Update on Corticosteroids for Treatment of DME

Steroids target multiple pathways in diabetic macular edema.

BY ANAT LOEWENSTEIN, MD

Diabetic macular edema (DME) is a common cause of vision loss in people with diabetes.[1] Because the inflammatory response in DME is complex, a therapy that targets more than one part of the inflammatory process could potentially provide a clinical advantage. By affecting multiple pathways, such a compound may be able to break the cycle of disease progression, whereas therapies that target only one inflammatory mediator may not.

Corticosteroids have great potential in this regard because they target both arms of the pathogenetic process, inhibiting the inflammatory mediators that affect vascular permeability and the blood-retinal barrier and also inhibiting vascular endothelial growth factor (VEGF). The rationale for treatment of DME with steroids includes their antiinflammatory, antiapoptotic, antiedematous, and antiangiogenic properties.

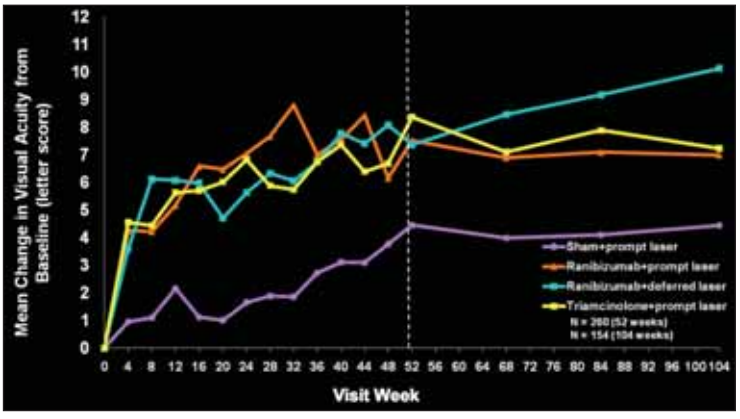

Figure 1. In DRCR.net Protocol I, IVTA plus laser was more effective than laser alone in eyes that were pseudophakic at baseline.

There are many types of steroids and methods of steroid delivery, and this leaves many open questions regarding their use in the treatment of DME, including identifying the best dosages and formulation, choosing the optimum method of delivery for each drug, and minimizing side effects. This article reviews results with a number of steroid formulations that have been or are being evaluated for use in DME.

INTRAVITREAL TRIAMCINOLONE

The Diabetic Retinopathy Clinical Research Network has investigated the use of intravitreal injection of triamcinolone acetonide (IVTA) for treatment of DME in two randomized clinical trials.

Protocol B [2,3] compared two doses of IVTA, 1 mg and 4 mg, to focal/grid laser photocoagulation using a modified ETDRS protocol. The results showed that after 36 months there was a clear benefit for laser alone over IVTA. In addition, the steroid groups experienced more side effects, including elevated intraocular pressure (IOP), which was sometimes profound, and development of cataract. In eyes that were phakic at baseline, 83% of patients in the 4 mg steroid group required cataract surgery over 3 years' follow-up.

Protocol I of the DRCR.net subsequently compared IVTA, ranibizumab, and laser alone.[4,5] Patients were randomly assigned to one of four groups: sham injection plus prompt laser, ranibizumab 0.5 mg plus prompt laser, ranibizumab 0.5 mg plus deferred laser, and IVTA 4 mg plus prompt laser. In this trial, ranibizumab with either prompt or deferred laser was more effective

through at least the primary outcome point of 1 year, compared with the two other groups.

In eyes that were pseudophakic at baseline (Figure 1), IVTA plus laser was more effective than laser alone; in this subgroup, visual acuity results in the three experimental groups appear to be similar. This suggests that a positive effect of steroids in the whole study population was masked by the development of cataract. Still, patients randomized to IVTA plus laser had a greater frequency of significant IOP elevation, and approximately 60% of patients in this group developed cataract, four times the percentage in the other groups.

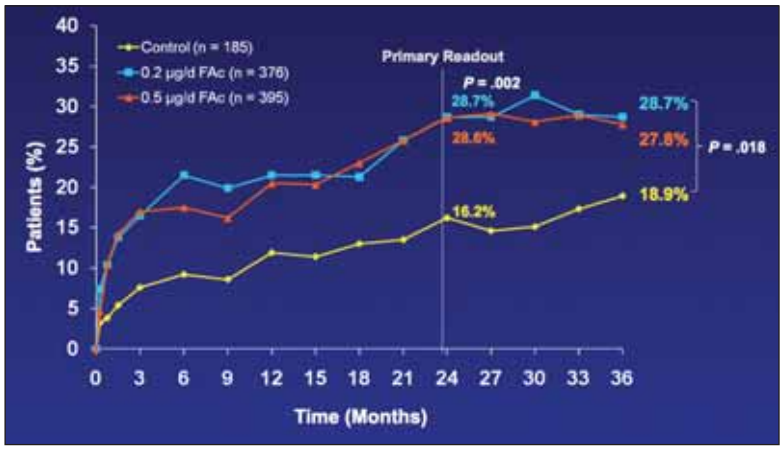

Figure 2. In the FAME trial, almost 30% of eyes receiving low- or high-dose fluocinolone implant achieved 3 lines or more improvement of visual acuity, compared with 16% of controls.

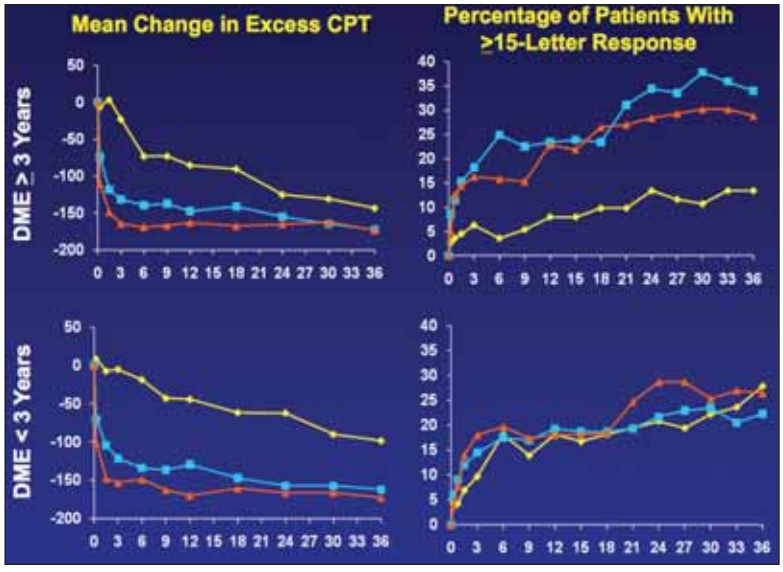

Figure 3. Subgroup analysis in FAME showed that patients with DME duration of more than 3 years experienced better results than those with DME of less than 3 years duration.

EXTENDED RELEASE

Intravitreal delivery of triamcinolone by means of an intraocular delivery device, the I-Vation sustained drug delivery system (Surmodics), has also been evaluated. This device, containing 925 µg of triamcinolone, has a novel helical design that is inserted through an incision smaller than 25 gauge and remains anchored to the sclera. Its safety and efficacy were prospectively evaluated in 31 patients in the phase 1 STRIDE trial.[6] Patients were randomized to a slow-release formulation (1 µg/day; 2-year release) or a fast-release formulation (3 µg/day; 10-month release). Stabilization of visual acuity and decrease in central retinal thickness on optical coherence tomography (OCT) were seen to approximately 30 months in the 3-year follow-up. The safety profile was good, with few patients requiring IOP-lowering medications. Most patients developed cataract, but the implant did not impede cataract surgery.

Two devices providing extended delivery of fluocinolone acetonide have been investigated for treatment of DME.

The Retisert (fluocinolone acetonide 0.59 mg implant, Bausch + Lomb) device, surgically implanted through a 3.5-mm incision in the pars plana, delivers a low level of this potent molecule to the posterior segment for up to 36 months. In a small study (n=80) in patients with DME, significant improvements were seen in macular edema, retinal thickness, and visual acuity at 36 months, but high rates of IOP elevation and cataract were reported. Almost 40% of patients required filtering surgery to control IOP, and more than 90% developed cataract.[7]

The Iluvien (fluocinolone acetonide implant, Alimera) is a smaller, nonbioerodable device that is injected in an office setting through a self-sealing wound with a 25-gauge inserter. The phase 3 FAME trial[8,9] compared this device, formulated in two doses (0.2 µg/day and 0.5 µg/day), to standard of care, which could include laser or anti-VEGF injection, in 956 patients.

Almost 30% of eyes receiving either the low-dose or high-dose formulation of the drug achieved three lines or more improvement of visual acuity, compared with 16% of controls, in the 3-year results of the study

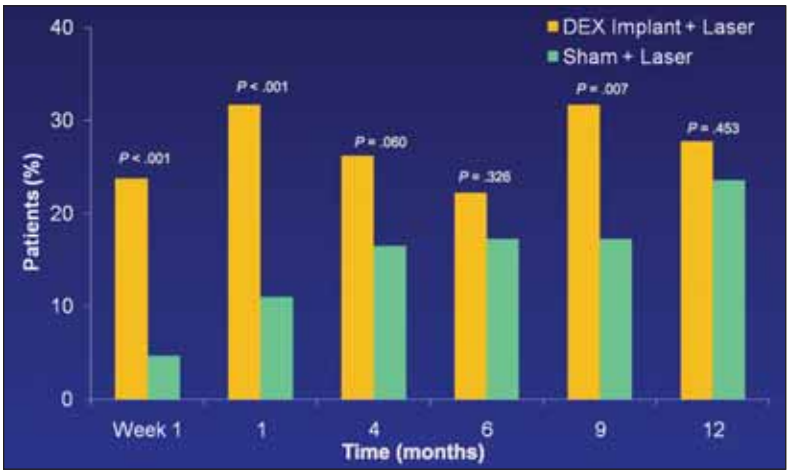

Figure 4. In the PLACID trial, more patients with the dexamethasone implant plus laser achieved a 2 line gain in visual acuity than with laser alone; after month 9 the difference was not statistically significant.

announced earlier this year (Figure 2).[8] This was paralleled by decrease in central retinal thickness to about 24 months. Subgroup analysis showed that patients with DME duration of more than 3 years experienced better results than those with DME of less than 3 years duration (Figure 3).[9]

Regarding safety, approximately 80% of patients in the steroid treatment groups underwent cataract surgery, but the IOP profile was better than with the larger fluocinolone implant, with less than 5% in the lower dose group and less than 10% in the higher dose group needing trabeculectomy. The 2-year follow-up results of this study have been submitted to the U.S. Food and Drug Administration for approval of this device for treatment of DME.

Dexamethasone is a potent inhibitor of cytokines released by human pericytes that has demonstrated high levels in the vitreous for more than 6 months in vivo. The Ozurdex (dexamethasone intravitreal implant, Allergan) device has been or is being evaluated in multiple posterior segment diseases, including central and branch retinal vein occlusions, age-related macular degeneration, and DME. The device is inserted in an office-based procedure using an injector. Patients are prepped with povidone iodine, and only topical anesthesia is required.

Several trials investigating the safety and efficacy of the dexamethasone implant have included patients with DME. A phase 2 trial[10,11] evaluated the device in two doses, 700 µg and 350 µg, in patients with treatment-resistant macular edema from multiple causes, including DME. In this trial, more patients receiving

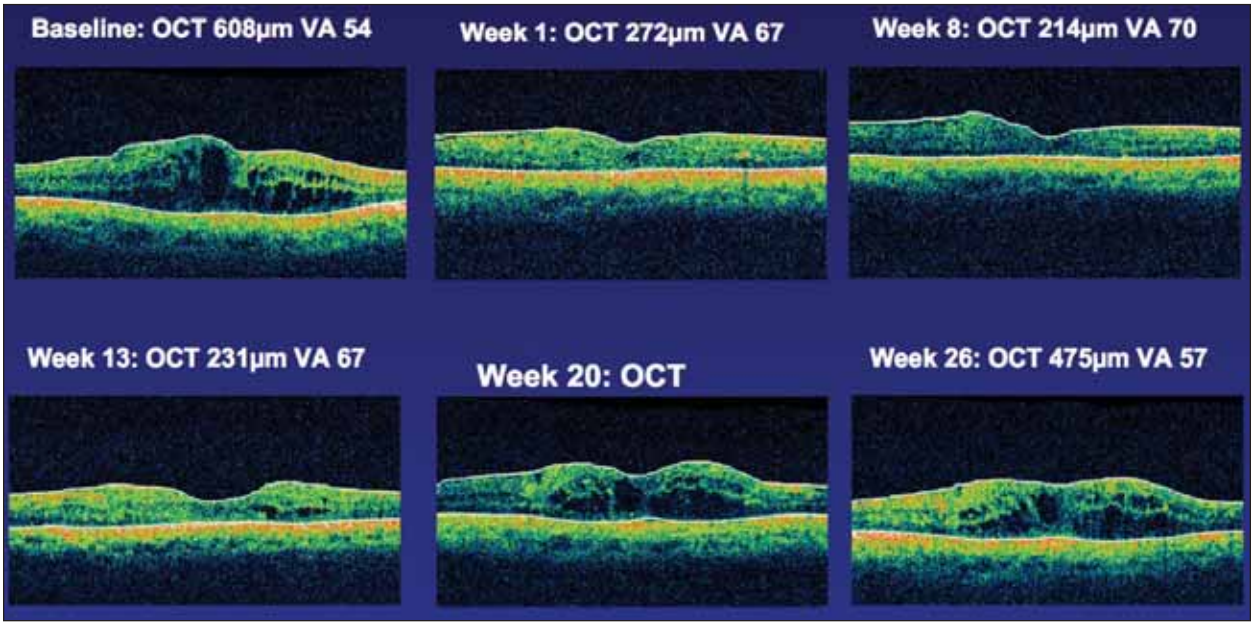

Figure 5. Case example of a patient in the CHAMPLAIN trial. This 60-year-old man had previous cataract extraction, laser photocoagulation, two pars plana vitrectomies, membrane stripping, and intravitreal triamcinolone acetonide. Baseline retinal thickness on optical coherence tomography (OCT) was 608 µm and visual acuity (VA) was 54 ETDRS letters. Both measures improved at 1 week after dexamethasone implant and maintained improvement until thickness increased again at week 20.

dexamethasone achieved two and three lines of improvement in visual acuity at 90 days after implant than patients who were observed. This was true for the whole group and also for the subgroup of DME eyes. Visual acuity improvement was paralleled by decrease in retinal thickness.

An ongoing phase 3 study, MEAD,[12] is comparing the dexamethasone implant in high and low doses (700 µg and 350 µg) to sham treatment. Recruitment is complete, and 3-year follow-up is planned. Many patients have received more than four injections, and it is anticipated that results will be announced in 2012.

Another phase 3 trial, PLACID,[13] compared the safety and efficacy of the dexamethasone implant plus laser with sham implant procedure plus laser in the treatment of DME. In this 1-year trial, patients in the dexamethasone group were eligible for a second implant at 6 months and a third at 9 months if they met retreatment criteria.

More patients with the dexamethasone implant plus laser achieved a two-line gain in visual acuity than with laser alone; after 9 months this difference was no longer statistically significant (Figure 4). Best corrected visual acuity improved more in patients with diffuse DME who received the implant plus laser vs sham plus laser over 12 months. Areas of leakage and retinal thickness decreased more in patients receiving dexamethasone and laser than those receiving laser alone. The anatomic response showed somewhat of a seesaw appearance in retinal thickness that requires further analysis. The safety profile of the device was excellent, with 1.0% of patients at month 12 experiencing elevation of IOP by 10 mg Hg or more. No patient required surgery for IOP management.

CHAMPLAIN[14] is an open-label phase 3b trial of the dexamethasone implant for the treatment of DME in vitrectomized patients. This trial includes patients with some very sick eyes, eyes that have had not only vitrectomy but also usually IVTA and other drugs (Figure 5) and that still have persistent DME.

In this 26-week trial, patients received a single injection of the dexamethasone implant. At weeks 8 and 13, approximately 30% of patients had an improvement of at least 2 lines of visual acuity, which was paralleled by a decrease in retinal thickness. The safety profile in these sick eyes was also very good, with no laser or surgery required for control of IOP.

CONCLUSIONS

Macular edema in diabetes is a multifactorial process, and it requires management that addresses the various aspect of its etiology. Steroids therefore have a theoretical advantage in rationale because they address more than one mechanism in the pathology of the disease.

Extended-release steroid delivery devices have shown promising efficacy results in DME, with varying length of effect. Safety profiles also differ among the different steroids and delivery devices. The optimal type, dose, device, and frequency of administration of corticosteroids for treatment of DME still remain to be established with longer follow-up in multiple clinical trials. ■

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