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Uveitic Macular Edema: Treatment Update

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Abstract

The aim of this review is to summarize recent developments in the treatment of uveitic macular edema (ME). ME represent a major cause of visual loss in uveitis and adequate management is crucial for the maintenance of useful vision in patients with chronic uveitis.

Keywords

Uveitic macula edema; uveitis; corticosteroids; immunosuppressive therapy; inflammation; inflammatory edema

INTRODUCTION

Although uveitis is relatively uncommon, it is a leading cause of vision impairment and blindness in the developed world. Furthermore, because it more often affects younger patients than, say, age-related macular degeneration, uveitis results in a disproportionate number of years of lost visual function¹.

“Uveitis” comprises many different disorders with a variety of causes, although the etiology nearly half of all cases remain unknown.

Uveitic macular edema (ME) is a complex condition. It is not a disease itself, rather the endpoint of a variety of cellular and molecular nonspecific inflammatory processes that lead to accumulation of fluid in the central retina. The vascular leakage is especially prominent at the macula and is generally located in the outer plexiform layers as demonstrated by optical coherence tomography (OCT).² The intraretinal fluid accumulates where there is loss of functional integrity in either the inner/outer blood-retinal barrier and disturbance in the pumping function of the retina pigment epithelium cell tight junctions. It seems that the most important pathogenic mechanism in uveitic ME is the loss of inner blood-retinal barrier integrity caused by the constant release of inflammatory mediators, including prostaglandins

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Conflict of Interest

Raquel Goldhardt declares that she has no conflict of interest. Bradley Simon Rosen

Human and Animal Rights and Informed Consent

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and leukotrienes, protein kinase C, nitric oxide and cytokines such as interleukins, tumor necrosis factor α , and vascular endothelial growth factor (VEGF) all generated by the underlying uveitic process³. Molecular mediators within the inflammatory system activate feedback loops that up-regulates the production of more such mediators in what can be seen as a vicious cycle.⁴ The pathogenesis still poorly understood due to a lack of an adequate animal model to study the process.

The relationship between angiogenesis factors and vascular leakage is well established. Vascular leakage results from breakdown of the blood-retinal barrier, which may be induced by VEGF or by other inflammatory mediators causing damage the retinal pigment epithelium (RPE), leading to failure of its pump, metabolic, and waste systems.⁵

Numerous treatment options targeting systemic and ocular inflammatory mediators have demonstrated efficacy in improving visual acuity in patients with uveitic ME. There is a strong relationship between the degree of the intraocular inflammation and response to therapy.⁶ Topical non-steroidal anti-inflammatory drugs (NSAIDs) block the cyclooxygenase enzymes and inhibit prostaglandins synthesis, thereby reducing inflammation.^{7,8} Other therapeutic options for recalcitrant and resistant cases include posterior sub-Tenon corticosteroids injections, systemic corticosteroids, intravitreal steroids, systemic carbonic anhydrase inhibitors, and anti-VEGF drugs, intravitreal delivery steroid systems, systemic or intravitreal steroid-sparing immunosuppressive drugs and systemic or intravitreal biologics, mainly anti-TNF α agents.

Mechanical and chemical deformations of the vitreous can make ME even more complex, since uveitic eyes may develop mechanical mechanism of macular swelling as well. The main vitreoretinal interactions reported are thickening of posterior hyaloid, vitreoretinal traction, epiretinal membrane, and retinal fibrosis. Accordingly vitrectomy can plays a role in managing select cases.⁹ Additional factors that may be important in the pathogenesis of mechanical vitreoretinal abnormalities include duration of inflammation, and history of smoking.^{10,11}

The degree of visual loss is influenced by the location, severity, and duration of ME. The early stages of uveitic ME may be more responsive to treatment than chronic forms. This may be because of permanent structural anomalies due to the constant release of inflammatory mediators and retinal atrophy which occur in chronic cases, or may represent the observation that one subset of uveitis may resolve spontaneously within a few months and create the appearance that acute cases respond better. Since a non-edematous macula has a better chance of maintaining visual acuity than an edematous counterpart.¹² The control of the uveitis is critical to prevent and treat the ME. Treatment of fluid is worthwhile even in the absence of visual improvement.

EPIDEMIOLOGY

The estimated annual incidence of uveitis is 17–52 cases per 100,000.¹³ Prevalence is approximately 38–714 per 100,000. Most available data pertains to populations in developed countries.

MEDICAL TREATMENT

Diagnostic efforts, while not uniformly fruitful, are requisite first steps. Distinguishing between infectious/non-infectious; acute/chronic; panuveitic/limited forms of uveitic entities help narrow diagnostic possibilities and better treatment to disease. Persistent subclinical inflammation, multiple vitreomacular mechanical interactions, membrane formation on the macular surface, retinal pigment epithelium detachment pump dysfunction etc. are all complications which can irreversibly alter vision and are legitimate treatment targets as well. Literature review of uveitic ME treatments commonly suggest the condition results in progressive visual loss⁶. Therefore, early treatment is advised even in patients with full visual acuity².

Mainstays of treatment for uveitic ME include systemic and topical corticosteroids and NSAIDs, each of which has better demonstrated efficacy in the prophylaxis and treatment of inflammatory ME related to surgery or to uveitis.^{7,14} In unilateral ME, local treatment is typically preferred, while the use of systemic immunomodulatory agents may be preferable to achieve remission in bilateral cases.

1. Nonsteroidal Anti-inflammatory Drugs

Although NSAIDs are regularly prescribed for inflammatory ME, their effect is often disappointing. NSAIDs inhibit production of cyclo-oxygenase (COX1–COX2), pro-inflammatory prostaglandins (PGs), and thromboxane.^{7,8} Recent randomized, double blind, placebo-controlled clinical trial by Allegri *et al* showed that administration of 0.5% indomethacin eye drops four times a day in eyes with a variety of uveitic ME subtypes was associated with a significant reduction in ME at the 6-month follow-up as measured by spectral-domain optical coherence tomography (SD-OCT).

Bromfenac is an attractive NSAID agent because it can achieve therapeutic levels in the retina after topical application onto the cornea, has minimal evidence of complications or side effects.¹⁵ It was shown to prevent macular edema and ocular inflammation after cataract surgery in non-insulin-dependent diabetic patients.^{16,17} Nepafenac 0.1% was recently shown to be a promising drug for treatment for acute pseudophakic CME.¹⁸ Bromfenac has better penetration into ocular tissue, and longer duration of anti-inflammatory activity compared to Nepafenac.¹⁹ Foster and associates reported in a retrospective comparative case series suggesting that Bromfenac alone is ineffective for uveitic macular edema, but may have a synergistic effect with intravitreal steroids.²⁰

2. Corticosteroids

Corticosteroids target neutrophil transmigration and decrease cytokine production, and broadly affect the immune system. The mechanism of action is complex and wide ranging. The primary anti-inflammatory activity occurs via the inhibition of prostaglandins and leukotrienes synthesis, and downregulation of cell adhesion and major histocompatibility molecules.²¹

Local steroid treatments include drops, periocular and intraocular injections, and long-term intraocular and periocular devices. Most drops have no effect, or a very modest effect on

macular edema. Accordingly drops should be employed for treatment of anterior manifestations of uveitis, and attempts to manage posterior segment complications should employ other means.

A. Periocular Corticosteroid Injections—Posterior subtenon injections were reported to have a beneficial though transient effect on ME. Different methods of periocular administration of corticosteroids (subtenon injections, subtenon cannula, and orbital floor injections) appear to have comparable efficacy and safety profiles.²² Other case series have shown similar outcomes and side-effect profiles. Cataract progression has been reported as a complication of periocular corticosteroids, with an occurrence as high as 17%.^{22–24} Pharmacologic effects from posterior subtenon corticosteroid injection lasts anywhere between 3 and 6 months. Single subtenon injections generally have limited influence on IOP increase and cataract development, though with repetition these side effects clearly increase.²⁵

B. Intravitreal Triamcinolone Application (IVTA)—In the last decade IVTA, usually ranging from 2 to 20 mg, has been widely adopted for various types of ME.²⁶ Intravitreal injection of triamcinolone appears more effective than periocular triamcinolone injections. However IVTA is linked to more side effects.²⁶ The rate of posterior subcapsular cataract formation is high, especially in the elderly population and with repeated injections. Intraocular pressure (IOP) rise has been observed in 20–60% of injected eyes. This phenomenon is more common in young patients with non-inflammatory ME and in those with multiple injections.^{27,28}

C. Corticosteroid Implants—The National Eye Institute (NEI)-funded Multicenter Uveitis Steroid Treatment (MUST) trial compared the efficacy and safety of local versus systemic treatments for severe forms of uveitis.²⁹ The study randomized patients (n=255) to either high dose oral corticosteroids for 1 to 4 weeks after which the doses were lowered, in some cases with cover by adjunctive immunosuppressive therapies, or to implantation with the fluocinolone acetonide 0.59mg intravitreal implant, which has duration of approximately 30 months.³⁰ The average visual acuity improvement over 2 years for patients in the implant group was slightly higher, but this difference failed to reach statistical significance. The implant ranked slightly higher in improvement of vision-related quality of life scales, but again, the difference between groups was not significant. Patients in the implant group had a higher risk of cataract formation, increased IOP, and glaucoma. Patients in the systemic treatment group had an increased need for prescription therapy to manage infection, but no other long-term complications. The study concluded there was no significant difference in efficacy and increased ocular complications when using the fluocinolone implant. Other smaller randomized clinical trials with good long-term follow-up showed improvement in visual acuity.^{31,32} The proportion of eyes with reduced CME was greater in the implanted group compared to non-implanted for all implant strengths.³¹ Pavesio *et al*/looking at only the lower dose found by 2-year follow-up, the proportion of improved CME was higher in the implant group (86.5%) compared to standard care (74.4%; $P=0.003$). However, use of implants remains limited due to concerns of costs and complications, including increased

intraocular pressure leading to filtration surgery and cataract progression.^{33,34} The range of patients requiring filtration surgery in these studies was 5.8 to 40%.

The dexamethasone intravitreal implant acts by binding steroid receptors in the cytoplasm and then by altering DNA expression in the cell nucleus. Dexamethasone is five times more potent than triamcinolone acetonide³⁵ but has a short half-life in the eye; hence the rationale for a sustained-delivery system. The duration of the sustained release is shorter than with the fluocinolone acetonide implant. The HURON study data showed the dexamethasone implant significantly improved visual acuity (15 or more letters) and reduced inflammation with a relatively good safety profile.³⁶ Kuppermann *et al* showed 27 patients who received implanted dexamethasone had a better outcome. He reported a 10-letter improvement in visual acuity in 54% compared to 14% of observed patients.³⁷ The follow-up however, was of short duration and conclusions on safety and efficacy must be tempered. A subgroup analysis for patients with persistent ME greater than 90 days showed that the overall study results applied to this group as well. The evidence is suggestive that intravitreal dexamethasone implants may be developed to become a viable intervention for uveitic ME.

Another case series data more focused on panuveitis (n=27), compared the efficacy and safety of the dexamethasone intravitreal implant with fluocinolone acetonide implant.³⁸ Reimplantation was 5 times more likely in the patients who received the dexamethasone implant, but this was most likely related to shorter activity duration and the length of the study. In regard to safety, 44% of patients with the fluocinolone acetonide implant required additional glaucoma medication, surgery, or laser, compared with no patients who received the dexamethasone implant. All patients in the fluocinolone acetonide implant group progressed to cataract and required surgery, compared with 50% of patients in the dexamethasone implant group. The two implants were equivalent in their ability to prevent recurrence of non-infectious uveitis, improve visual acuity, and reduced inflammation, but that the side effect profile was more favorable for the dexamethasone intravitreal implant.

D. Systemic Corticosteroids—Oral prednisone is often used to treat patients with significant vision-threatening uveitis bilateral inflammatory ME and for ME refractory to topical treatment. Relatively high dose “induction” therapy is generally recommended to achieve an anatomical recovery of the macula and they are typically continued until optimal visual acuity is achieved. When this stage is reached, steroid-sparing medications are started and the corticosteroids are tapered slowly. OCT studies have documented a more rapid decrease of ME with oral than with periocular corticosteroid treatment, making oral therapy the preferred route for some clinicians, especially if rapid recovery is essential.³⁹ However, side effects from systemic corticosteroid, including peptic ulceration, osteoporosis, aseptic necrosis of the hip, weight gain, muscle weakness, hyperglycemia, systemic hypertension, progression of glaucoma, and progression of cataracts convince others to avoid or minimize systemic corticosteroid therapy whenever possible.⁴⁰

3. Acetazolamide and Somatostatin Analogues

Acetazolamide is a carbonic anhydrase inhibitor. One sub-type of carbonic anhydrase, known as isoenzyme IV, is thought to be a membrane-bound fraction found in the atypical

region of the RPE cell. Inhibition of carbonic anhydrase reduces aqueous production and possibly also reduces leakage from the RPE. Data from 3 randomized studies looking at acetazolamide's efficacy in ME have been published.^{41–43} Acetazolamide had no significant effect on visual acuity in any of the studies. However, patients under 55 years appeared more likely to benefit from treatment than older patients.⁴² Acetazolamide was associated with adverse events including paresthesia, nausea, drowsiness, weight loss, chronic fatigue, cutaneous allergic reaction, and depression. Elevated liver enzymes, pain, and gastrointestinal distress have also been reported.

Octreotide is a somatostatin analog that works as a potent inhibitor of growth hormone releases as well as release of certain other agents. Studies suggest that somatostatin is synthesized by RPE housing receptors.^{44,45} Somatostatin analog may inhibit proliferation of human retinal endothelial cells and aid restoration of the inner blood-retinal barrier, which breaks down in posterior uveitis, leading to macular edema.

4. Anti-vascular Endothelial Growth Factor (Anti-VEGF) Treatment

Monoclonal antibodies against vascular endothelial growth factor (VEGF) were first developed as an intravenous treatment for metastatic colorectal cancer.^{46,47} VEGF has important roles in angiogenesis, which include up regulating methane monooxygenase and $\alpha\gamma\beta 3$ activity, and the creation of blood-vessel lumen and fenestrations.⁴⁸ In preclinical models, VEGF was shown to potentiate survival of existing vessels, encourage vascular abnormalities (that theoretically impede effective delivery of antitumor compounds), and stimulate new vessel growth. VEGF is an endothelial cell-specific mitogen, an angiogenic inducer, and a highly potent agent favoring retinal vascular permeability.⁴⁸ Moreover, VEGF has multiple pro-inflammatory effects, including a positive effect on chemotaxis and migration of monocytes and induction of B- and T-lymphocytes;⁴⁹ anti-VEGF therefore also has promise as an anti-inflammatory agent. Accordingly, intravitreal application of anti-VEGF drugs has been advocated as a powerful treatment option in ME.

The effect of anti-VEGF treatment of inflammatory ME have not yet been well investigated. The data on anti-VEGF efficacy in inflammatory ME are primarily derived from small clinical series and anecdotal reports based on a limited number of patients. In most cases, bevacizumab was injected into eyes with persistent ME, and quiescent uveitis. Three reports comprising 51 eyes, showed a significant but transient reduction in central retinal thickness in most patients.^{50–52} Twenty-nine eyes with ME showed a significant improvement in visual acuity and mean retinal thickness at one year.⁵¹ Weiss *et al* reported that patients with inflammatory ME responded well to bevacizumab treatment, unless there was extensive leakage from the choroid or leakage from the optic disk was detectable on pre treatment fluorescein angiogram (FA). In such patients, intravitreal triamcinolone, but not Anti-VEGF therapy, led to a reduction of ME.^{50,53} Anti-VEGF intravitreal injections have been associated with post injection uveitis.^{54–57} The pathogenesis of this type of uveitis is not understood. Possible explanations include contamination of the medications with bacterial endotoxins, formation of antibodies against immunogenic anti-VEGF molecules, and leaching of contaminants from disposable syringes, packaging materials or impurities.

Whether patients with uveitis have an increase risk on developing uveitis as a result of anti-VEGF activity remains to be further examined.

Due to the transient nature of anti-VEGF intraocular injections, this treatment modality is less suitable for ME in active chronic uveitis, and more practical in patients with persistent ME and quiescent uveitis. Given the safety profile of anti-VEGF further prospective randomized intervention studies of longer follow-up and larger sample size are needed before this agent can be broadly recommended as a treatment for uveitic macular edema.

5. Immunomodulatory Drugs

Immunomodulatory drugs have been explored in the management of uveitis complicated by macular edema with a view to greater efficacy and for an opportunity to reduce side effects from corticosteroids.^{58–60} Immunomodulatory drugs include mycophenolate mofetil, methotrexate, T-cell inhibitors like cyclosporine, interferons (IFNs) and anti-tumor necrosis factor (TNF)- α . There are no randomized controlled trials towards the efficacy of these agents in treatment of uveitic ME. The most common endpoint reviewed in the studies that do exist has been to reduce the use of systemic corticosteroids and to achieve a remission of uveitis. One study focused on ME in 19 uveitic patients who were unresponsive to standard immunosuppressive therapy and were then treated with mycophenolate mofetil.⁶¹ Mycophenolate mofetil proved safe and very effective in controlling ME and in reducing the uveitis relapse rate. When uveitis and/or macular edema are unresponsive to first and second line drugs, biologics can be considered. Many immunologic biologics are attractive treatment options because they offer a targeted suppression of immune effector response.⁶² Interferon (INF) influence both innate and adaptive immune responses⁶³ and play a role in the defense against viral infections and tumor growth. In autoimmune diseases, INFs appear as double agents, involved in both supportive and suppressive action. INFs have been used successfully in the treatment of multiple sclerosis and Behçet disease. Interferon- α has also been shown to be effective in treating inflammatory ME refractory to standard care.^{64,65} IFN- α -2a was effective in 15 out of 24 patients and partially effective in 6/24 patients with chronic inflammatory ME.⁶⁶ The response to therapy was very quick and the majority of patients showed an almost complete ME resolution within 2 weeks. Side effects were common and dose dependent. Patients commonly experienced flu-like symptoms, fatigue, and increased liver enzymes. Severe depression has also been reported. The authors suggested that the mode of action of INFs in improving macular edema might be enhancement of the barrier function of the vascular endothelium.

Tumor necrosis factor (TNF)- α is a key pro-inflammatory cytokine. High intraocular levels of TNF have been observed in experimental autoimmune and human uveitis.⁶⁷ Three anti-TNFs agents are currently available for clinical use: etanercept, infliximab, and adalimumab. Etanercept is considered pro-inflammatory in the eye and is not recommended for use in patients with uveitis. Infliximab demonstrated complete regression of ME (assessed by OCT) in 8/14 eyes in a small series and is considered a promising candidate agent deserving further study.⁶⁰ A recent report on the use of adalimumab described complete resolution of ME in 18/33 eyes with active uveitis and ME.⁶⁸

The safety of biologics, especially in long-term use, remains undetermined. Apart from acute allergic type reaction, which may occur in up to 5% of patients who receive immunologic agents intravenously, various infections, development of autoimmune and demyelinating diseases, occurrence of malignancies, and congestive heart failure have been reported. It goes without saying that these agents require further study before being considered safe or effective treatment options, but immunologic agents represent an exciting new frontier.

6. Intraocular Immunosuppressive Therapy

Intravitreal Methotrexate was given in 15 eyes to treat ME, 12 of 15 patients completed the final follow-up. At 6 months both mean visual acuity and macular thickness improved.⁶⁹

Intravitreal adalimumab showed neither improvement in macular edema nor side effects, and its role as an ophthalmologic agent remains to be established.^{40,60,70}

7. Vitamin E

Nussenblatt *et al* reported no effect over 18-month follow-up for 4 months of 1600 IU of vitamin E as an intervention compared to placebo.⁷¹

8. Macular Grid Laser

A case series of 6 eyes where macular grid laser was used to treat uveitic macular edema showed that best corrected visual acuity improved significantly for one eye, was stable in 3, and deteriorated in 2.⁷²

Vitrectomy—The possible efficacy of pars plana vitrectomy (PPV) in inflammatory ME has been studied for many years. Theoretically, the case for PPV in inflammatory ME is sound since many inflammatory mediators accumulate in the vitreous and a removal of these mediators may have good effect on ME. In addition, fibrosis of the vitreoretinal interface occurs often and may result in the formation of epiretinal membranes, and subsequently, macular edema. The presence of an epiretinal membrane is a known factor associated with medical treatment failure⁷³. Removal of this membrane can help to reduce ME. In practice, results are not clear cut. A worsening of visual acuity (22% of all eyes) was reported after PPV with ILM peeling and injection of triamcinolone in refractory ME, though 44% of the eyes in the same study showed decrease of ME on FA.⁷⁴ Another report showed positive effect of surgical posterior vitreous detachment on retinal thickness and visual acuity.⁷⁵ Also in pediatric uveitis, PPV might improve ME and lead to decrease of systemic immunosuppressive therapies.⁷⁶ The data is not convincing but the modality has not been adequately studied as a treatment for uveitic ME at this point in time.

CONCLUSIONS

Our ability to diagnose and treat patients with uveitis has advanced tremendously, and appears to be accelerating. The control of the uveitis is critical to prevent and treat the ME. Despite new treatment options, and expanding knowledge on the pathophysiology of inflammatory ME, treatment remains challenging.

Uveitis is a heterogeneous, relatively uncommon condition. As such it is difficult to conduct prospective randomized clinical trials.

Clinical judgment and our understanding of the disease process suggest that more aggressive treatment earlier in the disease process, improves results. Being mindful of, and striving to prevent the permanent structural changes and subsequent macular atrophy which regularly develop in patients with long-standing ME will generally lead to better results. Because of the unpredictable outcome, many potential pitfalls, and the need for sometimes, prolonged costly treatment (which may have significant side effects) patient counseling is imperative. Patients with uveitis can sometimes be paralyzed by the complexity of the choices presented to them, and often fail to accurately understand the significance of their condition, the mechanism their medications work through, need for compliance, and nature of adverse effect profiles. The most important aspect of the discussion regarding different treatment options, and something that should be clear to all clinicians as they consider treatment options is the natural history of the condition without adequate treatment.

Traditionally, modern treatment of uveitic ME has been achieved mainly through immunosuppression with steroid therapy. The dexamethasone implant has duration to 3 to 5 months, and may currently represent the most promising long acting steroid based implant option. Intravitreal triamcinolone acetonide is less potent than dexamethasone, but can last 3 months or longer.

Anti-VEGF and immunological biologic agents are both new and promising options for treatment of uveitic ME. Because of their relatively high cost, and the fact that neither their efficacy or safety profiles have been well established, it would be prudent to reserve these agents for truly refractory cases, preferably at centers for uveitis so that further knowledge can be effectively gathered.

PPV offers potential for select cases with pathologic vitreoretinal interface and deserves further investigation in clinical trials. In unilateral ME in which structural changes can be demonstrated, treatment with PPV should be entertained before long-term treatment with immunosuppressive drugs is initiated.

Several papers acknowledged that despite best efforts, there is no way of differentiating treatment-induced disease quiescence from spontaneous disease remission. Thus, current interventions are typically long duration and slow withdrawal. All patients need continued observation.

As we gain more experience and follow-up with the newer treatments that have become available, outcomes should improve. The medical literature provides tools for clinical judgment, but as yet no clear silver bullet for therapy. Treatment plans may rely on clinical judgment until better data and more definitive treatment options are available.

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