Redefining the Patient-Doctor Relationship to Improve Outcomes in Retinal Disease

Chronic conditions require dynamic treatment strategies.

BY KISHAN GOVIND, MD; VICTOR T. COPELAND, MD; AND SHREE K. KURUP, MD

Results from the 2003 National Assessment of Adult Literacy illuminated the dire state of health literacy in the United States, reporting that more than 75 million Americans possessed basic or below health literacy skills.[1] The physician-patient interaction is, therefore, time vitally spent educating the patient to become a collaborative partner. When discussing different treatment options, patients should be objectively informed of potential side effects from treatment, duration of therapy, expected therapeutic response, and time typically required to achieve that response. A discussion of all available treatment options is warranted, with the acknowledgement that there may be no single best treatment course in some conditions. This discussion aligns patient expectations with expected therapeutic outcome, and guards against physician bias.

RETINAL VENOUS OCCULSIVE DISEASE WITH MACULAR EDEMA

Retinal venous occlusive (RVO) disease is a common disease with prevalence of 5.2 per 1000 people. It presents primarily as either branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO).[2]

Although the underlying pathologic mechanisms differ, associated macular edema is frequently a driver of visual loss.[3] Regarding BRVO-related macular edema, the BVOS group established grid laser photocoagulation as a viable treatment for BRVO-related macular edema.[4]

BVOS guidelines recommended treating patients with vision at levels of 20/40 or worse secondary to macular edema and delaying that treatment for 3 months to allow for potential spontaneous edema resolution—parameters that remained the standard of care for many years.[4,5] For edema related to CRVO, however, the standard of care long remained observation due to lack of benefit from macular laser treatment.[6]

TREATING BRVO-RELATED MACULAR EDEMA IN THE ANTI-VEGF ERA

As in many other retinal diseases involving vascular occlusion, abnormally elevated VEGF levels have been found in both aqueous and vitreous from eyes affected by RVO.[7-8] Accordingly, much research has focused on utilization of anti-VEGF agents to treat RVO-related sequelae. The recent BRAVO and CRUISE phase 3 randomized controlled clinical trials studied the effect of intravitreal ranibizumab (Lucentis, Genentech) for treatment of RVO-related macular edema.[9-11] At 12-month follow-up, patients treated with monthly ranibizumab in the BRAVO study had an average gain of 16.6 to 18.3 letters (compared with 7.3 letters in the control group), and patients in the CRUISE study showed an average gain of 12.7 to 14.9 letters (compared with 0.8 letters in the control group).[9-11] These findings, in conjunction with low numbers of adverse events in both studies, spurred US Food and Drug Administration (FDA) approval of intravitreal ranibizumab for the treatment of macular edema secondary to RVO in June 2009.

As with other etiologies treated using ranibizumab, off–FDA-label use of bevacizumab (Avastin, Genentech) in the treatment of RVO-related macular

CASE REPORT: BRVO

Figure 1. Bilateral ptosis in 66-year-old black man with chronic BRVO OS and CPEO causing left exotropia and severely impaired vision (BCVA OS = 20/200).

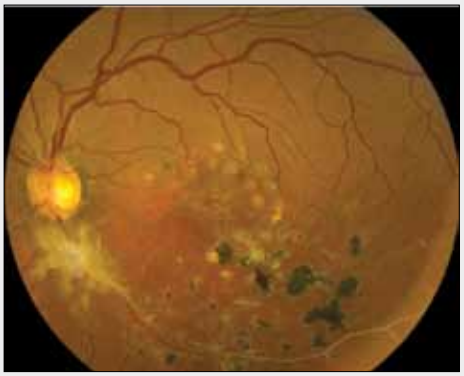

Figure 2. Color fundus photograph OS taken prior to therapy demonstrating BRVO with sclerotic vessels, focal laser scars, and CME.

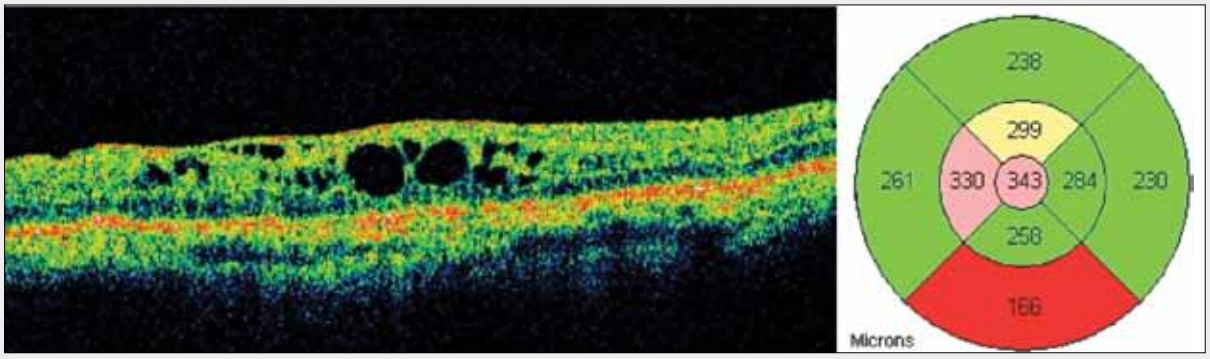

Figure 3. Time-domain OCT OS prior to treatment showing macular edema with chronic cystic changes.

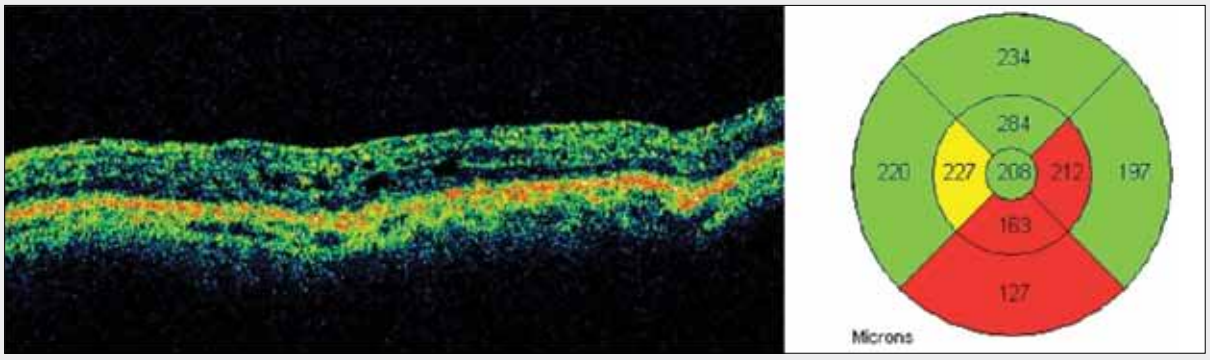

Figure 4. Resolution of macular edema with visual improvement (final BCVA = 20/80+) 9 months after final of 3 consecutive dexamethasone intravitreal injections. The patient also experienced resolution of exotropia and had lid surgery after.

edema is common practice. Several small, prospective clinical trials have reported that bevacizumab has similar efficacy to ranibizumab for RVO-related macular edema.[12-15] Monthly bevacizumab use was shown to result in at least 15 letter visual acuity improvement in 60% of patients (compared to 33.3% for sham treatment) with 12 month follow-up.[13] Aflibercept (Eylea, Regeneron) is the newest anti-VEGF agent used for treatment of RVO-related macular edema, and the COPERNICUS trial reported that 56.1% of eyes treated monthly with aflibercept gained 15 letters at 24 week follow-up.[16] The results of the COPERNICUS trial led to FDA approval of aflibercept for RVO-related macular edema in September 2012.

OTHER VIABLE TREATMENT OPTIONS

With the immediately apparent advantage that anti-VEGF agents provide compared with laser therapy, anti-VEGF agents have generally become accepted as first-line treatment for macular edema secondary to RVO. A subset of RVO patients, however, have been shown to be poorly responsive, or to have worsening of macular edema, when treated with anti-VEGF agents.[17-18] Feng and colleagues[19] recently reported a significant correlation in RVO patients between aqueous levels of the inflammatory cytokines interleukin 6, basic fibroblast growth factor, serum amyloid A, and central macular thickness. In light of such findings, patient nonresponse is explainable by acknowledging that venous occlusions are associated with a host of inflammatory factors beyond the VEGF spectrum—findings that establish the basis for corticosteroid use in treating RVO-related edema. The SCORE trial reported that 27% of patients receiving intraocular triamcinolone acetonide gained at least 15 letters of visual acuity (vs 7% for sham injection) at 1 year, but the rates of side effects such as cataracts and increased intraocular pressure were high.[20]

The sustained-release dexamethasone intravitreal implant (Ozurdex, Allergan) gained FDA approval for RVO-related macular edema treatment in June 2009 after the GENEVA trial demonstrated that 29% of patients experienced at least 15 letters of improvement (vs 11% with sham injection) at 30 days.[21] Although no significant cataract progression was reported after 1 injection, a significant increase in cataract progression was reported in patients receiving 2 dexamethasone implant injections 6 months apart (29.8% vs 5.7% in the control group).[21] Capone and associates[22] recently reported efficacy and safety results from a retrospective review of 289 patients receiving 2 or more (mean, 3.2) sequential dexamethasone-implant injections. They found results in their real-world clinical setting similar to those reported in the controlled phase 3 GENEVA trial. Notably, although 32.6% of patients had elevation of intraocular pressure (≥10 mm Hg), only 1.7% percent required glaucoma incisional surgery, and 80% of those patients had preexisting glaucoma or ocular hypertension prior to their first dexamethasone implant injection (Figure 4).[22]

WHICH OPTION TO CHOOSE?

With so many viable options available for treatment, how does one decide on a treatment course? In a commentary, Hahn and Fekrat[23] noted that the major obstacle to incorporating an evidence-based approach to the management of RVO-related edema is that the reported prospective clinical trials have differing primary endpoints. Additionally, although a single small retrospective series found favorable results when treating RVO-related macular edema that was nonresponsive to bevacizumab with the dexamethasone implant, there is a dearth of prospective clinical trials comparing different treatment options head to head.[24] In the absence of clearly defined treatment guidelines, we recommend incorporating the patient into the decision-making process. Patients must be educated that available intravitreal therapies for RVO-related macular edema may not be curative of the underlying pathologic processes and thus often require multiple treatments over an extended period, with no definite endpoint for treatment. Unlike the bimonthly regimen used to treat exudative age-related macular degeneration, patients must be informed that aflibercept is FDA-approved only for monthly application in RVO treatment, resulting in the same treatment interval as bevacizumab and ranibizumab. Similarly, although dexamethasone implantation results in longer treatment intervals and, therefore, fewer total injections, patients should specifically be educated regarding the risk of secondary glaucoma and cataract progression. Recent reports have found that the dexamethasone implant has the added benefit of clinically significant improvement in angiographic findings related to neovascularization, findings that merit inclusion in the physician-patient discussion regarding treatment course.[25]

UVEITIS AND ASSOCIATED MACULAR EDEMA

Just as the increasing number of available intraocular treatment options has redefined the treatment of RVO-related macular edema, the treatment of macular edema secondary to noninfectious uveitis has drastically changed due to new ocular and systemic therapies. An extensive, but not exhaustive, list of therapeutic classes that are available for treatment of uveitis and uveitic macular edema includes steroids, carbonic anhydrase inhibitors, anti-VEGF therapies, and immunomodulatory drugs (including antimetabolites, T-cell inhibitors, alkylating agents, and biologic agents).[26] When approaching treatment of patients with noninfectious uveitis and macular edema, major considerations include calming active inflammation and preventing recurrent inflammation, both of which will potentiate edema presence.[27]

STANDARD AND OTHER FORMS OF CORTICOSTEROIDS FOR UVEITIS

Corticosteroids are the mainstay of initial treatment for uveitis, as they serve multiple clinical purposes, including calming active inflammation, aborting potential episodes of recurrent inflammation, and buying time for potential systemic medications to take effect.

Although topical steroids are typically the first treatment option chosen, depot injection of periocular steroids is more advantageous for uveitic cystoid macular edema due to higher drug proximity to the macula resulting in increased intraocular concentrations.[28] Intravitreal triamcinolone acetonide is often used, but, as in its other applications, it carries a higher risk of glaucoma development and cataract progression.[29] The sustained release fluocinolone acetone implant (Retisert, Bausch + Lomb) offers more constant, sustained steroid presence in the posterior segment, but must be placed in the operative setting, and the implant itself is nonbiodegradable. Alternatively, the dexamethasone intravitreal implant is biodegradable and can be injected in an office setting, and, as such, has become more frequently used for pars planitis and posterior noninfectious uveitis treatment.[30,31] Oral prednisone carries many well-established systemic and ocular risks including peptic ulceration, osteoporosis, hip necrosis, weight gain, and progression of glaucoma and cataracts.

OTHER TREATMENT OPTIONS

Anti-VEGF agents have been utilized in uveitic macular edema with varying degrees of success. Although elevated aqueous humor levels of VEGF have been demonstrated in patients with uveitis and macular edema, treatments to lower VEGF levels alone do not address the upstream mediators of persistent inflammation that initially led to edema development.[32] Systemic therapy with immunomodulatory agents has a positive effect on inflammation in many patients with uveitis, although the effect on macular edema may be delayed. In such a situation, local therapies such as the dexamethasone intravitreal implant tend to buy time for the immunosuppressive agents to take effect and to allow referral to a uveitic center if needed.

DISCUSSING TREATMENT OPTIONS WITH THE PATIENT

As with patients with RVO-related macular edema, uveitic patients with uveitis have a multitude of available treatment options. The major limitation to the treating physician relates to the fact that most published literature involves case reports and retrospective reviews. In light of this, a thorough discussion with the patient must be undertaken, in which the physician is transparent about the available treatment options. It should be stressed that disease processes of RVO and uveitis are chronic in nature, and that, until more evidence is amassed, the treatment of such patients often revolves around a dynamic treatment strategy, which can be changed over time depending on the reaction to treatment. ■

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