INTRAVITREAL MONOTHERAPY FOR CRVO, OR INTRAVITREAL THERAPY PLUS LASER?

Which approach to treatment is best for patients with CME secondary to central retinal vein occlusion?

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Central retinal vein occlusion (CRVO) is a common retinal vascular disease. Population-based studies have reported 10- and 15-year cumulative incidences of 0.4% and 0.5%, respectively.[1,2] One of the key causes of vision loss in patients with CRVO is cystoid macular edema (CME); therefore, identifying the most effective treatment for this secondary condition is important. This article compares intravitreal monotherapy with intravitreal monotherapy in combination with laser therapy to establish which treatment approach makes the most sense for patients with CME secondary to CRVO.

MONOTHERAPY

Three treatment options are approved by the US Food and Drug Administration for macular edema secondary to CRVO: the dexamethasone intravitreal implant 0.7 mg (Ozurdex, Allergan), intravitreal ranibizumab (Lucentis, Genentech) injection, and intravitreal aflibercept (Eylea, Regeneron) injection. Intravitreal bevacizumab (Avastin, Genentech) and intravitreal triamcinolone acetonide have also been used extensively off label.

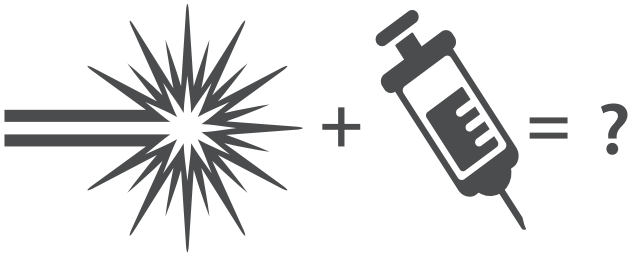
Despite pharmacologic therapy, many patients with CRVO continue to lose vision and require multiple injections due to recurrent CME. In the SCORE CRVO Study, which compared the use of intravitreal triamcinolone acetonide 1 mg versus intravitreal triamcinolone acetonide 4 mg versus observation, 25% of patients in the treatment groups lost 15 or more letters at 24 months, and 52% showed residual CME.[3] In the CRUISE study, 2.3% to 3.8% of eyes treated with either 0.3 mg or 0.5 mg of ranibizumab lost 15 or more letters, and 22.3% to 24.2% of eyes had residual CME.[4] In the COPERNICUS study, 5.3% of eyes treated with monthly aflibercept lost 15 or more letters, and 43% of eyes had residual CME.[5] In a retrospective study by the Pan American Collaborative Retina Study Group, of 86 eyes with CME secondary to CRVO, 11.6% lost 15 or more letters and 25% had residual CME despite treatment with intravitreal bevacizumab.[6]

COMBINATION THERAPY

Given the limitations of monotherapy, investigators have explored combination therapy in the treatment of

AT A GLANCE

- Although there are several pharmacologic agents available for the treatment of patients with CME secondary to CRVO, many patients experience recurrent CME and subsequent vision loss despite treatment.
- There is no evidence to support the superiority of combination therapy as primary therapy for CME secondary to CRVO.
- Intravitreal monotherapy remains the treatment of choice for these patients.



patients with CME secondary to CRVO. The fact that macular edema recurs suggests that active sources of VEGF production are present. Histopathologic studies and animal models have shown that VEGF upregulation occurs in areas of capillary nonperfusion.[7,8] Some have speculated that ablating these areas of capillary nonperfusion with laser may decrease secretion of VEGF and therefore break the cycle of recurring CME.[9]

MONOTHERAPY AND COMBINATION THERAPY HEAD-TO-HEAD COMPARISONS

In a prospective study in 10 eyes with CRVO, Spaide used ultrawide-field fluorescein angiography to detect areas of peripheral nonperfusion.[10] These areas were then photocoagulated, and the number of intravitreal injections of ranibizumab and visual acuity were compared 6 months before laser and 8 months after laser. Laser photocoagulation to peripheral areas of nonperfusion did not result in improved visual acuity or in a decreased number of injections. Spaide suggested that the "nonperfused" retina he saw in the ultrawide-field angiograms might actually have represented infarcted retinal tissue with minimal VEGF secretion.

In the RETAIN study, in 32 patients with CRVO treated with ranibizumab, eyes still requiring injections after month 40 received scatter laser photocoagulation to reduce the need for injections. The study authors reported that no eyes treated with scatter laser benefited in terms of edema resolution, reduction of number of injections, or improvement in visual acuity. They concluded that there was little evidence to support that scatter photocoagulation initiated at 40 months after the start of treatment with anti-VEGF therapy reduced the injection burden.[11]

Chhablani and colleagues compared 12 eyes with CRVO treated with intravitreal bevacizumab monotherapy with 11 eyes treated with intravitreal bevacizumab plus peripheral laser photocoagulation.[12] They found no differences between groups in numbers of injections or visual acuity, even when laser photocoagulation was initiated 1 month after the start of bevacizumab injections. Similarly, Rehak et al compared a group of 10 eyes with CRVO that underwent monthly intravitreal ranibizumab injections plus laser photocoagulation to areas of retinal nonperfusion with another group of 10 eyes treated with ranibizumab monotherapy.[9] The differences in visual outcomes between the two groups were not statistically significant.

In contrast are the results reported by Shimura et al.[13] In 25 eyes treated with 1.25 mg of bevacizumab; 20 eyes had recurrent CME and were injected again. These 20 eyes were then randomly assigned to undergo panretinal photocoagulation plus intravitreal bevacizumab reinjection or bevacizumab reinjection alone. The researchers reported that there were no differences in visual acuity or central macular thickness between the combination treatment group and the anti-VEGF monotherapy group. There was, however, a reduction in the number of injections in the combination group.

Increased levels of several cytokines and growth factors have been identified in the aqueous humor of eyes with CRVO.[14] These cytokines include VEGF, interleukin (IL) 1, IL-6, IL-8, interferon gamma inducible protein 10, monocyte chemoattractant protein 1, and platelet-derived growth factor. Several investigators have suggested that targeting multiple cytokines and growth factors with combination therapy may be synergistic and may lead to better visual outcomes and/or the need for fewer injections. Wang et al compared the use of intravitreal bevacizumab plus triamcinolone 2 mg versus bevacizumab 1.25 mg alone.[15] The authors reported that the combination was not better than bevacizumab monotherapy in terms of visual outcomes, resolution of macular edema, or frequency of retreatment. Singer and colleagues treated 62 eyes with an anti-VEGF agent in combination with the dexamethasone intravitreal implant 0.7 mg.[16] Their results showed a mean reinjection interval of 135 days and a peak change in best corrected visual acuity of +13.8 letters. Additionally, 48% of eyes had a gain of 3 or more lines. A caveat with this study is that there was no control arm.

> **"[Wang et al found that combination therapy] was not better than bevacizumab monotherapy in terms of visual outcomes, resolution of macular edema, or frequency of retreatment.**

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TREATMENT OUTCOMES NO BETTER WITH ADDED LASER THERAPY

Although several pharmacologic agents are available for the treatment of patients with CME secondary to CRVO, many patients experience recurrent CME and subsequent vision loss despite treatment. It may be natural to think that, if one agent does not produce optimal outcomes, then a combination of therapies may do the trick; however, there is no evidence to support the superiority of combination therapy over monotherapy as primary therapy for CME secondary to CRVO. For patients with CME secondary to CRVO, intravitreal monotherapy remains the treatment of choice at present. ■

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