# Combination Therapy for RVO

The complexity of this multifactorial disease state suggests a need for a tailored treatment approach.

BY SEENU M. HARIPRASAD, MD; VEERAL SHETH, MD; AND PAULPOJ CHIRANAND, MD

For the first time since the 1990s, the treatment options for retinal vein occlusion (RVO) are expanding. It has been more than 1 decade since the data and recommendations from the Central Vein Occlusion Study (CVOS)[1-5] were released and more than two decades since the Branch Vein Occlusion Study (BVOS),[6,7] the two landmark studies that set the standard of care for central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO).

RVO affects nearly 160,000 eyes each year, according to collected data from the Beaver Dam Eye Study.[8] Most of these (80%) are BRVOs, and although some younger patients present with RVO, particularly CRVO, it is most common among patients over age 65.

At the 2009 Retina Congress in New York, more data were released on these diseases than had been for some time, setting the stage for a paradigm shift in the way retina specialists will address this disease.

***BRVO.*** Patients with BRVO commonly complain of a sudden, painless decrease in vision or a visual field defect in one eye.[9] In acute BRVO, intraretinal hemorrhages, retinal or macular edema, and cotton wool spots are seen in the portion of the fundus affected by the involved retinal vein.[10] In chronic BRVO, hemorrhages may be absent and macular edema may be the only symptom present.

Retinal neovascularization may be seen in eyes with large areas of nonperfusion. This may lead to vitreous hemorrhage and tractional retinal detachments, which may create retinal breaks leading to combined rhegmatogenous and tractional retinal detachments. Neovascular glaucoma and neovascularization at the disc area are rare.[10] In patients with reduced vision, fluorescein angiography can help identify vision loss secondary to macular edema or macular ischemia.[9]

***CRVO.*** Patients with CRVO present in much the same way with sudden, painless loss of vision in one eye. Signs of CRVO include disc edema, with increased dilation and tortuosity of all retinal veins. Widespread deep and superficial hemorrhages, cotton wool spots, retinal edema, and capillary nonperfusion are also usually present.[1]

> Possible causes of RVO include external vascular compression, disease of the vein wall, inflammation, and intravascular thrombus formation.

CRVO can be ischemic or nonischemic. Ischemic CRVO is a seriously blinding disease, and anterior segment neovascularization leading to neovascular glaucoma is its major complication.[11]

Nonischemic CRVO is a comparatively benign disease, with permanent central scotoma as the major complications from cystoid macular edema. This type of CRVO less frequently results in the complication of ocular neovascularization. It is estimated that 12.6% to 33% of nonischemic cases may progress to ischemic CRVO within 4 years.[11,12]

## MACULAR EDEMA IN RVO

The exact pathogenesis of RVO is not known, but possible causes include external vascular compression, disease of the vein wall, inflammation, and intravascular thrombus formation.[13-15]

Once an obstruction has occurred, increased vascular pressure behind the occlusion can cause fluid and small molecules to leak across the vascular wall and into the surrounding retinal tissue, causing macular edema. Macular edema is a common complication of RVO.[16]

Low-grade, chronic inflammation may also play a role in exacerbating the disease process.[15,16]

This includes the production of inflammatory mediators (such as prostaglandins and IL-6), increased amounts

| TRIAMCINOLONE VS DEXAMETHASONE COMPARISON FOR CATARACT DEVELOPMENT AND IOP RISE REQUIRING THERAPY | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Retisert | SCORE – CRVO | | SCORE – BRVO | | DEX Clinical Trials | |
| **Dose** | | **1 mg** | **4 mg** | **1mg** | **4mg** | **700 µg** | **350 µg** |
| Cataract | 100% | 26% | 33% | 25% | 35% | 7% | 4% |
| IOP rise requiring medical therapy or surgery | 93% | 20% | 35% | 8% | 41% | 30%* | |
| *At 180 days post-treatment, increase in IOP was not significantly different from sham injection group. Change in IOP similar after second injection. | | | | | | | |

**Table 1. Complications data from the SCORE and intravitreal dexamethasone implant trials with a comparison to the intravitreal fluocinolone for uvetis (Retisert).**

of vascular permeability factors such as vascular endothelial growth factor (VEGF),[17] and may also include the loss of endothelial tight junction proteins.[18]

The results of the BVOS showed a benefit of laser for vision loss due to macular edema.[6] Conversely, the CVOS did not show a significant benefit—any reduction in macular edema from laser did not seem to affect visual acuity.[2,3] Interestingly, there was a trend in the CVOS that younger patients with CRVO responded better to laser.[2] The BVOS and CVOS both produced the gold standard recommendations for treatment (BVOS) or observation (CVOS), to which there has been little to no challenge—until now.

## NEW AND EMERGING DATA IN RVO

New data were released at the 2009 Retina Congress on both CRVO and BRVO regarding visual acuity results with steroids vs laser (SCORE [Standard Care vs Corticosteroid for Retinal Vein Occlusion]), sustained-delivery dexamethasone vs sham (Ozurdex, Allergan, Inc.), and anti-VEGF agents vs sham for BRVO and CRVO (BRAVO [A Study of the Efficacy and Safety of Ranibizumab Injection in Patients With Macular Edema Secondary to Branch Retinal Vein Occlusion] and CRUISE [Study of the Efficacy and Safety of Ranibizumab Injection in Patients with Macular Edema Secondary to CRVO].

***Intravitreal triamcinolone acetonide.*** The SCORE studies were sponsored by the National Eye Institute (NEI) and were designed to evaluate a preservative-free preparation of triamcinolone acetonide (Trivaris, Allergan, Inc.) in 1 mg and 4 mg concentrations in comparison with the standards of care for BRVO (laser in the absence of dense macular hemorrhage)[19] and CRVO (observation).[20] Both studies enrolled groups of patients similar to those in the BVOS and CVOS studies.

The use of intravitreal triamcinolone acetonide was not shown to provide significant visual acuity benefit over laser in the SCORE-BRVO study. In the first year, steroids appeared to have a better effect on visual acuity, but at year 2, the results evened out and there was no significant benefit. The side-effect profile in the 1 mg group was similar to that of laser, but side effects were significantly higher in the 4 mg group. Thus, the recommendation from the SCORE-BRVO trial was that laser should remain the standard of care in BRVO.

Patients in the SCORE-CRVO trial who were randomized to 1 mg and 4 mg of intravitreal triamcinolone achieved better visual acuity outcomes than those in the laser group. Twenty-seven percent of those in the 1 mg group and 26% of those in the 4 mg group gained three lines in 1 year, compared with 7% in the observation group. Those in the steroid groups lost far less vision than those in the observation groups. The side effects were lower in the 1 mg group, leading to a recommendation that 1 mg nonpreserved triamcinolone acetonide should be considered for patients with CRVO.

***Intravitreal dexamethasone implant.*** The 6-month[21] and 12-month[22] results for the only US Food and Drug Administration (FDA)-approved drug therapy for BRVO and CRVO, the dexamethasone 0.7-mg intravitreal implant (Ozurdex, Allergan, Inc.), were presented at the 2009 Retina Congress and the 2010 Macula Society meeting, respectively.

Two identical, prospective, multicenter phase 3 clinical trials were conducted to evaluate the safety and efficacy of the dexamethasone implant. Each trial consisted of a

# Combination Therapy for BRVO and CRVO

BY SEENU M. HARIPRASAD, MD

## CASE NO.1

A 92-year-old woman presented with a 2-month history of branch retinal vein occlusion (BRVO) in her right eye and secondary vision loss. The patient had not been treated previously, and her vision in the right eye at presentation was counting fingers at 2 feet. On fundus photography and fluorescein angiography (FA), intraretinal hemorrhages were seen along with cotton wool spots along the inferotemporal arcade and the inferior macula (Figures 1, 2, and 3). These findings are consistent with BRVO.

## TREATMENT

Optical coherence tomography (OCT) at presentation demonstrated massive thickening with subfoveal serous retinal detachment (Figure 4). These findings precluded effective laser treatment at this time, so we chose to inject the patient with the intravitreal dexamethasone 0.7 mg implant (Ozurdex, Allergan, Inc.).

The patient returned for a follow-up visit 3 weeks later. On OCT, the macular edema was seen to have improved markedly, and the serous retinal detachment had resolved (Figure 5). Her visual acuity remained the same as before injection with the dexamethasone implant (counting fingers at 2 feet), and her intraocular pressure (IOP) had remained stable (preinjection IOP: 14 mm Hg; postinjection IOP: 12 mm Hg).

At this visit, we applied focal grid laser in her right eye. The decreased edema allowed a more accurate treatment

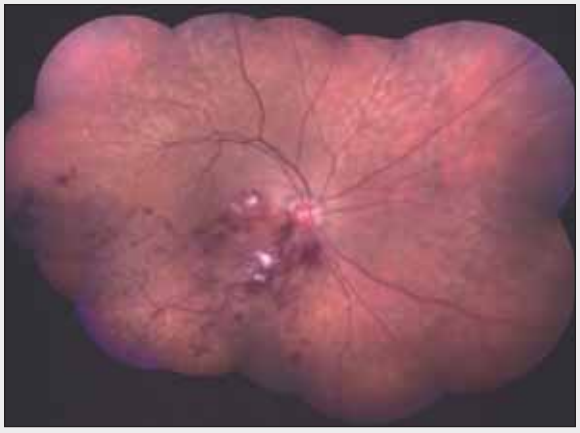

**Figure 1. Fundus photograph of the right eye shows intraretinal hemorrhages and cotton wool spots along the inferotemporal arcade and inferior macular consistent with BRVO.**

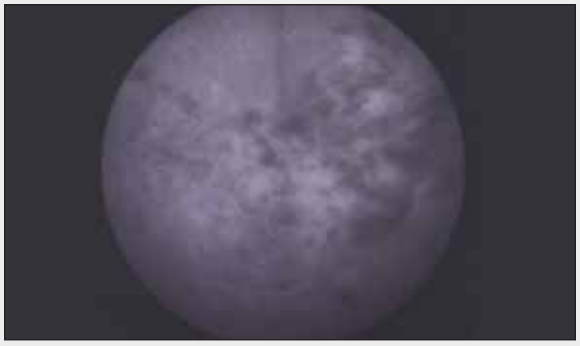

**Figure 3. FA of the right eye showing a perfused macula.**

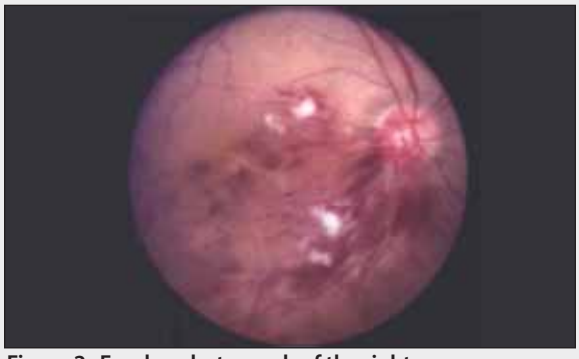

**Figure 2. Fundus photograph of the right eye.**

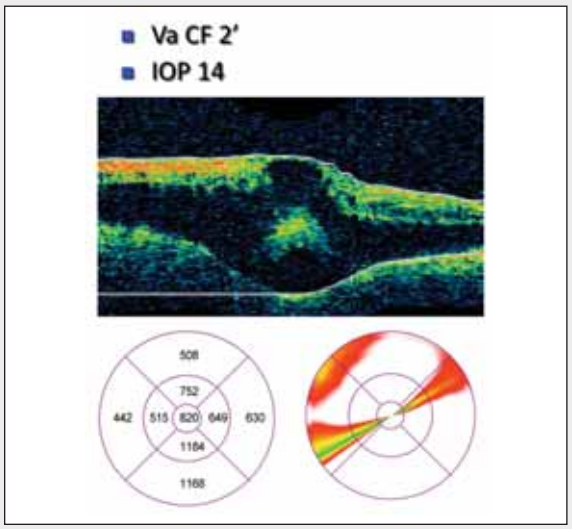


**Figure 4. Right-eye OCT before implant shows massive thickening with subfoveal serous retinal detachment.**

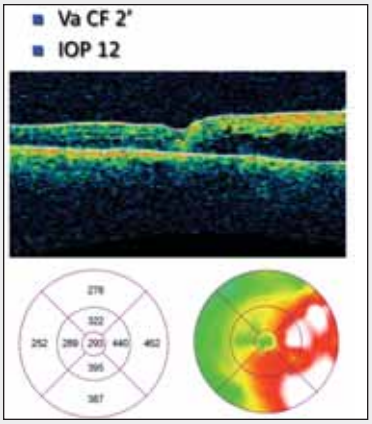


Figure 5. Right-eye OCT after injection shows marked improvement in macular edema with resolution of subfoveal serous retinal detachment.

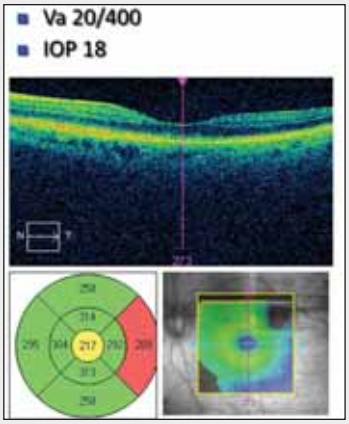


Figure 6. Foveal architecture is restored in the right eye.

with less power to a smaller geographical area. Two months following laser treatment, the foveal architecture was restored (Figure 6), and vision improved to 20/400. IOP at this follow-up visit was 18 mm Hg. At most recent follow-up, her vision had improved to 20/100.

## CASE NO.2

A 47-year-old man from Abu Dhabi presented with central retinal vein occlusion (CRVO) and macular edema in both eyes. The patient has severe hypertension from kidney disease. His history revealed vision loss for at least 7 months, and he had not received any prior treatment. At presentation, the patient's vision in the right eye was 20/400 with an IOP of 8 mm Hg and 20/70 in the left eye with an IOP of 8 mm Hg. The macular edema in both eyes is seen on OCT in Figure 7. Fundus photography and FA showed intraretinal hemorrhages consistent with CRVO and macular edema (Figure 8).

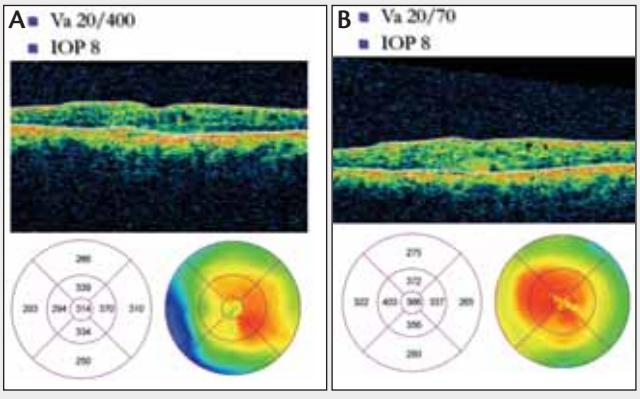


Figure 7. OCT before implant shows marked macular edema in the right eye (A) and moderate edema in the left eye (B).

## TREATMENT

We injected the intravitreal dexamethasone implant in the patient's right eye 2 weeks after presentation and in his left eye 3 days later. Two weeks following the right eye injection, visual acuity in his right eye improved to 20/50 and the macular edema decreased on OCT (Figure 9A). His IOP at 2 weeks was 10 mm Hg. At this visit we applied gentle focal grid laser for the subtle macular edema immediately outside the fovea in the right eye. The visual acuity in the left eye had improved to 20/50 with an IOP of

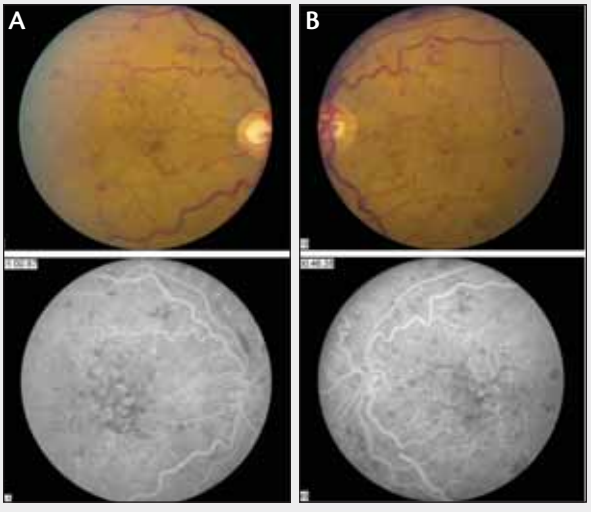


Figure 8. Fundus photography and FA of both eyes. Note intraretinal hemorrhages and macular edema seen on FA.

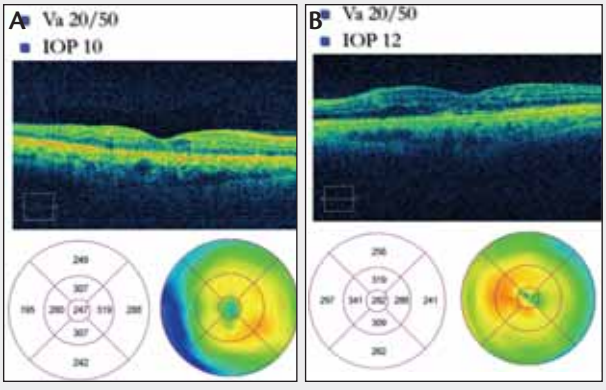


Figure 9. Both OCTs show improvement in macular edema approximately 2 weeks following injection with the intravitreal dexamethasone implant.

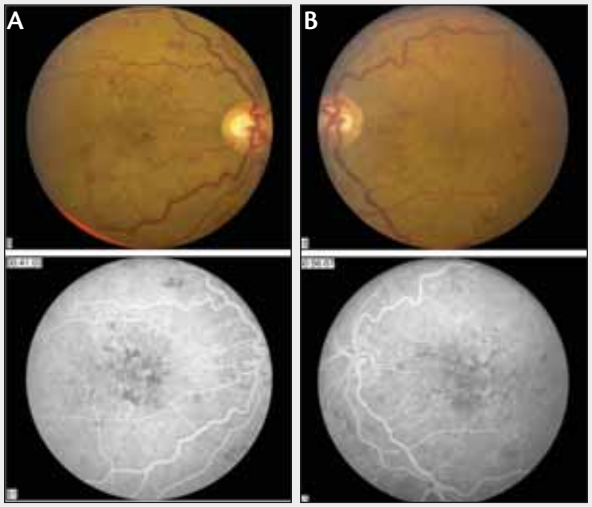


**Figure 10. Fundus and FA of both eyes. Note the decreased tortuosity and decreased intraretinal hemorrhages after implantation with the dexamethasone implant.**

12 mm Hg and a decrease in macular edema (Figure 9B). On fundus photography and FA, we saw decreased vascular tortuosity and decreased intraretinal hemorrhaging in both eyes (Figure 10). We applied laser to the left eye 3 days later for mild residual macular edema.

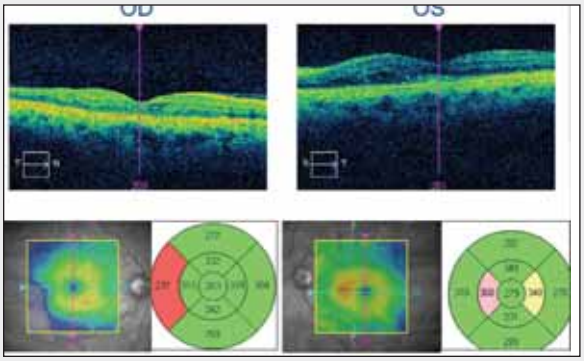

**Figure 11. OCTs of both eyes approximately 2 weeks after combination therapy with dexamethasone and laser. Macular edema has significantly improved.**

Approximately 2 weeks after combination therapy with the intravitreal dexamethasone implant and laser in both eyes, the patient returned for follow-up. The patient's OCT scans showed significant improvement in macular edema (Figure 11).

At the most recent follow-up, approximately 3 months later, the patient's vision had stabilized to 20/50 in both eyes with complete resolution of macular edema.

6-month, randomized, sham-controlled, parallel-group, double-masked phase followed by a 6-month open-label extension. In the masked phase of the trial, patients were randomized 1:1 to either sham or the intravitreal dexamethasone implant. In the open-label phase (the second 6 months) all patients who were eligible received the dexamethasone implant.

Both the 6- and 12-month data showed that more patients (30%) injected with the dexamethasone implant (n=427) gained three lines of vision in 1 to 2 months than sham-treated patients (7% to 12%; n=426).[9] Improvement with the implant peaked at day 60; 29.3% of patients who received the dexamethasone implant gained three or more lines of vision vs 11.3% of sham-treated patients, a difference that was statistically significant ($P$<.001). In this trial, patients with CRVO and BRVO were pooled into one group.

Side effects were relatively low with dexamethasone; intraocular pressure (IOP) rise was only 25% higher in the treatment groups with normalization with appropriate topical treatment in essentially all patients, and rates of surgical intervention were very low at 6 months. These data were similar in the 12-month reinjection study. In regard to cataract, the 6-month data showed that one patient required cataract removal at 1 year; at 12 months, four patients required cataract extraction. The side effect profiles of the SCORE and dexamethasone implant studies are seen (compared with the intravitreal fluocinolone implant for uveitis [Retisert, Bausch + Lomb] in Table 1 on page 2.

***Intravitreal ranibizumab.*** The BRAVO[23] and CRUISE[24] studies evaluated the use of intravitreal ranibizumab (Lucentis, Genentech, Inc.) in two doses (0.3 mg and 0.5 mg) for BRVO and CRVO compared with observation and rescue laser (BRAVO) or observation (CRUISE). All the treatment groups in BRAVO were eligible for rescue laser at 3 months and the observation group was eligible for injections of 0.5 mg ranibizumab if vision was worse than 20/40 and central foveal thickness was greater than or equal to 250 µm. Rescue laser was not available in CRUISE.

Patients enrolled in BRAVO had visual acuity at baseline of between 20/63 and 20/80 and the average retinal thickness showed significant edema at 500 µm. The response to ranibizumab was rapid (7 days). At 6 months, there was a significant difference in three-line gainers in the ranibizumab-treated group compared with the sham group; 55.2% of those in the 0.3-mg group gained three lines and 61.1% of those in the 0.5-mg group gained three lines, compared with

# Anti-VEGF for Recurring Macular Edema

BY DANTE PIERAMICI, MD

A 63-year-old woman presented with an acute loss of vision over several recent weeks in her left eye from a central retinal vein occlusion (CRVO). The baseline visual acuity was 20/200, and central retinal thickness (CRT) on optical coherence tomography (OCT) was 685 µm. Clinical examination showed no signs of neovascularization of the iris, and fundus examination showed a dense intraretinal hemorrhage in all four quadrants, swelling of the optic nerve, and macular edema. Fluorescein angiography confirmed swelling of the optic nerve, with cystoid macular edema in the late phases of the angiogram. OCT testing confirmed marked cystic edema of the retina, as well as areas of subretinal fluid (Figure 1).

The patient appeared to have what is typically called a perfused CRVO. Although there was no evidence of neovascularization of the iris or neovascularization of the angle, the patient had significantly decreased visual acuity secondary to severe macular edema.

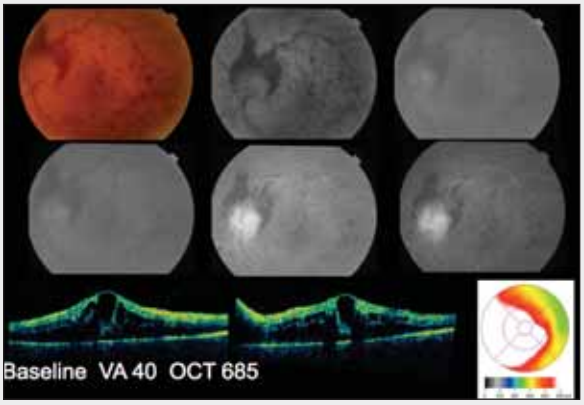


**Figure 1. Fluorescein angiography confirms swelling of the optic nerve, with cystoid macular edema in the late phases of the angiogram. OCT testing confirms marked cystic edema of the retina and areas of subretinal fluid.**

## TREATMENT

The OCT at the top of Figure 2 shows a large amount of intraretinal and subretinal fluid with swelling at the optic nerve edge. We injected intravitreal ranibizumab (Lucentis, Genentech, Inc.) and within 1 week (Figure 2, second row) a marked decrease in the intraretinal edema is evident; however, there is still persistent subretinal fluid. At 1 month following treatment (Figure 2, third row), subretinal fluid is still present, but the edema and retina continue to thin, and there is associated improvement in visual acuity. It is interesting to note that the subretinal fluid is slightly more resilient to the anti-VEGF agent. Additionally, macular edema can resolve significantly despite the patient not subjectively noticing the improvement for some time.

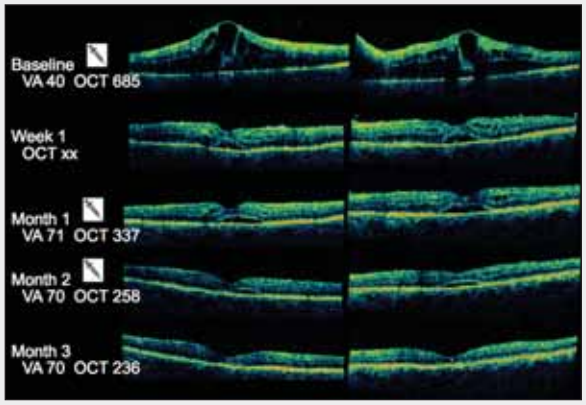


**Figure 2. OCT scans from month 1 to 5.**

For this patient, we injected again at 1 month. We saw additional reduction in edema at 2 months (Figure 2, fourth row) and injected again. By 3 months, the OCT appeared fairly normal, and the visual acuity improved from 20/200 at baseline to 20/40 (Figure 2, fifth row).

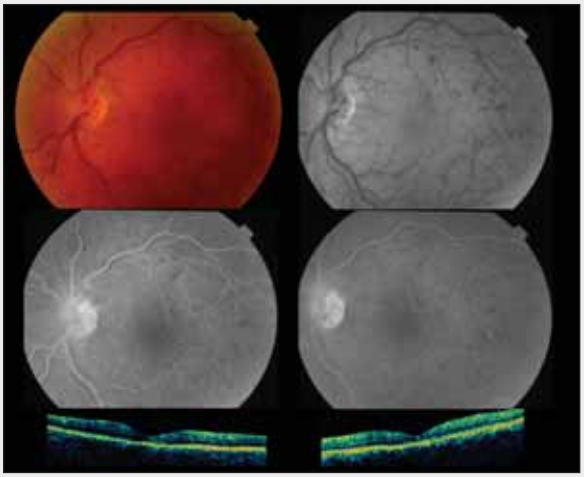

**Figure 3. At month 3, not only did we see improvement on OCT, but we also saw marked improvement in the fundus photographs and fluorescein angiogram.**

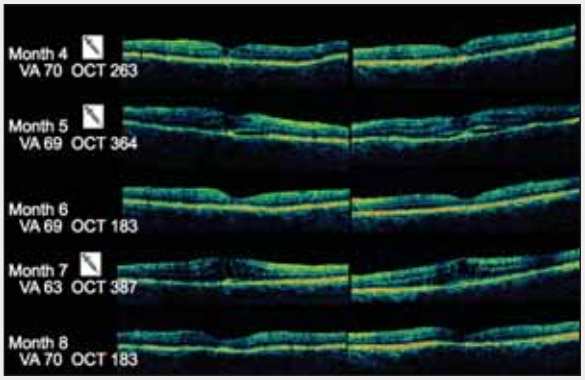


**Figure 4. OCTs scans from month 4 to 8.**

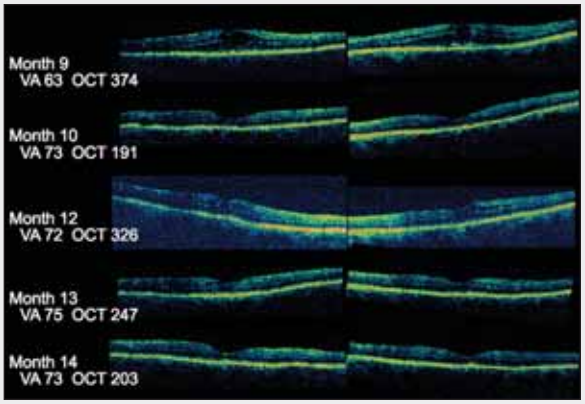


**Figure 6. OCT scans from month 9 to 14.**

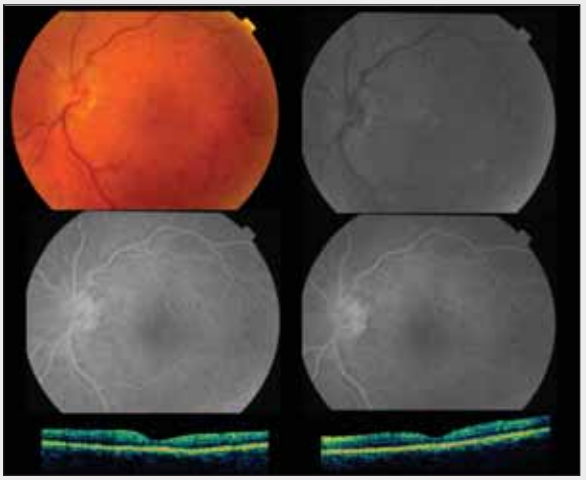

**Figure 5. The fundus and fluorescein images from month 6 show the marked improvements and collateralization at the optic nerve head that correlate with the OCT findings.**

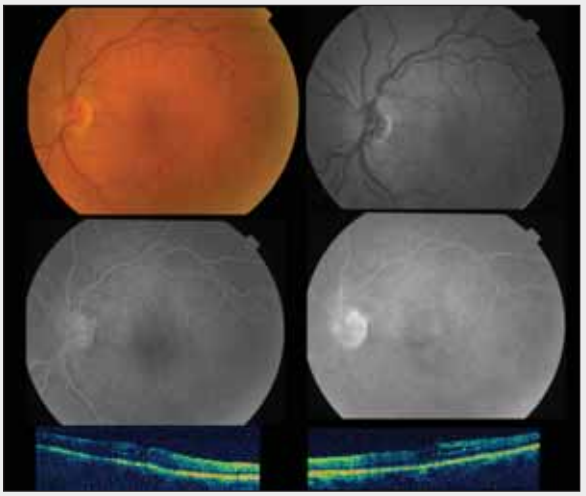

**Figure 7. The fundus and fluorescein images from month 12 show that the patient is continuing to do well, as noted on OCT.**

At month 3, not only did we see improvement on OCT, but we also saw marked improvement in the fundus photographs and fluorescein angiogram (Figure 3). There is clearly rapid reduction in the intraretinal hemorrhaging and optic nerve swelling. The fluorescein angiogram confirms decreased swelling of the optic nerve and the macula.

Anti-VEGF agents seem to have an effect on antipermeability of fluid, but they also seem to reduce leakage of intraretinal hemorrhage and leakage of the optic nerve. Early collateralization that is apparent on the optic nerve head is seen in this patient.

Because the patient was doing well at 3 months, observation could be an option at this point. After discussion with the patient, however, we chose to inject again at month 4 (Figure 4, top row). Interestingly, at 5 months there was an increase in subretinal fluid (Figure 4, second row). After injecting again at 5 months, the edema was fairly resolved by month 6 (Figure 4, third row), after which we chose to observe. At month 7 the edema recurred along with slight reduction in visual acuity (Figure 4, fourth row). For this patient we decided to treat again, and by month 8 (Figure 4, fifth row), the edema and visual acuity began to improve. The fundus and fluorescein images from month 6 show marked improvements and collateralization at the optic nerve head that correlate with the OCT findings (Figure 5).

Although we saw some recurrence of the edema at month 9 (Figure 6, top row), we decided to continue the period of observation. By month 12, the patient continued to do well (Figure 6, third row) and over the next year, although there was some fluctuation in OCT findings, the visual acuity and fundus findings continued to improve out to 2 years (Figures 7-9). After more than 1 year without

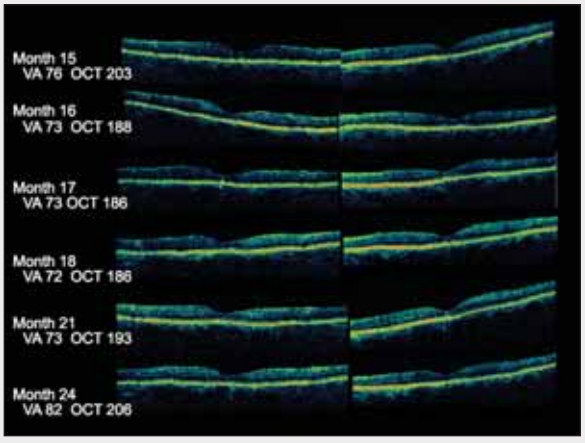


**Figure 8. Although the OCTs from month 15 to 24 show some variability, the readings continue to be good.**

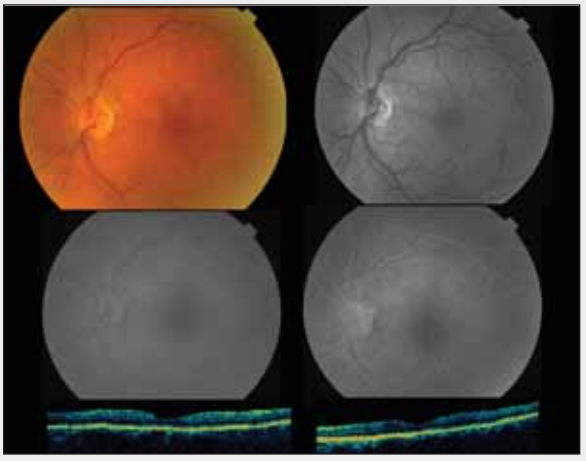

**Figure 9. The eye is clear and the visual acuity is good at 24 months.**

another injection, the patient's visual acuity is nearly 20/20, and the OCT is normalized.

## DISCUSSION

Although many of our patients do not have the recurring edema that was seen with this patient, approximately one-third of CRVO cases will require extended treatment.

What should the clinician do for cases that require 3 to 4 years of treatment? If a patient is responding to treatment and tolerates the injections well, I consider this a reasonable approach.

The other option for patients who require a long course of treatment may be a combination approach. It may help patients to add a steroid injection or a sustained-delivery device such as the intravitreal dexamethasone implant (Ozurdex, Allergan, Inc.) to extend the treatment period.

Another option in combination therapy is to use laser along with anti-VEGF injections. It is believed that recurrence of edema is caused by increased or persistent VEGF expression, so patients with recalcitrant edema might benefit from the addition of panretinal laser photocoagulation to the areas of ischemia. Although there are no data to show that this approach is successful for these patients, from our knowledge of the effect of laser, this seems a reasonable approach. The use of laser may reduce peripheral or night vision, so it is important to discuss these side effects with the patient.

It is important to note that we must be aware of the possibility of iris or retinal neovascularization, particularly during periods when we withhold intraocular VEGF therapy.

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28.8% in the sham group. The foveal thickness measurements were reduced significantly for the ranibizumab-treatment groups at all time points during the 6-month study.

Patients randomized to treatment with either 0.3 mg or 0.5 mg ranibizumab had rapid resolution of macular edema at day 7 (400 µm reduction from baseline mean of 680 µm).

In CRUISE, 46.2% of patients who received 0.3 mg of ranibizumab and 47.7% of patients who received 0.5 mg of ranibizumab gained three lines or more compared with 16.9% of patients in the sham group. The mean foveal thickness (mean baseline measurement of 680 µm) was reduced by almost 400 µm by day 7 in the treatment groups. At the 6-month point, foveal thickness was reduced by at least 430 µm in both treatment groups, while it was reduced by only 168 µm in the sham group.

The side effect profile of ranibizumab in both trials was excellent and consistent with those of the ranibizumab trials for age-related macular degeneration (AMD).

Our treatments for macular edema secondary to RVO have expanded and improved, and the benefit to our patients is significant.

## RATIONALE FOR COMBINATION THERAPY FOR RVO

Macular edema secondary to RVO is often more difficult to treat than exudative AMD. With AMD we are treating the primary action of the disease—neovascularization. When we are treating macular edema secondary to RVO, we are still unable to address the primary mechanism of the disease—the vein occlusion. Although we have many more treatment options available to us in 2010, they only suppress the macular edema, thereby buying time so that the body can recanalize the vessel that is occluded. In RVO, it is clear that the body wants to heal itself, but this process can sometimes take from 9 months to a year—or it may never happen. Thus, the goal in treating RVO is to maximize the treatment with the fewest side effects and discomfort to the patient. Using a combination approach may offer the best treatment while reducing the side effects of any one therapy.

The factors that come into play with macular edema secondary to RVO are multiple. We know that in macular edema a significant amount of VEGF is produced. Thus, VEGF suppression seems a likely path to success; however, there are data showing that the VEGF produced in macular edema secondary to RVO is far more extensive. Based on this knowledge, it is reasonable to assume that more frequent injections could be required.

The results from the BRAVO and CRUISE studies are the most positive that we have seen with any pharmaceutical intervention, and the side effects were minimal. What are the downsides to monthly (or potentially even more frequent) injections of anti-VEGF? The negatives include inconvenience to the patient, more frequent office visits, increased burden on office flow, and high cost. As we know, monthly injections of ranibizumab add up to $24,000 per year. These costs could also potentially rise based on the need for more frequent injections to control the production of VEGF.

We also know from the SCORE-CRVO and the sustained-delivery dexamethasone trials that steroids are effective in mediating the inflammation that causes macular edema secondary to RVO. The downsides to triamcinolone acetonide use are the side effects of cataract and increased IOP. The only steroids that we currently have available for intraocular use are triamcinolone acetonide and dexamethasone. The side effect profile of triamcinolone acetonide has been shown in some case reports to be unfavorable for phakic patients and those patients who are at risk for high IOP. In the SCORE-BRVO study, the 12-month data showed that three patients in the standard-of-care group had cataracts vs none in the 1-mg triamcinolone acetonide group vs four in the 4-mg triamcinolone acetonide group. Between 12 and 24 months, cataracts increased significantly in the 4-mg group. Thirty-five patients in the 4-mg group required cataract surgery vs eight in the 1-mg group and six in the standard-of-care group.[19]

The 6-month data for the dexamethasone intravitreal implant, however, showed a more favorable profile, with only 4% of patients having cataract progression over the course of 6 months and only one patient in the study requiring cataract removal. At 1 year, only four patients required cataract removal.

Finally, the dexamethasone intravitreal implant study, BRAVO, and CRUISE all evaluated monotherapy. If we accept that laser treatment is effective in BRVO, it is likely that when combined with laser, fewer injections of the chosen pharmacotherapy can be given, minimizing the inconvenience to the patient and the side effects of a single treatment, while increasing the duration between patient visits. Furthermore, it is possible that a combination approach may prove to be more effective than monotherapy due to a multi-pronged approach to treating the disease.

## COMBINATION STRATEGIES USING FDA-APPROVED TREATMENTS

Our options for combination therapy for treating macular edema secondary to RVO using FDA-approved treatments will likely include the following: 1) immediate injection of one or several ranibizumab injections followed by laser when there is clearance of any hemorrhaging; 2) injection of the dexamethasone implant followed by laser; and 3) combination of an injection of anti-VEGF and dexamethasone implant with or without laser.

Pretreatment with an injection prior to laser is important for several reasons. First, the geographic area requiring treatment in the macula often is "smaller" after an injection compared with when one does not pretreat with an injection. Second, in a fresh RVO with macular edema, the retina is thick and boggy, requiring more laser power and decreasing the accuracy of the treatment. With pretreatment, either with anti-VEGF or steroid, we can thin the macula (eg, from 600 µm to 400 µm), and when the laser is applied the precision of burn placement is more accurate with less power required.

## CONCLUSIONS

This past year in retina has been landmark. We have gone from having no FDA-approved pharmacologics to having one approved (dexamethasone intravitreal implant) and one with excellent data to show that it is effective in our patients with macular edema secondary to RVO (ranibizumab), and FDA approval seems likely. How do we make choices as to what combinations will bring the best benefit to our patients? Currently, we do not have hard data to support any one combination over another. We do know, however, that some choices are obvious; for example, in a patient who has advanced glaucoma or a patient with a crystal clear lens, an anti-VEGF agent would be more favorable than steroid. For pseudophakic patients with no history of glaucoma, the dexamethasone implant may be more favorable because of its long durability.

Further data are needed to develop solid algorithms for treating RVO. Many factors come into play: severity and location of macular edema, natural history, response to therapy, side effects, and cost.

Although there will be continued debate over which combination is best until we have these hard data, there is no doubt that our treatments for macular edema secondary to RVO have expanded and improved and that the benefit to our patients is significant. ■

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