American Academy of Ophthalmology
The Eye M.D. Association

Sustained Delivery Fluocinolone Acetonide Vitreous Implants

Long-Term Benefit in Patients with Chronic Diabetic Macular Edema

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Purpose: To present the safety and efficacy of intravitreal implants releasing 0.2 μg/day fluocinolone acetonide (FAc) in patients with chronic versus nonchronic diabetic macular edema (DME). To assess ocular characteristics, anatomic changes, and re-treatment and ancillary therapies that may explain the differential treatment effect seen with intravitreal implants releasing FAc 0.2 μg/day in patients with chronic and nonchronic DME. An overall benefit-to-risk assessment for the FAc 0.2-μg/day and FAc 0.5-μg/day doses has been reported previously.

Design: Preplanned subgroup analysis of chronic (duration of diagnosis, ≥3 years) and nonchronic (duration of diagnosis, <3 years) DME in patients from 2 randomized, sham injection-controlled, double-masked, multicenter clinical trials.

Participants: Patients with persistent DME despite 1 or more macular laser treatment were randomized 1:2:2 to sham injection (n = 185), FAc 0.2 μg/day (n = 375), or FAc 0.5 μg/day (n = 393).

Methods: Patients received study drug or sham injection and after 6 weeks were eligible for rescue laser. Based on re-treatment criteria, additional masked study drug could be given after 1 year.

Main Outcome Measures: Percentage of patients with improvement of 15 letters or more from baseline. Secondary outcomes included other parameters of visual function and foveal thickness.

Results: At month 36, the difference between FAc 0.2 μg/day and sham control in the percentage of patients who gained 15 letters or more was significantly greater in chronic DME patients (FAc 0.2 μg/day, 34.0% vs. sham, 13.4%; $P<0.001$), compared with patients with nonchronic DME (FAc 0.2 μg/day, 22.3% vs. sham, 27.8%; $P = 0.275$). The greater response in patients with chronic DME was not associated with baseline ocular characteristics, changes in anatomic features, or differences in re-treatment or ancillary therapies. The ocular adverse event profile for FAc 0.2 μg/day was similar regardless of DME duration.

Conclusions: This is the first published analysis correlating duration of diagnosis of DME with treatment effect. In patients with chronic DME, FAc 0.2 μg/day provides substantial visual benefit for up to 3 years and would provide an option for patients who do not respond to other therapy. *Ophthalmology 2014;121:1892-1903 © 2014 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/3.0/).*

*Supplemental material is available at www.aaojournal.org.

The prevalence of macular edema, the primary cause of impaired vision in patients with diabetes, is increasing.[1–3] Since 1985, the mainstay of treatment for diabetic macular edema (DME) had been focal or grid photocoagulation.[4] Surgical techniques, such as pars plana vitrectomy, with or without internal limiting membrane removal, also have shown efficacy in some patients.[5,6] Based on the discovery that vascular endothelial growth factor (VEGF) plays a central role in the increased vascular permeability associated with DME,[7] the first pharmacotherapy, the anti-VEGF antibody ranibizumab, was approved in 2012 for treatment of DME.[8] This approval was based on the results of 2 phase 3 clinical trials (A Study of Ranibizumab Injection in Subjects with Clinically Significant Macular Edema with Center Involvement Secondary to Diabetes Mellitus [RIDE/RISE]), which compared 2 doses of ranibizumab to sham injection, with rescue laser available 3 months after randomization.[9] Before these trials, the Diabetic Retinopathy Clinical Research Network undertook protocol I, which compared ranibizumab plus prompt or deferred laser versus triamcinolone plus prompt laser versus sham injections plus prompt laser.[10]

http://dx.doi.org/10.1016/j.ophtha.2014.04.019
ISSN 0161-6420/14

In the RIDE and RISE trials, patients initially randomized to the sham control arm were crossed over to monthly injection of ranibizumab 0.5 mg after the primary time point of 2 years. However, in both trials, after treatment with ranibizumab for 1 year, the crossover group was unable to achieve the margin of vision improvement achieved by patients who were randomized initially to ranibizumab treatment arms.[11] In the combined dataset, the proportion of patients gaining 15 letters or more 12 months after first ranibizumab injection was 32.4% for those initially randomized to 0.3 mg ranibizumab, 31.7% for those randomized to 0.5 mg ranibizumab, and 7.3% for patients randomized to sham treatment after crossover to 0.5 mg ranibizumab. Furthermore, in the Diabetic Retinopathy Clinical Research Network protocol I trial, patients received a median of 10 or 12 ranibizumab injections over 2 years in the prompt laser and deferred laser groups, respectively. However, more than 50% of ranibizumab-treated eyes did not achieve a visual acuity improvement from baseline of 10 letters or more at year 2.[12] Similarly, in RIDE, after 3 years of monthly injections, 43.2% and 37.0% of patients in the 0.3- and 0.5-mg ranibizumab arms, respectively, achieved an improvement of fewer than 10 letters of visual acuity.[11] In RISE, these percentages were 30.4% and 42.4%, respectively. In recognition of the need for additional treatments for DME, the Diabetic Retinopathy Clinical Research Network has initiated a phase 2 clinical trial assessing the combination of steroid and anti-VEGF for persistent DME.[13]

Two identically designed phase 3 clinical trials, the Fluocinolone Acetonide for Diabetic Macular Edema (FAME) studies, FAME A and FAME B, compared 2 doses of a nonbioerodible intravitreal implant-releasing submicrogram doses of the corticosteroid fluocinolone acetonide (FAc) with sham injection over a 3-year period.[14,15] All patients were eligible for laser photocoagulation 6 weeks after randomization. A preplanned subgroup analysis was performed that assessed the primary outcome of 15 or more Early Treatment Diabetic Retinopathy Study (ETDRS) letters of improvement from baseline as a function of median duration of diagnosis of DME at baseline. This revealed enhanced benefit in that patients with chronic DME (duration, $\geq$3 years) demonstrated a significant treatment effect as compared with patients with nonchronic DME (duration, $<$3 years).[15] This result was highly statistically significant and was reproduced in both phase 3 trials. On the basis of these results, FAc 0.2 μg/day (ILUVIEN; Alpharetta, GA) received marketing authorizations after a positive opinion in the decentralized procedure involving the United Kingdom, Germany, France, Spain, Austria, and Portugal, with Italy in the process of completing administrative steps. These data have also been submitted to the United States Food and Drug Administration.

This study explored the possible contribution of baseline features and treatments received during the trial to the differential treatment effect and examined the relationship between anatomic changes and visual acuity outcomes. Additionally, new analyses related to the calculation of duration of DME are presented, which add to the understanding of these results, and outcomes are examined in the context of insufficient responses observed in other phase 3 DME studies among patients with chronic DME. We hypothesized that microenvironmental changes occurring in chronic DME may need a treatment strategy that targets multiple mediators. This report primarily focuses on comparisons between the approved dose of FAc 0.2 μg/day and sham control injection among patients with chronic or nonchronic DME. An overall benefit-to-risk assessment for the FAc 0.2-μg/day and FAc 0.5-μg/day doses has been reported previously.[15]

Methods

The FAME A and B studies were performed under a single protocol as 36-month, randomized, double-masked, sham injection-controlled, parallel-group, multicenter studies.[14] Both 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. The studies were compliant with the rules and regulations under the Health Insurance Portability and Accountability Act of 1996. Each patient provided written informed consent. These studies are registered at www.clinicaltrials.gov (no. NCT00344968).

Study Population

Selection criteria for the study have been described.[14] The study enrolled patients who had a time-domain optical coherence tomography foveal thickness of at least 250 μm despite at least 1 prior focal or grid macular laser photocoagulation treatment and best-corrected visual acuity (BCVA) in ETDRS letter score between 19 and 68 (Snellen equivalent range, 20/50−20/400). Enrollment was stratified by baseline BCVA score (letter score, $\leq$49 and $>$49). Patients with glaucoma, ocular hypertension, or intraocular pressure (IOP) of more than 21 mmHg or those receiving IOP-lowering medication were excluded. A total of 956 patients were randomized 2:2:1 to receive FAc 0.2-μg/day intravitreal implant, FAc 0.5-μg/day intravitreal implant, or sham injection in 1 eye. After 6 weeks, all patients were eligible for laser photocoagulation. After 12 months, all patients were eligible for re-treatment with randomized study drug or sham injection if they lost 5 letters or more of BCVA or experienced an increase in retinal center point thickness (CPT) of 50 μm or more from their best reading in the previous 12 months. Other therapies such as anti-VEGF and intravitreal triamcinolone acetonide, now considered part of the standard of care, were not allowed to be included in the protocol because at the time of the trial, they were not approved for DME. Some patients were prescribed these off-protocol therapies to control their disease; these patients were not removed from statistical analyses.

Assessments

Over the 3-year treatment period, study visits were scheduled at screening, baseline, 1 week, 6 weeks, and 3 months after treatment initiation, and every 3 months thereafter. One masked investigator carried out the assessment, and another masked investigator carried out the injections. Best-corrected visual acuity was measured with the ETDRS chart at 4 m or with an electronic visual acuity tester at 3 m. Anatomic assessments included measurement of CPT and macular volume with optical coherence tomography (Stratus OCT; Carl Zeiss Meditec; Dublin, CA) and measurement of area of fluorescein leakage and area of cystoid edema with fluorescein angiography. The severity of diabetic retinopathy was graded with the ETDRS Retinopathy Eye Scale after masked assessment of angiograms and fundus photographs by an independent reading center.