Dexamethasone Implant for Treatment of DME in Vitrectomized Patients

A prospective, 6-month, open-label study shows promising results.

BY LEONARD FEINER, MD

Ocular pharmacokinetics and pharmacodynamics are altered in the vitrectomized eye. The normally two-chambered eye is essentially rendered one-chambered, and this increases the rate of clearance of medications from the vitreous cavity. Thus, the dose of drug delivered to the retina, as well as the duration of delivery of the drug, are reduced. The half-life of many commonly used intravitreal medications, including some used in the treatment of diabetic macular edema (DME), are reduced in human vitrectomized eyes.

Yanyali and colleagues[1] reviewed the records of 11 eyes of 10 patients who received three monthly injections of bevacizumab (Avastin, Genentech) after vitrectomy for persistent DME. They found no improvement in terms of anatomic improvement on optical coherence tomography (OCT) or in visual acuity. The authors hypothesized that one of the reasons for this lack of efficacy was the rapid clearance of drug from the vitreous cavity.

Dexamethasone is a potent steroid that is highly effective in reducing inflammation in the eye. It reduces the production of many inflammatory factors, including vascular endothelial growth factor (VEGF). Dexamethasone also has an extremely short half-life in the eye.

A solid polymer drug-delivery system known as Novadur (Allergan, Inc.) was developed to facilitate long-term intraocular delivery of pharmaceutical agents. Ozurdex (Allergan, Inc.), a biodegradable implant built on the Novadur delivery platform, enables extended release and prolonged effect of dexamethasone in the vitreous cavity. The device is delivered into the eye using a pen-like 22-gauge needle injector. After delivery, encapsulated dexamethasone is released as the polymer breaks down by simple hydrolysis. This enables sustained, low-dose delivery of the steroid to the tissues of the eye.

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PRECLINICAL, CLINICAL EVALUATION

In vitrectomized and nonvitrectomized rabbit eyes,[2] the Ozurdex device was injected, and the concentration of dexamethasone was measured over 1 month's time. Investigators found that the concentration was similar, regardless of the vitrectomy status of the eye.

This finding led to the rationale to use Ozurdex to treat postvitrectomy patients with persistent macular edema. We performed a study to evaluate the safety

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and efficacy of Ozurdex dexamethasone intravitreal implant 0.7 mg in the treatment of patients with DME after vitrectomy.[3]

In this prospective, multicenter, 6-month, open-label study, 56 patients with DME and a history of pars plana vitrectomy at least 3 months before baseline were enrolled. Patients received one intravitreal injection of the 0.7 mg dexamethasone implant in the vitrectomized eye and were followed for 26 weeks: follow-up visits were on day 2 and at weeks 1, 4, 8, 13, 20, and 26.

The primary efficacy endpoint was anatomic: the change in central retinal thickness (CRT) from baseline to week 26 as evaluated on OCT. Change from baseline at every time point was also evaluated. Secondary outcomes included change in best corrected visual acuity (BCVA) over time, the percentage of patients who improved by 2 lines of BCVA or more, change in leakage on fluorescein angiography, standard safety evaluations including adverse events, and intraocular pressure (IOP).

Patients enrolled in the trial were 18 years of age or older and had diabetes, a history of vitrectomy at least 3 months before baseline, DME diagnosed by OCT, and a CRT of greater than 275 µm. Baseline BCVA was between 20/40 and 20/320. Patients with glaucoma or hypertension were excluded.

RESULTS

Fifty-five patients received the dexamethasone implant in this study. Patients' mean age was 62, their mean duration of DME was 43 months, and mean baseline CRT was 403 µm.

The implant significantly decreased CRT from baseline at every time point after injection. The peak effect was at the week 8 visit (-155.5 µm; $P<.001$), but there was still a statistically significant difference at the 26-week visit (-38.9 µm; $P=.004$).

Approximately 30% of patients gained two lines of BCVA or more, and the maximal effects in this prespecified endpoint were seen at the week 8 and week 13 visits. At the week 26 time point, 43% of patients had gained one line or more and 21% of patients had gained two lines or more of BCVA.

Ocular adverse events were consistent with other studies in which intravitreal injections were given. Conjunctival hemorrhage and hyperemia were the most common adverse events. Vitreous hemorrhage was seen in six patients, perhaps because of the large (22 gauge) needle size.

The two main safety concerns with long-term steroid implants are glaucoma and cataract progression. Increases in IOP were seen in 16% of patients, and antiglaucoma medications were initiated in eight patients during the study, but no patient required surgery. By week 26, no patient had an IOP of 25 mm Hg or greater.

Regarding cataract, as would be expected in a study of postvitrectomy patients, most patients were already pseudophakic at the start of the study. Of 12 patients who were phakic at baseline, two developed cataract progression by 26 weeks.

CONCLUSIONS

Treatment with the dexamethasone implant safely reduced CRT and improved visual acuity in this pilot study, with a peak effect at 8 to 13 weeks after implant injection.

This was a difficult-to-treat population, with chronic DME of mean duration of almost 4 years. The average patient was between 2 and 3 years postvitrectomy with a mean CRT of 403 µm. Sustained delivery of dexamethasone may be particularly beneficial for this difficult-to-treat group of patients. ■

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1. Yanyali A, Aytug B, Horozoglu F, et al. Bevacizumab (Avastin) for diabetic macular edema in previously vitrectomized eyes. *Am J Ophthalmol.* 2007;144(1):124-126.
2. Chin HS, Park TS, Moon YS, et al. Difference in clearance of intravitreal triamcinoloneacetonide between vitrectomized and nonvitrectomized eyes. *Retina.* 2005;25(5):556-560.
3. Feiner L, Gupta S, Patel SS, et al. Dexamethasone intravitreal implant for treatment of DME in vitrectomized patients: a prospective, 6-month, open-label study. Paper presented at: American Society of Retina Specialists annual meeting; Vancouver, Canada.