European Review for Medical and Pharmacological Sciences 2023; 27: 1759-1766

Efficacy of 190 mcg fluocinolone acetonide intravitreal implant: microperimetry and OCT real-life data

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Abstract. – OBJECTIVE: Fluocinolone acetonide is a valid alternative treatment for patients with chronic diabetic macular edema (DME) with poor response to anti-vascular endothelial growth factor (VEGF) therapy. The purpose of this study is to report the efficacy and safety of ILUVIEN® implant in pseudophakic eyes with persistent DME.

PATIENTS AND METHODS: This is a single-centre pilot-study of 8 patients with persistent DME treated with the ILUVIEN implant, despite previous anti-vascular endothelial growth factor and/or steroid treatment. Best-corrected visual acuity (BCVA), optical coherence tomography (OCT) central retinal thickness, intraocular pressure (IOP) and microperimetric data were evaluated at baseline and month 1, 3 and 6 post treatment.

RESULTS: All data are presented as mean and standard deviation. At baseline, 1, 3 and 6 months, we had BCVA of 0.26±0.22, 0.38±0.27, 0.48±0.27 and 0.46±0.24; IOP of 15.00±2.67, 15.50±3.16, 14.88±2.42 and 15.63±2.67 mmHg; macular thickness of 652±231, 487±278, 475±287 and 413±211 μm; macular sensitivity of 6.83±4.20, 6.13±3.72, 7.68±3.40 and 7.71±3.33 dB; bivariate contour elliptic area (BCEA) 95.4% 3.8±3.42, 6.06±10.06, 3.05±2.46 and 2.59±2.19°2.

CONCLUSIONS: According to the results of our study, fluocinolone acetonide (FAc) is a valid therapy option despite some limitations. It has been evidenced that FAc is more effective in patients with mild central macular thickening while in those with modest to severe central macular thickness (CMT), different therapy strategies should be considered.

Key Words:
Fluocinolone acetonide, Maculopathy, Diabetes, Diabetic macular edema, Intravitreal implant, Microperimetry, Optical coherence tomography.

Introduction

Diabetic macular edema (DME) directly impairs central vision and represents the most common cause of vision loss in working-age populations of developing countries affected by diabetes mellitus[1]. DME is the thickening of the retina due to the breakdown of the blood-retina barrier with an increase in vascular permeability[2]; this alteration leads to the exudation and accumulation of extracellular fluid and proteins in the macula[3]. Solid evidence[4,5] has been provided about the association between the persistent hyperglycemia and elevated glycated hemoglobin and a higher incidence of DME. Traditionally, laser Photocoagulation has been the gold standard therapy for DME for decades, but since the early 90's several studies[6] have shown that a substantial part of patients treated with retinal laser showed no improvement in visual acuity (VA). Thus, photocoagulation has been progressively replaced by anti-vascular endothelial growth factor (VEGF) medications that are currently the first-line treatment and result in a rapid decrease of macular edema and improvement of VA[7,8]. However, treatment regimen with anti-VEGF requires a large number of frequent injections that may be disruptive to the patient's quality of life[9], and may lead to a wide swing in ocular drug concentration and exposes patients to risks related to surgical processes. Moreover, a high percentage of diabetic patients have a poor response to anti-VEGF therapy and in some cases up to 55% of eyes have a chronic persistent DME[10,11]. In these patients, corticosteroid therapy can be a valid alternative treatment. Corticosteroid drugs reduce the expression of VEGF and the synthesis of pro-inflammatory mediators involved in the pathogenesis of DME. Moreover, treatment with steroids reduces the influx of leukocytes into the retina and inhibits all the inflammatory processes that are thought to be responsible for the retinal cell degeneration[12-14]. ILUVIEN® (SiFi Spa, Catania, Italy) is a small, cylindric and nonbiodegradable

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fluocinolone acetonide (FAc) intravitreal implant and it is designed to be injected into the vitreous cavity with a 25-gauge needle through the pars plana[15]. It contains 190 mcg of FAc that is initially released at 0.25 μg/day (average, 0.2 μg/day), and the implant lasts 36 months[16].

Recently, the scientific community has shown increasing interest in the study of macular pathologies by microperimetry (MP). The information derived from MP comes from the analysis of threshold sensitivity and fixation stability. Threshold sensibility is a functional test exploring the weakest possible luminous stimulus recognized by the patients in each area of the visual field. On the other hand, fixation stability represents an objective evaluation which maps eye movements 25 times per second and mathematically analyzes the resulting cloud of fixation points over a reference map. Nowadays, two methods are available to measure fixation stability; one calculating the percentage of points encompassed in a circle of 18 [P1 in the Macular Integrity Assessment device (MAIA) MP] and 28 (P2) radii centered in the cloud of fixation points, where a P1 value higher than 75% represents "stable fixation", "relatively unstable fixation" is reached whether P1 < 75% and P2 > 75%, while fixation pattern is defined as "unstable" if both P1 and P2 are less than 75%. The bivariate contour ellipse area represents a second fixation stability measurement methodology consisting in determining the area of an ellipse that encompasses a given proportion of fixation points during a fixation attempt. The Macular Integrity Assessment device (MAIA) is a microperimetry system that reports two bivariate contour ellipse areas with proportional values of 63% and 95%. As a database reporting threshold derived from normal eyes is available, it is possible to correlate patients' specific data to reference values[17].

Patients and Methods

This was a single-center, non-randomized pilot-study and it was conducted at the Ophthalmology Department of Fiorini Hospital in Terracina. Research and data collection adhered to the tenets of the Declaration of Helsinki and written informed consent was obtained from all patients before being included in the study and after an explanation of the nature of the participation.

The study recruitment occurred between September 2019 and March 2022.

Required Inclusion Criteria

- Males and non-pregnant females at least 18 years of age;
- Diagnosis of diabetes mellitus (type 1 or 2);
- Pseudophakia;
- Chronic DME based on investigator's clinical evaluation and demonstrated on fundus examination and OCT images;
- Previous photocoagulation or anti-VEGF treatment with no significant response;
- Previous injection of Dexamethasone implant;
- BCVA lower than 0.70 Snellen;
- Mean foveal thickness of at least 300 μm;
- Ability and willingness to comply with the treatment and follow-up procedures;
- Ability to understand and sign the informed consent form.

Exclusion Criteria

- Other causes of macular edema;
- Uncontrolled diabetes with glycosylated hemoglobin higher than 8%;
- Monocle patients;
- Prior intravitreal, subtenon, or periocular steroid therapy within 3 months prior to enrollment or prior treatment with intravitreal anti-VEGF injection within 2 months of enrollment.
- Glaucoma, ocular hypertension or history of uncontrolled IOP elevation with steroid use that did not respond to topical therapy, C/D ratio higher than 0.8.
- Any active viral, fungal, or bacterial infection which could be activated by a treatment with a steroid.

Patients were submitted to a baseline full ophthalmic evaluation including BCVA testing using Snellen charts, biomicroscopy, applanation tonometry and ophthalmoscopic fundus examination.

Patients also underwent spectral-domain OCT (Spectralis OCT Heidelberg Engineering, Germany). Central macular thickness (CMT) was determined by the built-in software, and it was defined as the minimum thickness of a central macular area of 1,000 micron in diameter centered on the patient's foveola.

Microperimetry (MP) was used to measure retinal sensitivity and the area of fixation with the evaluation of a bivariate contour elliptic area (BCEA). We considered the 95.4% BCEA[17] in order to evaluate fixation stability comparing the results of our patients with MAIA normative databases. The correlation between retinal

Table I. BCVA, macular thickness and macular sensitivities.

Follow-up	n	BCVA (Snellen decimal)	Macular thickness (µm)	Macular sensitivities (dB)
Baseline	8	0.26 ± 0.22	652 ± 231	6.83 ± 4.20
1 Month	8	0.38 ± 0.27	487 ± 278	6.13 ± 3.72
3 Months	8	0.48 ± 0.27	475 ± 287	7.68 ± 3.40
6 Months	8	0.46 ± 0.24	413 ± 211	7.71 ± 3.33

alteration and corresponding functional defects was obtained by the integration of ocular fundus images and a computerized threshold microperimetry. MP was performed with automatic fundus-related perimeter (MP-1 Nidek Technologies, Japan) in patients with dilated pupils. In our study the following parameters were used: a fixation target consisting of a 2 degrees diameter red cross, a white monochromatic background at 4 asb, stimulus size Goldmann III with 200 ms projection time, a customized grid of 45 stimuli covering 12° centered onto the fovea. Decibel range of attenuation was 0 to 20. A threshold strategy 4-2 double staircase was used. Stimuli with MP-1 were always projected exactly onto the predefined retinal position thanks to an eye tracker that compensated eye movements.

One month after the intravitreal implant, BCVA measurements, applanation tonometry, OCT and microperimetry were repeated at 3 and 6 months.

The primary endpoint of this study was to investigate changes in MP data before and after the treatment with 190 mcg FAc intravitreal implant; secondary endpoints were changes in BCVA, CMT and any intraocular pressure (IOP) elevation related to corticosteroid therapy.

Statistical Analysis

Patients' results are displayed as mean value of the considered parameter plus-minus mean deviation. The deviation from normality of the parameters is displayed as a *p*-value obtained with Student's *t*-test. A *p*-value lower than 0.05 is considered as statistically significant in order to refuse null hypothesis.

Results

There were 8 patients, 8 eyes, 4 women and 4 men; the mean age of the patients was 66±18 years. In total 8 patients met these criteria, and they received the 0.2 µg/day FAc intravitreal implant (ILUVIEN®, SiFi Spa, Catania, Italy). All patients were affected by chronic diabetic macular oedema. BCVA, foveal thickness, average retinal sensitivity of the 45 stimuli (Table I) and fixation stability through evaluation of BCEA 95.4%[17] (Table II) were considered in our study. We also evaluated IOP at every follow-up (Table III).

Before the injection, all the patients underwent the following treatments: peripheral laser photocoagulation and at least a cycle of 5 intravitreal injections of anti-VEGF at least 4 months before the intravitreal implant injection of FAc. All eyes were also treated with at least one injection of Dexamethasone implant to test steroid efficacy and response for that subject. All data are presented as mean value and standard deviation.

Baseline Characteristics

All 8 patients underwent the baseline examination except for microperimetry: one patient was not able to complete the examination due

Table II. Deviation from normality of patient's BCEA.

Follow-up	n	BCEA 95.4% (°2)	DN[1]	CN (n)[2]	ON (n)[3]
Baseline	7[4]	3.80 ± 3.42	$p = 0.077$	5	2
1 Month	8	6.06 ± 10.06	$p < 0.001$	6	2
3 Months	8	3.05 ± 2.46	$p = 0.375$	6	2
6 Months	8	2.59 ± 2.19	$p = 0.795$	7	1

[1]DN: deviation from normality, BCEA 95.4% deviation *p*-values; [2]CN: compatible with normality, subjects with BCEA compatible with normal values; [3]ON: outside normality, subjects with BCEA outside normal values; [4]One subject was not able to attend the exam due to extremely poor visual acuity.

Table III. Intraocular pressure values.

Follow-up	Intraocular pressure (mmHg)
Baseline	15.00 ± 2.67
1 Month	15.50 ± 3.16
3 Months	14.88 ± 2.42
6 Months	15.63 ± 2.67

to visual acuity being too poor. Mean measured BCVA with Snellen charts was 0.26±0.22. Mean IOP at baseline was 15±2.67 mmHg, no patient was in therapy with anti-glaucomatous drops. Mean OCT macular thickness at baseline was 652±231 µm. Mean macular sensitivity determined with the MP-1 was 6.83±4.20 dB, mean BCEA 95.4% was 3.80±3.42°^{2} (deviation from normality p=0.077, only 7 patients examined).

One-Month Follow-Up

After 1 month 8 patients completed the follow-up. Mean measured BCVA with Snellen charts was 0.38±0.27. Mean IOP was 15.50±3.16 mmHg, 1 patient had an IOP of 21 mmHg and we prudently chose to start therapy with brimonidine, 2 drops per day in the treated eye. Mean OCT macular thickness was 487±278 µm. Mean macular sensitivity determined with the MP-1 was 6.13±3.72 dB, mean BCEA 95.4% was 6.06±10.06°^{2} (deviation from normality p<0.001).

Three-Months Follow-Up

After 3 months, 8 patients completed the follow-up. Mean measured BCVA with Snellen charts was 0.48±0.27. Mean IOP was 14.88±2.42 mmHg, the higher IOP value was 18 mmHg, only 1 subject was undergoing therapy with brimonidine with a good intraocular pressure control (17 mmHg at the 3 months follow-up). Mean OCT macular thickness was 475±287 µm. Mean macular sensitivity determined with the MP-1 was 7.68±3.40 dB, mean BCEA 95.4% was 3.05±2.46°^{2} (deviation from normality p=0.375).

Six-Months Follow-Up

After 6 months, 8 patients completed the follow-up. Mean measured BCVA with Snellen charts was 0.46±0.24. Mean IOP was 15.63±2.67 mmHg, the higher IOP value was 18 mmHg, only 1 subject was undergoing therapy with brimonidine with a good pressure control (18 mmHg at the 6 months follow-up). Mean OCT macular thickness was 413±211 µm. Mean macular sensitivity determined with the MP-1 was 7.71±3.33 dB, mean BCEA 95.4% was 2.59±2.19°^{2} (deviation from normality p=0.795).

During the follow-up, retinal thickness reduced in the first postoperative period, and BCVA and retinal sensitivities improved as well; considering the 6 months follow-up period all the parameters analyzed demonstrated a reduction trend, further follow-ups are necessary to evaluate this tendency to the reduction of the edema (Figure 1).

Considering the IOP, all patients had no cortico-response on the basis of an unreported response to dexamethasone implant[18]. In none of the eyes did the implant interfere with vision, and postoperative infectious endophthalmitis, vitreous hemorrhage, or proliferative vitreoretinopathy did not occur. Due to the small number of patients enrolled, all improvement parameters verified with Student's t-test were not statistically significant. The only significant element was the BCEA 95.4% improvement whose deviation from normality (evaluated with t-test) becomes progressively less significant considering the 1 month, 3 months and 6 months follow-up and considering[17] 2.40±2.04°^{2}. Intraocular pressure variations through the follow-ups were not statistically significant.

Discussion

Diabetes mellitus is one of the most common causes of macular edema, which itself is the cause of visual impairment[19]. In order to consider the efficiency of the treatment it is important to evaluate the entity in the baseline of the DME and its duration: these two components represent an important factor for visual prognosis.

Diabetic macular edema can be divided into two subtypes: diffuse, when there is a generalized leakage from dilated capillaries throughout the posterior pole; focal, in case of localized retinal thickening caused primarily by a focal leakage from microaneurysm and dilated capillaries[20].

Imaging methods, such as OCT and A-OCT, are the main instruments to monitor macular edema and retinal thickness. Thanks to the OCT, we could evaluate early diabetic macular abnormalities and macular thickness in the baseline and the progression and changes after intravitreal therapy[21].

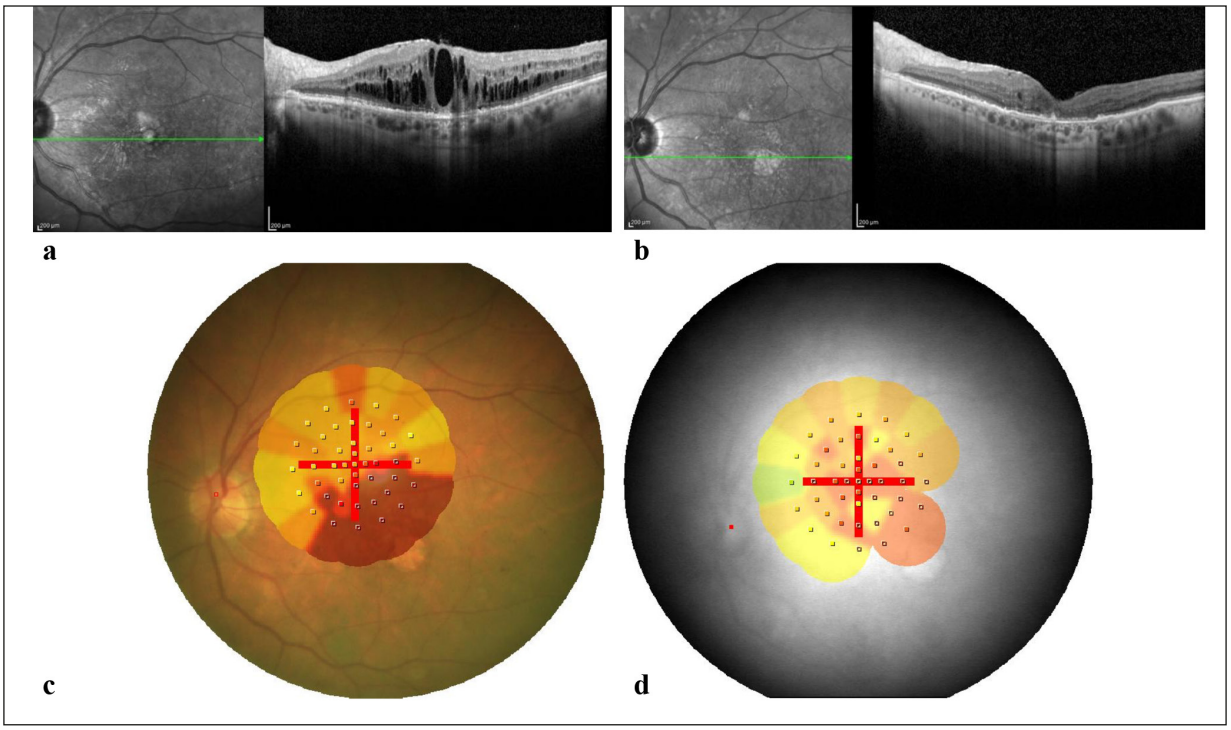

Figure 1. **a-b**, IR and OCT macula at baseline and 6 months examination of one of the 8 subjects. **c-d**, Microperimetry at baseline and 6 months examination of the same subject.

OCT findings help distinguish newly and well-established macular edema: cystoid spaces are considered newly developed when are located in the outer retinal layers, with preservation of the inner layers; well-established when forming large confluent cavities[22].

The functional impact of DME in clinical practice is usually quantified by BCVA, even if this parameter is just one of the aspects of macular function and is too subjective to be considered alone. For this reason, the effectiveness of the therapy has been analyzed with microperimetry as well.

MP-1 has proven to be an effective functional method in the examination of retina sensitivity changes, thus is a useful tool for a qualitative evaluation of the retinal function. Microperimetry has been successfully used in the diagnosis and follow-up of different macular disorders, including age-related macular degeneration, myopic maculopathy, macular dystrophies, and diabetic macular edema[23].

Different therapies are used to manage diabetic macular edema. Among these, corticosteroids have been used to reduce the breakdown of the inner blood-retinal barrier and extravasation from leaking vessels[24]. The exact mechanism of action of corticosteroids is still unknown, however, the rationale could be found in their ability to inhibit arachidonic acid pathway, of which prostaglandin is a product[25]. Moreover, steroids may also downregulate the production of vascular endothelial growth factor (VEGF), a known vascular permeability factor[26]. During the last few years, corticosteroids have been administered in different ways: first as intravitreal suspension, then as intravitreal implants. Intravitreal dexamethasone implants last for about 3 months, with different pharmacokinetics compared to FAc, which instead lasts for 36 months[27].

Intravitreal therapies might be useful for the treatment of diffuse DME, in fact this kind of edema has poor prognosis with laser photocoagulation; other treatments like vitrectomy are not always followed by improvement in visual function and require a significant surgical intervention with its inherent risk, recovery time, and expense[27].

In our study we have evaluated retinal sensitivities and fixation by means of MP-1 and retinal thickness by means of OCT, at the baseline, 3 months and 6 months follow-ups after administration of FAc intravitreal implant.

Our data confirms the efficacy of intravitreal (IVT) implant for the treatment of diffuse

macular edema in diabetic patients with an improvement of all the parameters evaluated. Nevertheless, it must be considered that the results are not statistically significant, except for the improvement of BCEA, due to the small number of patients enrolled in the study.

A comparison of the normative database of MAIA microperimetry for the BCEA 95.4%, shows less statistically significant deviations of fixation stability during the follow-ups. This suggests a gradually more stable fixation[21].

It has to be considered that the BCEA 95.4% encountered in the baseline appears with less significant deviations from normality in comparison to the follow-ups because of the lack of one patient examination, due to low VA and retinal sensitivity.

Limitations

The present study has weaknesses and limitations. Firstly, the follow-up time was relatively short and consequently evaluation of FAc implant safety was not significant. As reported from other research in literature, long term evaluation showed increased incidence of steroid-induced adverse events. Secondly, the number of patients enrolled was limited, also because all the patients that underwent the implantation had to be pseudophakic. Thirdly VA was evaluated with Snellen charts.

Conclusions

Our data suggest that intravitreal implant of FAc can be a useful treatment in patients with DME. According to our data, patients with modest retinal thickening due to the edema responded better to the treatment compared to those with major thickening. Thus, we can assess that FAc is efficient in keeping dry retinal layers. As reported in the USER study by Riemann et al[28] the same goes with BCVA: patients that began the study with lower VA, have improved less than those with higher VA[20].

Major DME, should be firstly treated with more aggressive therapies in order to decrease macular edema; once central foveal thickness (CFT) is reduced, FAc should be considered to control it for longer periods of time.

According to our data, the best way to approach patients with DME is to combine the treatment options in order to control macular edema more efficiently[27].

Macular sensitivity is probably a useful predictor of visual outcome in diabetic patients. Fixation and retinal sensitivity may give more information about central macular function because it documents any individual area where function is distorted[29].

The side-effects described in the literature like direct toxic effect on the retina and optic disk, retinal detachment and endophthalmitis were not observed. IOP elevation occurred in one case in the postoperative period and was not a major problem. IOP was successfully controlled by hypotonic anti glaucomatous drops (brimonidine).

OCT and MP-1 could be easily performed in routine clinical settings and may provide a complete method to evaluate treatment efficacy in many retinal diseases. Larger studies are needed to test the ability of microperimetry to make a point-by-point prediction of functional outcome after various forms of intervention, to see the real efficacy of FAc and to identify those patients that would benefit the most from this kind of treatment.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Authors' Contribution

Conceptualization: E.M.V.; methodology: F.A.; validation: A.F, F.T. and E.M.V.; formal analysis: F.A., A.C.; investigation: A.C.; resources: F.A.; data curation: F.A., A.F.; writing-original draft preparation: F.A., A.F. and A.C.; writing-review and editing: F.T.; visualization: F.A.; supervision: E.M.V.; project administration: E.M.V. All authors have read and agreed to the published version of the manuscript.

Funding

This research received no external funding.

Informed Consent

Informed consent was obtained from all subjects involved in the study.

Ethical Approval

The study was approved by the Ethic Committee of Senses and Organs Department ("La Sapienza" University of Rome) with the session 27.7.2022 n.7.3.

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