Long-term Benefit of Sustained-Delivery Fluocinolone Acetonide Vitreous Inserts for Diabetic Macular Edema

*Peter A. Campochiaro, MD,[1] David M. Brown, MD,[2] Andrew Pearson, MD,[3] Thomas Ciulla, MD,[4] David Boyer, MD,[5] Frank G. Holz, MD,[6] Michael Tolentino, MD,[7] Amod Gupta, MD,[8] Lilianne Duarte, MD,[9] Steven Madreperla, MD,[10] John Gonder, MD,[11] Barry Kapik, BS,[12] Kathleen Billman, BS,[12] Frances E. Kane, PhD,[12] for the FAME Study Group**

Objective: To assess the efficacy and safety of intravitreal inserts releasing 0.2 μg/day (low dose) or 0.5 μg/day (high dose) fluocinolone acetonide (FA) in patients with diabetic macular edema (DME).

Design: Two parallel, prospective, randomized, sham injection-controlled, double-masked, multicenter clinical trials.

Participants: Subjects with persistent DME despite at least 1 macular laser treatment were randomized 1:2:2 to sham injection (n = 185), low-dose insert (n = 375), or high-dose insert (n = 393).

Methods: Subjects received study drug or sham injection at baseline and after 6 weeks were eligible for rescue laser. Based on retreatment criteria, additional study drug or sham injections could be given after 1 year.

Main Outcome Measures: The primary outcome was the percentage of patients with improvement from baseline best-corrected visual acuity (BCVA) in Early Treatment Diabetic Retinopathy Trial (ETDRS) letter score of 15 or more at month 24. Secondary outcomes included other parameters of visual function and foveal thickness (FTH).

Results: The percentage of patients with improvement from baseline ETDRS letter score of 15 or more at month 24 was 28.7 and 28.6 in the low- and high-dose insert groups, respectively, compared with 16.2 in the sham group ($P = 0.002$ for each). Benefit occurred for both doses compared with sham at 3 weeks and all subsequent time points. The mean improvement in BCVA letter score between baseline and month 24 was 4.4 and 5.4 in the low- and high-dose groups, respectively, compared with 1.7 in the sham group ($P = 0.02$ and $P = 0.016$). At all time points compared with sham, there was significantly more improvement in FTH. Subjects requiring cataract surgery were more frequent in the insert groups, and their visual benefit was similar to that of subjects who were pseudophakic at baseline. Glaucoma requiring incisional surgery occurred in 3.7%, 7.6%, and 0.5% of the low-dose, high-dose, and sham groups, respectively.

Conclusions: Both low- and high-dose FA inserts significantly improved BCVA in patients with DME over 2 years, and the risk-to-benefit ratio was superior for the low-dose insert. This is the first pharmacologic treatment that can be administered by an outpatient injection to provide substantial benefit in patients with DME for at least 2 years.

Financial Disclosure(s): Proprietary or commercial disclosure may be found after the references.
Ophthalmology 2011;118:626–635 © 2011 by the American Academy of Ophthalmology.

**Group members listed online (available at http://aaojournal.org).*

Diabetic macular edema (DME) is the most common cause of moderate vision loss in working-age individuals in developed countries.[1,2] It is a major public health problem that is increasing because the prevalence of diabetes is increasing. The current standard of care, focal/grid laser photocoagulation, does not cause rapid improvement but results in slow improvement in a minority of patients.[3] A recent study showed that although approximately one third of DME patients treated with focal/grid laser therapy experience gradual improvement in best-corrected visual acuity (BCVA) of 2 lines or more, 20% worsen by 2 lines or more.[4] Thus, development of new treatments is an important priority.

Retinal hypoxia has been implicated in the pathogenesis of DME,[5] and it causes stabilization of hypoxia-inducible factor-1, which stimulates transcription of several genes that contain a hypoxia response element in their promoter region, including vascular endothelial growth factor (VEGF).[6,7] Vascular endothelial growth factor is a major target in DME, because intraocular injections of ranibizumab or bevacizumab, specific antagonists of VEGF, result in rapid reduction in edema and substantial improvement in visual acuity.[8–12] However, the products of other hypoxia-inducible genes, such as placental growth factor, also can cause vascular leakage. Furthermore, hypoxia,

ISSN 0161-6420/11/$–see front matter
doi:10.1016/j.ophtha.2010.12.028

ischemia, or the diabetic state induces influx of leukocytes into the retina,[13–15] another potential source of leakage-promoting proteins. Thus, suppression of inflammatory mediators and other permeability factors in addition to VEGF is a more comprehensive treatment strategy for DME.

Corticosteroids reduce expression of VEGF and other permeability factors and suppress influx of leukocytes into the retina,[16–21] providing good rationale for their use in DME. Treatment with systemic steroids is not feasible for a chronic ocular disease like DME because of their adverse effects throughout the body, but the eye is a relatively isolated organ, allowing consideration of local delivery. Enthusiasm for this approach was fueled by case series suggesting that intraocular injections of triamcinolone acetonide provided short-term benefits in some patients with DME.[22,23] A recent study compared focal/grid laser treatment with intraocular injections of 1 or 4 mg preservative-free triamcinolone acetonide with repeat treatments every 4 months for persistent or recurrent DME.[4] At 4 months, mean improvement in BCVA was significantly better in the 2 triamcinolone groups compared with the focal/grid laser therapy group, but at the 2-year primary end point, the focal/grid laser therapy group showed a mean improvement of 1±17 letters, which was significantly better than the triamcinolone groups (4-mg group, –2±18; 1-mg group, –3±22). These data suggest that bolus injections of triamcinolone acetonide may not provide a good long-term solution for treatment of DME, but do not rule out other steroid formulations that provide more controlled delivery. Sustained drug delivery systems may allow delivery of low doses over a long period, thereby avoiding frequent repeated injections and the wide swings in intraocular steroid concentrations that result.

Retisert (Bausch & Lomb, Rochester, NY) is a device that is sutured to the anterior eye wall and releases 0.59 μg/day of fluocinolone acetonide (FA) into the anterior part of the vitreous cavity.[24] It has been approved for the treatment of chronic noninfectious posterior uveitis.[25] Surgical implantation of sutured FA devices in patients with DME caused significant reduction in edema, but after 2 years resulted in cataract in 80% to 90% of phakic patients and required surgery for glaucoma in approximately 20% of patients (Pearson A, Levy B, and the Fluocinolone Acetonide Implant Study Group. Fluocinolone acetonide intravitreal implant to treat diabetic macular edema: 2-year results of a multicenter clinical trial. Invest Ophthalmol Vis Sci 2005;46:E-Abstract 1795).

Fluocinolone acetonide intravitreal inserts are nonbiodegradable cylindrical tubes (3.5×0.37 mm) that have the same polymer matrix as Retisert and also are loaded with FA, but do not require a surgical procedure. Instead, the device is inserted into the vitreous cavity through a 25-gauge needle in an outpatient clinic. Devices that release either 0.5 or 0.2 μg/day FA in vitro have been designed. A pharmacokinetic study showed that each provided excellent sustained delivery of FA in the eye for at least 1 year and reduced DME.[26] Herein, the results of 2 phase III studies are reported testing the effects of FA inserts in patients with DME with persistent edema despite at least 1 macular laser photocoagulation treatment.

Patients and Methods

The Fluocinolone Acetonide for Macular Edema (FAME) studies A and B were performed under a single protocol (C-01-05-001, sponsored by Alimera Sciences, Inc.) as randomized, double-masked, sham injection-controlled, parallel-group, multicenter studies conducted over a 36-month period. The FAME study A was conducted at 49 sites in the United States, Canada, 4 countries in the European Union, and India. The FAME study B was conducted at 52 sites in the United States, India, and 3 countries in the European Union. The studies adhered to the guidelines of the Declaration of Helsinki and the protocol and consent form were approved by each institution's governing institutional review board or ethics committee. Each subject provided written informed consent. The studies are registered at www.clinicaltrials.gov under the identifier NCT00344968.

Study Population

Consenting subjects with DME were screened by measuring BCVA by the protocol described in the Early Treatment Diabetic Retinopathy Study (ETDRS)[3] and foveal thickness (FTH; center point thickness) using the Fast Macular Scan protocol on a Stratus 3 optical coherence tomography (OCT) instrument (Carl Zeiss Meditec, Dublin, CA). Subjects were eligible if they had FTH of 250 μm or more despite at least 1 prior focal/grid macular laser photocoagulation treatment and BCVA in ETDRS letter score between 19 and 68 (Snellen equivalent range, 20/50–20/400). Enrollment was stratified by baseline BCVA (≤49 letter score [20/100], >49 letter score). Patients were excluded if they had glaucoma, ocular hypertension, intraocular pressure (IOP) of more than 21 mmHg, or if they were taking IOP-lowering drops. Detailed inclusion and exclusion criteria are shown in Table 1 (available at http://aaojournal.org). A total of 956 subjects were randomized in a 2:2:1 ratio to 0.2-μg/day FA intravitreal insert, 0.5-μg/day FA intravitreal insert, or sham injection. The assigned treatment was administered to only 1 eye, referred to as the study eye. Standard procedures were used for injections, including application of topical anesthetic, insertion of a lid speculum, cleaning the conjunctiva with povidone–iodine, and pressure on the injection site for approximately 2 minutes with a povidone–iodine- and lidocaine-soaked cotton tip. The same procedure was used for sham injections, after which the hub of a syringe was pressed against the conjunctiva to simulate administration of the insert.

Clinical Assessments

There were at least 16 study visits over a 3-year treatment period, including screening, baseline, 1 week, 6 weeks, and 3 months after initial study treatment, and every 3 months thereafter. Study assessments included BCVA (ETDRS charts at 4 m or electronic visual acuity tester at 3 m), time-domain OCT, fluorescein angiography, fundus photography, adverse events, and concomitant medications. Patients were allowed to receive rescue focal/grid laser therapy for persistent edema any time after the week 6 assessment, and subsequently, treatments were allowed as frequently as every 3 months for persistent or recurrent DME. Subjects were eligible for retreatment with their initially assigned study drug after month 12 if they experienced loss of 5 or more letters in BCVA or an increase in foveal thickness of 50 μm or more compared with the subject's best status during the previous 12 months. In the event of retreatment, there were 2 posttreatment visits at 1 day and 1 week. Although treatment with nonprotocol therapies was discouraged, subjects who were treated with other therapies were retained in the study.