The Outcomes of Switching from Short- to Long-Term Intravitreal Corticosteroid Implant Therapy in Patients with Diabetic Macular Edema

Sara Vaz-Pereira^{a, b} João Paulo Castro-de-Sousa^{c–e} David Martins^f
Joaquim Prates Canelas^{a, b} Pedro Reis^g António Sampaio^h Helena Urbanoⁱ
Paulo Kaku^j João Nascimento^k Carlos Marques-Neves^{a, b, l}

^aDepartment of Ophthalmology, Centro Hospitalar Universitário de Lisboa Norte, EPE – Hospital de Santa Maria, Lisbon, Portugal; ^bDepartment of Ophthalmology, Faculdade de Medicina, Universidade de Lisboa, Lisbon, Portugal; ^cDepartment of Ophthalmology, Centro Hospitalar de Leiria, Leiria, Portugal; ^dCICS-UBI, Health Sciences Research Centre, University of Beira Interior, Covilhã, Portugal; ^eFaculty of Health Sciences, University of Beira Interior, Covilhã, Portugal; ^fDepartment of Ophthalmology, Centro Hospitalar de Setúbal, Setúbal, Portugal; ^gDepartment of Ophthalmology, Hospital das Forças Armadas, Lisbon, Portugal; ^hInstituto de Microcirurgia Ocular, Lisbon, Portugal; ⁱDepartment of Ophthalmology, Centro Hospitalar de Lisboa Ocidental – Hospital Egas Moniz, Lisbon, Portugal; ^jDepartment of Ophthalmology, Hospital da Cruz Vermelha Portuguesa, Lisbon, Portugal; ^kInstituto de Retina de Lisboa, Lisbon, Portugal; ^lALM Oftalmolaser, Lisbon, Portugal

Keywords

Visual acuity · Diabetic macular edema · Fluocinolone acetonide intravitreal implant · Safety · Real-world study

Abstract

Background: First-line treatment for diabetic macular edema (DME) is usually with anti-vascular endothelial growth factor agents, followed by intravitreal corticosteroids as a second-line treatment option. Long-term corticosteroids may offer quality of life and effectiveness benefits over short-term implants. **Objectives:** To evaluate outcomes of patients with persistent or recurrent DME who switched from a short-term (dexamethasone) to a long-term (fluocinolone acetonide, FAc) corticosteroid intravitreal implant in a real-world setting. **Methods:** This is a retrospective study in 9 Portuguese centers. An FAc intravitreal implant was administered

according to product labeling. Effectiveness outcomes were mean change in visual acuity (VA; ETDRS letters), central retinal thickness (CRT; μm), and macular volume (MV; mm^3). The safety outcome was mean change in intraocular pressure (IOP; mm Hg). All were analyzed at months 1 and 3, and then quarterly until month 24 after implantation. **Results:** Forty-four eyes from 36 patients were analyzed. Mean duration of DME was 3.3 ± 1.9 years, and mean follow-up was 8 months. From baseline following FAc implantation, VA increased significantly at months 1 and 6 (mean +6.82 and +13.02 letters, respectively; $p = 0.005$), and last observation carried forward (LOCF; mean +8.3 letters; $p = 0.002$). CRT improved significantly at months 1 and 6 (mean -71.81 and -170.77 μm , respectively; $p = 0.001$), and LOCF (mean -121.46 μm ; $p = 0.001$). MV was consistently, but not significantly, decreased from baseline to LOCF (mean -0.69 mm^3 ; $p = 0.062$). The mean change in IOP was -0.25 and $+0.88$ mm Hg at months

1 and 6, respectively ($p = 0.268$), and $+1.86$ mm Hg at LOCF ($p = 0.036$). Increases were controlled with topical medication in most cases. **Conclusions:** The FAc intravitreal implant is effective in patients previously treated with short-term corticosteroid implants. Thus, after a suboptimal response to antiangiogenics or a short-term corticosteroid, a single FAc implant may be considered an effective and tolerable treatment that can improve long-term outcomes for patients with sight-threatening DME.

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Introduction

Diabetic macular edema (DME) is the most common cause of vision loss in patients with diabetic retinopathy [1]. With the growing prevalence of diabetes, an aging population, and the increased life expectancy of individuals with diabetes, the prevalence of DME is expected to rise [2]. In the Diabetic Retinopathy Barometer Study of 4,340 adults from 41 countries across 5 continents, the global prevalence of DME was 7.6%. Prevalence rates were highest in the Eastern Mediterranean region (11.0%) and lowest in the Western Pacific region (5.6%), and prevalence increased with age and time since diagnosis [3]. DME significantly impacts a patient's quality of life because functional ability declines at higher levels of visual impairment [4], and an estimated almost two-thirds of individuals with DME experience limitations in performing daily activities [5].

Without treatment, nearly half of all patients who develop DME will lose 2 or more lines of visual acuity (VA) within 2 years [6]. Thus, early diagnosis and effective treatment of DME are essential in preventing visual impairment and avoiding vision loss [4]. Current treatment guidelines generally recommend antivascular endothelial growth factor (anti-VEGF) therapy as first-line treatment for central-involving DME, with corticosteroids as a recommended second-line treatment option [7–9].

Randomized controlled trials (RCTs) of anti-VEGF therapy administered by intravitreal injection have shown favorable VA and retinal morphology outcomes when used as first-line therapy in patients with DME, with the best results generally achieved with monthly or bimonthly dosing regimens [10]. However, not all patients demonstrate optimal visual outcomes, and up to half show persistent edema after use of anti-VEGF therapy alone. This may be explained by suboptimal responses to therapy or suboptimal delivery of the medication. Indeed, in the former case, if ineffective treatment is resumed, or the

patient is left untreated, the risk of vision deteriorating increases [11]. In the latter case, ophthalmologists tend to prescribe anti-VEGF therapy as first-line treatment for DME in real-world settings [12]; however, their administration is less frequent than in anti-VEGF RCTs [10, 11].

Intravitreal injections of corticosteroids have been shown to be beneficial in the treatment of patients with DME [13, 14]. Corticosteroids have a dual effect as they inhibit the inflammatory response to a variety of inciting agents and reduce levels of VEGF: both of which play key roles in the pathophysiology of DME [15–19]. The corticosteroid fluocinolone acetonide (FAc), administered as an intravitreal implant (ILUVIEN 190 µg intravitreal implant in applicator; Alimera Sciences Limited, Aldershot, UK), is indicated in Europe for the treatment of vision impairment associated with chronic DME in patients considered to be insufficiently responsive to available therapies (i.e., persistent or recurrent DME despite prior treatment) [20, 21]. Each implant contains 190 µg of FAc with a daily release rate of 0.2 µg for up to 3 years.

Past studies have documented the effectiveness and tolerability of the implant after mainly first-line treatment with anti-VEGF therapies [22]. The objective of the current study was to assess the effectiveness and safety of the FAc intravitreal implant, in patients with persistent or recurrent DME despite treatment, after treatment with at least 1 dexamethasone implant.

Materials and Methods

Study Design

This was a retrospective, multicenter study of patients with DME treated with an FAc intravitreal implant, who attended one of 9 Portuguese public hospitals or private health clinics.

Patients and Study Procedures

For inclusion in the study, patients were required to have persistent or recurrent DME. Patients were judged to be insufficiently responsive to anti-VEGF treatment (or were unsuitable for anti-VEGF therapy) and were then treated with at least 1 dexamethasone implant and afterwards considered for treatment with an FAc intravitreal implant. Exclusion criteria were the presence of macular edema secondary to causes other than diabetic retinopathy, previous treatment with an FAc intravitreal implant, uncontrolled ocular hypertension, diagnosis of moderate-to-severe glaucoma, and the presence of active or acute intraocular inflammation or infection. A single FAc intravitreal implant was injected in the affected eye of patients according to product labeling [20].

Outcomes

Outcomes were analyzed at months 1 and 3, and then quarterly until month 24 after receiving the FAc intravitreal implant. Effectiveness evaluations included mean change in VA, mean

Table 1. Summary of patient demographics (44 eyes of 36 patients) and baseline characteristics

<i>Patients</i>	
Age, years	69.2±7.4
Sex	
Male	65.9
Female	34.1
<i>Eyes</i>	
Duration of DME, years	3.3±1.9
Lens condition	
Phakic	31.8
Pseudophakic	63.6
Aphakic	4.5
Previous vitrectomy	
Yes	22.7
No	77.3
Previous treatment for DME	
Bevacizumab	18.6
Ranibizumab	53.5
Aflibercept	25.6
Triamcinolone	37.2
Dexamethasone	100.0
Concomitant IOP-lowering medication use, <i>n</i> (%)	
	8.0 (18.2)
Mean (range) follow-up, months	8.0 (1.0–23.0)

Values are mean ± SD or % unless otherwise indicated. DME, diabetic macular edema; IOP, intraocular pressure; SD, standard deviation.

change in central retinal thickness (CRT), and mean change in macular volume (MV). Safety evaluations included mean changes in intraocular pressure (IOP) and times to IOP medication as well as cataract extraction.

Data and Statistical Analysis

To establish significance between paired samples, either a Student's *t* test or Wilcoxon test were used (the latter when variables did not follow a normal distribution, as determined by the Shapiro-Wilk test). A *p* value of <0.05 was defined as statistically significant. All statistical analyses were performed with SPSS (Statistical Package for the Social Sciences) version 25.0 for Windows. The last observation carried forward (LOCF) method was used to handle missing follow-up data. Data are reported as mean ± standard deviation unless otherwise stated.

Results

Patient Population

Patient demographics and baseline characteristics are shown in Table 1. In total, 44 eyes (31.8% phakic, 63.6% pseudophakic, 4.5% aphakic) of 36 patients with persistent or recurrent DME were analyzed. At baseline, pa-

Fig. 1. Visual acuity mean change from baseline following FAc implantation.

tients had a mean age of 69.2 years, and approximately two-thirds (65.9%) were male. Mean duration of DME was 3.3 ± 1.9 years, and patients were followed up for a mean period of 8 ± 5.6 months. Almost one-quarter (22.7%) of eyes had undergone prior vitrectomy, and 8 eyes (18.2%) needed IOP-lowering treatments. Other than dexamethasone, which all patients had received (mean 1.89 injections; range 1–4 injections), the most common previous treatment for DME was ranibizumab (administered to 53.5% of eyes).

Efficacy

At baseline, VA was 41.93 ± 20.83 letters. At month 1 after injection of the FAc intravitreal implant, the mean VA letter gain from baseline was +6.82, and this increased to +13.02 letters (*p* = 0.005) at month 6 and +8.3 (*p* = 0.002) at LOCF (Fig. 1).

Similarly, significant improvements in CRT were noted following FAc intravitreal implant injection. At baseline, CRT was 542.81 ± 149.56 μm, and this decreased by 71.81 μm at month 1, 170.77 μm at month 6 (*p* = 0.001), and 121.46 μm at LOCF (*p* = 0.001) (Fig. 2).

A consistent mean decrease in MV (−0.69 mm³) from baseline (10.09 ± 1.99 mm³) to LOCF was observed, although this did not reach statistical significance (*p* = 0.062) (Fig. 3).

Safety

At baseline, IOP was 14.3 ± 4.81 mm Hg and remained relatively stable at month 1 (14.1 ± 3.8 mm Hg; a change of −0.25 mm Hg from baseline) and month 6 (15.2 ± 7.1 mm Hg; +0.88 mmHg from baseline; *p* = 0.268) (Fig. 4).

Fig. 2. Central retinal thickness mean change from baseline following FAc implantation.

Fig. 4. Intraocular pressure mean change from baseline following FAc implantation.

Fig. 3. Macular volume mean change from baseline FAc implantation.

Fig. 5. Scatter plot of intraocular pressure (IOP) at baseline versus LOCF for all eyes.

LOCF revealed a small (+1.86 mm Hg; $p = 0.036$) change in pressure (Fig. 4). Figure 5 plots baseline IOP against IOP at LOCF for all patient eyes and shows 4 cases where IOP changed by ≥ 10 mm Hg from baseline levels (also summarized in Table 2). In 2 of these cases IOP was managed with IOP-lowering drops prior to administration of the FAc implant and one of the patient eyes then underwent IOP-lowering surgery at month 6. This patient was previously diagnosed with glaucoma. Of the remaining 2 cases, IOP was being managed with IOP-lowering drops, respectively, from months 12 and 15. At baseline, in the total group, there were 8 cases where IOP was being managed with IOP-lowering drops (in the majority of cases – 87.5% – with one to two drops of topical medication), and

Table 2. Mean IOP and treatments at baseline and LOCF ($n = 44$ eyes)

Parameter	Baseline	LOCF
IOP		
≥ 21 mm Hg	3	6
≥ 25 mm Hg	2	4
≥ 30 mm Hg	1	1
Change in IOP ≥ 10 mm Hg from baseline	0	4
IOP drops	8	11
IOP surgery	0	1

Values are number of eyes. IOP, intraocular pressure.

at LOCF there were 11 cases (i.e., 3 new cases during the follow-up period). On average, the time to first IOP-lowering drop was 3 months (range, 1–12 months) after injection of the FAc implant.

A total of 14 eyes (31.8%) were phakic at baseline. During the period of follow-up 6 of these eyes (42.9%) underwent cataract surgery which occurred on average at 6.7 months (range, 1–15 months) after injection of the FAc implant.

Discussion

In this retrospective, real-world study in patients with DME that persisted or recurred despite treatment, the injection of a single FAc intravitreal implant after an intravitreal injection of dexamethasone significantly improved VA and CRT outcomes. Safety signals were consistent with corticosteroid class effects, with small elevations in IOP that were controlled with topical medication in most cases. These results show the effectiveness and safety of the FAc intravitreal implant after a prior dexamethasone implant and are consistent with the previously findings reported [23]. Furthermore, the current findings are consistent with those reported in real-world clinical practices.

Previously reported RCTs show that the FAc intravitreal implant is efficacious in patients with persistent or recurrent DME, irrespective of lens status, for up to 36 months [10, 24, 25]. In real clinical practice, patients who received the FAc intravitreal implant had continuous and sustained exposure to treatment, irrespective of vitreous status, and achieved both functional and anatomical improvements [26]. While formal subgroup analyses were not done, outcomes in vitrectomized eyes in this study appear similar to those reported in the pivotal FAME studies, in which previously vitrectomized eyes were excluded [26]. Vitrectomy appears to increase both the distribution speed of an applied drug throughout the eye and the clearance of anti-VEGF agents and corticosteroids (triamcinolone); the latter effect can reduce drug exposure and impact on the success of anti-VEGF and corticosteroid treatment [26]. Such negative effects have not been observed to any clinically meaningful extent with the FAc intravitreal implant. Further real-world experience from the UK multicenter Medisoft audit study, the US Retrospective Chart Review in Patients Receiving ILUVIEN study (USER study), the ILUVIEN Registry Safety Study (IRISS), and the Pilot Study on the Effect and Safety of ILUVIEN® in Chronic Diabetic Macular Edema

Patients (RESPOND study) in Portugal, confirms the safety profile of the FAc intravitreal implant and supports the findings of the Fluocinolone Acetate for Macular Edema (FAME) studies [27–30]. In the Medisoft audit study, while overall IOP-related emergent events were observed at a similar frequency to those in the FAME studies, no adverse events were seen in patients with prior steroid exposure and no prior IOP events [27]. This finding supports the use of a prior steroid challenge to assess IOP responses and is the basis of the licensed indication in the US (i.e., the FAc implant is indicated for patients with DME who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in IOP) [21, 30]. The mitigating effect of the requirement for prior steroid challenge on IOP responses is evident from the USER study: fewer IOP events were reported after FAc implantation in the USER study (in which all patients had received a course of prior corticosteroids) than in the FAME study [30]. Similarly, in the IRISS study, mean IOP for the overall population remained within the normal range throughout the follow-up period, and more than three-quarters of patients required no IOP-lowering therapy following treatment with the FAc implant [28]. These findings have been replicated in several other center-specific studies, even including patients with more advanced disease than those studied in the FAME trial [22, 31]. Regarding the presence of cataract, we note that in Portugal the use of the FAc implant is not restricted by lens status, unlike the UK, where only eyes with a pseudophakic lens can be treated. Hence, the percentage of phakic eyes in the current study were higher than in the IRISS study (i.e., 31.8 vs. 16.4%, respectively) [28]. In our study, in the majority of cases (5 of 6) cataract surgery was conducted within the first year after the FAc implant was administered, providing new information on the timing of cataract extractions. Indeed, Yang et al. [32] showed that the decline in mean best-corrected VA associated with cataract development reached a minimum at around 18 months, suggesting that in real-world practice an earlier cataract extraction may be beneficial.

The administration of the FAc intravitreal implant soon after a suboptimal response to anti-VEGF injections (e.g., after 3–4 injections without positive anatomic gains [11]) may be considered earlier in the treatment of DME to avoid recurrences of edema, and could produce better long-term visual outcomes for patients [27]. Choosing when to switch to the FAc intravitreal implant can be highly individualized and influenced by several factors such as prior vitrectomy, which can decrease the durability of biological activity of anti-VEGF agents [11], as well

as clinician choice [33]. In this study, the decisions to switch from the dexamethasone to the FAc implant included suboptimal response with dexamethasone, the desire for a less burdensome treatment, and the need for steroid challenge before receiving the FAc implant.

Nonadherence to treatment is a common problem in the management of patients with DME and leads to poorer outcomes [34, 35]. The high frequency of anti-VEGF injections constitutes a heavy burden for patients and their families [11, 36]. Patients must also attend consultations with various other specialists, which may be a further barrier to follow-up [36]. A single FAc intravitreal implant has been designed to deliver inflammation-suppressing FAc that lasts up to 3 years. Experience from the UK suggests that this helps to decrease the clinical, healthcare, and patient burdens of frequent injections and visits [37]. Reducing these burdens could improve the quality of life of patients and caregivers, as well as treatment compliance [37].

As well as offering effectiveness and clinical benefits, the FAc implant has also been found to reduce healthcare usage in the 12 months after implantation, compared with the preceding 12 months in the same patient. Total costs were higher in the 12 months after implantation due to the cost of the implant itself, but it is possible that the FAc implant may cost less than its alternatives over its 3-year lifespan [38]. In support of these findings, two cost analysis models from the UK found that over 3 years of treatment, a single FAc implant offers considerable cost savings compared with ranibizumab (in phakic and pseudophakic eyes) [39] and aflibercept monotherapy (in phakic eyes) [40]. However, whether these findings also apply to the healthcare system in Portugal is not known.

The limitations of this study included its retrospective design, which increases the potential for selection bias and confounding; the relatively small study sample, which limits the generalizability of the findings; and the use of the LOCF method when the mean follow-up period was relatively short (8 months). Additionally, as this was a real-world study, VA rather than best-corrected VA was measured, which may have underestimated the real functional gain.

Conclusions

The FAc intravitreal implant is an effective treatment option for patients previously treated with the short-acting dexamethasone implant. FAc significantly improves VA and edema in patients with recurrent DME, with safety

signals consistent with corticosteroid class effects. Physicians and patients therefore have the choice to use the FAc implant earlier in the DME treatment process should they wish, and doing so may reduce the burden of the frequency of repeated injections for both patients and clinical staff.

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Statement of Ethics

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki [41], International Conference on Harmonization Good Clinical Practice Guidelines [42], and all applicable country-specific regulatory requirements. The subjects gave their informed consent and the study protocol was approved by each local ethics committee.

Disclosure Statement

Dr. Vaz-Pereira reports advisory board honoraria from Bayer and Novartis and travel grants from Alimera, Allergan, Novartis, and Bayer. Dr. Castro-de-Sousa reports consulting honoraria from Zeiss and Alcon and travel grants from Alimera, Alcon, and Zeiss. Dr. Martins reports advisory board honoraria from Novartis and travel grants from Alimera, Allergan, and Bayer. Dr. Prates Canelas has received travel grants from Alimera, Allergan, Novartis, and Bayer. Dr. Reis has received travel grants from Alimera, Allergan, and Bayer. Dr. Sampaio, Dr. Urbano, and Dr. Kaku report no conflicts of interest. Dr. Nascimento reports advisory board honoraria and travel grants from Alimera, Allergan, Novartis, Bayer, and Bausch + Lomb. Dr. Marques-Neves reports advisory board honoraria from Novartis and travel grants from Alimera.

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Author Contributions

All authors made substantial contributions to the conception, design, analysis, and interpretation of data for this study, and contributed to writing and revising the manuscript. All approved the final version.

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