Multi-modality Treatment Approaches to RVO-associated Macular Edema

Expert insights into the importance of utilizing all of the available options

- Diagnosis and Monitoring of RVO and Secondary Macular Edema
- Reframing How We Think About Treatment for RVO
- Macular Laser in the RVO Treatment Paradigm
- Dexamethasone Intravitreal Implant Following RVO: Rescue, Adjunct or Primary Therapy?
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.
For macular edema following RVO

- When OCT reveals macular edema that persists or recurs in RVO, consider inflammation
- Inject OZURDEX® (dexamethasone intravitreal implant) to help improve visual acuity

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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.

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%).

OCT images ©2013, Dr. Szilárd Kiss.

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:** OZURDEX® (dexamethasone intravitreal implant) is contraindicated in patients who have aphakic eyes with rupture of the posterior lens capsule.

**Posterior Segment Uveitis:** OZURDEX® is contraindicated in patients with advanced glaucoma.

**Advanced Glaucoma:** OZURDEX® 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.

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- 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 [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 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>
</tr>
</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>
</tr>
<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>
</tr>
<tr>
<td>Ocular hypertension</td>
<td>23 (5%)</td>
<td>3 (1%)</td>
</tr>
</tbody>
</table>

Increased IOP with OZURDEX® (dexamethasone intravitreal implant) peaked at approximately week 8. During the initial treatment period, 1% (3/342) 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 is known 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 the 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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We don’t have to think too far into the past to remember a time when we diagnosed and planned treatment for our retinal vein occlusion (RVO) patients without several of the advanced technologies we have today. Clinical exam, fluorescein angiography (FA) and OCT continue to be our best tools for evaluating RVO and associated macular edema, but our imaging capabilities have improved significantly.

■ Clinical Exam. RVO patients commonly report decreased vision and blurring in one eye, but it’s typically painless with sudden onset. They may also report distortion of images, and their visual disturbances may be limited to one part of the visual field. A dilated fundus exam often reveals the classic features of branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO), which include intraretinal hemorrhages and tortuosity and dilation of the retinal blood vessels. Macular edema, exudates and cotton wool spots may be present. If so, their location should be noted in the chart so any changes that occur over time or with treatment can be documented.

In addition to a measurement of visual acuity, which may or may not be affected depending on the location of the occlusion, a confrontation visual field test should be performed. Depression of the field in a certain quadrant could indicate macular edema or areas of ischemia. Ischemic RVO has a much poorer prognosis than non-ischemic. The pupillary light reflex should also be checked as the presence of an afferent pupillary defect may be a sign of ischemia.

Questions about cardiovascular disease, stroke, high cholesterol and diabetes are particularly relevant when eliciting the medical history of RVO patients. All of those conditions are associated with RVO, with hypertension being the number one associated risk factor. Many patients aren’t aware of the connection between these systemic conditions and retinal vein occlusion. As such, it’s important that we educate them about the link between these conditions and RVO and thus, the importance of getting certain risk factors under control. We should also encourage them to follow up with their primary care physician on a regular basis.

■ Fluorescein Angiography. When symptoms and clinical examination suggest RVO, FA is the next step. Ultra-widefield angiography (Optos) is preferred because it enables efficient imaging of the retinal periphery out to approximately 200 degrees. This reveals whether areas of the peripheral retina are ischemic, which is useful for determining a prognosis, and planning your treatment approach, follow-up steps and schedule. Peripheral ischemia should be monitored closely with suspicion. Ischemia induces production of vascular endothelial growth factor (VEGF) that in turn can lead to increased vascular permeability and macular edema, as well as neovascularization in the retina and iris.2,3
Ultra-widefield angiography has shown us that even if the macula is not ischemic, ischemia in the periphery can be extensive. Eyes with peripheral ischemia are likely to require repeat anti-VEGF injection therapy, whereas eyes without peripheral ischemia may not require anti-VEGF treatment at all, provided the patient’s vision isn’t being affected by the macular edema. Peripheral ischemia often exists without associated macular edema (Figures 1 and 2). However, when both are present, persistent ischemia can perpetuate a cycle of post-treatment resolution and recurrence of the edema.

Most photographers will capture some color fundus photos as part of performing FA. In general, their diagnostic value doesn’t extend beyond serving as documentation of what was observed during the clinical exam.

**OCT.** OCT provides us with a more efficient, less invasive and less costly way than repeat FA to evaluate and monitor RVO and associated macular edema over time. With the progression from time-domain to spectral-domain technology, we have gained the ability to capture volumetric scans of the retina, rather than only single-line scans. This allows generation of thickness maps that more precisely identify focal areas of retinal thickening.

In our clinic, for all patients in whom macular disease is suspected, we obtain a high-resolution, high-density scan through the center of the fovea. We also capture a cube scan that covers a 6-by-6-mm area of the macula. For RVO patients in particular, it’s important to look at the entire cube to determine whether focal areas of edema are present outside the fovea. It may be faster to look only at one scan through the fovea, but doing so can lead to the assumption that the entire macula is free of edema when it may not be. Making use of the thickness maps derived from the cube is also a good way to pick up all edematous areas. Edema outside the fovea can be observed rather than treated, but it should be monitored for changes over time.

After initial examination and baseline OCT and FA, most physicians choose to follow RVO patients with monthly OCT scans. Repeat FA is reserved for when it is unclear why a patient isn’t responding to treatment as expected or experiences worsening vision or if neovascularization is suspected. Once macular edema becomes quiescent or doesn’t require monthly treatment, and depending on the extent of ischemia, the interval between follow-up visits can be extended to every 3, 6 or 12 months. Even when the eye is quiet, it is prudent to examine any patient with a history of RVO once or twice each year.

**Advances in Imaging on the Horizon**

Further improvements that will enhance our ability to manage RVO patients are being researched and developed. Among them is the use of OCT for performing angiography for imaging retinal capillaries. Having a noncontact method for viewing the retinal vasculature would be a welcome addition. Swept-source OCT also promises to provide wider views of the peripheral retina. We can also look forward to the development of new visualization tools based on volumetric data.

**References**

The number of options retina specialists have for managing macular edema associated with retinal vein occlusion (RVO) has increased since observation was the prevailing approach and the only proven treatment, solely for branch occlusion, was laser photocoagulation. The increase in options has led to a focus on debating the question: Which treatment is best for RVO? I venture to say there is a better way to frame the issue.

First, we should understand that RVO, like any other chronic, complex disease, has a life cycle consisting of various stages. Oncologists, for example, have approached cancer this way for many years. Rather than simply diagnosing lung cancer or colon cancer, they delve deeper to categorize it at a specific stage, stage 1, stage 2, and so on, and use that insight to implement the appropriate treatment plan. Ideally, we would do the same with RVO. Clinically, we see the repercussions of RVO disease stages that follow the initial occlusive event — capillary permeability and leakage, edema, inflammation, vessel remodeling and recanalization, neovascularization if ischemia is present, and fibrosis. However, not all patients go through all the stages. Furthermore, although we know a multitude of chemical factors are involved, e.g., angiogenic and inflammatory cytokines, we’re still working to clearly define the stages at the cellular level and discern the relationships between them. Until we’re armed with that information, we aren’t able to predict, for instance, that a specific patient’s RVO is at the leakage stage and therefore an anti-VEGF agent alone will resolve his macular edema. In the meantime, what we can do is work with the life cycle of RVO in a roundabout way, by titrating our treatment options and perhaps combining them until we arrive at what works for the individual patient. By doing this, we not only provide the best possible current care but also adopt the mindset that will be most helpful to us as our knowledge of RVO and associated macular edema expands.

Here, I summarize other key aspects of my approach to macular edema secondary to retinal vein occlusion.

### Treatment Criteria

The treatment criteria used in the early studies of laser for RVO and in subsequent anti-VEGF studies are outdated. Rather than observe patients for 3 months to see if macular edema spontaneously resolves and visual acuity improves to 20/40 or better, I treat all patients who have edema and a vision complaint, even if their Snellen visual acuity is 20/20. One reason is that the longer we wait to treat, the less vision we can expect the patient to recover. Another reason is that Snellen acuity is not a true assessment of visual function. It doesn’t take into account the real-world aspects of what constitutes clear, comfortable vision for patients, such as contrast sensitivity and color perception. I often see RVO patients with 20/20 Snellen acuity who say they’re having trouble seeing.
Gauging Response to Treatment
My most frequent first-line therapy for RVO-associated macular edema is an anti-VEGF agent, as it is for most retina specialists. I gauge whether it is adequate for a given patient based on a post hoc analysis from the BRAVO and CRUISE studies of ranibizumab (Lucentis, Genentech). The analysis showed that in patients with central retinal vein occlusion, 90% of the response to treatment occurred within the first three injections. Therefore, if I see no response after three injections, I’m confident that monotherapy will not be adequate, and I move to the next option. If I see robust improvement in macular thickness and visual acuity by the third injection, I’m inclined to continue with the injections until the response plateaus.

I use another subanalysis from BRAVO and CRUISE, the RETAIN study, as guidance. This analysis showed that despite a good visual response, approximately 50% of patients continue to need anti-VEGF injections for edema as much as 4 years later. This indicates that at least half of patients are likely better off if we use additional treatment to keep the retina dry, thus reducing the treatment burden.

Updated Approaches to Laser Treatment
The role of traditional laser treatment is becoming less and less relevant. It does produce benefits, but, as we know, it is also photodestructive, producing scarring and scotoma. Scars can expand slowly over time, which is especially troubling for young patients.

On the other hand, some recent developments in laser technology are encouraging. For example, End-point Management (Topcon Medical), for use with the PASCAL and Streamline lasers, is an innovative way to precisely control laser output. Through photostimulation, the retinal pigment epithelium cells can be selectively targeted with subthreshold treatment to prompt the necessary biologic response for decreasing edema, without collateral tissue damage. It will be interesting to see what further studies reveal about the safety and efficacy of these types of technology.

Steroid Pharmacokinetics
All steroids and steroid delivery devices are not the same. The pharmacokinetics (PK) of each is an important consideration in the treatment of macular edema. Injecting a bolus of steroid, such as intravitreal triamcinolone, results in a large increase of drug in the eye followed by a sudden decrease, which is not a favorable PK profile. Beneficial effects are minimized, and complications are maximized. In comparison, the dexamethasone intravitreal implant provides an initial burst of drug elution followed by a gradual decrease over time, a much more favorable profile. Complications are more predictable, and therefore more easily managed.

Thinking in terms of the life cycle of RVO-associated edema, we can see how using an anti-VEGF agent is a sensible option at the relatively early stage of capillary permeability. When inflammation becomes more of a factor, based on how the eye responds to anti-VEGF, the steroid implant makes sense. Studies have confirmed the safety of using it multiple times as well. Should the fluocinolone intravitreal insert (Alimera Sciences) receive FDA approval for RVO treatment, it could be a useful next step, in particular for eyes with very diffuse edema that could benefit from the device’s 3-year steady-state release of steroid.

“I’m more likely to use the dexamethasone implant rather than anti-VEGF therapy in a vitrectomized eye, because its sustained presence in the eye has been show to be effective in this scenario.”

— Pravin U. Dugel, MD

Attention to Potential Complications
All of the available treatments for macular edema have side effects, which we must understand and manage. Anti-VEGF agents are certainly effective, yet they may increase the risk for systemic arteriothrombembolic events (ATEs). Even though there’s a lack of definitive data, we must be mindful of the trends. We do have to use caution in our patients who are at highest risk for ATEs, particularly patients 85 and older. Whether different anti-VEGF agents have different systemic safety profiles is not known. One theory that has been put forth suggests that the IgG1 protein could have an impact by allowing for greater systemic exposure. We are also learning that chronic anti-VEGF treatment may additionally have local side effects. This has been seen in neovascular AMD as geographic atrophy and fibrosis. The systemic and local side effects of chronic anti-VEGF treatment for RVO requires more study.

Our main concerns with steroid treatments are cataract formation and elevated IOP. As mentioned previously, using steroids with known favorable PK profiles improves our ability to predict and manage these side effects.
Whether we're using monotherapy or combination therapies, we must use them in the context of the risk/benefit ratio for the individual patient. For example, in an 85-year-old patient with a history of heart attack or stroke, I prefer to use an anti-VEGF agent without the Fc fragment for a short period of time, and I'm more likely to switch to the dexamethasone implant quickly.

"Our main concerns with steroid treatments are cataract formation and elevated IOP. As mentioned previously, using steroids with known favorable PK profiles improves our ability to predict and manage these side effects."

— Pravin U. Dugel, MD

I'm less likely to use the implant in steroid-responsive patients or patients with uncontrolled glaucoma, although several studies indicate the side effects are quite manageable in glaucoma patients with good IOP control. I do monitor such patients more closely than patients without these added risks. When deciding whether to use the dexamethasone implant in phakic patients, the risk/benefit equation is also an important consideration. For patients in danger of losing vision to fibrosis, for instance, the need for future cataract surgery becomes less of a concern. The clinical trials for both the dexamethasone and fluocinolone implants showed that eyes with these devices do very well with cataract surgery. As a final example, I'm more likely to use the dexamethasone implant rather than anti-VEGF therapy in a vitrectomized eye, because its sustained presence in the eye has been shown to be effective in this scenario.

**Further Progress to Come**

As we learn more about the pathophysiology of RVO and its sequelae, we'll be better able to select targeted treatment plans. We'll also continue to benefit from the knowledge that most diseases of the retina share a final common pathway, leading to vision loss. Therefore, lessons learned from new therapies for age-related macular degeneration and diabetic macular edema will be applicable to vein occlusion. Anti-platelet-derived growth factor is an example of this potential cross-pollination of seemingly disparate diseases. Its potent anti-fibrotic effect is now being studied in AMD and may be applicable in RVO in the future.

In conclusion, we've made meaningful progress in RVO treatment in the past several years, and I believe additional treatment options are on the horizon. However, a better understanding of this and other chronic retinal diseases begins with an understanding of the life cycle of the disease.

**References**

Anti-vascular endothelial growth factor (VEGF) therapy has certainly raised our expectations regarding treatment of macular edema secondary to retinal vein occlusion (RVO). However, there remains a distinct role for macular grid laser (MGL) treatment, either alone or as part of combination therapy.

We recently completed a textbook on current concepts in RVO management, which includes a discussion of the utility of MGL for treating macular edema, the most common cause of vision loss after RVO. This article is a summary of the body of literature and expert experience on which the book is based.

Macular Grid Laser as Monotherapy

As prospective, randomized, controlled clinical trials, the Branch Vein Occlusion Study (BVOS) and Central Vein Occlusion Study (CVOS) were the first to provide us with Level I evidence on the use of laser photocoagulation in the treatment of RVO and its sequelae. From the BVOS, we learned that argon MGL is preferable to observation for patients with macular edema secondary to branch retinal vein occlusion (BRVO) and vision of 20/40 or worse.

Patients in the BVOS were divided into four groups. One group included 139 eyes with vision loss from macular edema secondary to BRVO. Key inclusion criteria were onset of BRVO from 3 to 18 months prior to the study, presence of macular edema involving the fovea, and best-corrected visual acuity of 20/40 or worse. Eyes with foveal hemorrhage or foveal capillary nonperfusion were excluded, as were those with any other ocular disease that could compromise visual acuity. Patients were randomized to either observation or treatment with argon MGL (n=71). The treatment group received MGL treatment in the area of capillary leakage — as identified by fluorescein angiography (FA) — within the vascular arcades but not closer to the fovea than the outer edge of the avascular zone. Additional MGL was performed at 4 months if foveal edema remained with attendant decreased visual acuity.

The majority of treated eyes required only a single session of laser. At 3 years, 65% of the eyes that underwent MGL gained at least 2 lines of vision compared with 37% in the untreated group. Mean visual acuity at the 3-year follow-up visit was 20/40 to 20/50 in the treated group and 20/70 in the untreated group. BVOS thus established that MGL applied to discrete areas of leakage can be useful as monotherapy in eyes with macular edema secondary to BRVO. We have further confirmation of this finding from the Standard Care versus Corticosteroid for Retinal Vein Occlusion (SCORE) study. SCORE compared MGL with intravitreal corticosteroid injections for BRVO-related macular edema. In this large, prospective comparative clinical trial, MGL was shown to result in similar visual acuity gains when compared with steroid monotherapy, but with fewer complications.
Case Report

Macular Grid Laser Following Incomplete Response to Anti-VEGF Injections

Anti-VEGF therapy does not lead to complete resolution of RVO-associated macular edema in every patient. Adding macular grid laser treatment to the therapy regimen may dry the retina and allow cessation of anti-VEGF injections, as this case demonstrates.

The patient is a 48-year-old female with a history of hypertension and waxing/waning blurry vision in the left eye for 10 months for which she had not sought treatment. Her initial dilated fundus exam revealed macular edema in the superior foveal region OS secondary to non-ischemic BRVO with exudates extending through the fovea (Figure 1). Fluorescein angiography was consistent with a diagnosis of chronic BRVO with macular edema (Figure 2). OCT imaging was performed (Figure 3). Visual acuity was 20/20 OD and 20/20-2 OS. Given the visual acuity at this visit, the decision was made to observe the patient.

The patient returned for follow-up 3 months later. Visual acuity OS had declined to 20/25 and macular edema was still present. The patient was treated at this visit with intravitreal bevacizumab (Avastin, Genentech). One month later, visual acuity OS was reduced to 20/30, persistent macular edema was noted, and the patient was given a second bevacizumab injection. After another month, the edema OS improved slightly but vision did not, and the patient was given a third anti-VEGF injection.

Approximately 6 weeks after the third injection, edema in the affected eye had stabilized, but vision declined further to 20/40 (Figure 4). At this visit, the patient received a macular grid laser treatment OS. By 3 months post laser, macular edema in the treated eye had significantly improved and visual acuity increased to 20/30 (Figure 5) Since that time, no further treatment has been needed. Macular edema OS completely resolved, and VA improved to 20/20-1 (Figure 6).

According to the results of the CVOS, macular grid photocoagulation is not recommended for treating macular edema due to central retinal vein occlusion (CRVO). Out of the 150 patients enrolled in the macular edema portion of this study, 77 were randomized to receive argon MGL while the remainder were observed. Patients were included if they had confirmed CRVO for at least 3 months, foveal-involving macular edema verified by FA, visual acuity between 20/50 and 5/200 and intraocular pressure less than 30 mmHg. Exclusion criteria included foveal nonperfusion documented on FA as well as a history of retinal laser photocoagulation, diabetic retinopathy, retinal neovascularization or lens abnormalities (significant opacity, aphakia/pseudophakia).

In the treatment group, eyes received argon MGL applied to areas of capillary leakage not extending into the foveal avascular zone. Collateral vessels and/or hemorrhages were avoided. Patients received additional laser treatment after their first treatment if they gained nine or fewer letters of vision and had persistent macular edema at a follow-up visit. At the end of 1 year, all of the eyes in the observation group had some degree of edema. In contrast, 31% of patients in the treatment group experienced complete resolution of angiographically evident edema 1 year after MGL. Despite the disparity in anatomic outcomes, however, no significant difference in post-treatment visual acuity was observed between the two groups.

In the treatment group, eyes received argon MGL applied to areas of capillary leakage not extending into the foveal avascular zone. Collateral vessels and/or hemorrhages were avoided. Patients received additional laser treatment after their first treatment if they gained nine or fewer letters of vision and had persistent macular edema at a follow-up visit. At the end of 1 year, all of the eyes in the observation group had some degree of edema. In contrast, 31% of patients in the treatment group experienced complete resolution of angiographically evident edema 1 year after MGL. Despite the disparity in anatomic outcomes, however, no significant difference in post-treatment visual acuity was observed between the two groups.
Macular Grid Laser in Combination Therapy

It is notable that while MGL did not improve patients’ vision in the CVOS, it did reduce macular leakage. Since that study was conducted, intravitreal pharmacologic therapies (i.e., steroid and anti-VEGF agents) have proven to be effective, albeit short-term, treatments for macular edema associated with RVO. In light of these new therapeutic options, it makes sense to re-evaluate the potential utility of MGL applied in combination with intravitreal agents for CRVO.

In BRVO, in which laser monotherapy has been proven beneficial, combination therapy may have the added advantage of limiting toxicity and/or lessening the treatment burden as smaller doses or less frequent treatments may achieve similar results. Combination therapy may also be used to increase efficacy in patients who are not adequately responsive to monotherapy. In either situation, the benefit of combination treatments is due to the synergistic effects achieved. Each agent has a different pharmacokinetic profile and acts at a different point in the pathway leading to macular edema.

Unfortunately, only a small number of studies exploring RVO combination therapies have been published to date. Most are short-term, retrospective and/or involve small numbers of patients. Nonetheless,
as retinal specialists are increasingly using MGL in combination with other treatments, it remains a treatment paradigm very much worth exploring.

**MGL + Anti-VEGF**

Laser in addition to intravitreal anti-VEGF therapy is an often-used combination in clinical practice. Given the previously documented high levels of VEGF in the aqueous and vitreous of eyes with RVO, it is not surprising that anti-VEGF monotherapy is effective in combating the associated macular edema. Although the exact mechanism whereby MGL reduces macular edema is unclear, one possible explanation relates to a reduction in VEGF levels secondary to a decrease in retinal hypoxia induced by laser. When laser is combined with anti-VEGF agents, which bind to and directly inhibit VEGF, a synergistic anti-VEGF effect is produced. Furthermore, anti-VEGF agents mitigate some of the limitations of MGL, including the inability to treat in the presence of dense macular hemorrhage and the need for increased laser power in the setting of severe macular edema with an associated greater risk of collateral tissue damage. In contrast, because anti-VEGF injections work quickly and can be given regardless of the severity of macular hemorrhage or edema, they may quiet the eye to allow us to utilize MGL earlier with greater efficacy and safety.

The studies1 of anti-VEGF/MGL combination therapy published to date have shown mixed results. In some, the combination clearly outperformed standalone anti-VEGF treatment in achieving better anatomic and visual outcomes. In others, impressive anatomical improvements were not matched by gains in vision. In published studies in which injection frequency was tracked, however, combination laser/anti-VEGF treatment resulted in a reduced need for anti-VEGF injections.

**MGL + Corticosteroid**

Combining MGL with corticosteroid may also increase the efficacy of our treatment for RVO-related macular edema compared to either treatment alone. The literature1 confirms that in addition to VEGF, inflammatory factors play a role in RVO-related edema. A combination of steroid therapy with MGL may result in synergistic effects as it targets both the inflammatory component (steroids) while also addressing VEGF-related drivers of macular edema at multiple different points along the pathway (reduced VEGF production due to lessened retinal hypoxia from laser; reduced activity of effectors downstream of the VEGF receptor from steroids).

Only two prospective studies1 of an intravitreal triamcinolone/MGL combination for BRVO-related macular edema have been published. In one, MGL applied after an average of 1.13 steroid injections led to impressive structural and functional improvements. In a separate comparative study, both a combination therapy group (consisting of patients receiving steroid therapy after failed MGL) and a steroid monotherapy group demonstrated significant anatomic and functional improvements at early timepoints. However, these improvements were maintained at later timepoints only in the steroid monotherapy group. The inclusion of only patients refractory to MGL in the combination group may be a significant confounder in this study. Of note, in both studies,1 the rate of IOP elevation was similar to the rate with intravitreal triamcinolone monotherapy.

Two abstracts1 presented in 2012 described non-comparative studies in which the dexamethasone implant (Ozurdex, Allergan) was utilized in conjunction with MGL. Significant decreases in retinal thickness were observed in both studies, but corresponding visual gains were noted in only one study. The authors of a prospective study1 comparing subthreshold micropulse grid laser (Iridex) alone to micropulse laser plus intravitreal triamcinolone for macular edema in BRVO reported better visual results in the combination group.

While these initial results are promising, future studies will be required to further evaluate safety and efficacy of these MGL combination therapies as well as to establish the ideal timing, frequency and optimal settings for adjunctive laser therapy.

**Role of MGL May Be Expanding**

Although retina specialists have been utilizing MGL as a treatment for RVO-related macular edema for decades, recent technological developments in laser delivery may lead to even greater efficacy and safety. For example, image-guided laser platforms, such as Navilas (OD-OS), have the potential to drastically improve treatment accuracy. Moreover, improvements in diagnostic imaging capabilities and laser lenses offer further hope for improved MGL application. Indeed, in light of these technological advances and the potential for synergistic effects when used in combination with intravitreal therapy, it appears now may be an ideal time to revisit the role of MGL in the treatment of macular edema secondary to RVO.

**Reference**

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Since the Phase III GENEVA clinical trials demonstrated the safety and effectiveness of the dexamethasone intravitreal implant (Ozurdex, Allergan) for treatment of macular edema following retinal vein occlusion (RVO), how best to utilize the implant in clinical practice has been further studied. In addition, doctors have gained several years of experience using it, and VEGF therapies have been FDA-approved for the same indication. In light of what has been learned, where the implant fits into retina specialists’ approach to treatment of this group of patients has evolved.

Studies, Experience Lead to Expanded Use of Ozurdex

“We’re more comfortable using Ozurdex overall,” says Ron Gallemore, MD, PhD, Founder and Director of the Retina Macula Institute and Research Center in Los Angeles and Assistant Professor at the Jules Stein Eye Institute, UCLA School of Medicine. “The subset of patients that we consider good candidates for the implant is larger as well. We don’t hesitate to switch to it quickly when macular edema is resistant to intravitreal anti-VEGF therapy and a patient’s vision isn’t bouncing back after a few injections. In cases where the patient has a partial response to anti-VEGF therapy, but a hint of edema remains, we can often achieve a line or two more vision when we add Ozurdex. As many as 30% of our RVO patients are at least partially resistant to anti-VEGF treatment. Also, in our experience, using anti-VEGF injections and Ozurdex together can extend the interval between treatments compared with either of the two drugs alone.”

Dr. Gallemore and colleagues conducted a retrospective chart review involving RVO patients who received an Ozurdex implant to treat macular edema that had persisted after multiple bevacizumab (Avastin, Genentech) injections. On average, the patients receiving Ozurdex had a decrease in central foveal thickness of 146.8 ± 33.65 μm and improvement in visual acuity.1 The retrospective study was subsequently repeated as a prospective trial. In that study, in which eyes with RVO recalcitrant to anti-VEGF therapy were randomized to receive Ozurdex either every 16 weeks or prn, the implant significantly reduced retinal thickness and improved visual acuity.2 “A higher incidence of posterior subcapsular cataract was seen with repeat administration of Ozurdex,” Dr. Gallemore explains, “but, interestingly, multifocal electroretinogram showed statistically significant improvement in macular function after treatment with consecutive dexamethasone implants.”

The macular function improvement was seen in all of the patients who received Ozurdex, whether they received implants every 16 weeks or prn during the 48-week study. In the original GENEVA clinical trials, the implant was administered every 6 months, but the effect waned during that interval.3 However, the extension portions of GENEVA showed that further reduction of edema and recovery of vision can occur with repeat administration.4 “In the GENEVA extension trials, visual recovery was better for patients who were treated at the outset with Ozurdex, suggesting that earlier use of the implant may achieve better visual
results,” Dr. Gallemore notes. “That said, it’s also important to know that patients who were initially randomized to the sham group also had a reduction in edema and recovery of vision when they were switched to treatment with Ozurdex, indicating that even if treatment with Ozurdex is delayed, it can still be beneficial. Today, most doctors using Ozurdex for patients with RVO-associated macular edema administer the implant every 2-3 months, especially in eyes that had not responded to, or had an inadequate response to, anti-VEGF agents.”

Dr. Gallemore may choose Ozurdex as primary therapy in specific situations, including RVO patients who refuse to have frequent intravitreal injections and patients with a recent history of heart attack or stroke. “Anti-VEGF treatment is relatively contraindicated in patients who have recently suffered MI or a stroke,” he says. He may also choose the implant as initial therapy for pregnant women for safety reasons and for maximizing visual results in patients who’ve had a vitrectomy because he expects the sustained-release dexamethasone to remain in the eye longer than other intravitreally injected steroids or anti-VEGF agents.

Julia Haller, MD, Ophthalmologist-in-Chief of the Wills Eye Institute and Professor and Chair of the Department of Ophthalmology at Jefferson Medical College of Thomas Jefferson University in Philadelphia, agrees. “We know that anti-VEGF drugs have a short half-life in vitrectomized eyes, so for those patients, I’m more likely to use the dexamethasone implant, which is our only current FDA-approved therapeutic option that provides extended drug delivery,” she says. “Given their effectiveness, most of us start with anti-VEGF injections for treating RVO-associated macular edema, but it’s important to keep in mind that steroids have anti-VEGF properties as well. Therefore, there is room for both treatments, either both upfront or sequentially. In some cases, before I combine treatments, I may try a different anti-VEGF agent if the initial choice is not effective. In other cases, such as in eyes that are already pseudophakic, I tend to get Ozurdex on board much sooner than I may have in the past. The same applies to eyes with a severe occlusion and very poor visual acuity, which I know from experience will likely have hard-to-control, recurring macular edema.” (See “Case Report: Dexamethasone Implant Plus Anti-VEGF Agent as Initial Treatment,” on the adjacent page.)

Intravitreal triamcinolone is a reasonable option when the decision is made to use a steroid, Dr. Haller points out, but she prefers the dexamethasone implant. “Triamcinolone can be effective for a few weeks or a month or two, but the dexamethasone implant is more potent, yet with a more favorable safety profile in terms of cataract progression, IOP elevation and potential toxicity.”

Based on her own experience and the cumulative experience of other retina specialists, Dr. Haller says she’s more aggressive than in the past using Ozurdex for patients who are already using a topical IOP-lowering medication. “Once I started using Ozurdex in this group of patients, I realized how well it works and that the complications are very manageable. That put the implant on my radar screen more often as a solid option sooner rather than later. It’s very important to balance any potential implant-related complications with the need to eliminate the macular edema to preserve vision,” she says. She cites the recently published Shasta study as an indication that Ozurdex is being used safely and effectively in patients with controlled glaucoma.

**A Real-world Evaluation of Ozurdex Use**

Shasta is a 26-site, retrospective chart review study of patients with branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO) who received two or more dexamethasone implants. Patients who had previously received an Ozurdex implant as part of a clinical study were excluded. The 289 study subjects received a mean 3.2 implants (range of 2 to 9) during the study time period, either as monotherapy (for 29.1% of the patients) or in conjunction with other treatments. At baseline (i.e., at the time of their first implant), 31.5% of the patients had glaucoma or ocular hypertension, and 15.6% had a history of IOP elevation in response to steroid treatment documented in their charts.

According to Shasta data analysis, the percentage of patients who experienced a 2- to 3-line improvement in best-corrected visual acuity compared with baseline was similar after each implant. Overall, 62.9% of patients demonstrated at least a 2-line improvement in BCVA, and 48.1% of patients demonstrated at least a 3-line improvement at some point after treatment with Ozurdex.

With the reminder that Shasta is a retrospective study, lead author Antonio Capone, Jr., MD, considers its safety...
In eyes with severe retinal vein occlusion and very poor visual acuity on presentation, macular edema is often recurrent despite treatment. In some of these cases, a reasonable course of action may be combining therapies at the outset, as in this case.

The patient is a 45-year-old otherwise healthy male who presented with sudden loss of vision in his left eye. Visual acuity OS was counting fingers inferiorly at 6 feet. Clinical exam and color fundus photography (Figure 1) revealed a hemiretinal vein occlusion, which fluorescein angiography confirmed (Figure 2). Central retinal thickness was 624 µm as measured by Spectralis SD-OCT (Heidelberg Engineering) (Figure 3).

Given the severity of the occlusion and macular edema and the patient’s lack of other health issues, the decision was made to immediately administer an anti-VEGF injection and a dexamethasone intravitreal implant. The patient indicated he understood the risks and benefits. For example, he was willing to accept the risk of steroid-induced cataract in favor of receiving the two treatments in an effort to restore as much of his vision as possible.

The patient returned for monthly follow-up visits, receiving four additional anti-VEGF injections. By the first follow-up visit, central retinal thickness had decreased to 153 µm. Five months after the initial visit, extreme ischemia, which is known to up-regulate VEGF, was still present, so the patient received peripheral laser treatment, which was his last treatment of any type to date. As of 1 month post laser (6 months after presentation), the macular edema remained completely resolved and visual acuity had improved to 20/50.

— Julia Haller, MD

Figure 1. Color fundus image at presentation.

Figure 2. Fluorescein angiography (4:37:16) at presentation.

Figure 3. At the patient’s initial visit, central retinal thickness was 624 µm as measured by Spectralis SD-OCT.

Figure 4. Six months after initiation of therapy with a dexamethasone implant and an anti-VEGF injection, 1 month after a peripheral laser treatment, macular edema remained completely resolved.
findings the most notable from the perspective of clinicians. “Very few patients had meaningful pressure rises,” he explains. “32.6% had an increase in IOP from baseline of at least 10 mmHg, and a similar proportion required pressure-lowering medications, but the vast majority were effectively managed with drops. A very small percentage, 1.7%, required incisional surgery. Also, the steroid response was very predictable, it peaked at 6 weeks and no stair-step increase in pressure was seen with subsequent implants. All of this runs counter to what I think many doctors would anticipate with a steroid treatment.”

Dr. Capone, who practices with Associated Retinal Consultants in Michigan and is a Clinical Professor of Biomedical Sciences at Oakland University’s William Beaumont School of Medicine, comments further on Shasta, pointing out that it involves somewhat of a selection bias. “These were patients who had been treated in clinical practices, so most had received anti-VEGF, laser and/or other steroid therapy before receiving Ozurdex implants. Only 39 Shasta patients were treatment-naïve when they began receiving Ozurdex. As such, this cohort is much more laden with treatment-refractory patients than most prospective clinical trials, which typically enroll treatment-naïve patients. Therefore, more of them have blunted vision outcomes.”

Along the same lines, Dr. Capone continues, “Other studies have shown us that patients with protracted treatment-naïve macular edema don’t do as well as those whose edema is resolved sooner, and in patients who have a significant response to anti-VEGF monotherapy, the response is most dramatic with the first injection. There may be additional positive impact with subsequent injections, but we’re learning that if macular edema isn’t at least 50% resolved after one injection, it is appropriate to consider adjunctive or alternative therapy with Ozurdex promptly. Again, the longer the edema persists, the less vision we’re able to preserve.”

**Individualized Treatment is the Best Course of Action**

An advantage of the Shasta study relative to prospective studies is that it reflects results obtained with Ozurdex in the real world, Dr. Capone says. More guidance on how best to treat RVO-associated macular edema will likely come from several studies currently under way (such as NCT01427751) that directly compare the safety and effectiveness of anti-VEGF agents with the dexamethasone implant.

In the meantime, according to Dr. Haller, “Taking care of patients with this condition to the best of our ability means determining which approach is best for each individual in terms of safety, efficacy, potential complications and burden of care.”

**References**

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