Visual Acuity Outcomes in Diabetic Macular Edema With Fluocinolone Acetonide 0.2 µg/Day Versus Ranibizumab Plus Deferred Laser (DRCR Protocol I)

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BACKGROUND AND OBJECTIVE: Visual outcomes of the FAME study (0.2 µg/day fluocinolone acetonide [FAc]) and Protocol I (0.5 mg ranibizumab plus deferred laser) were compared using the area under the curve (AUC) analysis method.

PATIENTS AND METHODS: Best-corrected visual acuity (BCVA) data collected during a period of 3 years of follow-up for patients enrolled in FAME or Protocol I were used to calculate AUC of the change in BCVA over a time curve.

RESULTS: In the overall population, there was a greater treatment effect for ranibizumab plus deferred laser compared with FAc. However, for subgroups of pseudophakic eyes, eyes with chronic diabetic macular edema (DME), and pseudophakic eyes with chronic DME, ranibizumab plus deferred laser and FAc were not found to be significantly different. The ranibizumab group received a median of 14 injections during a 36-month period compared with a mean of 1.3 injections in the FAc group.

CONCLUSION: In pseudophakic and chronic DME subgroups, FAc was comparable to ranibizumab plus deferred laser with fewer injections.


INTRODUCTION

Diabetic macular edema (DME) is a severe, vision-threatening stage of diabetic retinopathy (DR) — a leading cause of vision loss worldwide. 1 Although intravitreal anti-vascular endothelial growth factor (VEGF)-A injections have been demonstrated as effec-
tive in managing DME, reducing progression of DR, and treating neovascularization, a broad spectrum of inflammatory events drives the pathogenesis and progression of DR and the multifactorial nature of DR at all levels of severity has been established in human eyes.

The importance of continuous therapy to maintain the disease-modifying effects of pharmacotherapy on DR has been demonstrated in two separate reports, in which a reduction in injection frequency of anti-VEGF therapy following a monthly injection regimen has resulted in worsening of DR.

The fluocinolone acetonide (FAc) 0.2 µg/day implant (Iluvien; Alimera Sciences, Alpharetta, GA) delivers the only continuous, multiyear therapy for DME as a daily micro-dose of FAc (0.2 µg/day) for 36 months. Sustained, low-dose intravitreal steroid released by FAc 0.2 µg/day implants has been shown to reduce neuroinflammation in animal models. In the FAME study, which compared efficacy in terms of change in best-corrected visual acuity (BCVA) for FAc 0.2 µg/day implant versus sham control in patients with DME, the FAc implant demonstrated significant vision improvement in patients with DME for up to 36 months and has also shown significant effects on slowing progression of proliferative DR and improving DR.

The area under the curve (AUC) method of efficacy analysis is an alternative measure of change in visual acuity (VA) that captures treatment benefit over an entire dosing/observation period, in contrast with typical measures of efficacy, which are based on a single time point measurement. For multiyear studies this is particularly relevant, especially considering the potential impact of short-term data fluctuations when outcomes are assessed using individual time points. In addition, real-world treatment regimens often do not match those employed in pivotal clinical trials for short-acting therapies requiring regular intravitreal injections.
AUC is being recognized as an important measure of therapy benefit for DR and has been previously used to assess the effect of anti-VEGF therapy on proliferative DR.\textsuperscript{3}

The current analysis used the AUC method to compare the efficacy of FAc 0.2 µg/day with sham control to evaluate the FAc 0.2 µg/day implant in the treatment of DME. In addition, a comparative analysis was conducted with the publicly available Protocol I dataset,\textsuperscript{11} where the AUC for the ranibizumab (Lucentis; Genentech, South San Francisco, CA) plus deferred laser arm was calculated. This arm was chosen because it had the best outcomes and is generally recognized as more closely reflecting the current standard of care.

The AUC method is intended to allow more robust statistical comparison between trials than conventional measures of efficacy; additionally, these studies have similar inclusion and exclusion criteria. However, differences between the studies, such as the lack of a chronic subpopulation in Protocol I, introduce limitations to the current analysis.

**PATIENTS AND METHODS**

The FAME study,\textsuperscript{12} consisting of two randomized, double-masked, sham injection-controlled, parallel-group, multicenter trials (FAME A and B), was conducted during a 36-month period, as previously described.\textsuperscript{13} Patients were randomized in a 2:1 ratio to FAc 0.2 µg/day or sham control injection. Treatment was administered to the study eye only (Figure 1).\textsuperscript{14} At each visit, BCVA was assessed using either Early Treatment Diabetic Retinopathy Study (ETDRS) charts at 4 m or an electronic ETDRS (E-ETDRS) test at 3 m.

The DRCR.net Protocol I trial\textsuperscript{15} was a randomized, multicenter study conducted during a 36-month period (Figure 2).\textsuperscript{2,16} Patients were randomly assigned to groups: sham injection plus prompt laser, ranibizumab 0.5 mg plus prompt laser, ranibizumab 0.5 mg plus deferred laser, or triamcinolone 4 mg plus prompt laser. Prompt laser was applied 3 to 10 days after the initial ranibizumab injection; deferred laser was applied at least 24 weeks following ranibizumab injection. In subjects with two eligible eyes, the right eye was randomly assigned to a treatment group; the left eye was assigned to sham plus prompt laser.

AUC was calculated from the observed change in BCVA letter score from baseline through Month 36 using the trapezoidal rule.\textsuperscript{3} For each subject, the summarized variable represented total AUC divided by the total number of days in the study. Individual patient AUC data were then used to calculate mean AUC for each subgroup.

AUC analysis was performed for individual FAc 0.2 µg/day trials (FAME A and B) and the combined study.

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**Figure 2.** DRCR.net Protocol I study design; data from sham and deferred laser treatment arms were incorporated into the current analysis. BCVA = best-corrected visual acuity; DME = diabetic macular edema.
population and compared with AUC for ranibizumab plus deferred laser in DRCR.net Protocol I. This arm was selected because it was considered to have an optimal BCVA outcome compared with the ranibizumab plus prompt laser and triamcinolone plus prompt laser arms. From baseline to Year 1, 75.5% of eyes in the ranibizumab plus deferred laser group, 69.0% of eyes in the ranibizumab plus prompt laser group, and 50.0% of eyes in the triamcinolone plus prompt laser group experienced a five-letter or greater improvement. From baseline to Year 5, 73.9% of eyes in the ranibizumab plus deferred laser arm experienced a five-letter or greater improvement compared with 66.1% of eyes in the ranibizumab plus prompt laser arm. Further analyses were conducted on pseudophakic eyes (FAME and Protocol I), chronic DME eyes (DME duration ≥ 3 years, FAME only), and pseudophakic plus chronic DME eyes (FAME only).

**RESULTS**

**Study Population**

In total, 953 patients were assessed in the FAME study with a mean age of 62.5 years; 188 participants were included in the ranibizumab plus deferred laser arm of Protocol I, with a mean age of 64 years. Baseline characteristics are further described in Table 1. 

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**Figure 3.** Summary of BCVA letter score and illustrative comparison of AUC analysis from (A) FAME A and (B) FAME B trials. AUC = area under the curve; BCVA = best-corrected visual acuity; ETDRS = Early Treatment Diabetic Retinopathy Study; FAC = fluocinolone acetonide.
Number of FAc Treatments

The number of FAc treatments administered during the FAME study was consistent across lens status and DME duration subgroups (Table 2).

FAME AUC Outcomes

A significant AUC-based treatment effect was observed for the FAc 0.2 µg/day implant versus sham control for FAME A and B independently ($P = .03$ and $P < .001$, respectively) (Figure 3).

FAME Versus Protocol I Ranibizumab Plus Deferred Laser

There was a significantly greater treatment effect for ranibizumab plus deferred laser compared with 0.2 µg/day FAc during the course of 36 months (8.43 letters/day compared with 5.18 letters/day, respectively; $P = .002$) (Figure 4).

For pseudophakic and chronic DME subgroups, the AUC with FAc 0.2 µg/day compared with ranibizumab plus deferred laser was not found to be significantly different ($P = .77$ and $P = .19$, respectively) (Figure 5). For pseudophakic plus chronic DME eyes treated with FAc 0.2 µg/day and pseudophakic eyes treated with ranibizumab plus deferred laser, AUC was not significantly different ($P = .90$) (Figure 6).

DISCUSSION

The comparison of VA outcomes provided by the AUC method is more representative of the treatment effect over time than comparisons based on a single time point. This is especially true in larger studies, in which individual time points for comparison may vary considerably.

AUC significantly favored FAc 0.2 µg/day during a period of 36 months compared with sham control in the FAME study. This outcome was replicated in the individual FAME A and B trials. In the overall FAME study population, the 36-month AUC was significantly greater for ranibizumab plus deferred laser than for FAc 0.2 µg/day ($P = .002$), partly because AUC was depressed in the FAc 0.2 µg/day group as a result of cataract development during the 12- to 18-month time period and consequent loss of VA (Figure 4). In a separate analysis of the FAME data, approximately 50% of patients (n = 188) treated with FAc 0.2 µg/day in the overall FAME study group underwent cataract extraction during the follow-up period. Of the patients who underwent cataract extraction during the follow-up period, 52% (n = 97) had chronic DME. Only 17% of patients in the sham group of the FAME study received cataract extraction during the follow-up period.
In this analysis of the FAME results and Protocol I, the visual outcomes achieved in pseudophakic cases treated with FAc 0.2 µg/day were not significantly different to those treated with ranibizumab plus deferred laser ($P = .77$). There was also no significant difference between the visual outcomes achieved in chronic DME treated with FAc 0.2 µg/day and those of all Protocol I participants treated with ranibizumab plus deferred laser ($P = .19$).

Cataract development and elevation of intraocular pressure (IOP) are known side-effects of intravitreal corticosteroid treatment; the incidence of these ocular adverse events was greater in FAc treatment compared with ranibizumab treatment. Cataract was the most common adverse event in the FAME study, affecting 42.7% of all patients and 81.7% of phakic patients treated with the FAc 0.2 µg/day implant; IOP elevation considered an adverse event was observed in 37.1% of FAc 0.2 µg/day-treated patients compared with 11.9% of sham-control patients. In the first year of Protocol I follow-up, only 6% of patients treated with ranibizumab plus deferred laser who were phakic at baseline required cataract extraction; seven eyes treated with ranibizumab plus deferred laser (4%) had either IOP elevation 10 mm Hg or greater, IOP increased to 30 mm Hg or greater, or initiation of IOP-lowering medication.2

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**Figure 5.** Summary of BCVA letter score and illustrative comparison of AUC from mean BCVA scores for FAc 0.2 µg/day and ranibizumab plus deferred laser: (A) Pseudophakic cases; (B) Chronic DME (DME duration ≥ 3 years) eyes and overall patient population. AUC = area under the curve; BCVA = best-corrected visual acuity; DME = diabetic macular edema; ETDRS = Early Treatment Diabetic Retinopathy Study; FAc = fluocinolone acetonide.
The clinical benefit of FAc 0.2 µg/day appears to be comparable to that of ranibizumab plus deferred laser in pseudophakic and chronic DME eyes, as demonstrated by AUC analysis, with a lesser treatment burden. During the 36-month evaluation period, patients who received FAc 0.2 µg/day required a mean of 1.3 treatments irrespective of DME duration or baseline lens status. In contrast, the ranibizumab group required a median of 14 injections. Treatment with the FAc 0.2 µg/day implant therefore provides an alternative to anti-VEGF therapy which, in selected patients, could provide similar benefit with a reduced treatment burden.

A limitation of this analysis is its post-hoc nature and the fact that it involves clinical data from two different studies. Although conclusive statements cannot be made based on meta-type analyses, these comparisons are still valuable given that there are no head-to-head clinical trials comparing these two agents, which are both approved to treat DME in the US and chronic DME in Europe. Even with these limitations, it should also be recognized that the ranibizumab plus deferred laser arm was specifically chosen because this is the ranibizumab arm in Protocol I with the optimal outcome. Rather than combine the data for ranibizumab from the two arms, we felt that using only the arm with the best outcome offset some of the other limitations of this analysis. The ranibizumab plus deferred laser arm was also the most clinically relevant and reflective of the FAME study protocol in terms of additional therapies. Indeed, in the FAME study, rescue laser was only allowed 6 weeks after FAc was administered and subsequent treatments were allowed as frequently as every 12 months for persistent or recurrent edema. In Protocol I, focal/grid laser treatment was applied either promptly (3 to 10 days after the initial ranibizumab injection) or was deferred for at least 24 weeks. Additionally, with any comparisons between the FAME study and other phase 3 clinical trials for DME pharmacotherapies, it is important to recognize differences in the study population. For example, chronic and chronic-pseudophakic subgroups were not analyzed in Protocol I. Unlike most phase 3 studies, the population enrolled in FAME did not include any treatment-naive DME patients. This means that the FAME study population may have had more severe DME with potentially irreversible damage, which would only reduce the treatment effect seen.
Although there were no approved pharmaceutical therapies for DME when the key phase 3 clinical study (FAME) was initiated, three pharmaceutical therapies have since been approved for the treatment of DME.22-24 However, no comparison between FAc and these additional pharmaceutical therapies has yet been performed. The results of the Protocol I analysis of ranibizumab and laser treatment are now publicly available.11 This meta-analysis comparison of the two studies was undertaken after the publication of the Protocol I analysis. The treatment burden, visual outcomes, and adverse events associated with each treatment were compared to allow clinicians to adjudicate the respective benefits of each treatment for their patients.

Analyses of the impact of FAc treatment on DME are ongoing. However, there is an improvement in treatment burden with the FAc implant, which will have an impact on patient compliance and quality of life. An economic benefit may also be observed as a result of better DME management and fewer treatments.25

REFERENCES


TABLE 1
Baseline Characteristics2,13

<table>
<thead>
<tr>
<th></th>
<th>FAME Sham Control</th>
<th>FAc 0.2 µg/day</th>
<th>Protocol I Ranibizumab Plus Deferred Laser</th>
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<tbody>
<tr>
<td>Participants, n</td>
<td>185</td>
<td>375</td>
<td>188</td>
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<tr>
<td>Age (Mean), Years</td>
<td>61.9</td>
<td>63.0</td>
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<td>Male, %</td>
<td>58.4</td>
<td>57.3</td>
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<td>Duration of Diabetes (Median, Interquartile Range), Years</td>
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<td>16 (11–22)</td>
<td>17 (11–22)</td>
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<td>HbA1c (Median, Interquartile Range), %</td>
<td>7.4 (6.7–8.4)</td>
<td>7.6 (6.7–8.6)</td>
<td>7.5 (6.7–8.4)</td>
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<td>Lens Status, % Phakic / % Pseudophakic</td>
<td>65 / 35</td>
<td>63 / 37</td>
<td>71 / 29*</td>
</tr>
</tbody>
</table>

*28% posterior chamber intraocular lens, 1% anterior chamber intraocular lens
FAc = fluocinolone acetonide; HbA1c = glycated hemoglobin

TABLE 2
Fluocinolone Acetonide Treatments Administered During the FAME Study by Lens Status and Duration of DME

<table>
<thead>
<tr>
<th>Lens Status</th>
<th>Number of FAc Treatments (Mean ± SD)</th>
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<tr>
<td>Pseudophakic</td>
<td>1.3 ± 0.5</td>
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<tr>
<td>Phakic</td>
<td>1.3 ± 0.6</td>
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<tr>
<td>Chronic (≥ 3 years)</td>
<td>1.3 ± 0.6</td>
</tr>
<tr>
<td>Non-chronic (&lt; 3 years)</td>
<td>1.3 ± 0.5</td>
</tr>
</tbody>
</table>

FAc = fluocinolone acetonide; SD = standard deviation; DME = diabetic macular edema

in the population.

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14. Singer M. Efficacy assessment of the 0.2 mg/day fluocinolone acetonide (FAc) intravitreal implants vs. sham control using the area under the curve (AUC) method. Poster presented at: American Society of Retina Specialists 34th Annual Meeting; August 9-14, 2016; San Francisco, CA.


