Retinal vascular occlusive diseases constitute a significant cause of visual impairment in the elderly worldwide. This article focuses on strategies for managing patients with retinal vein occlusion (RVO) and retinal artery occlusion (RAO).

RVO IN A NUTSHELL

Central RVO (CRVO) and branch RVO (BRVO) are caused by thrombosis of a retinal vein. RVO is the second most common vision-threatening retinal vascular disease after diabetic retinopathy.1-3 Systemic risk factors include arteriosclerosis, hypertension, diabetes, lipid abnormalities, and vascular inflammatory diseases.4 Because of characteristic alterations in the arteriovenous crossing anatomy, hypertension is the leading risk factor for BRVO;4 yet the necessity for hypercoagulability testing in younger patients and patients with bilateral RVO remains controversial.5

Move Over Laser

The most common cause of vision loss in patients with RVO is macular edema (ME). Coexisting macular ischemia is the primary determinant of visual outcomes in patients with RVO.1-3 Historically, grid laser photocoagulation was the gold standard therapy for BRVO; however, intravitreal pharmacotherapy has largely replaced laser as the intervention of choice for both BRVO and CRVO. Intravitreal injection of anti-VEGF agents has become first-line therapy for ME secondary to RVO since numerous prospective studies revealed their remarkable therapeutic effects.6-19 More than half of patients with nonischemic RVO will achieve rapid improvement in visual acuity and reduction in retinal thickness shortly after initiation of anti-VEGF therapy, and these improvements are largely maintained with adequate retreatment.5-19 Visual acuity changes from baseline and number of injections required in selected prospective clinical trials are outlined in Figures 1 and 2. Early initiation (ie, < 3 months from onset) of anti-VEGF therapy appears to lead to the greatest improvement in visual acuity.12,17,19

An Anti-VEGF Drug is an Anti-VEGF Drug?

At this point, evidence from randomized controlled trials has

AT A GLANCE

- RVO is the second most common vision-threatening retinal vascular disease after diabetic retinopathy.
- Although giant cell arteritis is a relatively uncommon cause of central retinal artery occlusion, it is essential to rule it out in patients 50 years and older.
- Multiple therapeutic interventions for RVO have emerged with significant potential for clinical improvement, whereas optimal therapies with proven visual benefit for retinal artery occlusions have yet to be found.
not shown definitive differences in efficacy and safety among anti-VEGF agents.\textsuperscript{18,20}

The SHORE study demonstrated that an as-needed (PRN) regimen with monthly follow-up, after 7 monthly injections, was as effective as a monthly treatment regimen.\textsuperscript{11} Although many trials mandate a loading period, one to two injections might be sufficient before switching to PRN in cases that demonstrate complete resorption of fluid.\textsuperscript{21} Switching anti-VEGF agents or switching to a steroid agent should be considered in eyes that do not show anatomic response.\textsuperscript{22}

During initial therapy, follow-up intervals beyond 2 months are not recommended in patients with CRVO. Mean visual acuity was maintained with bimonthly monitoring in CRYSTAL but not with quarterly monitoring in COPERNICUS.\textsuperscript{12,19} Switching anti-VEGF agents, particularly to aflibercept (Eylea; Regeneron), may be beneficial for extending treatment intervals. In the NEWTON study\textsuperscript{23} and other studies, refractory ME unresponsive to ranibizumab (Lucentis; Genentech) or bevacizumab (Avastin; Genentech) was anatomically improved with aflibercept, and treatment intervals were able to be extended.\textsuperscript{24-26}

**Laser Plus Pharmacotherapy**

The addition of grid or peripheral scatter laser to pharmacotherapy in the treatment of patients with RVO is of unclear benefit. In BRVO, the 2-year BRIGHTER and 4-year RETAIN studies demonstrated that addition of laser to ranibizumab did not provide better visual outcome or reduce the need for treatment.\textsuperscript{10,17} The RELATE study, which evaluated targeted scatter laser for areas of nonperfusion identified by wide-angle fluorescein angiography in addition to pharmacotherapy, also did not find clear benefit of adding laser in the treatment of RVO.\textsuperscript{14}

**Corticosteroid Use**

Intravitreal corticosteroids are also an effective alternative for treating ME secondary to RVO.\textsuperscript{27-31} Intravitreal injection of triamcinolone in SCORE resulted in superior visual outcomes in patients with CRVO compared with standard care.\textsuperscript{27,28} The dexamethasone intravitreal implant 0.7 mg (Ozurdex; Allergan), in the GENEVA trial and in a head-to-head comparison versus ranibizumab in the COMRADE B and C trials, led to rapid visual acuity gain for 2 months (comparable to ranibizumab); however, visual acuity gain was not sustained after month 3 in any of the trials, resulting in inferior overall performance to ranibizumab from month 3 to 6.\textsuperscript{29-31} These findings may be a result of undertreatment in the dexamethasone arm compared with anti-VEGF therapy.\textsuperscript{29-31}

In clinical practice,
ocular hypertension and cataract formation or progression may occur with steroid use. Studies suggest that intravitreal steroids may be useful for treatment of recalcitrant ME unresponsive to anti-VEGF therapy. \textsuperscript{32,33}

Novel formulations and approaches to steroid therapy may open new avenues for therapeutic intervention. Recently, suprachoroidal injection of triamcinolone for the treatment of ME secondary to uveitis has been reported to lead to functional and anatomic improvement with no increase in intraocular pressure during 26 weeks of follow-up. \textsuperscript{34} The application of this delivery method could potentially reduce steroid-induced ocular complications while achieving therapeutic effect similar to intravitreal delivery methods, but with fewer injections.

**Surgical Intervention**

Internal limiting membrane peeling and intravascular tissue plasminogen activator (tPA) injection have been explored with mixed results. One study explored the use of vitrectomy with injection of tPA into the central retinal vein using a 47-gauge microneedle in patients with CRVO. \textsuperscript{35} In a preliminary report, 12 eyes demonstrated a marked decrease in ME and a significant increase in mean visual acuity, equivalent to 16.3 letters after 6 months. \textsuperscript{35} In the age of intravitreal pharmacotherapy, however, surgical intervention is more a salvage treatment option for ischemic CRVO than a first-line choice.

**THE INS AND OUTS OF RAO**

Central retinal artery occlusion (CRAO) and branch retinal artery occlusion (BRAO) are typically caused by an embolus or thrombus, which often leads to severe irreversible vision loss caused by inner retinal ischemia of the macula. \textsuperscript{36-38} In CRAO, the two most common locations of the occlusion are where the central retinal artery pierces the dural sheath of the optic nerve and immediately posterior to the lamina cribrosa. \textsuperscript{39} Other causes of RAO include giant cell arteritis, nocturnal hypotension, and inflammatory etiologies. \textsuperscript{40,41}

Visual prognosis is usually poor for patients with CRAO. A 3-line improvement can be expected in only 10% of cases due to spontaneous reperfusion, and final visual acuity is typically no better than 20/200 in 80% of all CRAO types. Cilioretinal artery sparing may act as a protective factor. \textsuperscript{36,42,43}

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**Figure 2.** Scatter plot illustrating the relationships between mean number of anti-VEGF injections per year and mean changes in BCVA from baseline in BRVO (A) and CRVO (B). This graph is intended to provide a rough estimate of the number of anti-VEGF injections required to gain or maintain visual acuity each year. Treatment arms in different clinical trials cannot be directly compared due to differences in the study populations, disease duration, and inclusion and treatment criteria.
Although giant cell arteritis is the cause of CRAO in less than 5% of cases, it is essential to rule it out in patients 50 years and older by measuring erythrocyte sedimentation rate and C-reactive protein, as the immediate initiation of steroid therapy may prevent further visual loss or bilateral involvement.\(^{40,44}\)

Fluorescein angiography is recommended in patients with CRAO to evaluate residual retinal circulation, to identify the cilio-retinal arteries, and to evaluate potential defects in choroidal filling that may reflect occlusion of the posterior ciliary arteries.\(^{36}\) In addition, inflammatory causes of RAO, such as vasculitis or Susac syndrome, must also be considered, as specific intervention with systemic steroids or immunomodulatory agents may improve clinical parameters and/or prevent recurrent episodes.

**Nonarteritic RAO**

The treatment of nonarteritic CRAO or BRAO involving the fovea is always a challenge, particularly given the short length of estimated retinal survival time.\(^{45}\) Historically, conservative treatments have included ocular massage, carbogen inhalation, anterior chamber paracentesis, treatment with a carbonic anhydrase inhibitor, and a combination of these therapies. However, none of these therapies has been shown to alter the visual outcome compared with the natural course of the disease.\(^{36}\)

More aggressive approaches include intravenous or selective arterial administration of thrombolytic agents, with the aim of dissolving fibrin-platelet occlusion.\(^{46,47}\)

The multicenter, prospective, randomized, controlled EAGLE study found similar visual outcomes but a higher rate of adverse reactions in patients with CRAO receiving local intraarterial fibrinolysis compared with those receiving conservative treatment.\(^{47}\) This result may be linked to the fact that only 15.5% of emboli were composed of fibrin in histologic studies, while 74% were cholesterol and 10.5% were calcific material, neither of which is dissolvable with tPA.\(^{48}\)

As for further workup and management, medical evaluation for risk factors such as diabetes mellitus, arterial hypertension, hyperlipidemia, ischemic heart disease, and cerebrovascular disease is recommended.\(^{36-38}\) Nearly 80% of patients with CRAO in the EAGLE study had a previously undiagnosed vascular risk factor.\(^{49}\) In acute RAO, urgent evaluation for stroke risk, including carotid and cardiac evaluation, is recommended.\(^{36-38,49}\)

## CONTINUED IMPROVEMENTS

The management of RVO has been transformed with the emergence of intravitreal pharmacotherapy, including anti-VEGF agents and steroids. Future therapies may build on the current success of pharmacotherapy while reducing treatment burden and offering alternative routes of administration. Although therapeutic intervention for RVO has seen significant advances, optimal therapies with proven visual benefit for RAO remain elusive. Further research in areas such as regenerative therapy and neuroprotection is needed to enable improved outcomes in the treatment of this condition.

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- Financial disclosure: Consultant (Bioptigen/Leica, Zeiss, Thrombogenics, Genentech, Santen, Alcon, Allergan, Novartis, Alimera); Research Grants (Thrombogenics, Regeneron, Genentech, Alcon, Aetna, Boehringer-Ingelheim); Patent (Bioptigen/Leica)

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Financial Support: NIH/NEI K23-EOY22947-01AT (JPE); Ohio Department of Development TECH-13-059 (JPE); Research to Prevent Blindness (Cole Eye Institutional Grant); unrestricted travel grant from Alcon Novartis Hida Memorial Award 2015 funded by Alcon Japan Ltd (AU).