Uveitic macular edema: a stepladder treatment paradigm

The purpose of this review is to evaluate the treatment modalities that are commonly employed for the treatment of uveitis-related macular edema. Herein, the different drug classes used to treat the condition are described. In addition, the effectiveness, benefits and risks of the different routes of drug administration are discussed. Although some treatments have been evaluated in prospective clinical trials, most clinical research has been retrospective in nature. Thus, there is a need for more prospective controlled trials in order to determine which treatment, if any, is superior. A well-defined and nationally accepted treatment approach is needed in order to more effectively manage uveitic macular edema.

Keywords: clinical trials • corticosteroids • macular thickness • treatment • uveitic macular edema

Immediate detection and treatment of macular edema is crucial. If left untreated, visual acuity (VA) can rapidly deteriorate leading to vision loss. Macular edema is an end point for a variety of disease processes including uveitis. Macular edema often presents in patients with active uveitis, however there are many cases where macular edema persists in a quiet eye. Although uveitis-related macular edema is a prevalent issue, there is limited pathophysiological understanding. Even though some prospective and many retrospective trials have evaluated treatment options, a nationally accepted approach for treating macular edema has yet to be determined. In addition, there is limited consensus on how to best treat macular edema in a patient whose uveitis is in remission. Only through prospective, randomized, controlled clinical trials will clinicians be able to determine the most effective way to treat this blinding disease.

Etiology

There are a number of conditions that can lead to development of macular edema including Type I and/or Type II diabetes and vein occlusion in the vasculature surrounding the macula. Cataract and laser surgical procedures, like Yttrium Aluminum Garnet (YAG) capsulotomy, also put patients at risk for developing macular edema postoperatively. After surgery, edema often develops within 3–12 weeks but resolves on its own in some patients [1]. Macular edema can also be drug induced [2]. Pharmacologic contributors include epinephrine like antiglaucoma drops which can lead to retinal-blood barrier breakdown and resultant cystoid macular edema (CME) [1]. Less often, macular edema cases are reported in association with intraocular tumors, for example, choroidal melanomas. Although surgical trauma, diabetic retinopathy and venous occlusive disease are all causes of macular edema [1,3–4], this review will focus on uveitic macular edema specifically.

Uveitic macular edema

Macular edema is the most common complication in uveitis patients. Macular edema often develops secondary to uveitis, resulting in vision threatening complications [5]. Patients with macular edema can be asymptomatic or present with inflammation, swell-
ing and blurred or decreased central vision [6]. Chronic macular edema can result in epiretinal membrane formation [7]. Macular edema can be associated with virtually all types of uveitis, most notably, birdshot retinochoroidopathy, sarcoid associated uveitis, pars planitis and iridocyclitis [8]. Macular edema is typically associated with intermediate and posterior uveitis; however in some instances, for example, in HLA-B27+ patients, an association with anterior uveitis is possible [9].

Pathogenesis
Although the pathogenesis of uveitic macular edema is not completely understood, some progress has been made in the past few decades in evaluating, studying and understanding this disease. Macular edema develops when there is a breach in the blood-retinal barrier causing fluid accumulation in the outer plexiform layer of the retina and/or the cystic spaces [3,9]. In the normal eye, retinal capillary endothelial cell tight junctions, retinal pigment epithelium (RPE) tight junctions and the RPE pump function regulate the volume and composition of the extracellular component of the retina and subretinal space [9,10]. If the balance of passive diffusion into the eye is greater than the active transfer out of the eye, edema ensues. Integrity of vasculature, mechanical forces, the RPE pump and inflammatory mediators can all affect this balance [10].

Pathogenesis often depends on the underlying entity causing macular edema. With uveitic macular edema, inflammatory processes cause hyperpermeability of retinal blood vessels and subsequently extravasation of fluid, proteins and macromolecules into the retinal interstitium. Prostaglandins, cytokines and other inflammatory markers also play a role [9]. Inflammatory processes can cause the RPE pump to dysfunction which also contributes to fluid accumulation. Ultimately, fluid accumulation causes macular thickening, and if left untreated, retinal thinning and fibrosis ensue. Once this point is reached, therapy is usually futile and damage is irreversible [3].

Clinical methods of detection
Optical coherence tomography (OCT) and fluorescein angiography (FA) are the most commonly utilized diagnostic tests for macular edema [11]. FA is widely available and is used to examine retinal and choroidal perfusion in both normal and diseased states [1]. FA is especially useful for the detection of retinal vascular leakage [9]. The amount of fluorescein leakage provides insight to the extent and pathological state of the retinal vasculature [1]. Once the retinal-blood barrier is breached, fluid accumulation causes macular thickening which can be detected via OCT.

Several research studies have compared the two techniques [12–15]. In 58 patients, OCT and FA were done on 121 eyes to compare their effectiveness in diagnosing CME in uveitis patients. Analysis revealed that OCT was just as useful as FA in detecting CME. However, OCT better detected axial distribution of fluid [13]. In a similar study, it was found that OCT was more sensitive in detecting CME and that it superiorly detected subretinal fluid and complications associated with chronic CME [12]. A study by Kempen and colleagues suggests that OCT should be used initially due to its lower cost and higher safety [15]. However, if macular edema is clinically suspected and it is not detected on an OCT, FA should be done, in addition, to ensure the diagnosis is not missed. Vitreous fluorometry has also been utilized to detect CME but is less frequently used compared with other techniques [16,17].

Treatment of uveitic macular edema
Foster and colleagues previously described a stepladder treatment algorithm for treating uveitis that may also be effective in treating associated macular edema [18]. However, there are many documented cases in which patients experience persistent macular edema in the absence of active inflammation [9]. Clear guidelines for the treatment of uveitic macular edema have yet to be established. This raises the important question of whether or not a particular treatment regimen provides the most benefit to patients with vision threatening macular edema.

Anti-inflammatory agents, including corticosteroids and nonsteroidal inflammatory drugs (NSAIDs), are the hallmark treatment for patients with uveitic macular edema. However, immunosuppressive agents and surgical therapy have also been used to treat patients who are unresponsive to conventional therapy. Medications and other therapeutic agents can be administered systemically or by periocular and/or intravitreal routes. Alternative therapies including interferon, octreotide, hyperbaric oxygen, acetazolamide and tocolizumab can be used in patients who fail more conventional therapies.

Corticosteroids
Corticosteroids are the mainstay treatment for uveitis and can also be useful in treating uveitis-related macular edema. Corticosteroids are potent, fast acting, and relatively inexpensive compared with other forms of therapy [20]. Corticosteroids’ therapeutic value stems from their ability to suppress inflammatory mediators and vascular permeability factors involved in macular edema [6]. Corticosteroids target neutrophil transmigration, decrease cytokine production, inhibit prostaglandin and leukotriene synthesis, downregulate cell
adhesion and major histocompatibility molecules and decrease induction of VEGF \([7]\). Corticosteroids also promote the integrity and hamper the breakdown of epithelial tight junctions that maintain the eye-blood barrier \([3]\). Topical, systemic and intravitreal corticosteroids can be used in the treatment of uveitis and associated macular edema.

Topical corticosteroids are not the optimal route of administration because the macula is located in the posterior segment of the eye \([18]\). Systemic corticosteroids are useful for treating uveitic macular edema with an underlying systemic condition. However, systemic corticosteroids have numerous harmful side effects including endocrine dysfunction, insomnia, psychosis, peptic ulceration, osteoporosis, hypertension, metabolic dysfunction impaired immune response and more \([18]\). Intravitreal corticosteroid injections are thought to be most optimal because they can bypass the blood-eye barrier and induce delivery of a higher concentration of drug to the posterior segment of the eye \([18]\). In addition, intravitreal drug delivery is rapid, can have lasting effects of 8–16 weeks, and systemic side effects are limited \([8,18]\).

**NSAIDs**

NSAIDs are a safer alternative to corticosteroid treatment. NSAIDs’ mode of action is inhibiting cyclooxygenase enzymes and prostaglandin synthesis, thereby limiting inflammation \([21]\). It has been noted that using oral NSAIDs as an adjuvant therapy to periocular steroids can reduce recurrence of uveitic macular edema \([8]\). In a chart review of patients at Massachusetts Eye Research and Surgery Institution, it was determined that NSAIDs alone are inadequate for treating macular edema. However, NSAIDs administered in conjunction with intravitreal injections of bevacizumab or triamcinolone acetate may improve visual acuity and reduce uveitic macular edema \([22]\).

A different study by Allegri and colleagues assessed the effectiveness of topical NSAID drops in patients with uveitic macular edema. In a randomized, double-blind, clinical trial, 0.5% indomethacin (INDOM) or placebo eye drops were administered to 46 eyes of 31 patients with uveitic macular edema \([21]\). Subjects were randomized to receive commercial 0.5% INDOM drops (n = 16 subjects, 23 eyes) or placebo drops (n = 15 subjects, 23 eyes) four times a day. Patients were followed for a 6 month treatment period. In the group receiving 0.5% INDOM, there was a notable reduction in central foveal thickness (CFT) \((p < 0.0001)\) and a significant improvement in visual acuity. Although 0.5% INDOM reduced macular edema, not all eyes achieved total resolution. The conclusions of this study are limited because only a small number of patients were examined and follow-up lasted only 6 months.

**Periocular injections**

Although corticosteroids and NSAIDs are useful for particular types of uveitis including postsurgical, they usually have limited therapeutic effects on uveitis-related macular edema because the macula is located in the posterior segment of the eye \([18]\). Periocular injections are beneficial for treating uveitic macular edema because therapy is local. Periocular injections can be administered to the subconjunctival space, the orbital floor or the retrobulbar posterior sub-Tenon’s space as an alternative to topical therapy \([7]\). Local therapies are advantageous because they lead to fewer systemic side effects \([18]\). In a study published by Riordan-Eva and Lightman, the effect of 54 orbital floor injections of either methylprednisolone or triamcinolone in 33 eyes was examined. A positive response was observed in 48% of the injections which lasted on average 9 weeks \([23]\).

In a study by Jennings et al., the effect of posterior sub-Tenon’s corticosteroid injections was observed in 12 eyes \([24]\). Visual acuity and blood-retinal barrier permeability were evaluated pre- and postinjection. In half of the treated eyes, visual acuity improved (at least 2 lines on the Snellen chart) and lasted for approximately 1 month. However, the effects on blood-retinal barrier permeability were inconsistent.

A similar study by Yoshikawa and colleagues, examined the effect of posterior sub-Tenon space injections in 39 eyes with macular edema secondary to uveitis \([25]\). Visual acuity results also revealed improvement in about 50% of treated eyes. Complications reported included cataract in 6 eyes, glaucoma in 1 eye and blepharoptosis in 1 eye. Although periocular injections are frequently used in the treatment of uveitic macular edema, there are few published studies that evaluate their effectiveness. Risk factors of periocular injections include proptosis, optic nerve injury, hemorrhage, globe perforation and choroidal/retinal occlusion \([7]\).

**Intravitreal injections**

Intravitreal corticosteroid and anti-VEGF injectable agents that have been used in the treatment of uveitic macular edema include triamcinolone and bevacizumab. Many retrospective studies have evaluated their ability to improve uveitic macular edema \([26–29]\). Bevacizumab, an anti-VEGF antibody, has been used off-label for many ocular pathologies including uveitic macular edema \([27]\). In a study by Coma and colleagues, the safety and efficacy of bevacizumab (Avastin®; Genentech, Inc, CA, USA) was assessed in 14 patients in uveitis remission but with persistent macular
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intraocular pressure rhage and endophthalmitis. Intravitreal corticosteroid related adverse events. Injection related risk factors include retinal detachment, vitreous hemorrhage and endophthalmitis. Intravitreal corticosteroid risk factors include cataract formation and elevated intraocular pressure.

Suprachoroidal injection

Soon, a new corticosteroid route of administration will be explored. In a Phase II, randomized clinical trial, the safety and efficacy of triamcinolone acetonide injected into the suprachoroidal space will be assessed in patients with uveitic macular edema. By administering the therapeutic agent directly into the suprachoroidal space, it is thought that there will be minimal exposure to the anterior segment of the eye and thus, fewer side effects. In order to determine the therapeutic value of suprachoroidal injections for uveitic macular edema, results will need to be evaluated following the completion of the trial. Because ocular steroid injections require repeated administration and put the patient at risk for injection related side effects, longer lasting corticosteroid eluting devices have been developed.

Devices

Corticosteroid eluting devices have been developed for treating a variety of ocular conditions including uveitis and associated macular edema. After undergoing clinical trials, three devices are currently available to ophthalmologists, Ozurdex® (Allergan Inc., CA, USA) which releases dexamethasone, Retisert® (Bausch & Lomb, NY, USA) and Illuvien® (Alimera Science, GA, USA) both of which release fluocinolone acetonide. Cao and colleagues, in a retrospective chart review, examined the therapeutic effect of the dexamethasone intravitreal implant (Ozurdex; Allergan, Inc., CA, USA) in 27 patients with inactive uveitis but persistent macular edema. Analysis revealed a mean reduction in macular thickness (278.9 μm compared with 478.7 μm at baseline) and visual acuity improvement within 3 months of implantation. In addition, 51.8% of eyes achieved ≥2-line improvement, 33.3% achieved ≥3-line improvement and 29.6% achieved ≥4-line improvement on the Snellen chart. Others have shown similar results. Although these results show great promise, the long-term efficacy has yet to be demonstrated in controlled clinical trials.

The Multicenter Uveitis Steroid Treatment (MUST) Trial Research Group randomized patients with noninfectious intermediate, posterior or panuveitis to receive the fluocinolone acetonide implant or systemic therapy. At baseline, a significant amount of patients also had uveitic macular edema. The proportion of these patients in each treatment group was about equal. At baseline, the proportion of eyes with macular edema in the implant group versus the systemic therapy group was 41% and 39%, respectively. At 6 months follow-up, the proportion of patients with macular edema decreased to 20% in the implant group and 34% in the systemic therapy group. These results indicate that in this study, macular edema was superiorly controlled in the implant group.

A different randomized controlled trial by the Fluocinolone Acetonide Study Group, the safety and efficacy of the FA implant, Retisert, was evaluated. FA
implant therapy was compared with standard therapy, in other words, systemic prednisolone or similar corticosteroid, in patients with noninfectious posterior uveitis [42]. At 2 years follow-up, the number of patients with a reduction in CME (≥1 mm² by FA) was greater in the implant group (86.5%) versus patients receiving standard of care (74.4%). Also, the rate of macular edema reduction was faster in the implant group. Shen and colleagues also reported reduced uveitic CME in patients after Retisert implantation as determined by OCT [43]. These studies suggest that corticosteroid eluting devices may have a therapeutic role in uveitic macular edema.

A similar device, Illuvien, showed benefit in patients with diabetic macular edema and just gained US FDA approval for this indication in 2014 [44]. Prospective, randomized, controlled, clinical trials are currently ongoing to assess its effectiveness in uveitis patients, including those with macular edema [36]. Researchers are hopeful that after the completion of the trial, analysis will show Illuvien is effective in treating uveitis and associated macular edema. The benefits of Illuvien are that effects may last up to three years and the device can be implanted without the use of an operating room [36].

**Immunosuppressive drugs**

Systemic immunosuppressive drugs like mycophenolate mofetil, azathioprine, methotrexate and cyclosporine A, are also used in the treatment of uveitic macular edema, especially in patients with an underlying systemic condition. In a retrospective study by Doycheva and colleagues, remission of cystoid macular edema was achieved in only half of patients who received mycophenolate mofetil (MMF) for the treatment of uveitic macular edema [45]. In uveitis patients without macular edema at the start of MMF therapy, 50% developed macular edema during the treatment period. This chart review demonstrates that MMF is not effective in all uveitic macular edema cases and that MMF cannot prevent the development of uveitic CME. The value of this review is limited by the small sample size of 38 patients analyzed in the study. Immunosuppressive therapy may be warranted in patients who are intolerant or nonresponsive to steroids [46]. However, few studies have been done to assess the effectiveness of immunosuppressive therapy on uveitic macular edema specifically.

**Biologic response modifiers**

In 2004, Murphy and colleagues were the first to explore the therapeutic role of anti-TNF-α agents in uveitis [47]. Since then, there have been several reports that have noted uveitic CME improvement after anti-TNF-α therapy [48-50]. The ability of anti-TNF-α agents to treat uveitis-related macular edema was recently explored in a study by Schaap-Fogler and colleagues [51]. A case review of 23 patients treated with anti-TNF-α agents (n = 9, 15 eyes) versus conventional immunosuppressive treatment (n = 18, 27 eyes) revealed anti-TNF-α agents may be an effective therapy for uveitic macular edema. Improved macular thickness was seen in both groups at 3 months follow-up. A maximal improvement of macular thickness was noted at month 6 in the TNF-α group. Maximal visual acuity improvement was seen at 3 months in both groups and a decline was seen at 12 months in both groups. Although this study suggests TNF-α may play a role in treating uveitic CME, further investigation is needed.

Tocilizumab (TCZ), a humanized antibody that binds to IL-6 receptors, may also be effective in treating uveitis-related CME [52,53]. In a retrospective study by Adán and colleagues, five patients with uveitis related CME received 8 mg/kg TCZ at 4 week intervals [53]. All patients had previously failed conventional therapy and at least one biologic agent. Mean follow-up was 8.4 months. Mean baseline CFT was 602 ± 236 μm. Mean CFT was 386 ± 113 μm at month 1 (p = 0.006), 323 ± 103 μm at month 3 (p = 0.026) and 294.5 ± 94.5 μm at month 6 (p = 0.014). At 6 months follow-up, a best-corrected visual acuity (BCVA) improvement of ≥2 lines was noted in 50% of eyes. BCVA did not worsen in any patients and no adverse events were reported. Although these data suggest that TCZ may play a role in treating patients resistant to conventional therapy, the value of this review is limited by the small sample size and short follow-up period.

Interferon (IFN) has also been noted to have an effect on uveitic CME [54,55]. In a study at the University of Heidelberg, IFN-β was compared with methotrexate in the treatment of uveitis-related macular edema [54]. Nineteen patients were randomized to receive either 44 μg of IFN-β subcutaneously three times weekly or methotrexate once weekly. At the end of three months follow-up, visual acuity improvement was greater in the interferon group. Also, macular thickness decreased by 206 μm in the IFN group compared with 47 μm in the methotrexate group. In a different retrospective study by Deuter and colleagues, IFN-α’s ability to treat macular edema was evaluated [55]. IFN-α was administered subcutaneously to 24 patients with noninfectious uveitis and macular edema. These patients had previously failed other therapies including corticosteroids, acetazolamide and immunosuppressive agents. Analysis revealed that CME completely resolved within three months in 15 patients (62.5%), partly resolved in six patients (25%) and did not resolve in three patients (12.5%).
Reported side effects included increased liver enzymes in one patient and fatigue and flu-like symptoms. These results indicate that further investigation may be warranted to evaluate the ability of interferon to treat uveitic macular edema.

Alternative/surgical therapies
For uveitic macular edema patients who are unresponsive to medication, surgery is an option. Pars plana vitrectomy (PPV) is a surgical procedure that is especially useful in medically unresponsive patients with epiretinal membrane or vitreomacular traction [56]. Whether or not this procedure is superior to immunosuppressive therapy remains to be seen. The only randomized controlled study was done by Tranos and colleagues [18,56]. Posterior uveitis patients with CME who were unresponsive to corticosteroids and immunomodulatory therapy were randomized to PPV or other medical treatment. The medical treatment group was treated with a variety of systemic corticosteroids including azathioprine, acyclovir, cyclosporine, etc. After 6 months follow-up, VA improved more drastically in the surgical group. The data suggest that PPV may benefit CME patients; however a trial with a larger sample size would be useful to definitively evaluate this procedure.

Octreotide has also been used in macular edema patients who are unresponsive to other therapies [57,58]. Octreotide, a somatostatin analogue, inhibits the release of growth hormone [57]. Although octreotide’s mechanism of action in treating CME is not fully understood, it has shown potential. In five patients (9 eyes) with quiet inflammation but persistent CME, 100 mg of octreotide acetate (Sandostatin; Novartis Pharmaceuticals Corp, NJ, USA) was administered subcutaneously 3 times a day [57]. After a mean follow-up of 12.4 months, CME was greatly improved or completely resolved in 7 of 9 eyes. Visual acuity also improved in 7 eyes. Two eyes did not respond to therapy and no adverse events were reported. Although these results show potential, further clinical investigation is needed in order to determine octreotide’s therapeutic value.

Carbonic anhydrase inhibitors like acetazolamide have also been utilized for treating patients who are unresponsive to conventional therapy. By inhibiting carbonic anhydrase and γ-glutamyl transferase, acetazolamide can alter the polarity of ionic transport systems in the RPE [1]. This results in increased fluid transport across the RPE and reduced edema [8]. However, controlled clinical trials have shown that acetazolamide inadequately improves vision in patients with uveitic macular edema [8]. Therefore, this is no longer a popular option. Hyperbaric oxygen has also been used as a treatment in CME based on the belief that hypoxia plays a role in the pathogenesis of CME [59]. However, this treatment is controversial and seldom used.

Conclusion
Although various treatment options exist, macular edema remains a significant physiological complication in many uveitis patients. Due to its blinding effects, rapid detection and treatment is of high importance. Many existing therapies have shown to be useful in treating patients with uveitis-related macular edema including steroids, immunomodulatory agents and surgical procedures. In addition, new treatments are emerging which have the potential to provide benefit to patients. However, further assessment is needed to determine long-term safety and efficacy. A nationally accepted approach for treating uveitis-related macular edema has yet to be determined.

Future perspective
The question of which therapy is most effective in treating uveitic macular edema remains unanswered. Research has been hindered by the fact that an efficient animal model for macular edema does not exist [6]. In addition, the pathogenesis is not well understood making the development of more specific treatments difficult [8]. More well-designed, prospective, randomized, controlled clinical trials are essential in order to determine the best treatment approach. In designing these prospective trials, researchers will have to address several challenges.

One of these challenges will be determining what value defines a significant reduction in macular thickness. Because of inter-measurement OCT variability, researchers have questioned whether or not a 10% change in retinal thickness is clinically relevant [60]. The MUST Trial Research Group has proposed a way to evaluate decreased retinal thickness [61]. However, more studies are needed to determine the best method.

When designing future clinical trials researchers should include a larger number of patients. A large sample size will help determine whether or not one treatment is superior to others in a majority of cases, or whether it is dependent on a case by case basis. In addition, clinical trials with longer follow-up periods are necessary to determine the optimal duration of treatment. Longer follow-up will also enable researchers to determine long term side effects. Although the road to a nationally accepted approach for treating uveitic macular edema is not an easy one, researchers must not give up the fight against this blinding disease.
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**Executive summary**

- Uveitic macular edema is a devastating condition that is blinding if left untreated.
- Several treatment options exist for uveitic macular edema including corticosteroids, NSAIDs, corticosteroid eluting devices, immunomodulatory therapy and surgery. These therapies can be administered orally, topically and by periocular or intravitreal routes.
- Many retrospective studies have evaluated uveitic macular edema therapies and have demonstrated that many improve visual acuity and decrease macular thickness.
- More prospective, randomized, controlled clinical trials with a larger sample size and a longer follow-up period are needed to determine the best treatment approach for uveitic macular edema.

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**References**

Papers of special note have been highlighted as: • of interest


• Reveals the detrimental effects uveitic macular edema can have on visual acuity.


• Provides insight on the clinical methods of detection for uveitic macular edema.


• Describes Foster and colleagues step-ladder treatment algorithm that may also be useful in treating patients with uveitis-related macular edema.

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