Treatments, Triggers, and Decisions in Retinal Disease Diagnosis and Management

Focus on Macular Edema

Highlights from a roundtable discussion during the 2014 meeting of the Macula Society in Key Largo, FL.
For macular edema following RVO*

Less “here we go again.”

*Branch or central retinal vein occlusion.

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 noninfectious uveitis affecting the posterior segment of the eye.

Dosage and Administration

FOR OPHTHALMIC INTRAVITREAL INJECTION ONLY. 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.

Advanced Glaucoma: OZURDEX® (dexamethasone intravitreal implant) is contraindicated in patients with advanced glaucoma.

Aphakic Eyes with Rupture of the Posterior Lens Capsule: OZURDEX® is contraindicated in patients who have aphakic eyes with rupture of the posterior lens capsule.

ACIOL and Rupture of the Posterior Lens Capsule: OZURDEX® is contraindicated in eyes with ACIOL (Anterior Chamber Intraocular Lens) and rupture of the posterior lens capsule.

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

Warnings and Precautions

Intravitreal Injection-related Effects: Intravitreal injections have been associated with endophthalmitis, eye inflammation, increased intraocular pressure, and retinal detachments. Patients should be monitored regularly following the injection.
• When OCT reveals macular edema that persists or recurs in RVO, consider inflammation

• Inject OZURDEX® (dexamethasone intravitreal implant) to help improve visual acuity¹

IMPORTANT SAFETY INFORMATION (continued)

Warnings and Precautions (continued)

Potential Steroid-related Effects: Use of corticosteroids 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.

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

Adverse Reactions
The most common ocular adverse reactions reported by greater than 2% of patients in the first 6 months following injection of OZURDEX® for retinal vein occlusion and posterior segment uveitis include: intraocular pressure increased (25%), conjunctival hemorrhage (22%), eye pain (8%), conjunctival hyperemia (7%), ocular hypertension (5%), cataract (5%), vitreous detachment (2%), and headache (4%).

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.

Please see Brief Summary of full Prescribing Information on next page.
Hypersensitivity:
Lens) and rupture of the posterior lens capsule. OZURDEX ® is contraindicated in eyes with ACIOL (Anterior Chamber Intraocular Lens) and rupture of the posterior lens capsule.

Ocular or Periocular Infections: OZURDEX ® (dexamethasone intravitreal implant) is contraindicated in eyes 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.

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WARNINGS AND PRECAUTIONS

Intravitreal Injection-related Effects: Intravitreal injections 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].

Potential Steroid-related Effects: Use of corticosteroids 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.

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

ADVERSE REACTIONS

Clinical Studies Experience: Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice. Adverse reactions associated with ophthalmic steroids include elevated intraocular pressure, which may be associated with optic nerve damage, visual acuity and field defects, posterior subcapsular cataract formation, secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera.

The following information is based on the combined clinical trial results from 3 initial, randomized, 6-month, sham-controlled studies (2 for retinal vein occlusion and 1 for posterior segment uveitis): Adverse Reactions Reported by Greater than 2% of Patients in the First Six Months

<table>
<thead>
<tr>
<th>MedDRA Term</th>
<th>OZURDEX® N=497 (%)</th>
<th>Sham N=498 (%)</th>
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</thead>
<tbody>
<tr>
<td>Intraocular pressure increased</td>
<td>125 (25%)</td>
<td>10 (2%)</td>
</tr>
<tr>
<td>Conjunctival hemorrhage</td>
<td>108 (22%)</td>
<td>79 (16%)</td>
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<tr>
<td>Eye pain</td>
<td>40 (8%)</td>
<td>26 (5%)</td>
</tr>
<tr>
<td>Conjunctival hyperemia</td>
<td>33 (7%)</td>
<td>27 (5%)</td>
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<tr>
<td>Ocular hypertension</td>
<td>23 (5%)</td>
<td>3 (1%)</td>
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Increased IOP with OZURDEX ® (dexamethasone intravitreal implant) 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. Following a second injection of OZURDEX ® in cases where a second injection was indicated, the overall incidence of cataracts was higher after 1 year.

USE IN SPECIFIC POPULATIONS

Pregnancy
Teratogenic Effects: Pregnancy Category C: Topical dexamethasone has been shown to be teratogenic in mice producing fetal resorptions and cleft palate. In the rabbit, dexamethasone produced fetal resorptions and multiple abnormalities involving the head, ears, limbs, palate, etc. Pregnant rhesus monkeys treated with dexamethasone sodium phosphate intramuscularly at 1 mg/kg/day every other day for 28 days or at 10 mg/kg/day once or every other day at 3 or 5 days between gestation days 23 and 49 had fetuses with minor cranial abnormalities. A 1 mg/kg/dose in pregnant rhesus monkeys would be approximately 85 times higher than an OZURDEX ® injection in humans (assuming 60 kg body weight).

There are no adequate and well-controlled studies in pregnant women. OZURDEX ® (dexamethasone intravitreal implant) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether ocular administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Caution should be exercised when corticosteroids are 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.

PATIENT COUNSELING INFORMATION

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. If the eye becomes red, sensitive to light, painful, or develops a change in vision, the patient should seek immediate care from an ophthalmologist. Patients may experience temporary visual blurring after receiving an intravitreal injection. They should not drive or use machines until this has resolved.

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**MODERATOR**

Pravin U. Dugel, MD, is a managing partner at Retinal Consultants of Arizona; a founding member of Spectra Eye Institute; and a clinical associate professor in the department of ophthalmology, Keck School of Medicine, University of Southern California, Los Angeles. Dr. Dugel may be reached at pdugel@gmail.com.

**PANELISTS**

Francesco Bandello, MD, PhD, is chair of the department of ophthalmology, Ospedale San Raffaele, Milan, Italy. Dr. Bandello may be reached at bandello.francesco@hsrit.

Anat Loewenstein, MD, is chair of the department of ophthalmology, Tel Aviv Sourasky Medical Center, and vice dean, Sackler Faculty of Medicine, Tel Aviv University, Israel. Dr. Loewenstein may be reached at anatlow@netvision.net.il.

Jordi Monés, MD, PhD, is director of the Institut de la Màcula i de la Retina, Barcelona, Spain. Dr. Monés may be reached at jmones@institutmacularetina.com.

Rishi P. Singh, MD, is a staff physician at the Cole Eye Institute, Cleveland Clinic; an assistant professor of ophthalmology at Case Western Reserve University; and the medical director of Clinical Systems Office, all in Cleveland, Ohio. Dr. Singh may be reached at drrishisingh@gmail.com.

Several key questions arise regarding the management of patients with retinal vein occlusion (RVO) and macular edema: When is anti-VEGF monotherapy appropriate? When should switching or combining therapies be considered? What is the role of corticosteroids? What safety issues should be considered when assessing treatment options? During a recent roundtable, a panel of experts gathered to discuss these important questions.

– Pravin U. Dugel, MD, moderator

**RETINAL VEIN OCCLUSION (RVO)**

Pravin U. Dugel, MD: How do you identify patients who need something more than anti-VEGF monotherapy? Is it appropriate to begin treatment with the dexamethasone intravitreal implant (Ozurdex, Allergan)?

Anat Loewenstein, MD: I sometimes begin treatment with Ozurdex as opposed to an anti-VEGF agent, but I cannot say I have identified specific disease characteristics that suggest a patient will respond better to Ozurdex than to an anti-VEGF agent. My decision to begin with the steroid is based more on the patient’s desire to avoid monthly injections or his or her medical history. A patient who has had a recent stroke, for example, will definitely receive Ozurdex.

Dr. Dugel: For what percentage of your patients do you initiate treatment with Ozurdex?

Dr. Loewenstein: Quite a lot, about a third.

Dr. Dugel: For the other two-thirds of your patients,
at what point do you decide someone needs more than anti-VEGF therapy?

**Dr. Loewenstein:** Typically, I administer 3 injections of an anti-VEGF agent. If I do not see a response, or if I see a partial response but the patient does not want to continue with monthly injections, I switch to Ozurdex (see also BRVO: Nonresponse to Anti-VEGF Therapy).

**Francesco Bandello, MD, PhD:** My approach is similar. I start with 3 injections of an anti-VEGF agent unless a patient has had a cardiovascular event or must travel a great distance to my office and is not likely to return for monthly injections. For those patients, initial therapy with Ozurdex is an appropriate choice.

**Dr. Dugel:** How do you manage patients who have a poor or partial response to anti-VEGF therapy?

**Dr. Bandello:** If a patient’s response is poor, I may use Ozurdex as adjunctive therapy. In some cases, patients receive both injections—first the anti-VEGF agent and then the Ozurdex—at the same visit.

**Dr. Dugel:** Dr. Singh, what is your usual approach to treating RVO?

**Rishi Singh, MD:** I administer an anti-VEGF agent as needed for most patients as initial therapy. I do not use a loading dose. I monitor patients closely during the first few months to determine if there has been a response to treatment. I am more likely to start with Ozurdex if a patient is pseudophakic and does not have risk factors for glaucoma.

**Dr. Dugel:** You would expect to see a fairly early response with anti-VEGF therapy.

**Dr. Singh:** Yes. In fact, sometimes I see patients as soon as 2 weeks after the initial injection to assess their response, particularly patients who have chronic disease, poor vision, or very high retinal thickness values.

**Dr. Dugel:** Dr. Monés, how do you treat RVO?

**Jordi Monés, MD:** I also usually begin with an anti-VEGF agent, unless a patient has had a recent cardiovascular event or does not want to return for monthly injections. For those patients, initial therapy is Ozurdex. I try to avoid using a steroid in young patients because of the risk of cataract, but if a patient is pseudophakic, I am comfortable using the steroid.

Because RVO is a chronic condition and compliance with monthly injections can be an issue, I am likely to switch from anti-VEGF monotherapy to combined therapy after 2 or 3 anti-VEGF injections, especially if a patient is pseudophakic or if the response has been suboptimal.

**Dr. Dugel:** Two recent reports have influenced how I treat RVO. First, a subanalysis of the BRAVO/CRUISE study showed that 90% of a patient’s total response to ranibizumab (Lucentis, Genentech) occurs within 3 injections (Figures 1-4). Second, the RETAIN study showed that after 4 years of treatment with ranibizumab, patients do well and their vision is good, but approximately 50% still need to be treated on a regular basis. Based on those findings, my approach is exactly as you have described.

I believe RVO has a life cycle. When leakage is the primary component, anti-VEGF monotherapy usually works well. As the disease progresses, however, it becomes multifactorial with an inflammatory component, and then monotherapy is not ideal. Do you agree?

**Dr. Loewenstein:** I think that is true in many patients, but there is not good evidence to identify when the disease becomes inflammatory.

**Dr. Bandello:** I do not completely agree that RVO is chronic. It is an acute event that may have a vascular compensation. The acute event resolves when you add a steroid. In other words, adding a steroid may have a beneficial effect on blood flow and secondary vascular compensation.

**Dr. Dugel:** Is that only in some patients?

**Dr. Bandello:** Yes. If another closure does not occur, resolution is definitive. In many cases, however, that is not possible, and additional treatments are needed.

**Dr. Loewenstein:** In the GENEVA trial, about 17% of patients needed only 1 treatment with Ozurdex, and the effect was sustained for about 4 months.

**Dr. Dugel:** Unfortunately, we do not know which patients will have this response, and that is part of the challenge.

**Dr. Singh:** The RETAIN study followed patients from the BRAVO and CRUISE trials and evaluated their long-term outcomes. However, those outcomes are relevant only for patients who have chronic disease. Patients with good visual acuity and without macular edema would have been dropped from evaluation and would not have been included in the final analysis. I enrolled many patients in CRUISE and followed them in HORIZON. I am seeing them now in practice 4 to 5 years later. About half of...
them do not come back to see me, because their macular edema has resolved. The other half come in every 2 months like clockwork and are still receiving injections for treatable but recalcitrant disease. Their visual acuities fluctuate a great deal between injections, and these patients will likely need chronic evaluation and management.

**ROLE OF LASER IN RVO**

**Dr. Dugel:** Is there a role for macular laser photocoagulation to treat RVO?

**Dr. Monés:** With effective pharmacologic agents now available for RVO, I rarely use macular laser to treat this disease. My rationale is to avoid the potential for irreversible burns, which may not affect visual acuity but do affect visual function. I use thermal laser only for cases with focal macular edema, although this occurs more often in diabetic macular edema. In some cases I try to extend the effect of the intravitreal therapy by using micropulse laser, which does not create a burn.

**Dr. Loewenstein:** Macular grid laser therapy does not have much utility in central RVO, but it sometimes has a role in diabetes and in branch RVO (BRVO). If the macular edema does not respond to anti-VEGF therapy or Ozurdex, I perform a fluorescein angiogram. If the macular edema is perfused, I sometimes apply a light grid in that area. I do not use the laser at the periphery for macular edema.

**Dr. Bandello:** I do not use laser for macular edema.

**ARE ALL STEROIDS ALIKE?**

**Dr. Dugel:** We may soon have two steroid delivery devices—Ozurdex and the fluocinolone acetonide intravitreal implant (Iluvien, Alimera Sciences)—in addition to triamcinolone delivered as a bolus. This is a critically important point. Are all steroids the same?

**Dr. Loewenstein:** They differ in many respects. For example, Ozurdex’s duration of action is between 3 and 4 months, whereas triamcinolone’s duration of action is shorter. In addition, more side effects, such as cataracts and increased intraocular pressure (IOP), are associated with triamcinolone, as seen in the SCORE trial. There are no data for the use of Iluvien for RVO.

**Dr. Singh:** Data from recent clinical trials suggest that elevated IOPs are common with all steroids, including triamcinolone, dexamethasone, and fluocinolone. Although the rate of incisional glaucoma surgeries was low (less than 1% in the Ozurdex RVO studies), the relevant
By Anat Loewenstein, MD

A 72-year-old woman with a history of hypertension and heart disease reported decreased vision in her left eye for 3 weeks (Figure 1). After 3 injections of bevacizumab, no response was detected (Figure 2). Figure 3 shows the response to Ozurdex at 3, 13, and 17 weeks. The favorable response was sustained for 3 months following Ozurdex treatment.

Figure 1. Branch retinal vein occlusion upon presentation.

Figure 2. No response was seen after 3 injections of bevacizumab.

Figure 3. The patient’s response to treatment with Ozurdex at 3 weeks (A), 13 weeks (B), and 17 weeks (C).
question is: What is the risk for the reward of improved anatomy? Potency seems to be a key driver of this, with triamcinolone, dexamethasone, and fluocinolone (in that order) showing increased rates of potency, and, thus, increased rates of elevated IOPs and the need for incisional glaucoma surgery.

Dr. Monés: I find it difficult to determine when to use Iluvien because of the risk of glaucoma. I think it is appropriate to consider doing a trial with short-term steroids before using such a long-lasting steroid.

Dr. Dugel: I evaluate a steroid’s utility based on the pharmacokinetic profile of the delivery system more than the steroid’s composition. A bolus injection of any steroid has the highest risk of adverse effects with the least amount of efficacy. The Ozurdex implant is biodegradable. Small cavitations develop in the pellet within days, increasing the surface area. It is not of zero-order kinetics. An initial elution burst is followed by a gradual decline. Iluvien, which is not biodegradable, is of near-zero-order elution kinetics. In my opinion, we would want the Ozurdex profile as soon as we clinically recognize that the disease has become multifactorial. If Ozurdex is not sufficient, then Iluvien, if approved for RVO, may be considered.

STEROID SAFETY—OCULAR HYPERTENSION

Dr. Dugel: Whenever steroids are considered for treatment, the potential adverse effects, such as ocular hypertension and cataract, must also be considered. Dr. Loewenstein, do you use Ozurdex to treat patients who have a history of glaucoma or who are using IOP-lowering medications? If so, how do you monitor them, and when do you become concerned about IOP issues?

Dr. Loewenstein: The safety profile of Ozurdex is excellent. I have treated patients who had elevated IOPs, and the pressures were easily controlled with topical medications, even in patients who received 6 or 7 injections. Typically, I ask patients to come to my clinic for a pressure check about 2 weeks after their injection, because it takes time for the pressure to increase. Then, they go to their usual ophthalmologist for another reading after a month. If a patient’s glaucoma is controlled by medication, I am comfortable using Ozurdex.

Dr. Bandello: IOPs should be closely monitored, because ocular hypertension can develop at any time during treatment. For example, a patient’s IOP may be within normal limits for 1, 2, or 3 months, but in the fourth month, it may rise. Maintaining control of IOP is important for patients treated with Ozurdex.

Dr. Dugel: What surprised me in the SHASTA study was that about one-third of the patients had a diagnosis of ocular hypertension or glaucoma, and Ozurdex was still used. Dr. Bandello, how would you monitor a patient who has no history of glaucoma? How would you monitor a patient who has a history of glaucoma and is using 1 pressure-lowering medicine?

Dr. Bandello: When I use Ozurdex to treat a patient who has no history of glaucoma, I see him or her every 2 months for a pressure check and also for an examination to see the evolution of the disease on optical coherence tomography (OCT). If I have any doubt about a patient’s pressure, I recommend that he or she have regular pressure checks. If a patient has glaucoma that is controlled with therapy, I follow the same regimen. I feel there is no increased risk if a patient’s pressure is controlled.

Dr. Dugel: Dr. Monés, do you perform any provocative tests?

Dr. Monés: I do not perform provocative tests for patients receiving Ozurdex. I am comfortable with its IOP profile. In fact, I rarely see patients before 6 weeks, because if the pressure is going to rise by 2 months, I will anticipate it. If a patient has a risk of glaucoma, however, I will likely see him or her at 3 weeks instead of 6 weeks.

If a patient has glaucoma that is being controlled by 1 or a few topical medicines, I have no problem injecting Ozurdex. If a patient has advanced glaucoma and is on maximal medical therapy, I prefer not to use steroids.

Dr. Singh: In the GENEVA study, the highest percentage of patients whose IOPs rose more than 10 mm Hg were seen at day 60, so I think it is reasonable to assess patients at day 60, and that is my current point to reevaluate them for glaucoma. I also like to view the OCT at 2 months.

I have been controlling IOPs successfully with medical management in patients who have received an Ozurdex implant. IOPs less than 30 mm Hg or maybe a few points above 20 mm Hg typically respond to 1 IOP-lowering medication. None of my patients has required an incisional glaucoma procedure, possibly because these drugs are delivered intermittently and not on a standardized dosing schedule as was followed in the studies (see also Balancing Effective Use With IOP Control).

Dr. Loewenstein: The glaucoma specialists with whom I have consulted are not overly concerned by pressures of 26 or 27 mm Hg in patients who do not have glaucoma. When the effects of the Ozurdex implant wear off, the pressure comes down.
Dr. Singh: Sometimes, the question arises: Does a patient have glaucoma or ocular hypertension? Our glaucoma colleagues help differentiate these two diagnoses. In the absence of nerve fiber layer defects or visual field losses from glaucoma, the best course may be to monitor the patient's IOP, because the time course for an IOP increase is self-limited until the steroid clears.

Dr. Dugel: It appears glaucoma may not be as concerning as initially thought, because Ozurdex has a predictable pharmacokinetic profile. Dr. Singh's comment about glaucoma specialists should ring true to us. As retina specialists, we tend to think of glaucoma as a single entity, but just as we differentiate the various types of retinal detachments, glaucoma specialists differentiate the various types of glaucoma and their severity. For example, neovascular glaucoma can be quite difficult to manage, while steroid-induced glaucoma is more easily managed, especially if the pressure will decrease in a predictable fashion.

STEROID SAFETY—CATARACT
Dr. Dugel: Do you consider a patient’s phakic status when deciding whether or not to treat with a steroid?

Dr. Bandello: If a patient is young, I try other options, but when a patient is mature, I do not consider cataract a serious problem.

Dr. Dugel: What do you tell your patients about the risks associated with steroid treatment?

Dr. Bandello: I explain everything. I say, “We are now using a therapy that produces a homogeneous effect, and I am happy to use it in your case. Your intraocular pressure may increase, but that usually can be treated with eye drops. There may be some opacification of the lens, but we can perform cataract surgery to resolve that issue.”

Dr. Dugel: So, cataract is not an issue for you, and you do not restrict your use of a steroid to pseudophakic patients.

Dr. Bandello: Absolutely not.

Dr. Loewenstein: I have not seen many cataracts, but if a cataract develops, I agree with Dr. Bandello. We just perform the cataract surgery. It is a nice solution, because the steroid controls the inflammation that may occur after cataract surgery.

Dr. Singh: When we know patients will eventually need cataract surgery, having them pretreated and well managed from a retina perspective improves their outcomes.

We know this because studies have shown that patients with preexisting retinopathies are the ones who develop macular edema following cataract surgery. For example, in patients with diabetic retinopathy, 16.7% develop macular edema following uncomplicated cataract surgery.9 At the Cleveland Clinic, we are performing a postvitrectomy study of patients who are receiving Ozurdex at the time of surgery, and I am impressed by the extent of inflammation control. From my perspective, I think it is safe to send a patient whose RVO has been well managed to have cataract surgery.

Dr. Monès: I would avoid Ozurdex in someone who is younger than 35 years.

Dr. Dugel: Dr. Monés, would you use Ozurdex to treat a mature patient with RVO?

Dr. Monès: Patients between the ages of 35 and 60 years are in a somewhat gray zone. The older the patient, the fewer issues I have with a transparent lens. In older patients, I explain the treatment as a combined treatment and that the patient will receive the injections plus cataract surgery. Patients tend to accept that. To them, this course of treatment is not a problem or an adverse event, and they will see well after treatment.

Dr. Dugel: In my opinion, patients who have macular edema, regardless of their age, have a blinding disease. If my solution to that blinding disease is Ozurdex and the side effect is a 20% risk of cataract formation, from my point of view, that is not a problem. If a patient is going to be blind, I do everything I can do to save his or her sight. As Dr. Singh noted, what impressed me from all of the steroid device studies is that patients actually do much better after cataract surgery when they have Ozurdex on board.

DIABETIC MACULAR EDEMA
Dr. Dugel: Dr. Monés, what is your usual approach to treating patients who have DME?

Dr. Monès: Patients with DME tend to resist compliance, which is a factor I must consider in my treatment plan. These patients see so many doctors already—primary care physicians, endocrinologists, cardiologists, nephrologists—that convincing them to adhere to a schedule of frequent anti-VEGF injections may be difficult. For these patients, I am likely to begin therapy with Ozurdex, or I may start with an anti-VEGF agent and then switch to Ozurdex. I am also mindful that chronic anti-VEGF treatment of people with diabetes may not be advisable, especially those with cardiovascular risk factors.
Dr. Dugel: When deciding on a treatment plan, do you differentiate between young and mature patients?

Dr. Monés: I have found young patients respond beautifully to anti-VEGF therapy. They tend to be more angiogenic, with more of a proliferative disease risk. In mature patients with type 2 diabetes, the DME is usually more inflammatory than vascular, and these patients may not want to come to the clinic so often, so I am more likely to treat with Ozurdex earlier.

Dr. Dugel: Dr. Singh, we know Ozurdex is not yet approved for treating DME in the United States, but speaking hypothetically, where would it fit in your treatment plan?

Dr. Singh: If Ozurdex is approved for DME, I will probably use it as I do in RVO, as a second-line therapy, especially in pseudophakic patients without a history of glaucoma. Based on my experience with intravitreal triamcinolone, I have found a steroid restores the anatomy faster than the typical anti-VEGF agent does.

Dr. Dugel: Which patients would you treat with Ozurdex first line?

Dr. Singh: I was referring to patients with center-involving DME versus a patch of clinically significant macular edema in the periphery. I prefer to use laser in cases involving the periphery.

Dr. Dugel: Dr. Bandello, what is your usual approach to treating DME?

Dr. Bandello: Classifying DME is difficult, and that is why I start with anti-VEGF therapy. If I do not see a response, then I switch to the steroid.

Dr. Dugel: How many times do you administer anti-VEGF before switching?

Dr. Bandello: If I do not see a response after 3 injections, I switch to the steroid. I believe patients who are best suited to treatment with Ozurdex are those with chronic edema and poor visual acuity. Anti-VEGF therapy is less effective in those patients. On the other hand, I have found anti-VEGF therapy is more effective when the disease is acute. The ideal patient for anti-VEGF therapy is a young patient with florid proliferative diabetic retinopathy and associated significant macular edema.

I should also mention, I still use laser to treat DME, which is the main difference between how I treat DME versus RVO.

Dr. Loewenstein: My approach is similar to Dr. Bandello’s. I start with 3 injections of an anti-VEGF agent and if the response is not good enough, I switch to Ozurdex. If a patient does not want to come in for monthly injections, I start with Ozurdex. For chronic disease, I might use Ozurdex upfront. If I am treating a vitrectomized eye, which happens in patients with diabetes, I use only Ozurdex, as shown in the CHAMPLAIN trial.11

Dr. Dugel: Many of us say we treat according to DRCR.net Protocol I, but in Protocol I, the first opportunity to not treat the patient was at week 16.12 At that time, the patient had to have a flat OCT and 20/20 visual acuity. In that study, 25% of patients qualified to not be treated. Of those 25%, 90% had a recurrence of DME. The first opportunity to decrease the visitation burden for the patient—to not to be seen every 4 weeks—was at week 64. Very few of my young patients with diabetes would commit to coming to my office for an injection every 4 weeks for more than a year. That regimen is difficult to sustain.

I consider treatment in terms of the life cycle of the disease. Early on, I believe the disease is more local and permeability-based. For those cases, if the leakage is away from the macula, laser treatment is sufficient. When it becomes diffuse and impinges on the macula, it probably becomes more of a diffuse permeability issue. At that point, an anti-VEGF agent may be the most appropriate intervention. As the life cycle progresses and the disease becomes more inflammatory, anti-VEGF monotherapy is not sufficient. I think the FAME A and FAME B studies confirmed that.13 Patients tended to respond well to having a steroid on board. Those of you who have experience with that in Europe, would you agree?

Dr. Bandello: Absolutely.

Dr. Loewenstein: Absolutely.

Dr. Dugel: FAME A and B also showed an absolute disconnect between OCT and visual acuity. How do you interpret that?

Dr. Bandello: These patients have a chronic condition, so that is a typical response. Even though the therapy reduces retinal thickness, the photoreceptors were destroyed before treatment. The main hypothesis is that hard exudates formed in the middle. Because of reabsorption of fluid and atrophy in the middle of the fovea, the patient cannot see, even though you have a beautiful OCT.

Dr. Monés: The edema may resolve, but the outer layer
By Rishi P. Singh, MD

A 68-year-old man with proliferative diabetic retinopathy presented with a recent branch retinal vein occlusion in the left eye, and macular edema (Figure 1). The patient had posterior chamber IOLs in both eyes and no history of glaucoma. Visual acuity was 20/50. The patient received 6 injections of bevacizumab over 7 months (Figure 2). His visual acuity ranged from 20/50 to 20/40, and the anatomy was not worse. IOPs ranged from 23 mmHg to 25 mmHg, suggesting ocular hypertension but not glaucoma. The decision was made to switch to Ozurdex because of poor anatomical and visual response. One month after the Ozurdex injection, visual acuity was 20/40, and the cystoid edema had resolved almost completely (Figure 3). Three months after treatment with Ozurdex, visual acuity had improved to 20/25, and the anatomy again showed normalization of the retinal contour and no evidence of macular edema (Figure 4).

Figure 1. A patient with no history of glaucoma presented with proliferative diabetic retinopathy, a recent branch retinal vein occlusion in the left eye, and macular edema.

Figure 2. The patient received 6 injections of bevacizumab over a 7-month period. Visual acuities were 20/50 and 20/40; IOPs ranged from 23 mm Hg to 25 mm Hg.

Figure 3. One month after Ozurdex injection, visual acuity was 20/40.

Figure 4. Three months after Ozurdex injection, visual acuity improved to 20/25, the retinal contour has normalized, and there is no evidence of macular edema.
atrophies. Especially in long-standing disease, the functional correlation with OCT is minimal.

**Dr. Loewenstein:** I think Dr. Dugel was referring to the dichotomy between long and short duration (3 years or 1.7 years), which was evident by visual acuity results but not as evident by OCT results. This suggests the steroid may have a protective effect on visual acuity.

**Dr. Dugel:** That is exactly where I was going. OCT is a good barometer for VEGF levels, but it may not be as reliable for measuring inflammation.

**Dr. Singh:** We should also keep in mind that off-protocol lasers were permitted in the FAME trials.

**Dr. Loewenstein:** Not only lasers, but also anti-VEGF agents and Ozurdex.

**Dr. Singh:** The fact that OCT findings do not correspond with visual acuity makes sense. The more chronic the disease, the greater the outer retina disruption and the higher the likelihood there will not be an improvement. In addition, about 70% of patients in some of the study arms received laser treatment, maybe 2 or even 3 treatments. Those retinas may have laser-induced injuries that may prevent the visual acuity from responding as well. It was not quite a pure steroid-versus-laser trial, which clouds the results and how we can use them (see also *Trial Results Versus Real-World Experience*).

**Dr. Dugel:** Outcomes achieved during a trial often differ from the posttrial outcomes that are seen in the clinic. In a practical sense, this means the optimal treatment strategy with a drug or device may not become apparent until it is widely used outside the setting of controlled clinical trials. For example, if a patient’s IOP will rise predictably 60 days or so after Ozurdex injection and then it will decrease—a finding that was not apparent in the clinical trials—we may be less likely to perform an invasive procedure, such as laser photocoagulation or surgery, during that time frame. As a result, I think glaucoma surgery and intervention rates may be lower than they were in the clinical trials.

Similarly, if we know a patient with Ozurdex on board will do well following cataract surgery, we may elect to intervene earlier. The GENEVA1 and MEAD2 study results were skewed because the cataracts that developed made the vision worse. If we knew these patients would do well, we probably would perform cataract surgery earlier. So in real life, do you think our results will be better?

**Dr. Loewenstein:** The results for treating RVO with Ozurdex will be better in the clinic, because we will not have to wait 6 months to retreat as we had to do in the clinical trials. Now, when we see a recurrence, which usually happens between 4 and 5 months, we inject again, so the results are better.

Regarding RVO and the issue of treating early, in the GENEVA trial, most eyes had a longer duration of macular edema prior to enrollment, and this created a bias toward poor results.1 As we know from each trial of each drug, treating earlier produces better outcomes. In real life, when we do not need to wait a long time, we see better results.

**Dr. Dugel:** Consider this scenario: A patient reports poor vision. Upon examination, you see BRVO with some macular edema. The patient’s visual acuity is 20/40. Do you treat?

**Dr. Monés:** Yes.

**Dr. Loewenstein:** Yes.

**Dr. Dugel:** Suppose the patient reports not seeing as well as in the past, but visual acuity is 20/20. Upon examination, you see BRVO with some macular edema. What do you do?

**Dr. Singh:** I always treat the patient when macula edema is present, because the risk of adverse events is low following intravitreal injections.

**Dr. Dugel:** So when macular edema is present, regardless of the vision, will you treat the patient?

**Dr. Singh:** Yes. If the retina is dry and the anatomy is normalized, but the visual acuity is not improving, I may say, “There is not much to do here. We have given it our best shot.” This usually occurs in patients with more chronic edema. In the absence of that, however, for the most part, I treat everyone.

**Dr. Monés:** Visual acuity is sometimes misleading, especially in BRVO. Half of a patient’s visual field may be markedly impaired despite a visual acuity of 20/20, because there is a sharp line between edema and no edema. Yet, we are too driven by visual acuity. If the edema impairs visual function, I will treat. I avoid treating patients who have minimal, almost subclinical BRVO.

(Continued on page 14)
Dr. Dugel: What I am hearing—and again, I know we do not have this in the United States—is that you would treat a patient with an anti-VEGF agent 3 or 4 times. If you get a response, that is great. If you do not get an adequate response, then you would conclude that this multifactorial disease is farther along in its life cycle and now has an inflammatory component, which you would treat with Ozurdex.

Dr. Monés: Also, consider a patient in his or her 50s with chronic disease who responds well after 3 injections but says, “Doctor, how many years are you going to do that to me?” So even if the response is good, we switch when patients are resistant to being treated frequently.

Dr. Bandello: Or we may consider using the laser to try to stabilize the results. I think about the future for these patients, who may need to undergo lifelong therapy. Something needs to be done that that will stabilize the disease.

Dr. Loewenstein: Remember, however, that in the second and third years of the DRCR.net trials, patients needed fewer injections. Of course, the researchers reported averages. Some patients needed more injections and some need fewer. If a patient’s disease is controlled, he or she may not need many injections. If a patient continues to need many injections, however, regardless of the response, it is still best to avoid administering injections every month for 2 or 3 years.

Dr. Dugel: It is difficult to tell patients, “Stay with me every 4 weeks for a year, and it will get better,” because that initial year is very difficult to sustain.

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### TRIAL RESULTS VERSUS REAL-WORLD EXPERIENCE (CONTINUED)

(Continued from page 13)

**Dr. Loewenstein:** If a patient is asymptomatic and has some incidental edema and 20/20 visual acuity, I may have him or her return in 3 or 4 weeks, because in a small percentage of patients, edema resolves spontaneously. If a patient is symptomatic or has decreased visual acuity or significant edema, I treat upfront.

**Dr. Bandello:** I think this is a case where we need to consider many factors, including the patient’s attitude. Will he or she return for treatment? What is the status of the other eye? I consider many traits of a specific patient before deciding on a treatment course.

**Dr. Singh:** Trying to extrapolate clinical trial data to patients in our clinics just does not work. We see patients with Snellen acuities of 20/25 or 20/30, and these patients never would have been enrolled in the those trials. The majority of the trials purposely enrolled patients with poorer vision, because they were pressed to show 3 lines of gain in visual acuity. I do not think we, as physicians, can wait for our patients to decline before instituting therapy, especially because most studies show that waiting for loss of acuity usually also prevents long-term improvement. That is why, for me, visual acuity means absolutely nothing in the presence of macular edema alone.

**Dr. Dugel:** I think you are exactly right. The only situation in which I would not treat is if no edema is present and the patient does not want treatment. As advanced as we are with drugs and devices, our method of measuring visual function is still archaic and artificial. When in life do you sit in a dark tunnel with a bright light at the end? I agree that with our current drugs, I would treat earlier.

On the topic of real-world versus trial results, in your experience, what is Ozurdex’s duration of action?

**Dr. Monés:** 3 to 4 months.

**Dr. Bandello:** 2 to 4 months.

**Dr. Singh:** 4 months.

**Dr. Loewenstein:** 3 to 4 months.

**Dr. Dugel:** I agree with you. Those of us who have been working with the dexamethasone implant from the beginning truly believed it was a 6-month drug based on studies in animals. Then, SHASTA suggested it lasts about 5 months. Here is an important factor to consider: In the GENEVA study, there were no visits between day 90 and day 180. More than 50% of patients came in after day 180 and some as late as day 210. So I think that aspect of the study design biases us.

Do you have any hesitation about administering Ozurdex multiple times?

**Dr. Loewenstein:** I have no hesitation. I administer as many as 6 or 7 injections.

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Dr. Singh: Especially if that patient is working, the socio-economic impact is significant.

Dr. Dugel: The dropout rate is enormous. No matter how effective the treatment is, if patients are not coming in, it does not help.

To Dr. Monés’ point, if the DME responds to Ozurdex, it may not be apparent if the inflammatory or the anti-VEGF component is responsible, or both. Steroids are potent VEGF inhibitors. When an Ozurdex injection is administered, it is both an anti-inflammatory and an anti-VEGF agent.

Dr. Loewenstein: Micropulse, subthreshold laser is also a treatment option. At Tel Aviv Sourasky Medical Center, we used the Lumenis laser to treat many patients as part of a trial, and we have had very good results. \(^{14}\) We did not induce the kind of scarring typically associated with laser therapy.

**ANTI-VEGF SYSTEMIC SAFETY**

Dr. Dugel: When potential side effects of treatments for DME are discussed, the conversation usually focuses on steroid-induced glaucoma and cataracts. The systemic effects of anti-VEGF agents are usually not discussed. Are you concerned about these effects in young patients?

Dr. Bandello: During anti-VEGF therapy, patients receive a large amount of drug during a short period, rather than a small amount of drug continuously over a long period, which I feel would be preferred. With each injection, the concentration of anti-VEGF increases, and the peak is dangerous for the patient. This is a lifelong problem for patients who need chronic therapy.

Dr. Singh: I agree. Many clinicians believe CATT validated the safety of ranibizumab and bevacizumab (Avastin, Genentech) and extrapolate the results of that study of exudative age-related macular degeneration to DME and RVO. \(^{15}\) However, the study was not powered for safety.

At the 2014 meeting of the Association for Research in Vision and Ophthalmology, Avery and colleagues presented some relevant and interesting data on systemic suppression of VEGF with these drugs, which seems to differ according to the drug. \(^{16}\) The impact on the side effect profile is unknown, but it is interesting to know it is there.

Dr. Dugel: Should potential systemic effects be considered when deciding whether or not to use chronic anti-VEGF monotherapy or Ozurdex?

Dr. Singh: Absolutely. I think about it every time I am deciding on a course of treatment for a young patient, especially because treatment may need to continue for 20, 30, or even 40 years.

Dr. Monés: In my opinion, any patient with diabetes, especially long-standing diabetes, has the potential to develop cardiovascular disease. When a patient has had diabetes for 20 years, the vasculature is not normal. So, yes, I am concerned. I have systemic safety in mind at all times.

**CONCLUSION**

Dr. Dugel: I believe this discussion has confirmed our intuition that we are on the precipice of a paradigm shift in how we manage RVO and DME. This shift was initiated by our improved understanding of the inflammatory component in the life cycle of these diseases. We look forward to having a larger therapeutic armamentarium that will allow us to customize our treatment strategies based on disease progression and each patient’s individual risk/benefit considerations.
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