Optical Coherence Tomography (OCT) Features Predicting the Response of Diabetic Macular Oedema to Treatment with Fluocinolone Acetonide Intravitreal Implant, a Cohort Study

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Synopsis
We demonstrated the resolution of inflammatory OCT features at 12-months post fluocinolone acetonide treatment, with the aim that this information may be used in the future to create guidance for use of fluocinolone acetonide by clinicians.

Abstract
Purpose
We aimed to list the OCT features associated with good response to treatment with Iluvien (fluocinolone acetonide). Among these features we looked to describe the commonest OCT signs in patients with diabetic macular oedema and furthermore to correlate the change in visual acuity with the OCT changes.

Methods
This is a retrospective observational study including 17 eyes of 14 patients who were treated fluocinolone acetonide 0.19 mg intravitreal implant as a second line of treatment. OCT scans were obtained and LogMAR visual acuity data were collected on regular visits for 12 months before and 12 months after receiving the fluocinolone acetonide implant.

Results
At the end of the 12 months post-fluocinolone acetonide follow up period, there was a mean reduction of the CMT by 43.9 µm from the baseline (visit -12 months) and 158 µm from the time of treatment with fluocinolone acetonide, these are equivalent to 12% and 42%, respectively. The change in visual acuity was equivalent to +5 ETDRS letters compared to the baseline (visit -12 months) and +7.2 ETDRS letters compared to the time of treatment with fluocinolone acetonide.

We observed a significant reduction in inflammatory features seen in that time.

Conclusions
We showed that fluocinolone acetonide significantly reduced macular inflammatory signs, particularly the proportion of eyes with disorganization of retinal inner layers (DRIL) and hyper reflective foci at 12 months post-treatment.

Key words: Diabetic macular oedema, Fluocinolone Acetonide, fluocinolone acetonide, OCT

Introduction
Diabetic macular oedema (DMO) is a prevalent complication of diabetic retinopathy leading to a reduction in visual acuity. In the UK, there are currently an estimated 4.9 million people living with diabetes, with the figure predicted to rise to 5.5 million by 2030\(^1\). The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) reported that at 25-year follow up, 17% of patients developed visually significant DMO\(^2\). This represents a significant treatment burden on the National Health Service (NHS).

Historically, following the Early Treatment Diabetic Retinopathy Study (ETDRS), focal/grid laser photocoagulation was considered the gold-standard treatment for DMO\(^3\). Current treatments include both anti-VEGF injections and corticosteroid implants, with patients exhibiting heterogenous response to treatment, and requiring long-term duration of treatments. The fluocinolone acetonide (FAc) 0.19mg intravitreal drug-delivery system (ILUVIEN\(^\text{®}\); Alimera Sciences, Inc., Alpharetta, GA, USA) has been introduced to provide a safe and efficient long-term therapeutic approach, with up to 72-month duration\(^4\).

The quality-adjusted life years (QALYs) in patients treated with fluocinolone acetonide was reported to be 5.78 years over a 15-year study horizon. fluocinolone acetonide was estimated to be
cost-effective compared to dexamethasone in pseudophakic patients with chronic DMO. Furthermore, in the age of COVID, with the increasing attempt to limit face-to-face appointments, a long-lasting 3-year implant with virtual follow up is an attractive treatment option.

Despite the obvious advantages, there is a lack of clear guidance indicating which patients are likely to respond, meaning clinicians are unable to effectively select patients likely to benefit from this expensive treatment. We aimed to elucidate the OCT features which can be predictive of successful responders, thus allowing the development of a recognised protocol for more careful selection of patients by clinicians.

We analysed the presence of a number of inflammatory features seen on OCT prior to treatment, and their change post-treatment. The benchmark Fluocinolone Acetonide in Diabetic Macular Oedema (FAME) trial set the primary outcome as improvement of visual acuity by ≥15 ETDRS letters at year 3. Our cohort of patients were followed up for a maximum of 12 months post-implant, meaning we were unable to do a direct comparison of results due to the difference in follow-up intervals. However, we observed a significant reduction in inflammatory features seen in that time, which was in line with results seen in the literature.

**Materials and Methods**

**Objectives**
- To list the OCT features associated with good response to treatment with fluocinolone acetonide.
- To describe the most common OCT signs in patients with diabetic macular oedema.
- To correlate the change in visual acuity with the OCT changes.

**Study Design**

This is a retrospective observational study including 17 eyes of 14 patients who were treated fluocinolone acetonide 0.19 mg intravitreal implant as a second line of treatment.

OCT scans were obtained using Spectralis® device (Heidelberg Engineering, Heidelberg, Germany) and LogMAR visual acuity data were collected on regular visits for 12 months before and 12 months after receiving the fluocinolone acetonide implant.

The study was conducted at Peterborough City and Hinchingbrooke Hospitals, which are part of North West Anglia NHS Foundation Trust in the East of England.
Inclusion Criteria
- Patients diagnosed with diabetic macular oedema who were treated with either anti-VEGF intravitreal injections or dexamethasone intravitreal implant as a first line of treatment.
- Patients who completed 12 months of follow up since treatment with fluocinolone acetonide implant.

Exclusion Criteria
- Patient treated with macular laser.
- Patients diagnosed with ischaemic maculopathy.

Data Entry and Analysis
The OCT parameters were collected in each visit from a single cross section scan which passes through the fovea. All data points from each visit were entered and analysed on a spreadsheet specifically designed using Microsoft Excel 365 (Microsoft Corporation, Redmond, Washington, USA). Subretinal fluid measurements were done in micrometres using the Heidelberg OCT analysis software (Heyex – 2). Visual acuity annotation is done using the ETDRS system.

Definitions of Terms
- Retinal cystoid spaces:
  - Demarcation: is how much retinal tissue is visible in between the cystoid space, better demarcation is indicated by more visible retinal tissue.
  - Reflectivity: is how bright the contents of the cystoid space are, if the brightness is similar to the vitreous cavity this indicates low reflectivity.
  - Hyper reflective foci: discrete multiple round hyper reflective spots that have a greater reflectivity compared to the vitreous.
  - Disorganization of Retinal Inner Layers (DRIL): loss of demarcation between horizontal retinal layers with altered thickness of the retina.

Limitations
1. OCT quality can be poor in cases of media opacities. Where this was an issue, we indicated that the particular data was not available.
2. Follow up intervals vary between patients, we grouped data from visits within the fixed follow up intervals: -12, -9, -6, -3, 0, 3, 6, 9 and 12 months.

Data collection and analysis was made in line with the Declaration of Helsinki guidance, the study did not involve any experimental component, and the ethical approval was granted by the Cambridgeshire-East Research Ethical Committee.

No grants or waivers were used for the completion of this study. Patient consent was obtained, as the data collection was done in retrospect, after the completion of treatment.
Results
Mean age 69.2 years (SD = 10.6, range = 50-80 years), 35% of the participants are females and 65% are males. All patients were pre-treated with anti-VEGF injections and/or dexamethasone 0.7mg intravitreal implant. Mean number of injections is 27.1 (SD = 14.63), minimum number of injections is 1 and maximum is 51.

The baseline visual acuity and OCT data were obtained from the visit preceding treatment with fluocinolone acetonide implant by 12 months (visit -12 months), mean baseline visual acuity (LogMAR) was 0.48 and CMT is 381 µm. Figure 1 shows the mean change in VA and CMT throughout the duration of the study.

At the end of the 12 months post-fluocinolone acetonide follow up period, there was a mean reduction of the CMT by 43.9 µm from the baseline (visit -12 months) and 158 µm from the time of treatment with fluocinolone acetonide, these are equivalent to 12% and 42%, respectively. The change in visual acuity was equivalent to +5 ETDRS letters compared to the baseline (visit -12 months) and +7.2 ETDRS letters compared to the time of treatment with fluocinolone acetonide.

We looked at the following morphological features of the cystoid macular oedema on OCT scans: number demarcation and reflectivity of cystoid spaces. At baseline 53% of the eyes had more than 10 cystoid spaces, then went down to 18% at the end of the 12 months post-fluocinolone acetonide follow up period (Figure 2). Proportion of eyes with both well and poorly demarcated cystoid spaces reduced from 29% and 35%, respectively at baseline to 6% and 18%, respectively at 12 months post-treatment (Figure 3). The proportion of eyes with both hyper and hypo-reflective cystoid spaces reduced from 24% and 41%, respectively at baseline to 6% and 24%, respectively at the end of the follow up interval (Figure 4).

Hyper reflective foci (HF), disorganization of retinal inner layers (DRIL) and epiretinal membrane (ERM) formation are known inflammatory features on OCT. At the time of injection with fluocinolone acetonide, the mean percentage of eyes with HF was 76%, DRIL was 29%, and ERM was 53%, these has all reduced down to 41%, 18%, and 18%, respectively, after 12 months from receiving fluocinolone acetonide implant (Figure 5).

Hard exudates (HEs) were present in 6% of the eyes at the time of treatment with fluocinolone acetonide, none of the eyes had hard exudates after 12 months from the implant date.

There was no significant difference in the percentage of eyes with a continuous ellipsoid layer at the time of treatment with fluocinolone acetonide (59%) and after 12 months of follow up (47%), p value = .021.

The percentage of eyes which required rescue therapy at 12 months post-injection was 29% (5 eyes), the average interval at which those eyes required the rescue therapy was 6.6 months, 3 eyes required rescue therapy with aflibercept intravitreal injection because of recurrence of CMO, and 2 eye required laser panretinal photocoagulation because of development of proliferative retinopathy (Table 1).

<p>| Table 1. Eyes requiring rescue therapy (RS) |
|---|---|---|---|</p>
<table>
<thead>
<tr>
<th>Eye</th>
<th>Days until RS</th>
<th>Number of previous injections</th>
<th>Reason for RS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye 1</td>
<td>301</td>
<td>49</td>
<td>DMO recurrence</td>
</tr>
<tr>
<td>Eye 2</td>
<td>72</td>
<td>43</td>
<td>PDR</td>
</tr>
<tr>
<td>Eye 3</td>
<td>72</td>
<td>37</td>
<td>PDR</td>
</tr>
<tr>
<td>Eye 4</td>
<td>244</td>
<td>1</td>
<td>DMO recurrence</td>
</tr>
<tr>
<td>Eye 5</td>
<td>305</td>
<td>17</td>
<td>DMO recurrence</td>
</tr>
</tbody>
</table>

Figure 5. Inflammatory signs. Figure showing the change in inflammatory signs seen on OCT scans over time.
Discussion
The Fluocinolone Acetonide in Diabetic Macular Oedema (FAME) study has set the primary outcome of treatment as improvement of visual acuity by ≥15 ETDRS letters at year 36. Our cohort of patients were followed up for a maximum of 12 months post implant, the mean visual acuity change was found to be half of what was reported by the FAME study, we believe this could be due to the difference in the follow up intervals, and that fluocinolone acetonide is a sustained release implant.

A good response to treatment with fluocinolone acetonide is reported to be achieved in patients with a complete anatomical response after one injection of dexamethasone implant for those patients in whom the retina layers are preserved. Our study focused on the value of OCT as a predictive tool for response to fluocinolone acetonide by comparing the morphology before and after treatment.

The inner retinal layers are the most commonly affected by diabetic maculopathy, whether that is in the form of cystoid space, DRIL or hyperreflective foci. We noticed that there was a significant reduction in the proportion of eyes with DRIL and hyper reflective foci at 12 months post-treatment with fluocinolone acetonide. Also, we found that proportion of eyes with ERM reduced significantly, this is in line with the findings in literature, and demonstrates the effects of steroids in reducing inflammatory signs associated with diabetic maculopathy.

In conclusion, fluocinolone acetonide was found to significantly reduce macular inflammatory signs. Our cohort of patients will be interviewed for the change in their quality of life after completing the second year of follow up, and will be submitted for publication. The literature in patients with DMO has demonstrated the sensitivity of NEI-VFQ-25 score improvements to visual acuity gains.

Data Availability Statement
The data that support the findings of this study are available on request from the corresponding author, AH. The data are not publicly available due to their containing information that could compromise the privacy of study participants.

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Conflict of Interest
None.

Funding
None.

References:
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1. The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) reported that at a 25-year follow up, what percentage of patients developed visually significant DMO?
   - 47%
   - 37%
   - 27%
   - 17%

2. Fluocinolone acetonide intravitreal implant provides a safe efficient long-term therapeutic approach to diabetic macula edema of what duration?
   - 72 months
   - 60 months
   - 48 months
   - 36 months

3. Which of the following is not a common retinal layer finding affected by diabetic maculopathy?
   - Disorganization of Retinal Inner Layers
   - Cystoid Space
   - Subretinal haemorrhages
   - Hyporeflective foci

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4. Which of the following retinal findings were seen to have significantly reduced at 12-months post-treatment with fluocinolone acetonide intravitreal implant?

☐ Epiretinal membranes
☐ Cataracts
☐ Hyperreflective foci
☐ Both A and C

5. What reduction of central macula thickness was seen at the end of the 12-month period from the time of the treatment with fluocinolone acetonide intravitreal implants?

☐ 62%
☐ 52%
☐ 42%
☐ 32%

6. Hard exudates were seen in 6% of eyes at the time of no treatment with fluocinolone acetonide intravitreal implants, what percentage of eyes had hard exudates after 12-months from the implant date?

☐ None
☐ 2%
☐ 4%
☐ 6%

7. What was the mean percentage of eyes with epiretinal membranes reduced to after 12-months from receiving fluocinolone acetonide intravitreal implants?

☐ 38%
☐ 28%
☐ 18%
☐ 8%

8. The change in visual acuity seen after treatment with fluocinolone acetonide intravitreal implants was which of the following?

☐ +7.2 EDTRS letters
☐ +6.2 EDTRS letters
☐ +5.2 EDTRS letters
☐ +4.2 EDTRS letters

9. Proportion of eyes with hyper- and hypo-reflective cystoid spaces reduced from 24% and 41% respectively, to which of the following?

☐ 12% and 30%
☐ 10% and 28%
☐ 8% and 26%
☐ 6% and 24%

10. The quality-adjusted life years (QALYs) in patients treated with fluocinolone acetonide intravitreal implants were reported to be which of the following?

☐ 7.776
☑ 5.776
☐ 3.776
☐ 1.776