Etiology and treatment of the inflammatory causes of cystoid macular edema

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Abstract: Cystoid macular edema in its various forms can be considered one of the leading causes of central vision loss in the developed world. It occurs in a wide variety of pathologic conditions and represents the final common pathway of several basic processes. Therapeutic approaches to cystoid macular edema depend on a clear understanding of its contributing pathophysiologic mechanisms. This review will discuss the mechanism of ocular inflammation in cystoid macular edema with a particular focus on the inflammatory causes: post-operative, uveitic, and after laser procedures. A variety of pharmacologic agents targeting inflammatory molecules have been shown to reduce macular edema and improve visual function. However, the long-term efficacy and safety of most new therapies have yet to be established in controlled clinical trials.

Keywords: ocular inflammation, cystoid macular edema, uveitis

Introduction
Cystoid macular edema (CME) is a painless disorder, which affects the central retina or macula. Since its first recognition and description in 1974,¹ CME has been recognized as the most common cause of decreased vision postoperatively in uneventful cataract surgery.² CME is caused by cystic accumulation of intraretinal fluid in the outer plexiform and inner nuclear layers of the retina as a result of the breakdown of the blood–retinal barrier (Figure 1).³ CME can be a serious consequence of numerous ocular procedures and conditions, including cataract surgery, ocular inflammatory disease, retinal vascular diseases, and tractional disorders (Table 1).⁴ It is not a disease itself, rather the endpoint of a variety of processes that lead to the accumulation of fluid in the central retina.⁵ Clinical CME has historically been defined as a reduction in vision to 20/40 or less that is attributable to ophthalmoscopically or angiographically visible CME.⁶ It can present with symptoms of blurred or decreased central vision, and painless retinal inflammation or swelling. In postoperative CME, vision loss is usually temporary, with infrequent incidences of permanent visual loss.⁷ CME is often asymptomatic and may only be detected with fluorescein angiography (Figure 2) or optical coherence tomography (Figure 1).⁸ Studies suggest that the rate of clinical CME is in the range of 1%–2%,⁹ whereas the incidence of angiographic CME may be as high as 9%–19%.¹⁰,¹¹

Uveitic CME, on the other hand, generally has a worse prognosis and the huge negative impact of inflammatory CME on visual acuity has become evident in recent years. In a large cross-sectional survey of 581 patients with uveitis, 35% of all uveitis eyes had a visual acuity of 20/60 or less, of which CME had caused 42%. Clinically significant
CME developed in 30% of patients with uveitis. Furthermore, the authors found that vision loss is especially severe among elderly patients and those with chronic disease.\textsuperscript{12}

**Pathophysiologic mechanism of ocular inflammation and CME**

Arachidonic acid is metabolized by cyclooxygenase to prostaglandins which are the most important lipid derived mediators of inflammation (Figure 3).\textsuperscript{13} Surgical trauma causes a trigger of the arachidonic acid cascade, which in turn generate prostaglandins by activation of cyclooxygenase-1 (COX-1) and COX-2. Phospholipids in the cell membrane are the substrate for phospholipase A to generate arachidonic acid from which a family of chemically distinct prostaglandins and leukotrienes are produced.\textsuperscript{14} Clinical symptoms of prostaglandin production include hyperemia, miosis, impaired vision, pain and diminished visual acuity secondary to CME.\textsuperscript{15}

Prostaglandin synthesis can be reduced by inhibiting phospholipase A\textsubscript{2}, which inhibits the release of arachidonic acid from cell membrane phospholipids, or by inhibiting the conversion of arachidonic acid to prostaglandins via the COX pathway. Different classes of anti-inflammatory medications may block different portions of this pathway. Corticosteroids interfere with the activity of phospholipase A\textsubscript{2}, thereby inhibiting the release of arachidonic acid and the production of all arachidonic acid metabolites, including prostaglandins.\textsuperscript{16}

In contrast, nonsteroidal anti-inflammatory drugs (NSAIDs) nonspecifically and irreversibly inhibit the synthesis of prostaglandins by interfering with the activity of COX-1 and COX-2 (Figure 3).\textsuperscript{16}

Most commonly, macular edema results from pathologic hyperpermeability of retinal blood vessels, particularly the retinal capillary bed. Increased vascular permeability results in extravasation of fluid, proteins, and other macromolecules into the retinal interstitium.\textsuperscript{17} Numerous molecules may induce the retinal vascular hyperpermeability that leads to macular edema. Depending on the underlying disease entity, these may include prostaglandins and leukotrienes, protein kinase C, nitric oxide, and various cytokines such as vascular endothelial growth factor (VEGF), tumor necrosis factor $\alpha$, insulin-like growth factor-1, and interleukins.\textsuperscript{18,20}

A factor that often contributes to vascular leakage is the endothelial damage resulting from leukocyte adherence to vessel walls (leukostasis), a phenomenon mediated by nitric oxide, adhesion molecules, and other inflammatory mediators.\textsuperscript{20,21}

**Table 1** Pathologic conditions causing macular edema

<table>
<thead>
<tr>
<th>Inflammatory disorders</th>
<th>Intraocular surgery, uveitic syndromes, laser procedures</th>
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</thead>
<tbody>
<tr>
<td>Retinal vascular disease</td>
<td>Diabetic retinopathy, retinal vein occlusion, hypertensive retinopathy</td>
</tr>
<tr>
<td>Choroidal vascular disease</td>
<td>Choroidal neovascularization</td>
</tr>
<tr>
<td>Tractional maculopathies</td>
<td>Epiretinal membrane, vitreomacular traction syndromes</td>
</tr>
<tr>
<td>Drug reactions</td>
<td>Epinephrine, prostaglandin analogs, nicotinic acid, tamoxifen, glitazones</td>
</tr>
<tr>
<td>Inherited retinal dystrophies</td>
<td>Retinitis pigmentosa</td>
</tr>
<tr>
<td>Retinal detachment</td>
<td>Exudative, rhegmatogenous</td>
</tr>
<tr>
<td>Intraocular tumors</td>
<td>Choroidal melanoma</td>
</tr>
<tr>
<td>Optic nerve head abnormalities</td>
<td>Diabetic/hypertensive papillopathy, neuroretinitis, optic nerve pits/colobomas</td>
</tr>
<tr>
<td>Idiopathic</td>
<td></td>
</tr>
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</table>
Regardless of the various pathogenic mechanisms causing macular edema, the resulting visual acuity depends on many factors in addition to macular thickening, including duration of edema, perfusion of macular capillaries, photoreceptor impairment and/or loss, retinal pigment epithelium (RPE) dysfunction, and media opacities. It is perhaps not surprising that many studies have found poor correlation between macular thickness and visual acuity in eyes with macular edema of various etiologies.

Inflammatory conditions causing macular edema

Intraocular surgery

CME following cataract surgery (Irvine–Gass syndrome) remains the most common cause of visual loss following cataract surgery, and a higher incidence is seen when surgery is complicated by vitreous loss, vitreous adhesions to the cataract wound or other anterior segment structures, iris damage, or retained lens material. Furthermore, the risk of developing postoperative CME is substantially higher in patients with pre-existing conditions known to produce vasoactive stimuli, such as diabetic retinopathy and uveitis. Prostaglandins, as described above, have been implicated in causing macular capillary hyperpermeability in this setting.

The risk of pseudophakic CME appears to be lower with phacoemulsification surgery than with either extracapsular cataract extraction or intracapsular cataract extraction, perhaps because of reduced postoperative inflammation. The amount of inflammation, and hence the risk of CME, is also greater with higher phaco power (>1 J). Surgical complications dramatically increase the risk of CME. A ruptured posterior capsule is associated with an 11.5% to 20% incidence of clinical CME in patients undergoing phacoemulsification. Retained lens fragments further increase the risk of clinical CME to as much as 29% after phacoemulsification.

Uveitic syndromes

Uveitis can occur in association with autoimmune disorders, infection, and exposure to systemic medications or toxins. Uveitis is the fifth most common cause of visual loss in the developed world and is estimated to be responsible for up to 20% of legal blindness worldwide. CME is the most frequent complication of uveitis and it develops typically in patients with intermediate and posterior uveitis components, but may also be seen with isolated anterior uveitis, particularly in patients positive for human leukocyte antigen (HLA)-B27. CME may occur in a wide variety of uveitis syndromes, whether autoimmune (eg, Pars planitis, birdshot chorioretinitis and Vogt–Koyanagi–Harada disease), infectious (eg, toxoplasmosis), toxic (eg, rifabutin-associated), or idiopathic (eg, sarcoidosis and idiopathic vitritis) in etiology.

Research on CME and ocular inflammatory disease has been hampered by the lack of adequate animal models and its pathogenesis is not completely understood. The most important pathogenic mechanism is loss of inner blood–retinal barrier integrity caused by a variety of inflammatory mediators generated by the underlying uveitic process, including prostaglandins, leukotrienes, and various cytokines such as interleukins, tumor necrosis factor α, and VEGF.
The reliable prognostic factors distinguishing CME eyes with a potential for improvement from the eyes with definitively damaged visual acuity are not yet known. Poor contrast sensitivity, impaired color vision, chronicity of CME and advanced age of patients were all associated with impaired visual outcomes as well as macular ischemia and flat optical coherence tomography (OCT) indicating thin and atrophic macula.  

Laser procedures
The development of new or worsening macular edema is a known complication of panretinal photocoagulation (PRP) for retinal vascular disease such as diabetic retinopathy. Although the mechanism is not clearly understood, laser-induced inflammatory mediators and transudation from increased macular blood flow may both play pathogenic roles. Focal laser photocoagulation prior to or concurrent with PRP and dividing the PRP into multiple sessions can decrease the incidence of this complication. Approximately 1% of patients may develop CME after Nd:YAG capsulotomy. This complication often occurs one to five months later and is believed to be related to opening the posterior capsule rather than to the energy of the Nd:YAG laser.

Treatment options for inflammatory cystoid macular edema
Initial approach
Anti-inflammatory agents are the mainstay in the treatment of postoperative and uveitic CME. Topical therapy with corticosteroid and NSAIDs are commonly used for the treatment of macular edema. Corticosteroids (Table 2) have been shown to inhibit the inflammatory mediators and vascular permeability factors that have been associated with macular edema. Corticosteroids also can retard the loss of endothelial tight junction proteins that are important for maintaining the blood–retina barrier.

A safer alternative to corticosteroids for the treatment of ocular inflammation are the NSAIDs (Table 3), which are comprised of several chemically heterogeneous classes of drugs which possess potent COX inhibitory activity. Topical NSAIDs are classified into six groups based on their chemical composition: indoles, phenylacetic acids, phenylalkanoic acids, salicylates, fenamates, and pyrazolones. Salicylates, fenamates, and pyrazolones are considered too toxic to be used in the eye. Most of the NSAIDs are weakly acidic drugs, which ionize at the pH of the lacrimal fluid and therefore have limited permeability through the anionic cornea which has an isoelectric point pl of 3.2. Reducing the pH of the formulation increases the unionized fraction of the drug which enhances permeation. Being acidic, NSAIDs are inherently irritant and reducing the pH of formulation further increase their irritation potential, as well as decrease their aqueous solubility. In addition, the anionic nature of NSAIDs lends to the formation of insoluble complexes with cationic quaternary ammonium preservatives, such as benzalkonium chloride. Thus, it has proved difficult to formulate topical NSAID formulations that are comfortable when applied topically to the eye.

Studies comparing NSAIDs with corticosteroids have demonstrated no significant difference in the results between these treatments. However, NSAID treatment appears to be more effective than topical corticosteroids in re-establishing the blood aqueous barrier. Many studies that analyzed the effects of NSAIDs on postoperative inflammation included the concurrent administration of corticosteroids, suggesting that NSAIDs and corticosteroids have the potential for synergistic activities. The beneficial effects of NSAIDs over corticosteroids include stabilization of intraocular pressure, provision of analgesia and reduction of the risk of secondary infections.

If topical therapy fails
Steroid agents
Resistant cases of postoperative CME and most cases of uveitic CME require higher macular concentrations of corticosteroid agents, usually achievable with posterior sub-Tenon injection. Cases further unresponsive to sub-Tenon corticosteroid injection may require intraocular drug concentrations attainable only with systemic or intravitreal delivery. Systemic corticosteroids are typically reserved for bilateral CME complicating noninfectious uveitis, and should be used with caution given the potential for significant systemic complications. In active inflammation, anti-inflammatory treatment is imperative. A recent OCT study documented a more rapid decrease of CME with oral administration than with periocular steroid injections, so an

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>Manufacturer</th>
<th>Formulation</th>
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<tbody>
<tr>
<td>Difluprednate</td>
<td>Durezol</td>
<td>Sirion therapeutics</td>
<td>0.05% emulsion</td>
</tr>
<tr>
<td>Loteprednol etabonate</td>
<td>Lotemax</td>
<td>Bausch and Lomb</td>
<td>0.5% suspension</td>
</tr>
<tr>
<td>Prednisolone acetate</td>
<td>Pred Forte</td>
<td>Allergan</td>
<td>1% solution</td>
</tr>
<tr>
<td>Rimexolone</td>
<td>Vexol</td>
<td>Alcon</td>
<td>1% suspension</td>
</tr>
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Table 3  Commercially available topical NSAIDs<sup>49–52</sup>

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>Manufacturer</th>
<th>Chemical class</th>
<th>Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketorolac</td>
<td>Acular</td>
<td>Allergan</td>
<td>Phenylalkanoic acid</td>
<td>0.5% solution</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>Voltaren</td>
<td>Novartis</td>
<td>Phenylactic acid</td>
<td>0.1% solution</td>
</tr>
<tr>
<td>Nepafenac</td>
<td>Nevanac</td>
<td>Alcon</td>
<td>Arylactic acid</td>
<td>0.1% suspension</td>
</tr>
<tr>
<td>Bromfenac</td>
<td>Xibrom</td>
<td>Bausch and Lomb</td>
<td>Phenylactic acid</td>
<td>0.09% solution</td>
</tr>
</tbody>
</table>

initial treatment with oral steroids might be preferred when the rapidity of recovery is essential.<sup>59</sup>

Intravitreal triamcinolone acetonide (IVTA) used in variable dosages had a short-term effect on CME and improved vision transiently but, despite repeated injections, most patients had no sustained improvement of acuity compared with baseline.<sup>60</sup> The side-effect profile of IVTA is significant with corticosteroid-induced intraocular pressure rises. The rate of posterior subcapsular cataract formation is higher than previously reported, and there is a small but potential risk of endophthalmitis.<sup>51</sup>

Steroid-sparing drugs

In cases of severe uveitis with CME requiring long-term treatment with moderate or high doses of corticosteroid, the use of steroid-sparing immunosuppressive drugs, in collaboration with an internist or rheumatologist, should be considered.<sup>57</sup> Harding and colleagues evaluated the use of intravitreal methotrexate (MTX) to provide an alternative for intraocular steroid therapy in patients with unilateral intermediate or posterior uveitis and/or CME who are also known steroid responders. They found that intravitreal MTX can improve visual acuity and reduce CME.<sup>62</sup>

Intraocular devices

A new treatment approach for patients requiring frequent intravitreal triamcinolone acetonide injections or chronic treatment with systemic corticosteroids and/or immunosuppressive agents is the use of an intraocular steroid sustained-delivery device. An implant containing 0.59 mg fluocinolone acetonide demonstrated efficacy in clinical trials in patients with chronic noninfectious posterior uveitis and was recently approved by the US Food and Drug Administration (FDA) for this indication.<sup>63</sup> The implant significantly reduced uveitis recurrences, improved visual acuity, and decreased the need for adjunctive therapy. However, the fluocinolone acetonide intravitreal implant is associated with a high rate of complications such as increased intraocular pressure, cataract, retinal detachment (RD), and endophthalmitis.<sup>63</sup> A large, randomized, controlled clinical trial (MUST Trial) sponsored by the US National Eye Institute is currently underway comparing the fluocinolone, implant with conventional therapy.

The dexamethasone intravitreous drug delivery system (DDS) is composed of a biodegradable copolymer of lactic acid and glycolic acid. As dexamethasone is released, the polymer slowly degrades into carbon dioxide and water. Since the implant dissolves completely, sequential implants can be placed into the eye over time without the need for surgical removal. Dexamethasone DDS was evaluated in patients with persistent macular edema resulting from uveitis or Irvine–Gass syndrome in a randomized, prospective, single-masked controlled trial. The authors found improvements in visual acuity and fluorescein leakage in this subgroup of patients.<sup>64</sup>

Antivascular endothelial growth factor, interferons, and somatostatin analogues

VEGF is a major regulator of angiogenesis and vascular permeability and is strongly implicated in the development of CME of various origins. The anti-VEGF drugs inhibit the breakdown of the blood-retinal barrier and recent data suggest that intravitreal anti-VEGF therapy with bevacizumab may be associated with anatomic and visual improvement in uveitis patients with CME resistant to medical therapy that persists despite control of the uveitis.<sup>19</sup> Unfortunately, the beneficial effect was of short duration. These results suggest that, despite its limited inflammatory activity, VEGF may play a role in the pathogenesis of uveitic CME and that targeting this molecule may potentially be an option for treating recalcitrant CME in the setting of uveitis remission.

Interferons are implicated in inducing as well as in treating autoimmunity and reduced intraocular inflammation, especially in Behçet’s disease.<sup>65</sup> German studies have shown promising results of interferon-α (IFNα) in eight patients with CME and inactive uveitis. Side effects of the IFNα treatment are frequent and include flu-like symptoms, fatigue, hepatotoxicity and psychological disturbances.<sup>66</sup> In addition, a beneficial effect of IFNβ on uveitic CME was noted in a retrospective study of 13 patients with multiple sclerosis-associated intermediate uveitis.<sup>67</sup>
Missotten and colleagues reported on patients with persisting macular edema in uveitis in an otherwise quiescent eye and found that the somatostatin analog octreotide long-acting repeatable (LAR) had an edema-reducing effect in 70% of treated CME episodes. Successful response was related to duration of CME before start of treatment.  

Surgical treatment

Vitrectomy surgery has a role in the management of selected patients with chronic inflammatory CME. In eyes with chronic CME and vitreous adhesions to anterior segment structures following complicated cataract surgery, vitrectomy with removal of all vitreous adhesions generally results in anatomic and visual benefit. The current literature contains no convincing data that vitrectomy favorably modifies the course of CME in patients with chronic, recurrent uveitis.

Conclusion

Macular edema is a condition of enormous medical and socioeconomic importance because of its high prevalence and occurrence in a large number of pathologic conditions. It is the endpoint of a variety of pathophysiologic processes that can be effectively managed by recognizing and addressing the pathogenic factors that are operative in a given clinical setting. So far, there are no clear guidelines for the treatment of subclinical cystoid macular edema and every practitioner has their own strategy using a variety of pharmacologic agents, as well as vitreous surgery when needed. Although treatment options continue to expand with the development of new drugs and surgical procedures, long-term efficacy and safety of most new approaches have yet to be established in controlled clinical trials.

Disclosures

The authors have no conflict of interest to disclose.

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