

Practical Guidelines for RVO Management

The availability of multiple treatment options is both a blessing and a curse.

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Treatment strategies for retinal vein occlusion (RVO) continue to evolve. A decade ago, laser treatment alone was the standard of care.¹ Subsequently, clinical trial data indicated a role for the off-label use of intravitreal steroid injections. Not long after that, the availability of anti-VEGF drugs—used in both on- and off-label settings—prompted another shift, and now these drugs are considered the new standard of care. More recently, the approval of sustained-release steroid implants by the US Food and Drug Administration and the release of preservative-free triamcinolone formulations add new treatment options for clinicians to consider.

The plethora of available options undoubtedly contributes to a great deal of confusion for clinicians. This article reviews the role of the various treatment options in the management of RVO and some caveats to consider when managing complex and chronic cases.

ANTI-VEGF DRUGS

Anti-VEGF drugs are markedly more effective in the treatment of RVO than any other treatment modality. Of the available options, they provide the greatest improvement in visual acuity (VA) and the most profound reduction of macular edema. Our research group has published and presented the results of a prospective and a retrospective study on the safety and efficacy of bevacizumab (Avastin, Genentech) in the treatment of RVO^{2,3}; following is a brief summary of the findings. For branch RVO (BRVO), bevacizumab improved VA an average of 3.0 lines and improved central macular thickness (CMT) by 39% from baseline to 1 year with injections every 6 weeks ($n = 23$). The mean number of reinjections was 1.6 during the first 6 months of follow-up and 0.8 during the subsequent 6 months.⁴ For central RVO (CRVO), a short-term study was performed to assess the short-term anatomic and VA response after treatment with bevacizumab ($n = 15$). After 1 month, mean CMT decreased from 887 μm to 372 μm , and VA improved from 20/600 to 20/200.⁵

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Similar reports have been noted with ranibizumab (Lucentis, Genentech) in major clinical trials. In the BRAVO study, which investigated ranibizumab in patients with BRVO, 55.2% ($n = 74$) and 61.1% ($n = 80$) of patients receiving 0.3-mg and 0.5-mg doses, respectively, had a VA improvement of greater than 15 letters over a period of 6 months with monthly injections.⁶ In the CRUISE study, which investigated 0.3-mg and 0.5-mg doses of ranibizumab in patients with CRVO, the results were less robust: 46.2% ($n = 61$) and 47.7% ($n = 62$), respectively, had a VA improvement of greater than 15 letters over a period of 6 months with monthly injections.⁷

More recently, aflibercept (Eylea, Regeneron) was approved for treatment of CRVO, and improvement of 15 letters or greater in VA was seen in 57.9% of patients in a clinical trial ($n = 66$).⁸

For financial reasons and because of insurance carrier requirements, retina specialists are often obligated to try monthly injections of bevacizumab as a first-line option. In some cases, a patient can develop tachyphylaxis in response to a particular anti-VEGF agent. In our clinic, we have found that changing to another agent may be effective in these situations.

In our experience, bevacizumab is less potent than ranibizumab, which is less potent than aflibercept; in cases of a suboptimal response, we move to the more potent agent. If that regimen is not effective, then a steroid may be added or used as an alternative. In some

cases, the side effects from one agent may lead to a switch. We have seen hair loss with bevacizumab; secondary glaucoma with bevacizumab and ranibizumab, which has also been noted in the literature⁹; and a few cases of hypotony following aflibercept. Immune reactions have been noted with all 3 agents; however, in our experience, changing agents typically eliminates the robust immune response. When immune reactions occur, we manage with a strong steroid (difluprednate; Durezol, Alcon Laboratories) every 15 minutes and check the patient 6 hours later, which is often enough time to see a slight improvement in the inflammatory response in noninfectious cases.

The Injection Train

One problem is how to taper off injections in patients with RVO. Cessation of either

anti-VEGF drugs or steroids can be associated with recurrent edema. In severe cases, the rebound edema can be more severe than the initial presentation, and VA may be reduced to below the initial level.¹⁰ In some cases, patients will have such profound rebound edema with ischemia that severe irreversible vision loss can occur

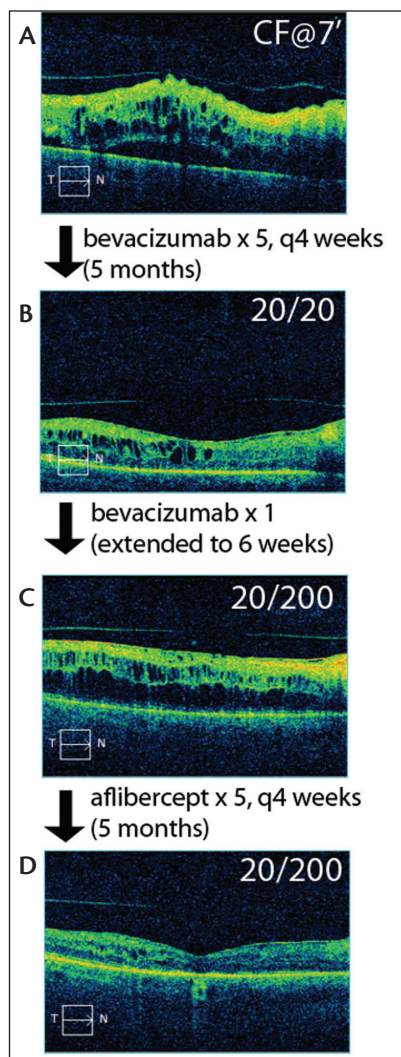


Figure 1. Rebound edema after a treat-and-extend protocol was used in a patient with CRVO (A-B). The patient's VA improved from counting fingers at 7 feet to 20/20 following 5 monthly bevacizumab injections (C). After extending treatment to an interval of 6 weeks, the patient's VA dropped to 20/200 (D). Macular edema improved after initiating treatment with aflibercept every 4 weeks, but vision never recovered beyond 20/200.

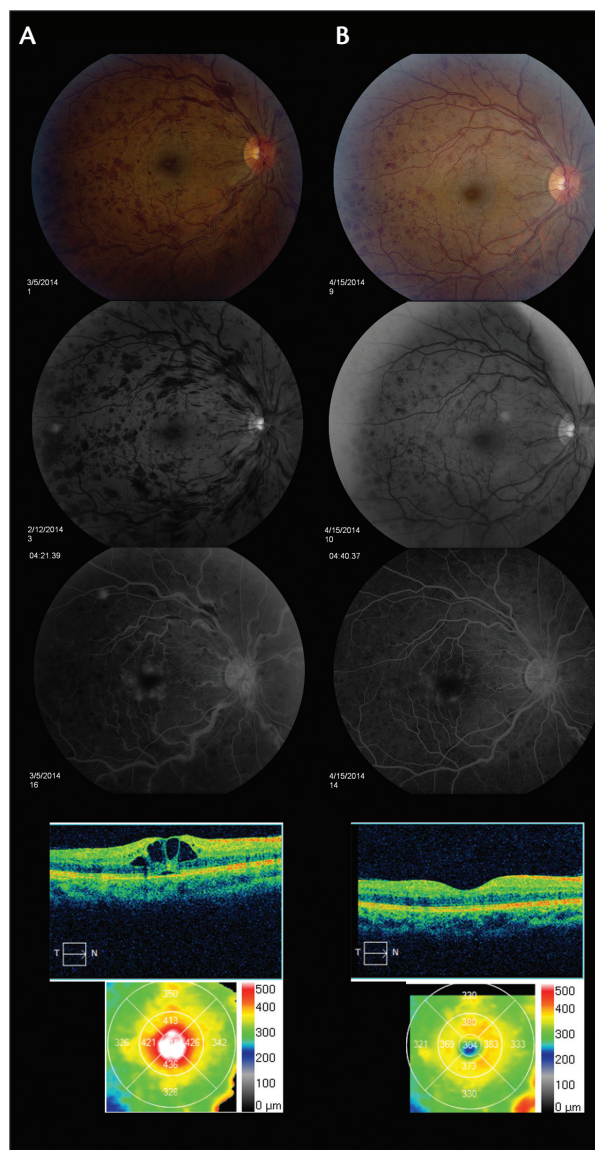


Figure 2. Topical therapy for mild CRVO with a combination of a strong topical steroid (difluprednate) every hour for 2 days, then every 2 hours thereafter; a nonsteroidal anti-inflammatory agent (bromfenac; Bromday, Bausch + Lomb) twice a day; and a carbonic anhydrase inhibitor (brinzolamide/brimonidine) 3 times a day induced a reduction in macular edema 7 days following treatment. Fluorescein angiography performed 2 months after treatment showed improvement.

(Figure 1). Treat-and-extend protocols can be effective, but patients must be monitored closely. Supplemental treatments may facilitate weaning off of injections, including laser (panretinal photocoagulation) to reduce macular leakage and peripheral ischemia, nonsteroidal antiinflammatory drugs, and steroid drops.

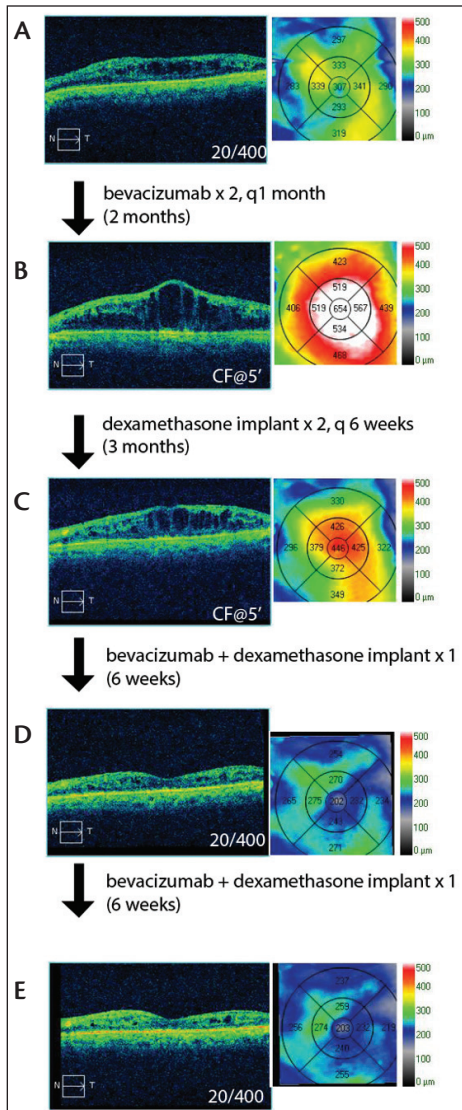


Figure 3. Combination injection with an anti-VEGF agent and a steroid for a patient with CRVO. The patient showed tachyphylaxis and rebound edema after 2 monthly bevacizumab injections (A-B). The patient had a partial response to 2 dexamethasone implants administered every 6 weeks (C), then marked response to combination bevacizumab injection and dexamethasone implant (C-E).

STERIODS

Steroids come in various forms, and all have been used for treating RVO in either on- or off-label fashions.

The topical steroid difluprednate can be effective in mild cases. We have used it in our clinic in an uncontrolled fashion in selected patients, often those scheduled for their first injection. We have often been pleased

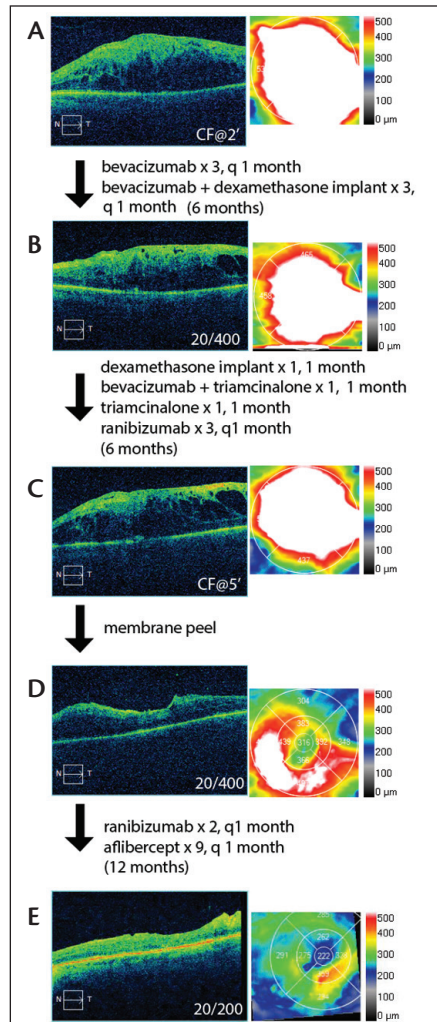


Figure 4. Surgical management with continued anti-VEGF and dexamethasone implant in a patient with CRVO. The patient showed initial improvement with anti-VEGF and steroid therapy (A-B), but subsequently developed tachyphylaxis in response to anti-VEGF and steroid treatments (B-C). The patient underwent vitrectomy with membrane peeling, resulting in continued decrease in macular thickness 1 day after surgery (D) and further improvement 1 year following surgery with continued injections (E).

to note a pronounced response from a loading dose of difluprednate, after which the injection can be canceled (Figure 2). In some cases, anti-VEGF injections are utilized after an initial partial response, in part because the long-term use of difluprednate may be associated with complications including cataract formation and glaucoma.

Strong topical steroids can be as effective as periocular or intravitreal steroid injections. In general, we limit the use of steroid injections to patients who have a less-than-desired response to anti-VEGF injections. We reported 2 studies, 1 retrospective and 1 prospective, on the dexamethasone implant (Ozurdex, Allergan) for the management of recalcitrant RVO after anti-VEGF therapy.^{2,3} In both studies, VA, macular edema, and retinal function improved with the implant. After 12 months, cataract progression was seen in 29.8% of phakic eyes that received 2 intravitreal dexamethasone implants. In a separate multicenter study, steroid-induced glaucoma was uncommon after 1 injection (12.6%) and more common with repeat injections (15.4%), but only 10.3% of patients required medications to control intraocular pressure.

In these anti-VEGF resistant cases, macular edema and retinal function (measured by VA and assessed with multifocal electroretinogram) were markedly improved following the implant.

On rare occasions, we use the dexamethasone implant alone, especially when anti-VEGF injections are contraindicated, such as in pregnant women or in patients with a

recent cardiovascular event (myocardial infarction or cerebrovascular accident within 4 months). Combination therapy with an anti-VEGF agent and either preservative-free triamcinolone acetonide or the dexamethasone implant may be used in selected cases when edema appears to be both VEGF- and steroid-dependent (eg, when only a partial response is seen with 1 or the other drug). An example case in which bevacizumab was used in conjunction with the dexamethasone implant is shown in Figure 3.

LASER

Laser treatment for the management of RVO has been abandoned in some clinical practices, but it still may have a role in selected cases. RVO with macular ischemia and leaking microaneurysms associated with chronic macular edema may be effectively managed with laser treatment. In our clinic, we also consider laser as an adjunctive treatment in recalcitrant cases. If widefield angiography reveals peripheral ischemia in a patient with CRVO, we apply panretinal photocoagulation to suppress this source of VEGF production. We have seen a few patients who had resolution of leakage with laser treatment following long-term use of anti-VEGF injections. Care should be taken, however, as some patients will have rebound edema and a decrease in VA after laser treatment, which can cause a burst of VEGF release related to the destructive effects of the laser treatment itself. Hence, we often perform laser treatment within a few weeks after the most recent anti-VEGF injection to neutralize any acute increase in VEGF production. Long-term treatment of an ischemic retina will reduce VEGF production, thereby reducing the need for frequent anti-VEGF injections.

VITRECTOMY

Selected patients will require vitrectomy surgery. Obvious cases are those that develop tractional or rhegmatogenous retinal detachments and those with chronic vitreous hemorrhage.¹² The more subtle cases are those with an epiretinal membrane (ERM) or vitreomacular traction, both of which limit the efficacy of injections and laser therapy. Figure 4 depicts such a case, in which the patient had an initial response to bevacizumab followed by a dexamethasone implant, but eventually became recalcitrant to therapy after developing an ERM. The VA decreased secondary to the ERM, requiring more frequent injections and a switch to different anti-VEGF agents. After electing to undergo a membrane peel, the patient had a prompt improvement of the macular contour. In cases such as this, further injections may or may not be required.

Following vitrectomy, the duration of effect of anti-VEGF agents may be reduced to a few days or

weeks, and more frequent injections—even as frequently as biweekly—may be required to maintain VA and to treat recurrent edema. In such cases, a dexamethasone implant may be ideal, as the duration of action is much less affected following vitrectomy, and injections as infrequently as every 6 to 12 weeks may still be efficacious in patients with persistently active leakage.

CONCLUSION

A multitude of treatment options are now available for the management of RVO. In complex cases requiring management for many months or even years, the retinologist will have to call upon several treatment options to achieve the best outcomes. In some cases, shifting between treatments because of tachyphylaxis or to avoid side effects will be necessary. Close follow-up and aggressive management of any recurrent edema is crucial for the best outcomes. ■

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