ABSTRACT

Devising treatment strategies for uveitic macular edema (UME) is challenging because the UME can persist even when the uveitic inflammation has been controlled by immunosuppressive agents. Increasing systemic immunosuppressive treatment may not lead to improvement of edema, and adjunctive therapy, often with corticosteroids, is frequently needed. Published reports describe various agents for UME, but there is no consensus as to which treatments are preferred. A Medline search was performed for clinical studies of the treatment of UME, and the Web site www.clinicaltrials.gov was consulted to see if there were relevant clinical trials. This article highlights results from those searches. The evidence level is overall low (usually level 2 or 3) for the treatment of macular edema in uveitis. Most studies showed no more than slight benefit to treatment possibly because visual improvement was limited by damage from prior edema. A variety of corticosteroids and various routes of administration have been studied. More recently biologic agents and other immunomodulatory drugs have been employed. Improved study designs with randomization, sufficient sample size, and follow-up are necessary to define the optimal management of UME. Outcome measures of standardized visual acuity using Early Treatment Diabetic Retinopathy Study charts and optical coherence tomography parameters will provide additional information on structure and function beyond the standard assessment of fluorescein leakage. (Adv Stud Ophthalmol. 2010;7(2):60-66)

Uveitic macular edema (UME) is particularly challenging because, even when the inflammation is controlled by immunosuppressive agents, UME can still be present, and increasing systemic immunosuppressive treatment often does not lead to improvement of edema. Case reports describing the use of various agents for UME have been published, but there is no clear guidance for which agents are superior. To address this question, a Medline literature search was performed, limiting the articles to those published in 2005 to 2010, in the English language (or with an English abstract), with the search term “uveitic cystoid macular edema” (CME) or uveitic macular edema. Clinicaltrials.gov also was searched for research trials involving uveitic CME and yielded 1 randomized controlled trial from 1996. Relevance and evidence levels were assigned to each article, based on the criteria outlined in Table 1. This article discusses the highlights of that literature search. The literature review revealed a small number of papers on risk factors for UME. Patients with intermediate uveitis appear to have a higher risk of UME.
Also, adults are more prone than children (odds ratio of 3.8 [95% confidence interval, 1.6-9] for those >50 years of age vs <50 years). The long-suspected higher risk of UME in smokers with uveitis has been quantified as a 4% higher risk for each cigarette smoked per day. Risk of UME is obviously assumed to be higher if there is uncontrolled inflammation. There is also an assumed higher risk in patients with an attached hyaloid and vitreomacular traction; therefore, vitrectomy also has been proposed as beneficial in UME related to uveitis, but unproven as a reliable therapy to improve vision.

Almost all patients with uveitis are initially treated with topical corticosteroids, which, in some cases, is sufficient to resolve the UME. For the remaining patients, the treatment strategies are highly variable. The majority of the Medline search returned articles concerning these treatment options for CME or UME.

**TREATMENT OPTIONS FOR UME**

**CORTICOSTEROIDS**

There are many drugs and routes of administration for the administration of corticosteroids. In addition to topical drops, there are regional injections given subconjunctivally or subtenon, iontophoresis, intravitreal injections of drugs, modified drugs, crystals, or matrices, intraocular implantation of drug-delivery devices, and oral and intravenous administration. Table 2 lists the corticosteroids that are approved by the US Food and Drug Administration in the United States for the treatment of uveitis by at least 1 route of administration.

There are no Level 1 studies involving corticosteroids that have uveitic CME as the primary outcome measure. There are Level 1 studies of corticosteroids in uveitis, but none specifically for CME or UME, including studies of topical corticosteroids.

One study compared regional use of corticosteroids for CME secondary to intermediate uveitis in 30 eyes by 3 different methods of posterior subtenon injection (via cannula, via needle using the remaining patients, the treatment strategies are highly variable. The majority of the Medline search returned articles concerning these treatment options for CME or UME.

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One study compared regional use of corticosteroids for CME secondary to intermediate uveitis in 30 eyes by 3 different methods of posterior subtenon injection (via cannula, via needle using the
Smith/Nozik technique, and via orbital floor injection). The results showed that the different methods of injection improved visual acuity equally, but that the cannula method, in which a blunt cannula is passed posteriorly along a long, tunneled track, achieved the greatest quantitative reduction in macular thickness (Level 2B).9

Intravitreal triamcinolone (various formulations) is commonly used for CME. Numerous studies on the use of this steroid in CME have been published (Table 3).10-16 Of note, the patient numbers are small in almost every study (range, 6–54). Doses ranged from 2 to 10 mg of intravitreal triamcinolone. The relevancy of these studies is labeled C (slight evidence for benefit) because, although intravitreal triamcinolone was often effective in reducing CME, it was less effective in improving visual acuity, likely because of pre-existing macular damage in many cases. No study confirmed that injection of intravitreal triamcinolone into the vitreous cavity was clearly beneficial to patients. This may have been due to study design, patient selection, or to an inherent limitation of this treatment for uveitic CME.

Surgically implanted fluocinolone acetonide-containing sustained-release drug-delivery device (SR-DDD; Retisert; Bausch & Lomb, Rochester, NY) was evaluated at 2 doses (0.59 or 2.1 mg) in a phase III study in which CME was a secondary outcome, measured as surface area of leakage on fluorescein angiography. The results showed significant reductions in leakage with both doses at year 1, but by year 3, the reduction was significant only in the lower-dose group, a finding perhaps related to technical difficulties with the higher-dose implant (Level 1A).17

Another, multicenter, European, open-label, superiority trial compared the 0.59-mg surgically implanted fluocinolone SR-DDD with standard care (N = 140) with a primary outcome of first recurrence of uveitis and, for those with CME, the proportion of patients with CME who had a reduction in CME area of more than 1 mm². In the implant group, 86.5% of patients had improvement in CME by this criteria, compared with 74.4% in the standard-of-care group (P = .003; Level 2C).18 Relevancy is considered “C” or “slight benefit” because the amount of reduction in leakage that was considered improvement was so small and because no other outcomes of importance such as visual acuity or optical coherence tomography (OCT) measures were studied in relation to CME.

**Table 3. Summary of Evidence for Intravitreal Triamcinolone for Uveitic CME**

<table>
<thead>
<tr>
<th>Year</th>
<th>Design</th>
<th>Patients, n</th>
<th>Treatment</th>
<th>Outcomes</th>
<th>EBM Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>Retrospective</td>
<td>54</td>
<td>IVTA 4 mg</td>
<td>VA Snellen</td>
<td>3C (M)</td>
</tr>
<tr>
<td>2005</td>
<td>Retrospective</td>
<td>30</td>
<td>IVTA 2 mg</td>
<td>VA Snellen</td>
<td>3C (M)</td>
</tr>
<tr>
<td>2005</td>
<td>Retrospective</td>
<td>12</td>
<td>IVTA 2 mg</td>
<td>VA Snellen</td>
<td>3C (M)</td>
</tr>
<tr>
<td>2007</td>
<td>Retrospective</td>
<td>7 Behcet</td>
<td>IVTA 4 mg</td>
<td>VA FA OCT</td>
<td>2C (#)</td>
</tr>
<tr>
<td>2008</td>
<td>Retrospective</td>
<td>6</td>
<td>IVTA 4 mg</td>
<td>VA OCT</td>
<td>2C (#)</td>
</tr>
<tr>
<td>2008</td>
<td>Retrospective</td>
<td>33 eyes</td>
<td>IVTA 10 mg</td>
<td>VA</td>
<td>3C (M)</td>
</tr>
<tr>
<td>2009</td>
<td>Retrospective</td>
<td>18</td>
<td>IVTA 4 mg</td>
<td>VA OCT</td>
<td>2C (O)</td>
</tr>
</tbody>
</table>

M indicates low rating because of methods; # indicates low rating because of results (slight evidence for benefit); Behcet = Behcet’s disease/syndrome; CME = cystoid macular edema; EBM = evidence-based medicine; FA = fluorescein angiography; IVTA = intravitreal triamcinolone; OCT = optical coherence tomography; VA = visual acuity.

Data from Kok et al10; Das-Bhaumik and Jones11; Angunawela et al12; Atmaca et al13; Dong et al14; Hogewind et al15; and Maca et al16.

**Pediatric Patient with Uveitic CME**

JG is a 190-lb, 11-year-old girl with decreased visual acuity beginning in January. In June, she reported seeing “floaters” and was referred to an ophthalmologist, who started her on 60-mg prednisone for active intermediate uveitis. After 6 weeks, the prednisone was tapered down to 10 mg by mouth.

Results from laboratory testing were all negative: Mantoux test, complete blood count, comprehensive metabolic panel, antinuclear antibodies, rheumatoid factor, and HLA-B27.

(continued on next page)
On examination, best corrected visual acuity was 20/70 OD, 20/100 OS, similar to her visual acuity at presentation. Anterior chamber cell was 1+ (right eye) and 2+ (left eye), with flare 1+ (both eyes). Intraocular pressure was 14 mm Hg in both eyes. Bilateral optic nerve edema was observed, along with bilateral 2+ vitreous cell and 1+ vitreous haze. She also had bilateral CME.

Fundus examination shows the CME, haze, and optic nerve edema. Mid-venous phase fluorescein and indocyanine green angiography (FA/ICG) are negative, with no evidence of choroid infiltrates, but massive retinal edema as well as focal leakage around the optic nerve and along the vessels is observed.

Fundus images show active inflammation, vascular leakage, and neovascularization. Intraretinal microcystic edema is observed as pinpoint dots with no choroidal leakage.

Central retinal thickness was measured by OCT: 753 µm (right eye) and 611 µm (left eye). Large cysts are present in both eyes. The outer retina looks intact.

Late-phase FA/ICG shows leakage off the disk in these vessels in both eyes. There are non-filling macular cysts as well as microcystic collections that are densely packed in the temporal macula of each eye.

The working diagnosis for the reduced vision is noninfectious, undertreated, anterior and intermediate uveitis with retinal leakage, retinal neovascularization, and CME.

What role do steroids have in treating this patient? How does her young age and weight affect your treatment choice? How long should a patient be followed before a treatment is determined to be unsuccessful? For further discussion of the challenges in managing this real-life situation, please go to www.JHASIO.com/retinaldiseases.

**BIOLOGIC AGENTS**

Several new biologic agents are being evaluated for UME. Systemic agents include interferons α and β and tumor necrosis factor (TNF) inhibitors (infliximab [Remicade; Centocor Ortho Biotech, Inc, Malvern, PA] and adalimumab [Humira; Abbott Laboratories, North Chicago, IL]); vascular endothelial growth factor inhibitors (bevacizumab [Avastin; Genentech, Inc, South San Francisco, CA] and ranibizumab [Lucentis; Genentech, Inc, South San Francisco, CA]) are delivered intravitreally.

Interferon α2a is currently only used for UME and uveitic CME and not other types of CME. Although most of the immunologic effects of interferon α are open to speculation, it is known to reduce vascular leakage by stabilizing the vascular wall. A small, German study of 24 patients with chronic uveitic CME were treated with 3 versus 6 million U interferon subcutaneously, daily, and then tapered over 6 months. Complete resolution as measured on OCT was observed within 3 months in 62.5% of patients; 25% had incomplete resolution or were unable to taper the dose. It was deemed ineffective in 12.5% of study patients (Level 2B).19

Ranibizumab was studied in a randomized, prospective, uncontrolled trial in which 7 patients received 3 monthly injections of 0.5 mg. After 3 months, visual acuity increased by a mean of 13 letters (P = .03) in the 6 patients who completed follow-up, and central retinal thickness decreased by a mean of 357 µm (P = .03). The improvement was maintained at 6 months, but reinjections were required (Level 2B).20 A retrospective study of 29 eyes receiving intravitreal bevacizumab as a single injection, 2 sequential injections, or in combination with triamcinolone acetonide injectable suspension (Trivaris; Allergan, Inc, Irvine, CA) found a small improvement in visual acuity after 1 year, but the visual acuity was not measured by standardized Early Treatment Diabetic Retinopathy Study parameters. Central macular thickness decreased from 383 to 294 µm (P = .0007; Level 2B).21 There have been several other studies of intravitreal bevacizumab for uveitic CME. Most had small numbers of patients (10–13) and offer 2C or 3C level of evidence. Nonetheless, this drug is of interest to clinicians because it can sometimes be used when ranibizumab is not an option due to cost/reimbursement considerations.

Intravenous infliximab was evaluated in a small, prospective study of 10 patients. Patients received 5 mg/kg as a single injection, and 5 patients were retreated once. After 2 months, decimal visual acuity increased from 0.41 to 0.82 (P <.00001) and macular thickness decreased from 428 to 218 µm (P = .00001; Level 2B).22 Despite the small patient numbers, this study showed fair evidence for a benefit from treatment with a TNF inhibitor, as has already been shown for the treatment of uveitic inflammation.
Several systemically administered and intravitreal drugs have been evaluated for UME and uveitic CME: mycophenolate mofetil (CellCept; Roche Laboratories Inc, Nutley, NJ), octreotide (Sandostatin; Novartis Pharmaceuticals Corporation, East Hanover, NJ), acetazolamide (Diamox; Wyeth, Collegeville, PA), and intravitreal methotrexate.

Mycophenolate mofetil was evaluated in a retrospective study of 19 consecutive patients who were treated for 1 year. Mean best corrected visual acuity improved from decimal 0.34 to 0.65 and fluorescein angiography-documented resolution of CME was observed in 18 of the 19 patients. Central foveal thickness decreased to 167 µm on OCT (Level 2B).23

Oral acetazolamide was evaluated in a randomized, masked, cross-over, placebo-controlled study of 40 patients. Acetazolamide resulted in a 0.5-disc area decrease (25%) in CME over placebo (P = .01) but had no effect on visual acuity (0.6 letters gained, P = .61; Level 1C).1 A later prospective study of 45 patients (52 eyes) evaluated the effect of acetazolamide at an initial dose of 500 mg/day. The patients were followed for a mean of 3.1 years, much longer than the earlier study. Visual acuity improved in both patients with quiescent uveitis (P = .012) and those with chronically active uveitis requiring additional systemic anti-inflammatory drugs (P = .025). Sixteen patients required a maintenance dose of 125 to 500 mg (Level 2B).24

A pilot study evaluated intravitreal methotrexate in 15 patients with uveitis and UME. Only single eyes were injected; patients were selected for the study because they had a unilateral exacerbation, visual acuity of 20/40 or worse, and a history of increased intraocular pressure in response to corticosteroid administration. Visual acuity improved at all time points, significantly so at the 3- and 6-month time points. Those with prior treatment with intravitreal triamcinolone had as much improvement as those with no history. Five patients relapsed after a median of 4 months but a similar improvement was seen after reinjection (Level 2B).25

A common question is the effect of vitrectomy on the efficacy of triamcinolone acetonide injectable solution (Kenalog-40; Bristol-Myers Squibb Company, Princeton, NJ). A retrospective review of 16 patients (20 eyes) found that, after intravitreal triamcinolone injection for chronic CME, mean visual acuity at last follow-up showed statistically significant improvement in non-vitrectomized eyes (mean baseline visual acuity: 1.14 ± 0.58; mean final visual acuity: 0.96 ± 0.66; P =

VITRECTOMY

Results from studies of vitrectomy for UME have been mixed. One small study evaluated pars plana vitrectomy in combination with intraoperative intravitreal triamcinolone injection in 19 patients. Angiographic improvement was observed in 58% of patients but was often transient; visual acuity improved in 42% of patients after 3 months and in 38% after 12 months. Cataract progressed in 85% of phakic patients postoperatively.26 However, a prospective, interventional, randomized, controlled, pilot study of 23 eyes (23 patients) found that mean visual acuity in those receiving vitrectomy improved significantly from logMAR 1.0 (± 0.62) at baseline to 0.55 (± 0.29) at 6 months (P = .011), with 5 (42%) eyes reaching vision of 20/40 or better. CME after vitrectomy was angiographically improved in 4 (33%) eyes, remained unchanged in 7 (58%) eyes, and deteriorated in 1 (8%) eye (Level 2B).27

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Patient with Bilateral Anterior and Intermediate Uveitis Associated with Multiple Sclerosis

AH is a 46-year-old woman who presents to a retina specialist because her vision did not improve after an intravitreal injection of triamcinolone acetonide. She was diagnosed with multiple sclerosis (MS) in 1994 and was diagnosed with bilateral anterior and intermediate uveitis associated with MS. Visual acuity is 20/200 OD and 20/25 OS. She had taken methotrexate and interferon β for her MS in the past but at this visit, she is no longer taking them. OCT shows vitreomacular traction with subfoveal fluid in her right eye and a small amount of leakage but a healthy macula in her left eye.

How would you treat this patient? As you follow her over several years, what do you consider when choosing among localized treatment: an immunosuppressive agent, a steroid, or a biologic agent? For further discussion of the challenges in managing this real-life situation, please go to www.JHASIO.com/retinaldiseases.
.02) compared to the almost unaltered mean visual acuity for vitrectomized eyes (mean baseline visual acuity: 0.76 ± 0.41; mean final visual acuity: 0.71 ± 0.48; P = .40; Level 3B).

**Current Clinical Trials**

A study evaluating 2 doses of a dexamethasone intravitreal implant (Ozurdex; Allergan, Inc, Irvine, CA) for intermediate and posterior uveitis has just been completed. The primary outcome measure is vitreous haze; secondary outcome measures include visual acuity, retinal thickness, and quality-of-life questionnaires (NCT00333814). Other current studies (from the www.clinicaltrials.gov Web site) include ranibizumab vs triamcinolone, ranibizumab alone, pegaptanib (Macugen; Eyetech Pharmaceuticals, Inc and Pfizer Inc, New York, NY) alone, bevacizumab vs triamcinolone, intravitreal diclofenac vs triamcinolone, and topical interferon γ-1b alone.

**Conclusions**

The evidence strength for treatment of macular edema in uveitis is overall low. Study deficiencies include small patient numbers, lack of UME as a primary outcome measure, and short duration of follow-up. Most clinical trials with higher quality designs have a primary goal of controlling inflammation. Benefits for the treatment of UME may be difficult to show if patients enter with damage from prior edema. Corticosteroids remain the most widely used treatment for ME in uveitis, often as an adjunctive agent combined with immunosuppressive therapy as the primary therapy for the uveitis. Other adjunctive agents specifically for UME and uveitic CME, and good studies to evaluate them, are clearly needed.

**References**


