Retinal vein occlusions (RVOs), which occur with a prevalence of 0.7% to 1.6%, are the second most common retinal vascular disorder after diabetic retinopathy and a significant cause of visual impairment in the elderly.1 RVO often presents as a sudden, painless loss of vision in the affected eye. The two main subtypes of RVO, central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO) are distinguished by the location of the obstruction. In CRVO, the central retinal vein is obstructed near the optic nerve, affecting most of the retina. In BRVO, the obstruction is located on one of the branches of the central retinal vein, affecting only a portion (typically a quadrant) of the posterior pole.2 The prevalence of BRVO (0.6% to 1.6%) is greater than that of CRVO (0.1% to 0.4%).3 Both CRVO and BRVO can be subdivided into ischemic and nonischemic types. Ischemic RVO (typically 10-disc diameter or more of capillary nonperfusion on fluorescein angiography) is associated with a significant loss of visual acuity at presentation and a poor prognosis, with 20/200 or worse in 90% of patients, suggesting that the initial damage is substantial and, most often, irreversible. Nonischemic CRVO is associated with a more favorable prognosis, with patients frequently recovering to 20/40 or better. Vision-threatening complications associated with RVO include vitreous hemorrhage, macular edema, macular ischemia, and neovascularization.

TREATMENT FOR RVO

Although many medical, surgical, and laser treatments for RVO have been tried, most have not been clinically validated in randomized controlled trials.4,5 Final visual acuity (VA) after RVO is strongly dependent on VA at presentation.5 No intervention for RVO has emerged as the standard of care, and current treatment is often limited to close observation and treatment of complications (such as macular edema) when indicated. The efficacy of many medical therapies for RVO, including anticoagulants, ocular hypotensive therapy, acetazolamide, and carbon dioxide inhalation, is unproven.2 Currently, there is also no safe and effective surgical treatment for RVO; randomized controlled trials testing hemodilution for CRVO have yielded conflicting results.8 Laser treatment for RVO-associated macular edema and retinal neovascularization was first introduced in 1976.9 Grid photocoagulation for macular edema, panretinal photocoagulation (PRP) for retinal neovascularization, and laser-induced chorioretinal anastomoses for non-ischemic RVO are currently in use. Results of several studies, including the CVOS (Central Vein Occlusion Study) and the BVOS (Branch Vein Occlusion Study), have yielded conflicting results on the efficacy of PRP and grid photocoagulation.10 In the CVOS, PRP was shown to be an effective treatment for neovascularization associated with CRVO, but an earlier study of PRP for neovascularization of ischemic CRVO showed no treatment benefit.11 Grid photocoagulation for macular edema was shown to be effective in the BVOS, but not in the CVOS. Laser-induced chorioretinal anastomoses, although still in use, is associated with significant treatment risks without significant improvement in prognosis.

More recently, intravitreal medications, such as anti-VEGF agents and corticosteroids, have been used to treat macular edema associated with RVO.12 Within the past 5 years, several studies have reported positive treatment effects after treatment with bevacizumab (Avastin, Genentech, Inc.) or ranibizumab (Lucentis, Genentech, Inc.). However, results from randomized controlled trials have not yet been published, and treatment effects may be temporary. Intravitreal triamcinolone (IVTA) and other corticosteroids have also been effective in several studies, including randomized controlled trials. Although intravitreal corticosteroids are associ-
ated with significant side effects, they remain a therapeutic approach for the treatment of RVO.

Due to the lack of a safe and effective monotherapy for RVO, one approach under investigation is the use of combination therapies. We identified 21 reports of combination therapies for RVO, including four clinical trials listed at clinicaltrials.gov and seven peer-reviewed publications. Additionally, 10 recent presentations at the Association for Research in Vision and Ophthalmology (ARVO) meeting were considered. These studies involve a total of 563 patients and most can be organized into three broad categories: bevacizumab/IVTA combinations, laser/IVTA combinations, and surgical/IVTA combinations.

BEVACIZUMAB/IVTA COMBINATION THERAPY

Although no randomized controlled trials testing the efficacy of the combination IVTA and bevacizumab for RVO are currently in place, there are preliminary indications that this approach may be effective. In one published case report, an individual with CRVO and chronic macular edema that had not responded to either IVTA or bevacizumab was effectively treated by simultaneous administration of both drugs. This observation is supported by the results from an uncontrolled case series of 13 eyes with macular edema due to RVO, which exhibited a mean gain of 5.5 letters in VA and a mean reduction in retinal thickness of 187 µm after receiving the IVTA/Avastin combination. Two small randomized controlled trials comparing this combination to bevacizumab monotherapy in 25 patients with CRVO are listed on clinicaltrials.gov. Neither of these listings, however, has been updated in over a year, and results have not been reported, even though both studies have passed their estimated completion dates.

LASER/IVTA COMBINATION THERAPY

We reviewed four reports of photocoagulation combined with IVTA in a total of 100 BRVO patients. The studies included two case series in which improved central retinal thickness was observed. However, two randomized controlled trials yielded mixed results. In one study, 25 eyes received IVTA alone and 12 eyes received IVTA and grid photocoagulation. A significant but short-lived reduction in central retinal thickness was observed in both treatment groups, but the IVTA monotherapy group had a greater improvement in VA. In the other study, 24 patients were randomized to receive IVTA with subthreshold grid laser photocoagulation (SGLT) or SGLT alone. After 1 year of follow-up, the combination group exhibited significantly improved VA relative to baseline while the laser-only group did not. These reports suggest that the photocoagulation/IVTA combination may be beneficial, but it is not yet clear that this therapy is more effective than IVTA alone, because no treatment benefit was shown in the trial that compared laser/IVTA to IVTA alone.

SURGICAL/IVTA COMBINATION THERAPY

A variety of surgical/IVTA combination therapy reports were reviewed, including three publications, one listing at clinicaltrials.gov, and five ARVO presentations. In a case series, 63 eyes received radial optic neurotomy (RON) and IVTA for CRVO, and VA improved by a mean of three lines in 68% of patients. Similar results were observed in a separate case series of 117 patients that received RON alone. In another series, 22 eyes received RON/IVTA and eight eyes received RON alone. A significant improvement in VA was observed in the RON-alone group but not in the combination group. In both studies, the group receiving IVTA had a higher incidence of ocular adverse events. Neither study demonstrated any treatment benefits for the adjunctive use of IVTA with RON. Another combination that has been investigated in several studies is IVTA and vitrectomy.

Although improved VA was observed in eyes receiving this combination in two uncontrolled longitudinal studies, no significant treatment effect was observed in either of these two randomized controlled trials. In an ongoing study, 47 eyes with CRVO or BRVO received vitrectomy with IVTA and bevacizumab. A study of the combination of hemodilution with IVTA has also been reported. Thirty eyes with CRVO were randomized to receive hemodilution or hemodilution/IVTA, and combination-treated eyes exhibited improved VA and reduced macular thickness relative to eyes treated with hemodilution alone. In a study comparing maculopexy assisted by gas and/or triamcinolone, BRVO eyes receiving gas-assisted maculopexy exhibited greater improvement than eyes receiving triamcinolone-assisted maculopexy. Additional combinations reported include vitrectomy, arteriovenous sheathotomy and IVTA, and RON with ILM peeling and IVTA.

Based on the combination therapies reviewed, the combination of IVTA and bevacizumab appears to be promising. However, limited data exist to support this hypothesis at this time, as results have not yet been reported for two small randomized controlled trials that are under way. A larger, well-designed randomized controlled trial will be necessary to demonstrate efficacy in a convincing way. Similarly, with the other combination approaches, large, multicenter randomized controlled trials will be essential to prove efficacy and establish clinical guidelines for the treatment of these common, sight-threatening conditions.

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