Fluocinolone Insert's Impact on Overall Risk of Procedures

In an analysis of FAME study data, risk of subsequent procedures was reduced in treated patients.

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Currently no pharmacologic therapy is approved by the US Food and Drug Administration (FDA) for treatment of diabetic macular edema (DME), an ocular complication of diabetes that results in significant visual disability for many of the 23 million people with diabetes in the United States.[1]

A fluocinolone acetonide intravitreal insert (Iluvien, Alimera Sciences) is currently being evaluated in a phase 3 clinical study (the FAME study) for treatment of DME. Preliminary results for the month-24 primary endpoint of this study were announced last year,[2] and the study will conclude this year with final visits at the 3-year data point.

The interim analysis of 24-month FAME data announced last year concentrated on the primary efficacy endpoint of 15-letter (three-line) improvement in visual acuity at 24 months. This article reviews additional data on the safety of the intravitreal insert regarding the number of subsequent ocular procedures required by study participants.[3]

FAME STUDY

Iluvien is an intravitreal insert for the sustained delivery of fluocinolone acetonide to the posterior segment. It is designed to be injected with a 25-gauge needle through the pars plana. The device is not secured to the sclera but remains free-floating. The Iluvien contains approximately 190 µg of fluocinolone acetonide. Depending on its formulation, the insert can deliver a low dose of approximately 0.2 µg per day, with a delivery lifespan of more than 2 years, or a high dose of approximately 0.5 µg per day, with a lifespan of approximately 18 months.

> The 24-month data readout indicated that Iluvien was effective in the treatment of DME.

In the FAME study, a total of 956 participants at 101 sites were randomized 2:2:1 to low-dose insert, high-dose insert, or sham treatment. All patients had DME involving the fovea, with central retinal thickness of 250 µm or greater on optical coherence tomography (OCT). All patients had previous laser treatment, and visual acuity was between 19 and 68 letters, inclusive, on the ETDRS chart. If progression of edema occurred, patients were permitted to undergo laser treatment 6 weeks after enrollment and retreatment with an additional study insert after 1 year.

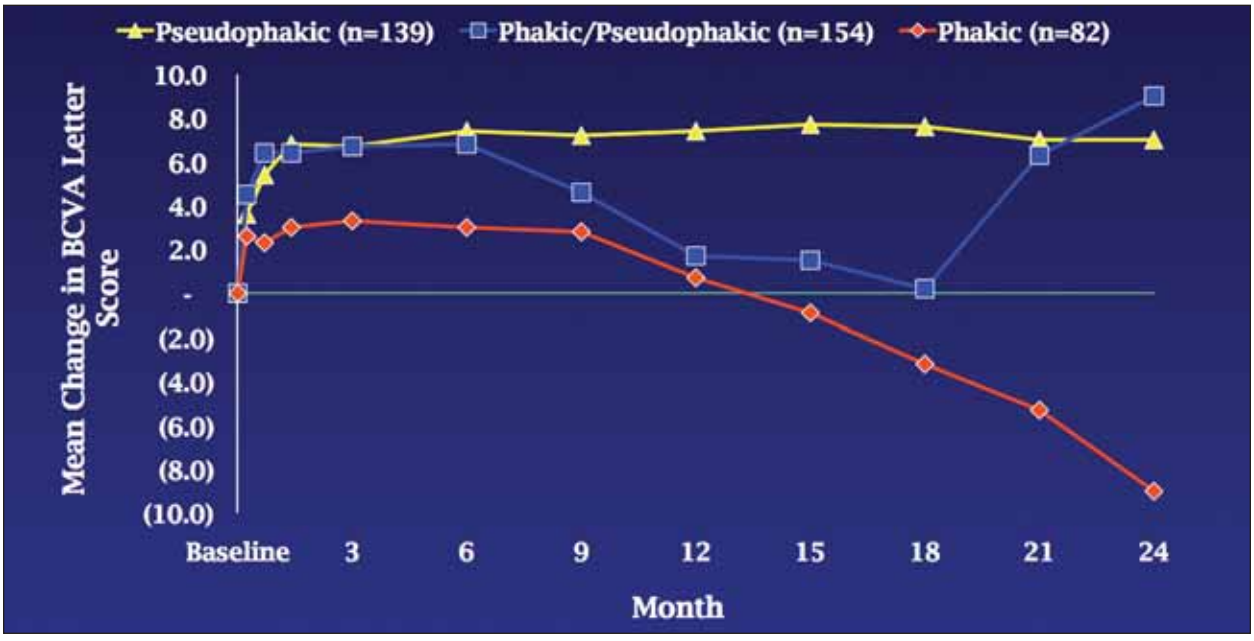

Figure 1. Those who remained phakic throughout the first 2 years had the worst vision at 24 months.

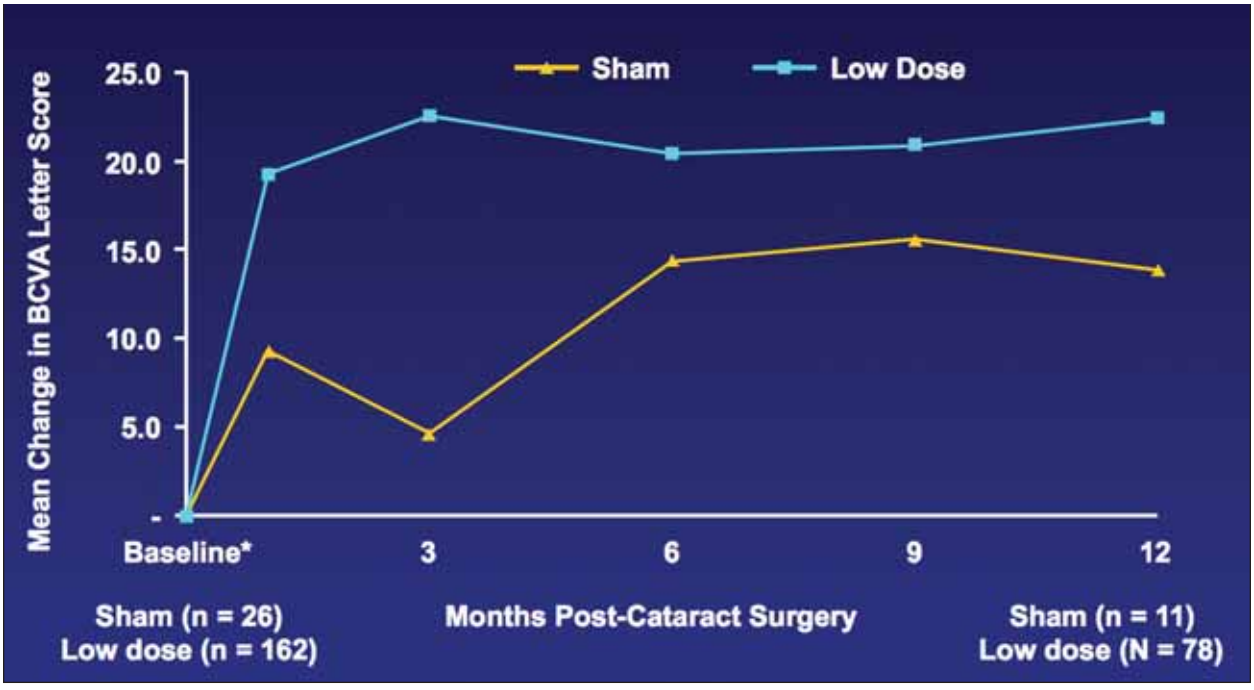

Figure 2. Those with sham implant who underwent cataract surgery had a mean decrease in visual acuity, perhaps because of a worsening of DME, followed by a gradual increase in vision.

The 24-month data readout indicated that Iluvien was effective in the treatment of DME, with 29% of treated patients (both treatment groups) gaining 15 letters of visual acuity compared with 16% of subjects in the sham group.

The two primary side effects of intraocular corticosteroids are development of cataract and elevation of intraocular pressure (IOP). The FAME investigators wanted to know whether Iluvien would mitigate these side effects. We evaluated the relative risk of all procedures associated with the treatment of diabetic retinopathy and elevation of IOP in FAME study participants.

CATARACT

The insert caused acceleration of cataract formation. By 24 months, approximately 75% of the patients who were phakic at enrollment had undergone cataract surgery. Cataract developed mostly between months 6 and 18.

In these patients, therefore, the visual benefit of the insert was delayed. Patients who entered the study pseudophakic (n=139) experienced rapid improvement in visual acuity that remained stable through 24 months. Patients who entered the study phakic and underwent cataract surgery during the course of the trial (n=154) ended up with modestly better visual acuity, on average, at 24 months than those who were pseudophakic at baseline. Those who remained phakic throughout the first 2 years (n=82) had the worst vision at 24 months (Figure 1).

Patients with DME are usually at risk for worsening of edema after cataract surgery, but that did not occur in patients in this study. Treated patients who underwent cataract surgery had rapid postoperative improvement by a mean of approximately 20 letters and were stable for 12 months. Those with sham implant who underwent cataract surgery had a mean decrease in visual acuity, perhaps because of a worsening of DME, followed by a gradual increase in vision (Figure 2).

INTRAOCULAR PRESSURE

Some patients experienced elevation of IOP. Elevation of IOP to greater than 30 mm Hg at any time during the study was recorded in 16.3% of patients in the low-dose group, 21.6% in the high-dose group, and 2.7% in the sham group. The need for surgical intervention to address elevated IOP was low: in the low-dose group, 2.1% underwent trabeculectomy, 1.3% underwent trabeculoplasty, and 1.3% had another glaucoma procedure. In the high-dose group, 5.1% underwent trabeculectomy, 2.5% had trabeculoplasty, and 2.5% had another glaucoma procedure. This profile represents at least 24 months of follow-up on all patients, but also includes 40% of patients for whom follow-up data was available beyond the 24-month visit at the time the database was locked.

ADDITIONAL TREATMENTS

Patients could receive additional laser treatment at the physician's discretion after week 6 if progression of edema occurred. A lower percentage of patients in the low-dose treatment group required laser (36.7%) than in the sham group (58.9%). The number of treatments per patient was 0.74 in the low-dose group and 1.34 in the sham group.

The need for additional intravitreal injections, either triamcinolone acetonide or antiangiogenic agents was also lower in treated patients. In the low-dose treatment group, 12.5% of patients received additional injections, and in the sham group 28.6%. The number of injections per patient was 0.19 in the low-dose group and 0.72 in the sham group.

CONCLUSIONS

Although the incidence of incisional IOP-lowering procedures was higher in the treatment groups, the overall incidence of ocular procedures per subject for diabetic retinopathy, IOP elevation, and cataract was lower in the treatment groups. Subjects in the sham group underwent 50% more procedures than those in the low-dose treatment group.

The month-24 results of the FAME study show that delivery of fluocinolone acetonide through the Iluvien intravitreal insert resulted in an overall reduction in the number of procedures needed for control of diabetic retinopathy and elevated IOP. Cataract formation was accelerated, but visual results after cataract surgery were good in treated patients.

This insert, delivering daily sub-microgram doses of fluocinolone acetonide, has the potential to become a long-duration treatment for DME. In June, Alimera Sciences submitted a New Drug Application to the FDA for consideration of the Iluvien for regulatory approval, and in August the FDA granted the company's request for priority review, which could result in an FDA action by the end of this year. We look forward to the widespread availability of this treatment modality for the ophthalmic community and our patients with DME. ■

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2. Alimera announces positive results from the two phase 3 FAME trials of Iluvien in patients with diabetic macular edema. http://investor.alimerasciences.com/releases.cfm. Accessed September 21, 2010.
3. Pearson PA. Fluocinolone acetonide insert (Iluvien) phase 3 studies: reduced overall risk of procedures to treat diabetic retinopathy and elevation of IOP. Paper presented at: American Society of Retina Specialists annual meeting; Vancouver, Canada.

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