UNDERLYING BASIS AND GOALS OF MACULAR EDEMA THERAPY*

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ABSTRACT

The pathophysiology of macular edema (ME), which encompasses a cascade of inflammatory events in retinal microvessels and the decay of tight junctions in cell walls, suggests a number of different therapeutic options. This article reviews several of these options, with particular emphasis on the underlying basis for their use and their effectiveness in meeting the goals of ME therapy. Options include topical nonsteroidal anti-inflammatory agents, carbonic anhydrase inhibitors, biologic agents with anti-inflammatory and/or antipermeability properties, various formulations of glucocorticoids, systemic therapy for better diabetes control, laser treatment, and vitrectomy. (Adv Stud Ophthalmol. 2007;4(7):182-186)

Macular edema (ME) is the result of a complex cascade of inflammatory events in the retinal microvessels and the decay of tight junctions in the cell walls. The cascade is initiated by vascular disease (ie, diabetes or central retinal vein occlusion) or primary inflammatory disease (ie, uveitis) and mediated by inflammatory cytokines that lead to vasodilation, leukostasis, diapedesis, increased vascular permeability, and the accumulation of various inflammatory proteins. Therapeutic options, many of which are currently being explored more completely, exist within this cascade.

The primary mediating cytokines are vascular endothelial growth factor (VEGF), tumor necrosis factor α (TNF-α), and interleukin 1 (IL-1). These, along with inflammatory disease states and surgery, also contribute to the breakdown of the proteins that maintain tight junction integrity—principally occludin, claudin, and zonula occludens-1 (ZO-1)—and ultimately to the breakdown of the blood-retinal barrier (BRB).

The goals of ME therapy are to reduce inflammation, downregulate the production of VEGF and other inflammatory mediators, and reduce BRB breakdown. The goals are closely related, as evidenced by the causative role of both inflammation and VEGF production in BRB breakdown and the migration of occludin, ZO-1, and other proteins from the tight junctions to inside the cells.

Treatment of ME can include 1 or more of the following: topical nonsteroidal anti-inflammatory drugs (NSAIDs); carbonic anhydrase inhibitors; biologic agents with activity against TNF-α and IL-2; topical, systemic, periocular, intraocular, and implantable glucocorticoids; anti-VEGF agents; systemic therapy for better diabetes control; laser treatment; and vitrectomy. The pathophysiologic basis of each of these modalities is addressed later in this article.

TOPICAL NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Topical NSAIDs have been used to treat post-surgical cystoid ME following cataract surgery. These agents inhibit the formation of prostaglandins, which are known to disrupt the blood-aqueous humor barrier, cause vasodilation, increase vascular permeability,
promote leukostasis, and increase intraocular pressure. Topical NSAIDs also decrease prostaglandin synthesis, particularly in the iris, ciliary body, and conjunctiva, by competitively inhibiting both cyclooxygenase isoenzymes, COX-1 and COX-2.

Some investigators are currently looking into ocular injection of NSAIDs as a potential therapeutic option even though the short half-life of intraocular NSAIDs suggests that these compounds may be most effective if utilized within a drug-delivery implant.

**Carbonic Anhydrase Inhibitors**

Carbonic anhydrase inhibitors, such as acetazolamide, are typically used in patients with cystoid ME due to retinitis pigmentosa or uveitis, but are less likely to produce a favorable response in patients with diabetic maculopathy or ME following retinal vein occlusion. The rationale for their use is that carbonic anhydrase is present in the retinal pigment epithelium (RPE), Müller cells, capillary endothelium, and cone inner segments.

Acetazolamide acts by increasing retinal adhesion between the retina and the RPE, stimulating ion and water transport from the retina to the choroid by solvent drag, and reducing leakage from the retinal vessels.

**Systemic Biologic Agents**

Monoclonal antibodies with activity against TNF-α (ie, infliximab) and IL-2 (ie, humanized anti-Tac) are used primarily in patients with uveitis. These agents, which are given systemically, reduce inflammation in numerous autoimmune diseases. Initially developed to circumvent some of the side effects seen with systemic therapy for autoimmune disorders, biologic agents are nevertheless associated with side effects such as lupus-like disease, infections, and skin reactions.

Although there are some data from controlled clinical trials evaluating biologic agents in uveitis, there are very limited data on their local use inside the eye in humans.

**Glucocorticosteroids**

The cascade of inflammatory events involved in the pathophysiology of ME is illustrated in the Figure. Corticosteroids are used to treat ME because they act at several crucial points in this cascade. Regardless of their formulation, corticosteroids suppress VEGF and inflammatory mediators, induce apoptosis in leukocytes recruited to the site of inflammation, and induce tight junction gene expression.

Studies have shown that intraocular injection of triamcinolone acetonide (TA) dramatically reduces VEGF expression in cultured RPE cells and the vitreous, and reduces ME in patients with diabetic retinopathy and cystoid ME. Glucocorticoids also preserve the BRB by multiple mechanisms, including decreased occludin phosphorylation to counter the enhanced effects of VEGF on vascular permeability, increased expression of tight junction proteins, and restoration of these proteins to their proper location in the endothelium. This restores the architecture of the tight junctions and allows ME to resolve.

Choosing which steroid to use depends on its anti-inflammatory potency, toxicity, method of delivery, and maximum level achieved in the vitreous. TA is 5 times more potent than cortisol, but only 20% as potent as betamethasone, dexamethasone, and fluocinolone acetonide (FA). Studies in retinal cell cultures indicate that dexamethasone and FA are the least toxic among the following steroids tested: dexamethasone,
betamethasone, FA, loteprednel etabonate, methylprednisolone, and TA.\textsuperscript{15-18}

Efforts to improve local delivery of corticosteroids and reduce the need for repeated intravitreal injections have led to the development of sustained-release intravitreal implants or drug delivery systems (DDSs) containing dexamethasone, FA, ganciclovir, and TA.\textsuperscript{19-21} Pharmacokinetics studies have shown maximum levels in the vitreous of 3 µg/mL for a dexamethasone DDS,\textsuperscript{19} 0.05 µg/mL for an FA implant,\textsuperscript{20} and 1.2 µg/mL for TA.\textsuperscript{21} When these values are looked at in relation to the potency of TA (with a corticosteroid equivalence number of 1 compared to a corticosteroid equivalence number of 5 for FA and dexamethasone), the maximum level equivalents are 15 for dexamethasone, 0.25 for FA, and 1.2 for TA.

When these corticosteroid drug level equivalents are plotted over time, the dexamethasone DDS produces very high initial levels of a potent steroid (dexamethasone) for a shorter period of time to quench the inflammatory cascade,\textsuperscript{19} followed by very low levels of dexamethasone released for up to 6 months after implantation,\textsuperscript{19} whereas the FA implant delivers very low levels of a potent steroid (FA) for a prolonged period of time to provide a chronic suppressive effect.\textsuperscript{20} Injection of a TA suspension results in levels of a weaker steroid (TA) that are somewhere in between.\textsuperscript{21-23}

An important aspect of the sustained-release systems is their ability to act as a drug reservoir in vitrectomized eyes and obviate the marked decline in drug half-life that occurs with standard intravitreal injections following vitrectomy. As demonstrated in a study of the dexamethasone DDS, there was no significant difference in retinal drug levels in vitrectomized versus nonvitrectomized rabbit eyes.\textsuperscript{24} This contrasts with the marked decrease in intravitreal half-life following a TA injection in a vitrectomized eye.\textsuperscript{25}

At present, several ongoing phase III studies are evaluating TA implants and intravitreal injections, a sustained-release FA implant, and a dexamethasone polymer DDS in patients with ME.

**ANTI-VEGF AGENTS**

The favorable effects of anti-VEGF agents on vascular permeability and angiogenesis have been well documented in numerous animal and clinical studies. Agents that have been evaluated in diabetic retinopathy and other VEGF-induced conditions include ranibizumab, bevacizumab, pegaptanib, and ruboxistaurin. Several others are in development.

In addition, several ongoing studies are evaluating intravitreal injections of ranibizumab, bevacizumab, pegaptanib, and VEGF-Trap specifically in diabetic ME. Results thus far with ranibizumab,\textsuperscript{26} bevacizumab,\textsuperscript{27} and pegaptanib\textsuperscript{28} are promising.

**SYSTEMIC THERAPY**

Systemic therapy to control glucose, blood pressure, and cholesterol is crucial in managing patients with diabetes and reducing their risk of progression to retinopathy and ME. As demonstrated in the United Kingdom Prospектив Diabetes Study, intensive glycemic and blood pressure control can reduce the risk of vision loss compared to less intensive control.\textsuperscript{29,30}

Similarly, the Early Treatment Diabetic Retinopathy Study underscored the increased risk for hard exudate formation and moderate vision loss in patients with elevated cholesterol levels, with higher risk associated with higher cholesterol levels.\textsuperscript{31}

**LASER TREATMENT AND VITRECTOMY**

Focal laser therapy is the only treatment that has been shown in a large-scale randomized controlled trial to be effective in diabetic ME and should be considered first-line therapy, particularly in cases where there is focal leakage.\textsuperscript{32}

Vitrectomy is an option to be considered when diabetic ME is due to posterior hyaloidal traction (PHT) and optical coherence tomography demonstrates retinal thickening, a taut posterior hyaloidal face, and an underlying shallow traction macular detachment.\textsuperscript{33} Surgery is also an option to be considered when diabetic ME due to PHT does not respond to laser treatment. As reports in the literature have noted, vitrectomy with removal of the posterior hyaloid face can lead to a resolution of diabetic ME and improve vision.\textsuperscript{34,35}

In patients who have failed to improve with pharma- cotherapy or who have continuous leakage, vitrectomy with removal of the posterior hyaloid, even in the absence of any PHT or taut hyaloid, can be therapeutic in that it has the potential to improve oxygenation in the retina and decrease VEGF levels.\textsuperscript{36-38} An important downside to this approach is that the half-life of any drug
given by standard intravitreal injection will be significantly reduced after vitrectomy, and the patient is also exposed to the additional risks associated with the vitrectomy procedure itself.25

**Conclusions**

The goals of therapy for ME are to reduce inflammation, VEGF production, and BRB breakdown. Reducing inflammation and restoring tight junctions are key elements in restoring the healthy anatomy of the macula.

Treatment of ME depends on its etiology, but therapeutic options to consider include topical NSAIDs, carbonic anhydrase inhibitors, systemic biologic agents, corticosteroids, anti-VEGF agents, systemic therapy to control glucose, blood pressure, and cholesterol levels, and/or laser therapy and vitrectomy.

**References**


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