Reduction in Retinal Thickness Fluctuations After Treatment With Fluocinolone Acetonide Implant for DME: A Post-Hoc Analysis of the USER Study

Christopher D. Riemann, MD; Alexander M. Eaton, MD; Antonio Cutino, COT

BACKGROUND AND OBJECTIVE: Assess fluocinolone acetonide implant (FAc) effects on diabetic macular edema (DME) retinal thickness fluctuations.

PATIENTS AND METHODS: A post-hoc chart review of the real-world USER study analyzed patients receiving 0.2 μg/day FAc implant. The percentage of eyes with central subfield thickness (CST) of 300 μm or less were compared pre- and post-FAc implant; mean retinal thickness amplitude (RTA), retinal thickness standard deviation (RTSD), and two case studies were analyzed.

RESULTS: One hundred thirty patients (mean age: 69.6 years) presented; CST was available for 120 of 160 treated eyes. Mean RTA decreased significantly post-FAc implant (P < .001) regardless of baseline visual acuity (VA). Correlations with last-observed VA (R²) were: RTA, 0.1197; retinal thickness standard deviation (RTSD), 0.1526; and area under the CST-time curve (AUC CST), 0.0981. After FAc implant, the percentage of eyes with CST of 300 μm or less was significantly greater versus baseline (P < .05).

CONCLUSIONS: Retinal thickness fluctuations significantly declined after FAc and correlated with improvement in VA. Both RTSD and RTA measures correlated more closely to last observed VA than AUC CST itself.

INTRODUCTION

Diabetic macular edema (DME) is the leading cause of vision loss in patients with diabetic retinopathy.1 During the past decade, evidence has emerged to suggest that chronic, low-grade intraretinal inflammation secondary to hyperglycemia in diabetes serves as a critical early contributor to the development of edema and pathogenic vascularization in diabetic patients.2,3 A variety of DME treatment options are available, including laser photocoagulation, anti-vascular endothelial growth factor (VEGF), steroids, and surgical therapy,4 with anti-VEGF being the first-line treatment option.5,6 However, many patients have a suboptimal response or are nonresponders to anti-VEGF therapy,7,8 with deteriorating clinical outcomes over time, often because of...
nonadherence to the therapeutic regimen. Consequently, patients with persistent DME despite anti-VEGF therapy receive second-line corticosteroid injections into the vitreous humor to reduce the levels of inflammatory cytokines responsible for macular edema.

The fluocinolone acetonide intravitreal implant 0.19 mg (FAc) (Iluvien; Alimera Sciences, Alpharet-
ta, GA) is the first treatment to release a sub-microgram dose of steroid into the vitreous humor over 36 months for the control of DME. The low-dose FAc (0.2 μg/day) implant was approved in the U.S. and European union for the indication of DME after demonstrating edema control in the key phase 3 Fluocinolone Acetonide in Diabetic Macular Edema (FAME) study. Results from the U.S. Retrospective Chart Review in Patients Receiving Iluvien (USER) Study and Medisoft audit have since confirmed the positive safety and efficacy profile of the FAc implant in the real-world setting.

In DME, optical coherence tomography (OCT) measurements of retinal thickness represent an important objective tool in the clinical evaluation of treatment response alongside subjective visual function.
acuity (VA).\textsuperscript{16,17} However, a reduction in retinal thickness is only modestly correlated with an improvement in VA, and it has been reported that there is a large variation in VA for any given retinal thickness.\textsuperscript{16-18} Furthermore, gradual deterioration of VA in the absence of macular thickening can occur over time.\textsuperscript{19} As demonstrated in refractory and regressed DME, mean OCT measured retinal thickness may not show a change over an extended period of follow-up; however, it may show significant variation from visit to visit.\textsuperscript{19} Therefore, it may be beneficial to assess edema control by evaluating fluctuations in retinal thickness. The retinal thickness amplitude (RTA) is calculated by subtracting the minimum from the maximum retinal thickness during a given period of time. Figure 1 illustrates how two hypothetical therapies may be considered to have equal efficacy based on mean retinal thickness values at the end of a treatment period, but very different efficacies based on RTA, where only one of the therapies has a consistent reduction in retinal thickness over a given period of time.

The literature surrounding the significance of retinal thickness variability over time is sparse, but a careful consideration of OCT stability may be a potentially useful measure for accurately assessing diabetic edema treatment efficacy and that measures of treatment durability over time may help guide man-
agement interventions. Frequent and/or large fluctuations in retinal thickening may decrease photoreceptor viability and have a negative effect on long-term visual function.\textsuperscript{20} If true, therapies with small retinal thickness fluctuations may be preferred.

The objective of this post-hoc analysis of the USER data was to describe the effect of FAc treatment on retinal thickness fluctuations in patients with DME in a large, real-world patient population.

\textbf{PATIENTS AND METHODS}

The USER study was a retrospective chart review of patients who received a 0.2 μg/day FAc implant for the treatment of DME, in accordance with the U.S. label, in at least one eye before January 1, 2016. Details of the USER study design and methods have been reported previously.\textsuperscript{15} The analysis of an existing dataset was approved by an institutional review board as a secondary use of the data.
Central subfield thickness (CST), derived from spectral-domain OCT performed using either the Cirrus (Zeiss, Oberkochen, Germany) or the Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany) machines, and VA were recorded for up to 36 months pre- and 24 months post-FAc treatment. All eyes with at least two OCT readings pre- and post-FAc follow-up were included in the analysis.

OCT retinal thickness signals were quantified in four ways: 1) RTA was calculated by subtracting the minimum from the maximum CST, pre- and post-FAc treatment. Mean RTA was analyzed for the full population and subgroups defined by diabetes type, lens status, last treatment, and baseline best-corrected VA (BCVA); 2) The mean standard deviation of retinal thickness (CST standard deviation over time; RTSD), was calculated for each subject pre- and post-FAc treatment; 3) The potential correlations with VA of area under the CST-time curve (AUC CST), RTA, and RTSD were analyzed; 4) The proportion of eyes with CST of 300 μm or less (considered nominally “dry”) in the USER study was also calculated for each timepoint both pre- and post-FAc treatment.

Comparison of pre- and post-FAc implant administration measurements were made; baseline was defined as the last assessment taken prior to FAc implant administration. Mean RTA was analyzed for the full population and subgroups defined by diabetes type, lens status, last treatment, and baseline best-corrected VA (BCVA); 2) The mean standard deviation of retinal thickness (CST standard deviation over time; RTSD), was calculated for each subject pre- and post-FAc treatment; 3) The potential correlations with VA of area under the CST-time curve (AUC CST), RTA, and RTSD were analyzed; 4) The proportion of eyes with CST of 300 μm or less (considered nominally “dry”) in the USER study was also calculated for each timepoint both pre- and post-FAc treatment.

Case Studies

Two illustrative case studies were evaluated using descriptive statistics.

### RESULTS

#### Patient Population

One hundred sixty eyes in 130 patients were included in the USER study. Patient baseline characteristics and demographics have been described previously.\(^{15}\) The mean age was 69.6 years; most patients had a diagnosis of type 2 diabetes mellitus (87.7%). The mean DME diagnosis duration was 4.4 years (range: 0 to 32 years; n = 160 eyes), and 91.3% of eyes (n = 146/160) had received prior treatment for DME; 76.9% (n = 123/160 eyes) had received anti-VEGF therapy. All patients met the U.S. labeling requirement of a prior corticosteroid exposure without a clinically significant IOP elevation. Greater than 75% of patients received an intravitreal corticosteroid. Of the remaining nearly 25%, the majority received topical steroid (18.1%) and one received a sub-Tenon’s injection; for the rest, physicians confirmed that the patients had undergone a steroid challenge without indicating the route or product.

#### Retinal Thickness Variability Measures

**Retinal Thickness Amplitude:** Measurements of RTA were calculated for the 120 eyes with CST data available. The mean RTA post-FAc implant administration was 96.4 μm, which was significantly decreased compared with pre-FAc implant administration RTA of 230.9 μm (A = 134.5 μm; P < .001). Mean RTA post-FAc implant administration was also significantly reduced compared with pre-FAc implant administration in each of the subgroups analyzed (Table 1).

**Retinal Thickness Standard Deviation:** Supporting the RTA findings, the RTSD after FAc implant administration was significantly lower than before FAc implant administration (35.44 versus 72.03, respectively; P < .0001; Table 2).
**Structure Function Analyses:** AUC CST, RTA, and RTSD versus VA. All measures of edema control had a significant correlation with the last observed VA; RTA and RTSD had a numerically greater correlation with the last observed VA than AUC CST ($R^2 = 0.1197$ and 0.1526 versus 0.0981, respectively; Figure 2).

**Retinal Thickness:** CST data downloaded from the machine-source OCT data were available for 120 eyes. The percentage of eyes with CST of 300 μm or less was significantly greater at all timepoints following FAc implant administration versus baseline ($P < .05$) and increased over time following FAc implant administration (Figure 3).

**Case Studies**

Two illustrative case studies are shown in Figure 4. In both cases, there was a substantial decrease in mean CST, RTA, and RTSD, and an improvement in mean VA after FAc implant administration. The cases also illustrate the effect of FAc implant treatment (continuous treatment) and discontinuous therapies on CST and RTA, and the inverse relationship with VA.

**DISCUSSION**

Results from this post-hoc analysis of the real-world USER study data show that the FAc implant provides a consistent, sustained decrease in retinal thickness over time. This was represented by 1) a significant reduction in RTA following FAc treatment to 96.4 μm versus 230.9 μm before FAc treatment ($P < .001$); 2) a significant reduction in mean RTSD following FAc treatment to 35.44 μm versus 72.03 μm before FAc treatment ($P < .001$); and 3) a striking rise in patients with nominally dry OCT-CST (<300 μm) over time. Encouragingly, the percentage of eyes with a CST of 300 μm or less in the USER study was similar to that observed in another real-world study of the FAc implant, the PALA-DIN study.21

Subgroup analyses showed that the statistically significant reduction in mean RTA and RTSD was present regardless of baseline VA. Whether RTA or RTSD results are more meaningful remains to be determined as they each reflect and assess fluctuations in retinal thickness but do so using different methods (the range between maximal and minimum CST and standard deviation of CST, respectively).

Although all the observed correlations were relatively low, the fact that both RTA and RTSD had a stronger statistical correlation with VA than AUC CST itself is an important finding. Recent evidence has shown that residual edema exposure during the first year of ranibizumab treatment for DME predicts poorer long-term VA outcomes.22 Given this, the current findings of reduced fluctuations in RTA, and therefore the associated reductions in edematous events with FAc implant, should lead to improved VA over the longer term. Clinicians and patients both intuitively understand that more frequent DME relapses are undesirable. This is the first large dataset to show that treatment consistency and durability over time are important and correlate directly to VA. The results of the present study suggest that the OCT and VA may commonly share an undesirable “yo-yo” effect in real-world patients.

The findings from the present analysis are supported by a recent retrospective cohort study in DME (n = 19 eyes in 15 patients) that demonstrated a significant decrease in central retinal thickness amplitude by 123.8 μm following FAc implant administration ($P < .001$).20 These two studies represent the first U.S. data showing the change in RTA before and after a given treatment for DME.

| Subgroup        | n* | Mean RTSD, μm | Pre-FAc | Post-FAc | P Value |
|-----------------|----|---------------|---------|----------|---------|
| VA at Baseline  | 120| 54.9          | 22.2    | <.001    |         |
| >20/40          | 51 | 77.0          | 37.3    | <.001    |         |
| 20/100–20/40    | 52 | 66.5          |         | .161     |         |
| 20/200–20/100   | 8  | 71.8          |         | .055     |         |
| <20/200         | 9  | 118.1         |         |          |         |

*Number of eyes

VA = visual acuity; FAc = fluocinolone acetonide implant; RTSD = retinal thickness standard deviation

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**TABLE 2**

| Subgroup        | n* | Mean RTSD, μm | Pre-FAc | Post-FAc | P Value |
|-----------------|----|---------------|---------|----------|---------|
| VA at Baseline  | 120| 54.9          | 22.2    | <.001    |         |
| >20/40          | 51 | 77.0          | 37.3    | <.001    |         |
| 20/100–20/40    | 52 | 66.5          |         | .161     |         |
| 20/200–20/100   | 8  | 71.8          |         | .055     |         |
| <20/200         | 9  | 118.1         |         |          |         |

*Number of eyes

VA = visual acuity; FAc = fluocinolone acetonide implant; RTSD = retinal thickness standard deviation
The ability of the FAc implant to reduce retinal thickness and its fluctuations over the treatment period may be attributed to the continuous micro-dosing of FAc 0.2 μg/day over a long period of time (up to 36 months). In humans, the concentration of FAc in the aqueous humor reaches a peak in the first week following implant administration and decreases over the following 3 to 6 months until reaching a stable concentration that is sustained for up to 3 years. As demonstrated in Case Study 2, the FAc implant reduced CST fluctuations and improved BCVA compared with the outcomes from prior management using dexamethasone implants. Treatment with anti-VEGF injections would be expected to cause fluctuations in treatment effects similar to the dexamethasone implant. This is because the half-life of these medications in the vitreous of humans ranges from 6.7 hours (bevacizumab [Avastin; Genentech, South San Francisco, CA]) to 10.4 hours (pegaptanib), and there are known adherence issues associated with anti-VEGF treatments that contribute to suboptimal clinical outcomes. The real-world challenges of treatment adherence by DME patients have been well described. Replicating randomized controlled trial (RCT) results in real-world patient populations remains elusive for anti-VEGF agents. This may not be the case with the FAc implant and ongoing analyses comparing real-world patient populations, Phase 4 patient registry patient populations, and RCT patient populations, all receiving the FAc implant, are underway.

Although OCT-measured retinal thickness is clinically useful, its relationship to VA is complex and not fully understood. It is believed that several variables affect VA in addition to retinal thickening, which accounts for up to 27% of variability in concurrently measured VA. These findings indicate that mitigating the extent (amplitude), frequency, and persistence of fluctuations in retinal thickness may translate into beneficial effects on visual outcomes. In contrast, results from the VIVID-VISTA study showed no detrimental effect of fluctuations in CST on BCVA in patients receiving intravitreal aflibercept injections for DME every 8 weeks. However, patients were only followed for 100 weeks in the VIVID-VISTA study, and aflibercept is still a short-acting drug approved for every-2-month dosing as opposed to ranibizumab (Lucentis; Genentech, South San Francisco, CA), which is approved for monthly dosing. Damage to photoreceptors in response to frequent DME relapse episodes may only become clinically apparent over the long term.

In this study, there was a significant increase in the percentage of eyes that achieved CST of 300 μm or less at all timepoints following FAc implant administration compared with baseline (P < .05). These findings were consistent with those observed in another real-world study (PALADIN) of the FAc implant, supporting the benefit of FAc treatment in DME. For optimal ocular health, reduced retinal thickness is essential, as well as increased control of retinal thickness fluctuations. Therefore, retinal thickness fluctuations should always be interpreted in the context of retinal thickness measurements (ie, CST) when assessing DME.

A theoretical limitation of both RTA and RTSD to measure signal variability before and after FAc is that a declining signal — CST decreased after FAc — would be expected to have smaller variability. For example, variability of 20 μm for an average signal of 200 before an intervention may be the same as variability of 10 μm for an average signal of 100 and probably does not represent a clinically relevant finding. In our data, both RTA and RTSD reductions were far in excess of the absolute reduction of CST after FAc.

A limitation of this study is that it is retrospective, and comparison of the current findings to other data in the literature is limited owing to the novel concept of studying variability in retinal thickness over time before and after treatment. However, results from this analysis will contribute to our understanding of edema control and ascertaining optimal management strategies. In this post-hoc analysis of real-world data from the USER study, DME was well controlled following FAc treatment, demonstrated by a significant reduction in retinal thickness fluctuations, a significant increase in the proportion of eyes with CST of 300 μm or less, and significant correlations of retinal thickness variability measures to VA outcomes. The clinical relevance of these findings needs to be investigated in future studies. The findings of the present study suggest that measures of OCT variability over time and perhaps other clinically important variables should be broadly considered as additional measures of treatment efficacy in DME and other retinal disease states.

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