MODULE 9.8
Corticosteroids

Corticosteroids have emerged as an alternative therapy for persistent diabetic macular edema (DME) or DME refractory to conventional laser photocoagulation and other treatments.[1] These agents have characteristics that result in the inhibition of vascular endothelial growth factor (VEGF) and possess anti-inflammatory properties (Figure 1).[2] Prostaglandins, are endogenous mediators of vascular permeability. Corticosteroids have been used in the treatment of cystoid macular edema (CME) because of their ability to inhibit the arachidonic acid pathway, which is responsible for the production of prostaglandins.[3] Corticosteroids also appear to downregulate the production of VEGF. Capillary leakage resulting in DME is thought to be mediated by both VEGF and inflammation. Numerous studies have demonstrated the beneficial therapeutic effect of corticosteroids such as triamcinolone and dexamethasone in the treatment of DME.

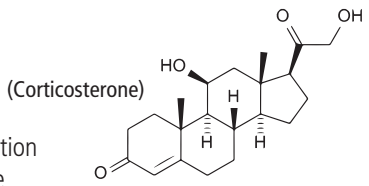
Peribulbar (inferotemporal, lateral to the lateral limbus either through the conjunctival reflection or percutaneously) or subtenon (between Tenon's capsule and the sclera) injections of corticosteroids have been used to treat DME either as monotherapy or as therapy adjunctive to laser.[1,4] Although these dosing techniques are not considered ideal for obtaining a therapeutic dose of the medication at the level of the retina,[5,6] short-term efficacy has been demonstrated with transient improvement in both visual acuity (VA) and retinal thickness.[6] However, this dosing method appears to be less effective than intravitreal therapy.

Intravitreal triamcinolone (IVTA; Alimera Sciences, Inc; Alpharetta, GA) has been widely used to treat DME, particularly diffuse macular edema that persists following laser treatment.[1] The Diabetic Retinopathy Clinical Research Network (DRCRnet) compared 2 doses of IVTA as monotherapy to focal/grid laser photocoagulation.[7] Eyes were randomized to either focal/grid photocoagulation (n = 330), 1-mg IVTA (n = 256), or 4-mg IVTA (n = 254). At 4 months, mean VA was better in the 4-mg triamcinolone group than in either of the other 2 groups ($P \leq .001$), but by 1 year there were no significant differences among groups in mean VA. At 2 years, mean VA was better in the laser group than in the IVTA groups ($P \leq .02$). Intraocular pressure increased from baseline by 10 mm Hg or more at any visit in 4%, 16%, and 33% of eyes in the laser, 1-mg, and 4-mg groups, respectively. Cataract surgery was performed in 13%, 23%, and 51% of eyes in these 3 treatment groups, respectively.

A second study by the DRCR.net evaluated intravitreal 0.5-mg ranibizumab or 4-mg triamcinolone combined with focal/grid laser compared with focal/grid laser alone for the treatment DME (sham injection + prompt laser (n = 293), 0.5-mg ranibizumab + prompt laser (n = 187), 0.5-mg ranibizumab + deferred (≥ 24 weeks) laser (n = 188), or 4-mg triamcinolone + prompt laser (n = 186).8 The 1-year mean change in the VA letter score from baseline was not significantly greater in the IVTA + prompt laser group (P = .31) compared with

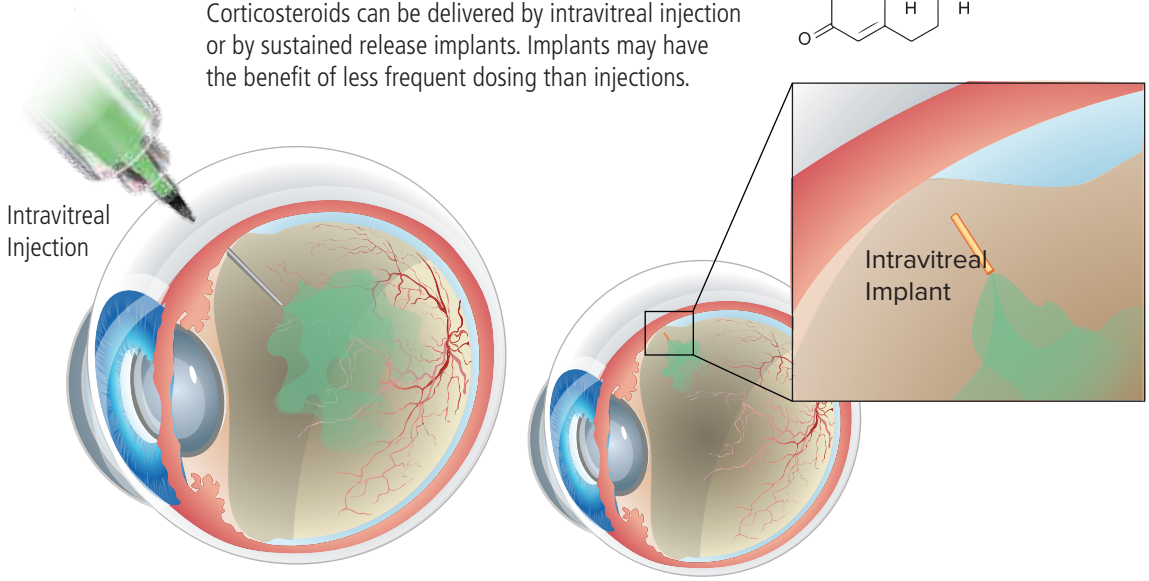
Corticosteroid Therapy

Corticosteroids work by targeting two of the different mechanisms that cause the disease: inflammation (or swelling) and VEGF expression.



(Corticosterone)

Corticosteroids can be delivered by intravitreal injection or by sustained release implants. Implants may have the benefit of less frequent dosing than injections.



the sham + prompt laser group. Reductions in mean central subfield thickness in the IVTA + prompt laser group were similar to both ranibizumab groups and greater than in the sham + prompt laser group. In a group analysis of pseudophakic eyes at baseline (n = 273), VA improvement in the IVTA + prompt laser group appeared comparable to that in the ranibizumab groups.

Adverse events (AEs) generally associated with IVTA injections include steroid-induced glaucoma, cataract progression, and an increasing risk of endophthalmitis.[1,2] To reduce the risks, complications, and frequent dosing required with intravitreal steroid injection formulations, intravitreal sustained-release implants using dexamethasone (0.7 mg; Ozurdex; Allergan, Inc; Irvine, CA) and fluocinolone acetonide (FA; 0.19 mg; Iluvien; Alimera Sciences, Inc; Alpharetta, GA) have been developed.[1,9,10] These devices have been recently approved by the FDA for the treatment of DME.[9] You'll learn more about these in Module 10.

Due to their mechanisms of action, corticosteroids being complimentary to those of anti-VEGF agents, the use of these two types of agents in combination may be beneficial for the treatment of DME. Soheilian and colleagues conducted a study 150 eyes with naïve CSME into three groups: intravitreal bevacizumab + sham laser, bevacizumab+ IVTA + sham laser, and macular laser photocoagulation+ sham injection (MPC). The addition of IVTA did not appear to have an adjunctive effect in this trial. The Diabetic Retinopathy Clinical Research Network is engaged in an ongoing study to assess whether the addition of steroids to an anti-VEGF treatment regimen in pseudophakic eyes has beneficial short-term effects in eyes with persistent DME and vision impairment, compared with continued anti-VEGF therapy alone.

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