Management of Retinal Vein Occlusion: What the Clinical Trials Tell Us

Demystifying the studies for some practical clinical guidelines.

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Retinal vein occlusions (RVOs) remain the leading cause of vision loss second only to diabetic retinopathy in patients with retinal vascular disease. The leading causes remain hypertension in patients over 65 years of age and a systemic coagulopathy in younger patients.[1] In addition to treating systemic disease, local therapy remains a mainstay for managing these patients. Initial clinical trials for the treatment of RVOs focused on the use of a laser, which demonstrated a statistically significant benefit over the natural course of the disease, particularly in patients with branch retinal vein occlusion (BRVO).[2] Laser treatment for central retinal vein occlusion (CRVO) was found to be of more limited benefit.[3] In the past decade, alternative treatment strategies have evolved including intravitreal steroid injections and, more recently, anti-VEGF therapies targeting VEGF-A, -B, and placental growth factor.[4-11] Although the anti-VEGF treatment strategies including the use of bevacizumab (Avastin, Genentech), ranibizumab (Lucentis, Genentech) and most recently, aflibercept (Eylea, Regeneron), have proved to be extremely effective, not all patients respond to anti-VEGF agents.[12-14] Furthermore, sequential injections are required, often on a monthly basis.

In this article, we review the clinical trials that have evaluated ranibizumab and aflibercept as treatments for RVO.

RANIBIZUMAB

Ranibizumab was evaluated as a treatment for patients with BRVO and CRVO in the BRAVO and CRUISE clinical trials. Patients with BRVO (n = 397) and CRVO (n = 392) were randomized on a 1:1:1 ratio to treatment with ranibizumab (0.3 or 0.5 mg) vs sham, with laser rescue therapy allowed for BRVO.[2] In both studies, entry criteria included baseline visual acuity of 20/40 to 20/320 and central macular thickness (CMT) greater than or equal to 250 µm. Patients received monthly injections for 6 months followed by 6 additional months in which all patients were eligible for 0.5 mg ranibizumab injections, as needed. After 6 months, the BRAVO study found an improvement of ≥15 letters in 55.2% (n = 74) and 61.1% (n = 80) of the 0.3 mg and 0.5 mg treatment groups, respectively. This compared with 28.8% (n = 38) in the sham group. CMT improved, on average, by 337.3 ±38.3 µm and 345.2 ±41.2 µm in the 0.3 mg and 0.5 mg treatment groups, respectively, and 157.7 ±38.6 µm in the sham group. Similarly, over 6 months, the CRUISE study found an improvement of ≥15 letters in 46.2% (n = 61) and 47.7% (n = 62) in the 0.3 mg and 0.5 mg treatment groups, respectively, compared with 16.9% (n = 22) in the sham group. CMT improved, on average, by 433.7 ±51.2 µm and 452.3 ±44.7 µm in the 0.3 mg and 0.5 mg treatment groups, respectively, and 167.7 ±53.7 µm in the sham group. Treatment group improvements in visual acuity and CMT were significant in comparison to the sham group.[10,11]

AFLIBERCEPT

More recently, aflibercept has been evaluated in the management of both BRVO and CRVO, which is United States Food and Drug Administration (FDA)-approved for use in CRVO only. In the COPERNICUS study evaluating the efficacy in CRVO, 189 patients were enrolled with entry criteria of visual acuity from 20/40 to 20/320 and

CMT >250 µm. Patients were randomized (3:2 ratio) to treatment with 2 mg aflibercept vs sham injection and treated every 4 weeks for a 24-week interval. Following the initial 6-month interval, all patients were treated on an as-needed basis for the next 6 months along with an extension unmasked 1 year thereafter. At the end of 6 months, a visual acuity increase of ≥15 letters was achieved in 57.9% (n = 66) of the treatment group vs 12.3% (n = 9) for the sham group. CMT decreased by 457.2 µm for the treatment group vs 144.8 µm for the sham group. Treatment group improvements in visual acuity and CMT were significant in comparison to the sham group.[8] A randomized, controlled prospective study is currently enrolling to test aflibercept in patients with BRVO.[15]

DEXAMETHASONE INTRAVITREAL IMPLANT

The dexamethasone intravitreal implant was evaluated for the treatment of RVO in several concomitant clinical trials such as GENEVA. In these studies, 1267 patients with BRVO or CRVO were randomized to treatment with OZURDEX vs sham. Entry criteria included baseline visual acuity of 20/50 to 20/200 and CMT ≥300 µm. Patients were randomized on a 1:1:1 ratio to receive a single 0.7 mg dexamethasone intravitreal implant, 0.35 mg dexamethasone intravitreal implant, or a sham injection. A crossover study after 6 months extended the study to 12 months and enrolled 1256 of the patients, of which 997 patients received the open-label 0.7 mg dexamethasone intravitreal implant having met the criteria of best-corrected visual acuity of <84 ETDRS letters or central macular thickness of >250 um. At the 6-month interval, the study found that a visual acuity increase of ≥15 letters was achieved in 22% and 19% of the 0.7 mg and 0.35 mg treatment groups, respectively, vs 18% for the sham group. CMT decreased, on average, 119 ±203 µm and 123 ±212 µm for 0.7 mg and 0.35 mg treatment, respectively, and 119 ±188 µm in the sham group. Neither the changes in visual acuity nor CMT for treatment groups were significant when compared with the sham group at the 6-month interval. After 3 months, however, there were significant improvements in visual acuity (0.7 mg, 22%; 0.35 mg, 23%; sham, 13%) and CMT (0.7 mg, 208 ±201 µm; 0.35 mg, 177 ±197 µm; sham, 85 ±173 µm). Patients with greater than 90 days' duration of macular edema associated with BRVO observed a significantly greater response rate, which can be seen in a metaanalysis of the data. After 12 months, cataract progression was seen in 5.8% of phakic eyes that received at least 1 dexamethasone intravitreal implant (0.35 mg or 0.7 mg). In patients treated with 2 0.7 mg dexamethasone intravitreal implants, an intraocular pressure (IOP) increase of ≥10 mm Hg from baseline was seen in 32.8% of eyes at some point during the study. Overall, 32.2% (n = 373) eyes required glaucoma drops within 6 months of treatment with the dexamethasone intravitreal implant (0.35 or 0.7 mg), 14 of which underwent surgery to manage the patients' IOP.

Patients treated with sham who then crossed over to treatment were able to achieve improved visual acuity following a dexamethasone intravitreal implant. The 12-month IOP data for all studied patients demonstrate an IOP response after treatment with the dexamethasone intravitreal implant.[16]

DEXAMETHASONE IMPLANT VS TRIAMCINOLONE ACETONIDE

The dexamethasone intravitreal implant has theoretical advantages over the injection of triamcinolone for the management of patients with RVO. There are several formulations of triamcinolone available for the treatment of RVO, none of which are on-label. The commercially available triamcinolone acetonide (Kenalog, Bristol-Myers Squibb) was developed for extraocular use and was approved for treatment of sympathetic ophthalmia, temporal arteritis, and uveitis. Initial small-scale pilot studies used the medication for treatment of RVO, and there are also several case reports regarding its use.[17-21] The concerns with triamcinolone acetonide include sterile endophthalmitis, steroid-induced glaucoma, and a short duration of action. A concentrated formulation of the triamcinolone acetonide injection was developed allowing injection of approximately 12 mg of triamcinolone crystals in a volume of 0.05 mL.[22] This treatment was found to last up to 3 months but was associated with a 50% incidence of steroid-induced glaucoma requiring 1 or more medications. There is also the concern of preservatives in the triamcinolone acetonide formulation of Kenalog.

Unpreserved triamcinolone formulations were subsequently developed (Trivaris, Allergan; and Triesence, Alcon) and administered with several small pilot studies and case reports published showing efficacy for RVO. One randomized, controlled study (SCORE) looked at the use of intravitreal triamcinolone (Trivaris) using 4 and 1 mg per 0.05 mL formulations that found improvements in visual acuity and central retinal thickness similar to grid photocoagulation for BRVO.[23] Given the greater complications associated with intravitreal triamcinolone, laser treatment was recommended as the continued standard of care treatment for macular edema in patients with BRVO. In contrast, for patients with CRVO (SCORE-CRVO), intravitreal triamcinolone (Kenalog) injection was deemed superior to observation and retreatment at 4-month intervals for up to 2 years and was advised.[24] In the SCORE study, the incidence of cataract

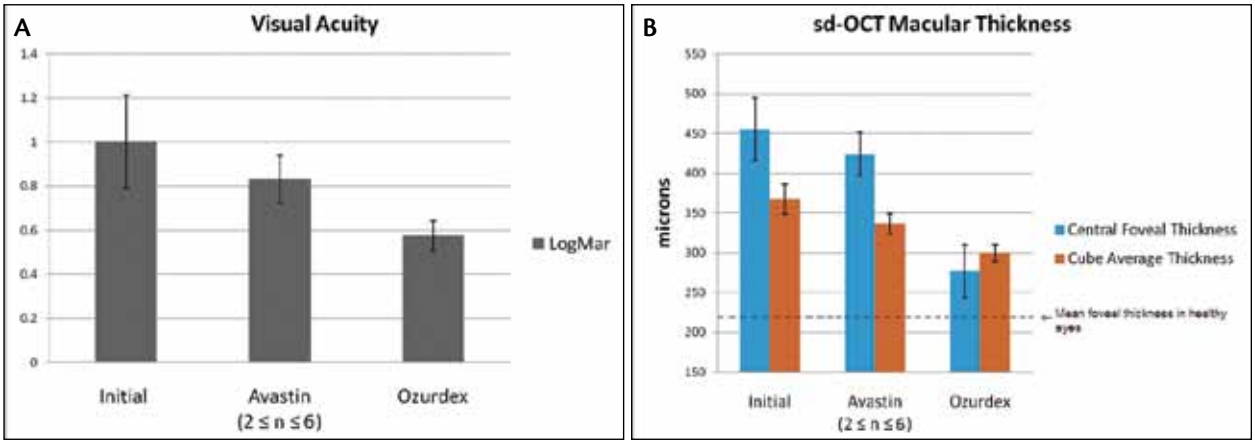

Figure 1. Mean change at baseline, following intravitreal bevacizumab and following the injection of the dexamethasone intravitreal implant in BCVA (A) and CMT (B).

was much higher than for the dexamethasone intravitreal implant (GENEVA), averaging 33% for SCORE-CRVO and 35% for SCORE-BRVO. More recently, Alcon developed its preservative-free formulation, Triesence, containing 4 mg per 0.1 mL of triamcinolone acetate and a preservative-free medium. This treatment has not been studied in a randomized, controlled fashion for the treatment of RVO but data suggest some efficacy. The downside of triamcinolone in all different formulations is evidence for retinal toxicity with suppression of the electroretinography scores and even cell death.[25] Furthermore, the higher potency of the steroid is associated with an increased risk of steroid-induced glaucoma[26] and cataract formation.[27] With these issues in mind, the dexamethasone intravitreal implant was developed allowing sustained release of steroid with a less toxic but also potent medication. Although there are no head-to-head studies, the apparent longer duration of action and decreased toxicity have made the dexamethasone implant a favorite. The lower cost of triamcinolone acetate and, in some settings, greater availability, may be reasons for its continued use.

DEXAMETHASONE IMPLANT VS ANTI-VEGF THERAPY

Although anti-VEGF therapy has become the mainstay for the treatment of RVO, there are patients who do not respond to anti-VEGF agents, become resistant, or even develop rebound edema following the use of anti-VEGF therapy. With this in mind, a retrospective review of patients resistant to anti-VEGF therapy was conducted. The dexamethasone intravitreal implant was found to be effective in all patients resistant to anti-VEGF drug therapy with a net visual acuity improvement of 0.26 ±0.07 logMAR and a CMT improvement of 146.8 ±33.65 µm in a study of 18 patients.[14] Figure 1 illustrates change in visual acuity and CMT following treatment with the dexamethasone intravitreal implant in patients resistant or partially responsive to anti-VEGF therapy. A randomized, controlled prospective study is now under way comparing these 2 treatment strategies.[28]

SUMMARY

Anti-VEGF therapy with ranibizumab and aflibercept has been shown to effectively treat macular edema and restore vision in patients with RVO. Ranibizumab is now FDA-approved for treating patients with BRVO and CRVO, while aflibercept is approved for CRVO alone. These drugs, on average, appear to achieve a greater improvement in visual acuity compared with steroid injections. The dexamethasone intravitreal implant, however, has the advantage of decreasing anti-VEGF injections overall and can rescue and restore vision in patients who have a partial response, become resistant, or are recalcitrant to anti-VEGF therapy alone. Each patient must be managed as an individual, and while reviewing the risks, benefits, and alternatives to each treatment option, the best strategy often becomes clear. Factors to consider include the patient's desires regarding frequency of injections and potential side effects for each medication while considering any history of steroid-induced glaucoma, prior inflammatory response to either steroids or an anti-VEGF agent, presence of cataract, and prior treatment history. Although anti-VEGF therapy continues to be the mainstay for the management of retinal vein occlusion, not all patients are responsive. In these cases, the dexamethasone intravitreal implant has been found to be effective and can rescue patients' vision and reduce macular edema safely and effectively. The dexamethasone intravitreal implant may be a reasonable choice as either primary or adjunctive therapy

for patients with RVO, and this conclusion is supported by data from randomized, controlled clinical trials. ■

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