Intravitreal Injection of Triamcinolone

An emerging treatment for diabetic macular edema

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Editor’s comment: From time to time, treatments for diabetes and its complications are promulgated, which seem to have sufficient nonrandomized clinical data to support their consideration for use in our patients. Rather than wait for randomized clinical trials to be published (and in some cases, this is unlikely to occur), descriptions of these treatments, their effectiveness, and their side effects will be published in Diabetes Care as a Commentary. In many situations, these therapeutic approaches would only be considered after more conventional therapy has been ineffective. Intraocular injections of glucocorticoids for macular edema fit these criteria.

Diabetic retinopathy is a major cause of visual impairment in the U.S. (1–3). Diabetic macular edema is a manifestation of diabetic retinopathy that produces loss of central vision and is commonly diagnosed by ophthalmologists. The Wisconsin Epidemiologic Study of Diabetic Retinopathy estimated that after 15 years of known diabetes, the prevalence of diabetic macular edema is ~20% in patients with type 1 diabetes, 25% in patients with type 2 diabetes who are taking insulin, and 14% in patients with type 2 diabetes who do not take insulin (1).

Diabetic macular edema, because of the frequency with which it is seen, is a condition that has considerable public health importance. Currently, the only demonstrated means to reduce the risk of vision loss from diabetic macular edema are intensive glycemic control, as demonstrated by the Diabetes Control and Complications Trial (DCCT) (4) and the U.K. Prospective Diabetes Study (5), and laser photocoagulation, as demonstrated by the Early Treatment Diabetic Retinopathy Study (ETDRS) (6).

In the DCCT, intensive glucose control reduced the risk of onset of diabetic macular edema by 23% compared with conventional treatment. Long-term follow-up of patients in the DCCT show a sustained effect of intensive glucose control, with a 58% risk reduction in the development of diabetic macular edema for the DCCT patients followed in the Epidemiology of Diabetes Interventions and Complications Study (7).

In the ETDRS, laser photocoagulation of eyes with diabetic macular edema reduced the risk of moderate visual loss by ~50% (from 24 to 12%, 3 years after initiation of treatment) (6). These results show that for some patients, laser photocoagulation is effective but that 12% of treated eyes developed moderate visual loss in spite of treatment. Furthermore, ~40% of treated eyes that had retinal edema involving the center of the macula at baseline still had edema involving the center at 12 months, as did 25% of treated eyes at 36 months (8).

The frequency of an unsatisfactory outcome following laser photocoagulation in some eyes with diabetic macular edema has prompted interest in other treatments. One such treatment is a procedure to remove the vitreous humor from the eye (vitrectomy surgery) (9–11). These studies suggest that vitreomacular traction, or the vitreous itself, may play a role in increased retinal vascular permeability. Removal of the vitreous or relief of mechanical traction with vitrectomy may, in some patients, be followed by substantial resolution of macular edema and corresponding visual rehabilitation. However, this treatment may be applicable only to a specific subset of eyes with diabetic macular edema. It also requires a significant and complex surgical intervention. Other treatments such as pharmacologic therapy with oral protein kinase C inhibitors and intravitreal injection of antibodies targeted at vascular endothelial growth factor (VEGF) are under investigation. Recently, delivery of corticosteroids via the vitreous cavity to treat diabetic macular edema has generated significant interest. The delivery route may be via either a sustained release, surgically placed intravitreal implant or via injection of corticosteroid, using a 27- or 30-gauge needle, directly into the vitreous cavity of the eye (intravitreal injection). The remainder of this commentary will discuss intravitreal injection of corticosteroid for diabetic macular edema.

The rationale for the use of corticosteroids to treat diabetic macular edema follows from the observation (12) that the increase in retinal capillary permeability that results in diabetic macular edema may be caused by a breakdown of the blood retina barrier mediated in part by VEGF, a 45-kDa glycoprotein. Antonetti et al. (13) demonstrated that VEGF may regulate vessel permeability by increasing the phosphorylation of tight junction proteins such as occludin and zonula occluden 1. This model provides, at the molecular level, a potential mechanism for VEGF-mediated vascular permeability in the eye. Similarly, in human nonocular disease states such as ascites, VEGF has been characterized as a potent vascular permeability factor (14).

Pharmacologic attenuation of the effects of VEGF is the rationale for the use of corticosteroids in the treatment of macular edema associated with diabetic retinopathy. Corticosteroids, a class of substances with anti-inflammatory properties, have been demonstrated to inhibit the expression of the VEGF gene (15). In
Intravitreal injection has been proposed as a way to efficiently deliver corticosteroid to the posterior portion of the eye, in close proximity to the retina. Triamcinolone acetonide is the corticosteroid currently used by ophthalmologists in the clinical setting because it is a readily available pharmacologic agent (Kenalog 40; Bristol-Myers-Squibb, Princeton, NJ). Currently, the typical dose of triamcinolone acetonide used to treat eyes with diabetic macular edema is 4 mg in a volume of 0.1 ml (17).

Triamcinolone acetonide has traditionally been used as a pericocular injection for the treatment of macular edema secondary to inflammation or following intraocular surgery (typically cataract surgery) (18,19). To achieve a higher intraocular concentration of corticosteroid to treat retinal disease, the intravitreal injection of triamcinolone acetonide was first proposed in the 1970s, in an animal model, as a pharmacological adjunct to prevent the formation of proliferative scar tissue (proliferative vitreoretinopathy) in order to improve outcomes following retinal detachment surgery (20). Since then, pure triamcinolone acetonide and the vehicle in Kenalog have been shown to have an acceptable safety profile in animal studies (21,22). Subsequent to the demonstration of the safety profile of intravitreal Kenalog in animal models, intravitreal triamcinolone in the form of Kenalog has been used clinically in a variety of retinal diseases, such as age-related macular degeneration (23–25).

Intravitreal triamcinolone acetonide was first proposed, in 1999, as a treatment for diabetic macular edema because of the safety profile demonstrated in animal models, prior clinical experience with other retinal diseases, and the rationale of attenuating the VEGF-mediated retinal capillary permeability that is presumed to contribute to diabetic macular edema. The use of intravitreal triamcinolone acetonide is now widespread among ophthalmologists who specialize in the treatment of retinal disease. The treatment has become common as a result of initial anecdotal experiences showing great promise in patients with diabetic macular edema as well as other ophthalmologic disorders, such as retinal vascular occlusion and certain inflammatory disorders. Some patients experience rapid and dramatic resolution of macular edema and improvement in visual acuity (26). Furthermore, the treatment is inexpensive and readily available, using commercially available Kenalog. The treatment is also easy to administer. It is typically performed in the outpatient setting using only topical anesthesia, and a small-bore needle (e.g., 27 or 30 gauge) is used to deliver the medication into the vitreous cavity of the eye via the pars plana portion of the globe. However, despite the extensive use of intravitreal corticosteroids, published data are limited. There have been no published controlled trials of intravitreal corticosteroids for diabetic macular edema. Two nonrandomized and noncontrolled case series have been published (Table 1).

Martidis et al. (17) reported results using intravitreal triamcinolone acetonide injection in 16 eyes with macular edema due to diabetic retinopathy. All 16 eyes had persistent macular edema after having received multiple sessions of laser photocoagulation. Using a diagnostic technique named optical coherence tomography (a diagnostic technique that can measure the thickness of the retina), anatomical improvement documented by the technique of optical coherence tomography (a diagnostic technique that can measure the thickness of the retina), DME, diabetic macular edema; FA, fluorescence angiography.

### Table 1—Efficacy of intravitreal steroids (published clinical studies)

<table>
<thead>
<tr>
<th>Study</th>
<th>No. eyes treated</th>
<th>Disease</th>
<th>Anatomical improvement</th>
<th>Mean baseline visual acuity</th>
<th>Mean visual acuity at end point</th>
<th>Mean follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martidis et al.</td>
<td>16</td>
<td>DME</td>
<td>11 of 16 eyes (69%)*</td>
<td>20/200</td>
<td>20/80</td>
<td>3</td>
</tr>
<tr>
<td>Jonas et al.</td>
<td>26</td>
<td>DME</td>
<td>21 of 21 eyes had less leakage (FA)</td>
<td>20/165</td>
<td>20/105</td>
<td>6.6</td>
</tr>
</tbody>
</table>

*Anatomical improvement documented by the technique of optical coherence tomography (a diagnostic technique that can measure the thickness of the retina). DME, diabetic macular edema; FA, fluorescence angiography.
ment. The potential toxicity of corticosteroids includes the development of cataracts and glaucoma. Furthermore, the treatment effect typically wanes, and patients who are initially successfully treated may require repeated injections. With each repeat injection, the patient is again subjected to the risks of the injection procedure and the risk of a steroid-related cataract and/or glaucoma increases.

Another unresolved issue with the use of this technique is that commercially available Kenalog is formulated specifically for intrabursal and intramuscular use and not for intravitreal use, necessitating "off-label" use of Kenalog by the ophthalmology community. There have been several anecdotal reports of inflammatory reactions, possibly to one of the excipients in the Kenalog formulation, following intravitreal injection of Kenalog. These sterile inflammatory reactions are often difficult to distinguish from a postinjection bacterial infection of the eye. Ultimately, the manufacture of a formulation for intravitreal use (i.e., preservative free, endotoxin free, and sterile) may alleviate some of the current concerns about the use of the Kenalog formulation.

One final unresolved issue concerning the use of intravitreal Kenalog is that the optimal dose to maximize efficacy and minimize side effects is not known. The commonly used dose of 4 mg/0.1 ml is principally being used because of convenience. At a shelf dosage of 40 mg/ml, Kenalog is easily aliquoted to a 4 mg/0.1 ml dose. A volume of 0.1 ml is readily tolerated when injected into the vitreous cavity. Other than the convenience of this dose, there are no data that support the use of 4 mg over any other alternative dose.

As a result of the potential for improvement in visual acuity in an ocular condition that does not often have good treatment options and for serious sight-threatening complications as described above, there is currently a need for a randomized trial to better define the efficacy and safety profile of this treatment. The Diabetic Retinopathy Clinical Research Network (www.drcr.net) is a National Eye Institute–sponsored research infrastructure dedicated to multicenter clinical research of diabetic retinopathy, macular edema, and associated disorders. One of the initial studies performed by this research network will be the study of intravitreal triamcinolone for the treatment of diabetic macular edema. This study is expected to begin the recruitment of patients in 2004 and will hopefully provide ophthalmologists answers in terms of the risk-to-benefit ratio of this new treatment for diabetic macular edema.

References


