

Pharmacokinetics of Sustained-delivery Fluocinolone Acetonide for DME

The Iluvien retinal insert provides sustained delivery for 1 year.

REVIEWED BY PETER A. CAMPOCHIARO, MD

The most common cause of visual acuity loss in patients with diabetic retinopathy is diabetic macular edema (DME).¹ Although focal/grid laser photocoagulation remains the gold standard treatment for DME, a recent trial² showed that, at least in the short term (4 months), patients receiving 4-mg intravitreal steroid injections had better mean visual acuity than those receiving laser. The outcome was reversed by month 16 in this 2-year randomized trial; however, the short-term result suggests that there is a rationale to consider the use of steroids in the treatment of DME.

Corticosteroids serve a number of physiologic functions in the body, and they act on more than one cellular receptor. Some of these receptors can have counter-acting effects. Therefore, it may be that higher doses of steroid have less desirable effects than lower doses. This provides a rationale for sustained delivery of low doses of steroid for the treatment of DME.

A sustained delivery device, Iluvien (Alimera Sciences) is in development for treatment of DME. The 3.5-mm-long tube is inserted into the vitreous cavity through the pars plana with a 25-gauge needle. The device is formulated to release either approximately 0.2 or 0.5 μ g of the corticosteroid fluocinolone acetonide per day. In vitro studies showed that the 0.5 μ g per day insert releases the drug at a higher rate than the 0.2 μ g insert. Early in vitro concentrations are higher with the 0.5 μ g

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device, but by 9 months to 1 year, the concentrations with the two devices are similar.³

In vivo studies of drug release and drug levels were in some cases contradictory with the in vitro work. In rabbits, the 0.5 μ g device was shown to release fluocinolone acetonide out to 9 months, similar to the in vitro curve, but at some time points the drug levels with the 0.2 μ g device were undetectable. Aqueous levels in the rabbit were mostly undetectable for both devices.

PHARMACOKINETIC STUDY

As part of the drug-development strategy, a clinical pharmacokinetic (PK) trial was designed to assess systemic levels of fluocinolone acetonide. This also provides an opportunity to assess certain safety and, to some extent, efficacy parameters in patients with DME. The 12-month safety and efficacy results of this ongoing, 36-month, open-label phase 2 trial have now been announced.⁴

The phase 3 trial of Iluvien in patients with DME is called FAME (Fluocinolone Acetonide for Diabetic Macular Edema), so this smaller PK study was dubbed FAMOUS. Thirty-seven subjects were enrolled, with 20 assigned to receive the smaller 0.2 µg insert and 17 to receive the 0.5 µg insert. In addition to assessing systemic exposure, anterior chamber levels of fluocinolone acetonide in patients with DME were also measured.

The patient eligibility criteria were similar to the FAME study. Patients had to have undergone at least one focal/grid laser treatment and still have persistent edema. As in the FAME study, visual acuity (VA) had to be better than 20/400, but unlike FAME there was no upper VA limit. As a result, the study includes some patients with baseline VA better than 20/50 who therefore could not improve by three lines of VA.

Both the low- and high-dose inserts provide sustained delivery of fluocinolone for at least 12 months.

RESULTS

The aqueous levels measured in patients in the study clearly show that both the low- and high-dose inserts provide sustained delivery of fluocinolone for at least 12 months. Over the course of a year there was little variability and a nice consistency of results for both doses. Patients with the 0.5 µg insert had significantly higher aqueous levels early in the study, for the first month, but after that the aqueous levels with the two models were not significantly different.

Efficacy was also assessed, although the numbers of patients are small. At baseline, by chance, the two patient groups were slightly unbalanced, with worse VA and more foveal thickening in the 0.5 µg group.

If patients who could not achieve a three-line improvement are excluded from analysis—thereby mimicking the eligibility criteria for the FAME trial—the numbers of patients are quite small, but the VA results are better. Mean 8- and 10-letter improvements were seen in the 0.2 µg and 0.5 µg groups, respectively.

Regarding safety, there was no significant change in intraocular pressure (IOP) in the 0.2 µg group, and no patients in that group required IOP-lowering drops. There was a modest increase in IOP in the 0.5 µg group, and five of the 17 patients in the group needed IOP-lowering drops.

Five patients in each group had incident cataract as

an adverse event, and two in each group required cataract surgery. There were no drug-related withdrawals from the study, but there were four deaths and two withdrawals for other reasons.

CONCLUSIONS

Twelve-month results in this small 36-month PK study show that the Iluvien device clearly provides sustained delivery of fluocinolone acetonide at least through the first year after insertion. It also shows that the aqueous levels are comparable between the two groups after the first month.

The efficacy and safety results through 12 months appear to be encouraging, and there seems to be a dose response.

IOP response appears to be a significant difference between the two groups. However, even in the 5 µg group, the IOP results compare favorably to those reported for Retisert (fluocinolone acetonide intravitreal implant, Bausch & Lomb). With that device, approximately 60% of patients required IOP-lowering medications within 34 weeks after implantation.⁵ Even for a study of this size, this difference in the important corticosteroid side-effect of ocular hypertension is striking.

At the end of 2009, the phase 3 studies of Iluvien will reach their primary endpoint, and at that time we will have definitive data on the efficacy and safety of Iluvien. ■

Peter A. Campochiaro, MD, is the George S. and Dolores Doré Eccles Professor of Ophthalmology and Neuroscience at the Wilmer Ophthalmological Institute of the Johns Hopkins Hospital School of Medicine. Dr. Campochiaro states that he receives research support from Alimera, Genentech, and Comentis, and he has an institutional consulting agreement with Genentech. He may be reached at +1 410 955 5106; fax: +1 410 614 7083; or via e-mail at pcampo@jhmi.edu.



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