the edema is greatly reduced and the macula is dry or close to dry.

Dr. Roth: When I switch to the dexamethasone intravitreal implant 0.7 mg, initially I see patients monthly for two reasons: to monitor the intraocular pressure (IOP) and to see the biological response. I, too, will supplement with an anti-VEGF agent if I feel more than just the steroid is necessary.

Dr. Capone: My approach is similar to what Dr. Drenser and Dr. Roth describe. I look for two things. First, I want to determine the treatment response interval, because every patient is different. In my experience, the dexamethasone intravitreal implant 0.7 mg lasts about 6 weeks in some patients and 3 to 4 months in others. Therefore, I need to determine the longevity of the therapy for each patient. Second, of course, I monitor the IOP. We know that if a pressure rise will occur, it usually occurs within the first three injections, so I monitor monthly. After three injections, I have information about both the therapeutic response and IOP. Therefore, I am likely to extend the treatment interval...
based solely on the edema response rate if pressure issues have been addressed.

**Dr. Roth:** I agree. After the first or second dexamethasone implant 0.7 mg injections, I see patients monthly. After the third or fourth dexamethasone injection, I see patients at 6-week intervals, because I usually find that if they respond well to dexamethasone, they respond for approximately 3 months. I perform one interim examination to assess their response and to check their pressures. If the response to dexamethasone lasts 3 months without a rise in IOP, then I see patients every 3 months and continue treating on that schedule. I very rarely treat patients with dexamethasone alone.

**Dr. Singh:** Dr. Drenser, how many of your patients with DME would you estimate are receiving anti-VEGF monotherapy, and how many are you managing with a combination of anti-VEGF therapy and something else?

**Dr. Drenser:** About 10% of my patients are receiving anti-VEGF monotherapy, and another 10% are being managed with the dexamethasone intravitreal implant 0.7 mg exclusively. About 40% of my patients are receiving an anti-VEGF agent with laser, and another 40% are receiving dexamethasone implant 0.7 mg with anti-VEGF with or without laser, depending on their vasculature.

**Dr. Capone:** My management philosophy is similar to that of Dr. Drenser’s, although I may have a higher percentage of patients receiving anti-VEGF monotherapy. I use the laser to consolidate gains in people who have some residual edema. I estimate about 80% of my patients are receiving anti-VEGF monotherapy (of whom about 10% have also had some laser), and about 20% are receiving either a steroid alone or a steroid plus anti-VEGF.

**Dr. Roth:** About 50% to 60% of my patients with DME are receiving anti-VEGF monotherapy; another 20% receive supplemental laser (usually, deferred laser for persistent edema), especially if the microaneurysms are not so close to the foveal center. The remaining 20% or so receive a steroid in combination with anti-VEGF therapy, either with or without adjunctive laser treatment. I estimate only 5% to 10% of my patients are receiving a steroid alone.

**Dr. Singh:** Dr. Roth, what laser system do you use?

**Dr. Roth:** I typically use an argon laser to create very small, very light, barely visible spots to treat focal microaneurysms. I rarely use a diffuse grid. Recently, we started to use micropulse laser in one of our office locations and we have been using more subthreshold micropulse laser in that office for the same purpose, but based on a micropulse protocol. I have not yet performed a formal study, but it seems to have a benefit in our hands, and we have been pleased with what we have seen so far.

**Dr. Singh:** Dr. Drenser, tell us about your laser experience. What modality do you use?

**Dr. Drenser:** I usually use a standard argon or green laser for focal laser treatments. I use a small spot size for a very light treatment. I like to have a barely perceptible burn, and I usually try to treat the microaneurysms focally. One effect we need to consider when managing DME with monotherapy is the progressive capillary dropout seen in a number of eyes after long-term treatment. I do not think I recognized how frequently this was occurring initially, and I think this is why the percentage of my patients receiving anti-VEGF monotherapy is low. At some point, even with good control of macular edema, I generally add a laser treatment. Sometimes, I use a light grid pattern based on angiographic findings, because I have found that eyes receiving long-term anti-VEGF therapy, despite having a good response, will frequently have increased capillary dropout or an increased foveal avascular zone to which I apply a light laser treatment.

**INSURANCE RESTRICTIONS AND ACCESS PROGRAMS**

**Dr. Singh:** Dr. Capone, you mentioned that sometimes you must initiate therapy with a specific anti-VEGF agent. Are you facing step-therapy mandates in your area from insurance carriers?

**Dr. Capone:** Yes, we are. In fact, two interesting insurance-related phenomena are influencing our patient care. One is the mandate for step therapy, which requires that we document nonresponse or inadequate response. The second is that some carriers do not allow us to use aflibercept more often than every 8 weeks after the first three injections. This is an interesting twist, particularly on the heels of the Protocol T study, which allowed monthly treatment, and patients received approximately nine injections in the first year, which is closer to monthly therapy than not.5

**Dr. Roth:** In New Jersey, we are not facing step therapy at this time, but it is probably inevitable in the future.
**Vitrectomized Eyes**

**Dr. Singh:** Dr. Capone, have you treated DME in vitrectomized eyes?

**Dr. Capone:** Yes, I have. Patients with vitrectomized eyes tend to have a shorter intraocular drug duration. For some patients, that precludes monthly anti-VEGF dosing. Many of those patients are likely to receive dexamethasone at 4 to 6 weeks.

We need to consider vitrectomy carefully, because of the impact on pharmacotherapy post-vitrectomy. It relegates some patients to anti-VEGF therapy every 2 to 3 weeks, which is impractical, or to conversion to dexamethasone with the hope they are not steroid responders.

**Dr. Roth:** In New Jersey, we are not mandated to order bevacizumab for a specific patient, so we can stock it in the office. If I feel a patient would benefit more from aflibercept or ranibizumab, I bring him or her back in a week, after we have had a chance to submit the relevant paperwork through the process of benefits investigation. We have a system in our office to make sure we get the green light before we start therapy. We decided as a group not to participate in the sampling programs, mostly to avoid mixing up samples and nonsamples and potentially mistaken billing for a sample. So, alternatively, I start with a bevacizumab injection, and if the response is good, I continue. Otherwise, I consider switching to one of the other anti-VEGF drugs.

**Dr. Singh:** In that setting, especially if an eye is pseudophakic or soon to be pseudophakic and has been vitrectomized, it is a good option. I introduce the dexamethasone intravitreal implant early on as a stand-alone treatment, or as an adjunct to anti-VEGF therapy as a means to reduce the need for frequent injections. As Dr. Capone mentioned, the treatment frequency required to suppress macular edema in vitrectomized eyes is difficult. Some people are not rapid VEGF producers, and treatment monthly or even every 5 or 6 weeks is sufficient. Most of the time, however, especially if a patient has a complete vitrectomy and there is no residual vitreous to act as a depot for the injected drug, the clearance is too rapid, and he or she will require frequent anti-VEGF injections.

**Dr. Singh:** Obviously, we are being told which drugs to use in some instances. Dr. Drenser, how are you managing that? Are you able to enroll patients into compassionate care programs?

**Dr. Drenser:** The more expensive drugs have such good programs that often the most needy patients are able to receive them. Finding an assistance program for bevacizumab is much more difficult. I have been happy with the programs that are in place through Good Days from CDF (formerly the Chronic Disease Fund) or Genentech Access Solutions. I have not had a significant delay of care when using these resources. Also, as Dr. Capone mentioned, the inability to store bevacizumab in the office but having samples of ranibizumab or aflibercept available makes it easier to immediately start treatment with those drugs.

**Dr. Singh:** Dr. Capone, you mentioned previously that when you start with anti-VEGF therapy, you must start with a particular anti-VEGF agent. Why is that? Is it strictly because of insurance?

**Dr. Capone:** In Michigan, the attorney general requires that we write a prescription for a specific patient to receive bevacizumab. Therefore, I cannot use it as a first-line drug at a patient’s first visit. I can either begin anti-VEGF therapy with a sample of aflibercept or ranibizumab, or have the patient return for bevacizumab. In all candor, now that we have some visual acuity guidance from Protocol T, particularly for patients with better vision, I would probably be inclined to use bevacizumab as a first-line drug if I had it in my office. So, the lack of availability influences which drug I use, at least for the first visit.

**Dr. Singh:** More from aflibercept or ranibizumab, I bring him or her back in a week, after we have had a chance to submit the relevant paperwork through the process of benefits investigation. We have a system in our office to make sure we get the green light before we start therapy. We decided as a group not to participate in the sampling programs, mostly to avoid mixing up samples and nonsamples and potentially mistaken billing for a sample. So, alternatively, I start with a bevacizumab injection, and if the response is good, I continue. Otherwise, I consider switching to one of the other anti-VEGF drugs.

**STERIOD AS FIRST-LINE TREATMENT**

**Dr. Singh:** Is there any particular patient for whom you would use a corticosteroid as a first-line agent versus anti-VEGF therapy?

**Dr. Roth:** Although uncommon, I might choose a steroid for first-line therapy if a patient had multiple strokes and was already nervous about what I consider a theoretical, remote risk of stroke with the use of intravitreal anti-VEGF agents. I would consider a corticosteroid in that case, especially if a patient is pseudophakic. The other possible situation is someone who has DME and has undergone recent cataract surgery. If I think there may be some inflammatory component within the umbrella of pseudophakic (Irvine-Gass syndrome) macular edema associated with their DME, I will prescribe a corticosteroid first (Figure 1).
Dr. Drenser: Typically, a corticosteroid is not my first choice because of the favorable safety profile of the anti-VEGF agents, but I might choose a steroid as first-line treatment for specific patients. One example would be a patient who was treated previously with an older steroid, such as triamcinolone, and achieved a good result that was sustained for a long period of time. Another example would be if I suspect an inflammatory cause from a recent surgery or an underlying immune disorder, then I would consider using a steroid for first-line therapy.

Dr. Capone: Although I consider a steroid as first-line therapy in much the same way as Dr. Roth and Dr. Drenser discussed, I will make a fairly controversial proposal: If a patient is pseudophakic and not a steroid responder, I believe there is no reason not to consider using the dexamethasone intravitreal implant 0.7 mg as primary therapy.

As we all are aware, many patients with diabetes are still of working age. For them, 12 or even nine visits a year are difficult if not untenable. The dexamethasone intravitreal implant 0.7 mg allows for effective management of their DME with a treatment regimen that is compatible with their lifestyle. When I discuss treatment frequency with patients, some folks tell me they would rather try the dexamethasone implant 0.7 mg. Colleagues in Europe sensitized me to this perspective. If a patient is pseudophakic, I have no problem trying dexamethasone implant 0.7 mg first if I know that coming into the office is a problem for him or her.

Similarly, some patients who go to our outlying offices for treatment live in rural areas. In northern Michigan, particularly in the winter, some retina specialists will entertain the use of dexamethasone implant 0.7 mg earlier because of the difficulties patients may encounter coming to the office monthly because of the distance and the weather.

CONTRAINDICATIONS TO STEROID TREATMENT

Dr. Singh: Dr. Roth, do you consider steroid response a contraindication to their use?

Dr. Roth: I think steroid response (ie, an IOP rise) is a relative contraindication but not an absolute contraindication, because some patients have been challenged with dexamethasone or triamcinolone, which probably has a higher incidence of IOP elevation and results in higher pressures, as well. If patients have had modest
Managing IOP Rise

**Dr. Singh:** How do you manage the IOP rise from dexamethasone?

**Dr. Drenser:** After the initial dexamethasone intravitreal injection, I typically bring patients back at 4 weeks to check their pressures. If a patient has a mild to moderate elevation, but has a healthy-looking nerve, is not using anti-glaucoma drops, and does not have a history of glaucoma, I manage the pressure myself with a topical IOP-lowering drug. I check the pressure again in 4 weeks.

A handful of my patients who have underlying, well-controlled glaucoma received the dexamethasone implant 0.7 mg, had a pressure rise, and needed their medications adjusted. If a patient is already seeing a glaucoma specialist, rather than try to change his or her current regimen myself, I will have the glaucoma specialist manage it. To date, I have not had a patient require trabeculectomy, nor has anyone had significant pressure spikes that could not be controlled. Most of my patients have not had difficulty with pressure rises. When they have occurred, they have been relatively mild and transient.

**Dr. Capone:** If a patient is using one ocular hypotensive drug, has a reasonably healthy nerve, and well-controlled pressures, and I want to use dexamethasone, I do not demur. I monitor these patients carefully. I have several patients who, with the addition of a second drug, have been able to continue dexamethasone treatments with good control. Conversely, I tend to stand down if the nerve does not look healthy and if the patient is using multiple ocular hypotensives. None of my patients has needed trabeculectomy to date.

**Dr. Roth:** When a patient has a rise in IOP, I have a low threshold to add a topical IOP-lowering medication. Usually, you can ride out a transient pressure elevation with the use of topical or even oral medical therapy without the need for surgical or laser intervention. I use dexamethasone cautiously or not at all in patients who have significant cupping and are using multiple aqueous suppressants already. I can remember only one patient who required trabeculectomy after dexamethasone.

If a patient is using one topical medication for glaucoma and responds well to the first dexamethasone injection but has a pressure rise after a second injection, I start another drop. Often, if a patient was using a prostaglandin analogue, I add the brimonidine tartrate/timolol maleate combination (Combigan, Allergan) prophylactically at the time I administer the next dexamethasone injection.

One caveat: If a patient has undergone a trabeculectomy, and if his or her pressures are very low, I am less reluctant to use the steroid, because the trabeculectomy is working and will keep the IOP low.

IOP elevations after those modalities, and if a steroid seems to be a good approach for them, either to reduce the number of visits required or in terms of efficacy and better vision, I will use it with careful monitoring and IOP-lowering medication. I have quite a few patients who experienced a pressure rise, but in whom I still use the dexamethasone intravitreal implant. They know they will get a bump in IOP, and I may use one, two, or three medications to lower it (Figure 2).

Another relative but not absolute contraindication is a minimal nuclear cortical cataract that does not appear to be progressing rapidly. I do not want to start those patients on a course of dexamethasone because, invariably, they will wind up with a cataract. At the same time, however, if using a steroid is the best treatment option for them, whether with dexamethasone alone or combined with anti-VEGF, then cataract surgery is a problem we can deal with in the future.

**Dr. Drenser:** I have very few patients with strong contraindications. Severe glaucoma is a risk factor, but if the steroid appears to be the best option, I will treat patients who have well-controlled glaucoma and work with their glaucoma specialists or closely monitor their pressures following treatment.

I have a detailed conversation with my phakic patients about the risk of precipitating cataract formation or exacerbating a mild to moderate cataract. I have some younger patients who were not doing well on anti-VEGF therapy, and we switched to the dexamethasone intravitreal implant. Despite eventually developing cataracts, they were so happy with dexamethasone’s efficacy and the decreased treatment burden, that they always chose the steroid over anti-VEGF therapy when they needed further treatment. I think the potential risk of glaucoma and/or cataract formation bothers the doctors more than the patients. I think that as long as patients know what to expect, they are comfortable with managing the potential risks.

**CONCLUSION**

**Dr. Singh:** How has our management of DME changed in the past several years?
Dr. Drenser: Certainly, it has changed for the better. We have much better results and much better control. I think the new generation of people with DME will have far less long-term scarring and damage, because we do not need to rely so heavily on laser alone to control the disease. Multimodality therapy enables us to tailor treatment to individual patients—their needs, how they are responding to one drug or another drug—and increases our management options tremendously. I can encourage patients to be optimistic about their future and their vision, because we can control their DME and give them good long-term results.

Dr. Roth: We are fortunate to be in a new era with multiple treatment modalities. We also have a much better understanding of DME, not only in terms of how patients respond to different therapies, but also with advances in imaging, which provide great insights into the disease and how different patients respond to different therapies.
One interesting note: When we first started treating DME with anti-VEGF agents and gave one or two injections to see what would happen, we often undertreated and were underwhelmed with the results. Now, we have data from studies that show us how to treat appropriately and obtain better visual outcomes. Even using the same drugs, we have a much better understanding of how to use them (Figure 3).

**Dr. Capone:** Compared with 2 years ago, I manage DME much the same way. I think the changes are largely a matter of nuance. One significant change is that I am much quicker to embrace the option of the dexamethasone intravitreal implant 0.7 mg earlier in the disease and for a broader range of patients than I was 2 years ago, because I am more familiar with the drug and more comfortable managing its side effects.

**Dr. Singh:** I want to thank my colleagues and contributors to this publication. Each has taken an approach that he or she finds effective with the common goal of improving vision and reducing long-term vision loss in patients with DME. It is reassuring that in 2015, we have many options from which to choose for this increasingly large group of patients. I look forward to additional research information that will help us tailor these therapies for individual patients and improve the risk/reward ratio.

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