Treatment of Uveitic Cystoid Macular Edema

Three case reports discuss the management of inflammatory CME.

BY PRANJAL THAKURIA, MD; AND C. STEPHEN FOSTER, MD

Uveitis is a common cause of preventable blindness in the developed world. Significant visual loss in patients with intraocular inflammation is most commonly a consequence of cystoid macular edema (CME).¹ More than 50 years ago, Irvine first described postoperative CME following cataract surgery.² It is now a recognized complication associated with a number of ocular diseases, such as uveitis, retinitis pigmentosa, diabetic retinopathy, and retinal vein occlusions.³ CME is more likely to occur in cases of posteriorly located inflammation, and the formation of epiretinal membranes may be an associated feature.⁴ In a study by Lardenoye et al,³ CME was noted in 33% of all uveitis patients in a tertiary referral center. Those with CME had an average Snellen visual acuity of 20/80, as compared with 20/50 in uveitis patients without CME. Patients with intermediate or panuveitis were most likely to have CME, and patients were most likely to have CME in the context of visual impairment (20/60 or worse). Overall, visual impairment was caused by CME in 42% of patients. Poor visual acuity in uveitic CME was related to increasing age and chronicity of inflammation.

The pathophysiology of uveitic macular edema is not fully understood. The accumulation of fluid in CME may be secondary to dysfunctional inner or outer blood-retina barriers, for example, through increased vascular permeability. This may be mediated by inflammatory cytokines, such as interferon-gamma, interleukin-2, interleukin-10, and tumor necrosis factor-alpha, as well as prostaglandins.⁵ Patients with uveitis and CME have higher concentrations of vascular endothelial growth factor (VEGF) in the aqueous humor as compared with those without CME.⁶ VEGF is a potent inducer of increased vascular permeability.⁷ The fluid accumulates in the outer retinal layers, although localization by optical coherence tomography (OCT) may not be precise.⁴ However, even in the setting of controlled inflammation, CME may persist, secondary to previous inflammatory insults to the retinal pigment epithelium, blood-retina barrier, and persistent cytokines.⁸ Chronic, untreated CME may lead to permanent visual loss and is associated with dam-

Figure 1. Patient 1: (A) Following a series of three bevacizumab and triamcinolone intravitreal injections, CRT decreased to 218 µm 7 months after starting octreotide. (B - C) Despite treatment, CRT increased to 617 µm and acuity decreased to 20/80.
age to photoreceptors or by ischemia, as well as with retinal thinning and fibrosis. Treatment of uveitic CME includes topical and systemic nonsteroidal antiinflammatory drugs (NSAIDs); corticosteroids delivered systemically, topically, regionally, or intraocularly; systemic carbonic anhydrase inhibitors; systemic somatostatin analogs; and VEGF inhibitors. There is no agreed-upon algorithm for treatment.

The following cases illustrate examples of the clinical course and treatment of uveitic CME.

**CASE PRESENTATIONS**

**Patient 1**

A 54-year-old woman presented in 2005 with decreased vision in the right eye. In 1985, she was diagnosed with Hodgkin’s disease, which was treated by nitrogen mustard, vincristine, procarbazine, and prednisone (MOPP) chemotherapy and radiation therapy. Following this, she had an episode of herpes zoster ophthalmicus in the right eye. She remained without any significant ocular symptoms for the next 20 years.

In 2005, she developed mild metamorphopsia in the right eye, with redness and a “tired feeling.” She was found to have Snellen visual acuity with correction of 20/80 in the right and 20/20 in the left eye. Slit-lamp examination of the right eye demonstrated 1+ conjunctival injection, fine keratic precipitates, no dendrites, 2+ flare, and 3+ cell. The left eye was unremarkable. Posterior segment examination revealed 2+ anterior vitreous cell, 1-2+ vitreous haze, and normal optic nerve in the right eye. She remained without any significant ocular symptoms for the next 20 years.

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She was treated for 14 days with intravenous acyclovir, topical prednisolone acetate, and 60 mg of prednisone daily, in a tapering schedule. After the course of intravenous acyclovir, the retinitis had improved, and she continued with oral acyclovir. The patient’s visual acuity improved to 20/25, and the retinitis was regressing, with a flat-appearing macula with no evidence of CME. Laser retinopexy was applied.

Approximately 4 months later, while on decreasing doses of topical steroid and continuing oral acyclovir, the patient noted gradual worsening of visual acuity in the right eye. At this time she presented to the Massachusetts Eye Research and Surgery Institution and was found to have acuity of 20/50 and evidence of active retinitis by examination and angiography. She again was started on intravenous acyclovir and systemic steroid. One week later, her visual acuity dropped to 20/60, and CME was present, with a central macular thickness (CMT) of 300 µm by OCT. She was transitioned to oral valacyclovir (Valtrex, GlaxoSmithKline), and topical nepafenac (Nevanac, Alcon Laboratories, Inc.) was initiated. Two months later, however, the CMT had increased to 400 µm. Pars plana vitrectomy with intravitreal injection of triamcinolone was performed for removal of vitreous debris as well as internal limiting membrane peeling for the CME, in November 2005.

The ensuing course was marked by various treatments for the edema followed by recurrent edema. Transseptal triamcinolone (40 mg) was given, but 1 month later the edema worsened, with more complaints of metamorphopsia. Intravitreal bevacizumab (2.5 mg; Avastin, Genentech) was given, with improvement of CMT to 299 µm. Two months later, the visual acuity was again 20/60, with 440 µm CMT. The NSAID therapy was modified by using topical bromfenac (Xibrom, Ista Pharmaceuticals) and adding oral diflunisal. Another transseptal 40-mg dose of triamcinolone was delivered. Visual acuity, however, continued to decrease to 20/100 due to continued CME, and 2 months later the patient received an intravitreal injection of...
triamcinolone acetonide (4 mg) and bevacizumab (2.5 mg).

There was a dramatic improvement in macular thickness following this injection; however, the patient developed a retinal detachment shortly after, in May 2006, and was treated with phacoemulsification, pars plana vitrectomy, scleral buckle, endolaser, and C3F8 gas. She was left aphakic. An epiretinal membrane was soon noted, and approximately 1 year later the CMT was 519 µm, with pinhole acuity of 20/70.

In October 2007, intravitreal bevacizumab (2.5 mg) was given, with minimal improvement. Thus, monthly intramuscular injections of octreotide (20 mg) were started. After 3 monthly doses of octreotide (Sandostatin, Novartis), macular edema remained, with CRT of 551 µm. The option of epiretinal membrane dissection was discussed, but the patient expressed preference for medical treatment. Following a series of three bevacizumab and triamcinolone intravitreal injections, the CRT decreased to 218 µm by 7 months after starting octreotide, and acuity improved to 20/30 with correction (Figure 1A).

Despite treatment, within a few months the macular edema had returned, the CRT was up to 517 µm, and the acuity was down to 20/80 (Figures 1B-C). Again, intraocular bevacizumab and triamcinolone were delivered.

Patient 2

A 6-year-old girl presented with a history of pauciarticular juvenile idiopathic arthritis (JIA) with positive antinuclear antibody (ANA), with associated anterior uveitis in both eyes.

In December 2005, at the age of 4, she had been on methotrexate for a year but was unable to be weaned off of topical steroid due to recurrent inflammation. She had Snellen visual acuity with correction of 20/100 in the right eye and 20/70 in the left eye. Slit-lamp examination demonstrated band keratopathy, 2+ anterior chamber cell in the left eye, and 2+ nuclear sclerosis cataracts in both eyes. The methotrexate dose was increased from 10 mg to 15 mg by mouth weekly. During an examination under anesthesia (EUA), IOP was measured at 9 and 10 mm Hg in the right and left eyes respectively, and B-scan ultrasonography demonstrated CME bilaterally; methylprednisolone 62.5 mg was given intravenously. A few months later, sub-Tenon’s triamcinolone injection was delivered bilaterally. The methotrexate was substituted by mycophenolate mofetil (400 mg) by mouth twice daily. The cataracts continued to progress, with 20/100 visual acuity in both eyes. The eyes remained quiet, and B-scan ultrasonography showed improved CME.

In July 2006, she underwent left eye cataract extraction, pars plana vitrectomy, and cyclitic membanectomy. She was given intraocular triamcinolone, and was left aphakic. Topical NSAIDs were started. She also underwent a cataract extraction and pars plana vitrectomy of the right eye, again without lens implantation. By February 2007, she had visual acuity of 20/60 in the right eye and 20/40 in the left with contact lenses. However, her joint inflammation was not well controlled on the mycophenolate mofetil (CellCept, Roche), and she was changed to methotrexate injections and systemic oral steroid. The steroid could not be tapered without flare of inflammation, and so infliximab (Remicade, Centocor, Inc.) was added, by intravenous infusion every 4 weeks. Her inflammation was controlled, and she remained without CME for several months, which was confirmed by OCT.

By June 2008, the interval between infusions had been extended to every 6 weeks due to limitations of insurance coverage. The vision worsened in the right eye to 20/100, and the CMT increased to 831 µm (Figure 2A). Due to continuing ocular inflammation and synovitis, the infliximab was increased in frequency to every 4 weeks and the methotrexate dose was increased. Although she was on topical NSAIDs, she continued to have persistent, albeit improved, edema, with CMT of 479 µm in September 2008. Plans for periocular steroid injections were made. In the interim of 10 days, however, there was

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Figure 3. Patient 3: (A) Prior to beginning treatment with implantable dexamethasone, CMT was 601 µm. (B) One week later, CME was reduced to 253 µm.
noted dramatic improvement, with acuity of 20/60 in the right and 20/40 in the left eye, and decrease of CMT to 179 and 200 µm respectively, (Figure 2B). The plans for steroid injection were cancelled, and the topical NSAID and immunomodulatory therapy were continued.

Patient 3
A 45-year-old woman presented in August 2005 with right eye redness, floaters, and pain, due to acute idiopathic anterior uveitis in the right eye. Her visual acuity was 20/30 in the right eye and 20/20 in the left. Examination showed 3+ anterior chamber cell. She was treated with topical steroids, and the inflammation resolved. However, in the next 9 months, she had two flares, which were treated with systemic steroids, and was referred to the Massachusetts Eye Research and Surgery Institution.

At her first evaluation here, she had visual acuity of 20/100 with correction in the right eye, improving to 20/70 with pinhole. Slit-lamp examination demonstrated anterior chamber flare. OCT demonstrated CMT of 478 µm. Serologic investigations were negative. She was treated with topical prednisolone acetate and topical bromfenac. Transseptal injection of triamcinolone (40 mg) was delivered to the right orbit. Three weeks later, she had tapered off of the steroid, the inflammation had resolved, and her acuity was 20/30 in the right eye. Systemic NSAID therapy with diflunisal 500 mg by mouth twice daily was commenced, and the topical NSAID was maintained.

A few weeks later, she experienced recurrent inflammation, and topical steroids were added for short-term management. By July 2006, her visual acuity had dropped to 20/200, with continued anterior inflammation and CMT of 480 µm. Transseptal triamcinolone was injected, and immunomodulatory therapy with mycophenolate mofetil was commenced. By the next month, there was resolution of inflammation and improved acuity of 20/30. The patient discontinued the mycophenolate mofetil due to a rash after 2 weeks. Diflunisal and bromfenac were continued, and the steroid was tapered off. Acuity remained 20/20 on this regimen with no inflammation for about a year. At that time, leukopenia was noted, with 2,800 white blood cells/cm³, and the diflunisal was stopped. This finding subsequently normalized. Bromfenac was continued through the duration of this case history.

After 1.5 years without a flare, there was recurrent anterior uveitis in the right eye in December 2007, with symptoms of redness and pain. Visual acuity was 20/40, with findings of 2 to 3+ anterior chamber cell, small posterior synechiae, trace posterior subcapsular cataract, and retinal thickening. A tapering schedule of topical steroid was initiated, as well as diflunisal, with improvement by 1 month with acuity of 20/30. Three months later, she had tapered off of steroid and had relapsed within 3 weeks with active, symptomatic inflammation. Visual acuity had declined to 20/100. Therapy options were discussed, including immunomodulatory therapies.

She was randomized into an implantable dexamethasone trial. At the start of the trial, she had CMT of 601 µm (Figure 3A). One week later, she was doing well with improvement in visual acuity to 20/30, with CMT of 253 µm (Figure 3B). Over the next several months, she remained stable on diflunisal and bromfenac with 20/20 vision. There has been no recurrence of leukopenia.

DISCUSSION REGARDING TREATMENT
Rothova,9 in a literature review of uveitic CME treatments, noted that one commonly sees progression of CME, which results in visual loss. Thus, starting treatment at an early stage is recommended.

Prolonged systemic NSAID has a beneficial effect.10 A retrospective study showed that patients treated with systemic NSAIDs compared similarly to those treated with transseptal steroid, with average improvement of three lines of Snellen visual acuity. Topical NSAIDs have demonstrated efficacy for the treatment of pseudophakic CME and are commonly used off-label for this purpose.11 Corticosteroids have been delivered by a number of routes, as described above. Periocular steroid injection is quick and effective and is commonly used for asymmetric cases. Systemic oral steroids can be given at 1 to 1.5 mg/kg, and tapered according to clinical course; however, this is associated with well-known systemic side effects.9 Intravitreal triamcinolone acetonide injections usually bring about a quick improvement of vision, but this can be transient.12 A review of the literature13 found a mean maximum improvement to 20/50 from a mean baseline of 20/100 with improvement of CME on OCT within the span of 6 days to 3 months. However, 76% had recurrence of CME within 6 months. Complications include bacterial endophthalmitis, with a rate of 0.5%, in addition to pressure elevation and cataract.13,14 Similarly, a small case series15 demonstrated efficacy in the treatment of uveitic CME in the pediatric population, with fast resolution of edema usually within a few weeks, and with relapse rate of 31% after a median 7 months. Possible roles for implantable steroids are illustrated by Patient 3.

Acetzolamide (Diamox, Wyeth Pharmaceuticals) has been found to be beneficial in about 25% of patients in the treatment of uveitic CME; however, it is suggested that it may not have a significant effect on acuity in patients with chronic uveitis.16 Better results may be seen in patients whose uveitis is in remission.17 Bevacizumab is a recombinant humanized anti-VEGF...
monoclonal antibody that has been used off-label in the treatment of age-related macular degeneration. A small case series suggests that intravitreal injection of bevacizumab can be an effective short-term treatment for uveitic CME in patients resistant to other medical therapy, with increased chance of improvement in acuity starting at 6 weeks. Limitations of this therapeutic strategy include the short half-life of bevacizumab in the eye, as well as its lack of significant antiinflammatory action.

The use of octreotide, a somatostatin analog, has been described in a case report and shown in a case series to be effective in reducing uveitic CME in up to 70% of episodes within an average of 2.7 months in quiescent eyes, but the edema recurred in about 65% within 6 months after discontinuing treatment. Somatostatin is an inhibitory hormone of growth hormone and has immunomodulatory function. It and its receptor are found in the eye and may be involved in retinal pigment epithelium-mediated fluid transport and may also inhibit retinal vascular endothelial proliferation. A retrospective study demonstrated that uveitic CME that is refractory to medical therapy may respond to pars plana vitrectomy with internal limiting membrane peeling and intravitreal triamcinolone. There was improvement in both CME and visual acuity; however, the effect was transient, greatest in the first 3 months. Cataract formation and increased intraocular pressure were notable complications. Additional benefits from the intravitreal triamcinolone or the membrane peeling was not clearly demonstrated.

### CONCLUSION

The cases described above illustrate our “stepladder” approach to therapy (Table 1). Patient 2 had significant resolution of edema by improved control of ocular inflammation. However, CME can persist in spite of uveitis being in remission. Immunomodulatory therapy should be increased only if one sees objective evidence of active inflammation, not just because CME is present. As discussed, CME can exist because of dysfunction of barrier or pump functions, or other factors, even if inflammation is not present. We advocate treating CME in a stepladder fashion, moving along with the addition of different therapies as needed to chase away the edema. This will work only if inflammation is in remission. The cases of Patients 1 and 3 demonstrate the often recalcitrant nature of CME in the setting of uveitis, which may be resistant to a number of treatment modalities.

**Pranjal Thakuria, MD, is a Clinical Fellow with the Massachusetts Eye Research and Surgery Institution (MERSI) in Cambridge, MA. C. Stephen Foster, MD, is the Founder and President of MERSI. The authors have no financial interest in this article. Dr. Foster can be reached at +1 617 621 6377; fax: +1 617 494 1430; or via e-mail: fosters@uveitis.org**

### TABLE 1. STEP-LADDER APPROACH TO TREATMENT OF UVEITIC CME

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