Persistent or Recurrent Diabetic Macular Edema After Fluocinolone Acetonide 0.19 mg Implant: Risk Factors and Management

MARIA VITTORIA CICINELLI, ALESSANDRO RABIOLO, PIERO ZOLLET, LUIGI CAPONE, ROSANGELA LATTANZIO, AND FRANCESCO BANDELLO

• PURPOSE: To investigate baseline characteristics of patients undergoing additional antivascular endothelial growth factor (VEGF) injections for residual or recurrent diabetic macular edema (DME) in the first year after 0.19-mg fluocinolone acetonide (FAc) implant.

• DESIGN: Prospective cohort study.

• METHODS: Ninety-four eyes of 66 patients received an FAc implant. Eyes with persistent or recurrent DME were managed with pro re nata anti-VEGF agents. Demographic data and medical history were collected at baseline. Best-corrected visual acuity and central macular thickness were measured every 2 months. The 3 outcomes explored were 1) the risk factors for administration of additional anti-VEGF agents, 2) the interval from FAc to first anti-VEGF injection; and 3) the number of anti-VEGF doses required to maintain regression of DME.

• RESULTS: Eighteen eyes (19.1%) of 13 patients received 1.3 ± 0.6 anti-VEGF injections. These eyes had significantly thicker central macular thickness at baseline and over the entire follow-up period ($P < .001$); best-corrected visual acuity was similar at every time point to eyes that were not receiving extra DME treatments. Eyes without preexistent panretinal photocoagulation (PRP) had a higher risk to undergo supplemental treatments (hazard ratio 1.5 [95% confidence interval 1.1-2.5, $P = .03$). The interval between FAc implant and the first anti-VEGF had a significant linear positive relationship with the number of dexamethasone implants before FAc implant ($P = .002$, $R^2 = 0.47$). No association was found between baseline factors and the number of injections given.

• CONCLUSION: Anti-VEGF agents are efficient treatment to maintain visual acuity in residual/recurrent DME after FAc. Patients with higher baseline central macular thickness and with no previous central macular thickness are more likely to require additional treatments to control DME. (Am J Ophthalmol 2020;215:14–24.

DIABETIC MACULAR EDEMA (DME) IS A MULTIFACTORIAL disease, and its pathogenesis involves complex vascular, inflammatory, and neurodegenerative mechanisms.[1–4] Vascular endothelial growth factor (VEGF) has been a valid therapeutic target in the last decade. The use of intravitreal VEGF antagonists, alone or in association with laser therapy, is an effective first-line strategy in terms of visual recovery and fluid reduction in patients with DME.[5–7] Intravitreal sustained-release corticosteroid implants are an alternative therapeutic option in patients with DME and are currently recommended in the case of unsatisfactory response to anti-VEGF therapy, in naïve pseudophakic or vitrectomized eyes at low risk for glaucoma, in patients with recent cardiovascular events, and in cases of poor compliance to an intense follow-up regimen.[8–10]

Both dexamethasone (DEX) 700 μg bioerodable (Ozurdex; Allergan, Inc, Irvine, California, USA) and fluocinolone acetonide (FAc) 0.19 mg non-bioerodable (Iluvien; Alimera Sciences, Inc, Alpharetta, Georgia, USA) drug-delivery systems (DDSs) are approved for the treatment of vision impairment associated with DME.[11,12] The efficacy of the 0.19-mg FAc implant in DME was demonstrated in the Fluocinolone Acetonide for Diabetic Macular Edema (FAME) A and B trials with functional outcome sustained up to 36 months.[12,13] Real-life studies and cost effective analyses have confirmed the long-term functional and anatomic effectiveness of FAc in DME with a substantial lowering of the treatment burden.[14–20]

In both the multicentric trials and the real-life registries, cases of persistent or recurrent DME in the first year after FAc have been recorded.[12] The clinical profile of patients experiencing persistence or reappearance of intraretinal and/or subretinal fluid has not been outlined. Also, details about the therapeutic outcomes of additional interventions after FAc implant are missing. In our practice, patients with persistent or recurrent DME after FAc are managed with anti-VEGF agents, administered with a pro re nata approach with a minimal interval of 4 weeks between consecutive injections.

AJO.com Supplemental Material available at AJO.com.

Accepted for publication Mar 16, 2020.

From the School of Medicine (M.V.C., A.R., P.Z., L.C., R.L., F.B.), Vita-Salute San Raffaele University, and the Department of Ophthalmology (M.V.C., F.B.), Istituto di Ricovero e Cura a Carattere Scientifico San Raffaele Scientific Institute, Milan, Italy.

Inquiries to Maria Vittoria Cicinelli, Department of Ophthalmology, University Vita-Salute, IRCCS Ospedale San Raffaele, via Olgettina 60, 20132, Milan, Italy; e-mail: cicinelli.mariavittoria@hsr.it

0002-9394/$36.00
https://doi.org/10.1016/j.ajo.2020.03.016

The purpose of the present study is to investigate the baseline demographic and clinical characteristics of patients undergoing additional anti-VEGF injections in the first year after FAc implant. The secondary aim is to clarify the functional and anatomical responses to additional anti-VEGF therapies. Finally, we aim to identify the factors predisposing to the need for additional treatments and those influencing the interval between the FAc implant and the first anti-VEGF retreatment.

METHODS

THIS WAS A PROSPECTIVE COHORT STUDY OF PATIENTS who received an FAc implant (Iluvien) for DME at the Medical Retina Unit of the Department of Ophthalmology, Ospedale San Raffaele, Milan, Italy, from July 2017 to October 2019. The study followed the tenets of the Declaration of Helsinki for research involving human subjects and all the subjects signed written consent approved by the local institutional review board before enrollment.

Inclusion criteria were: 1) age ≥18 years, 2) a diagnosis of diabetes mellitus (DM), either type 1 or type 2, and 3) a history of DME previously treated with intravitreal implant of FAc according to the Italian guidelines (ie, refractory DME in pseudophakic patients).[21] Exclusion criteria were 1) macular edema secondary to other causes than DME (eg, retinal vein occlusion, age-related macular degeneration, pseudophakic macular edema); 2) media opacities limiting fundus examination and imaging; 3) any intraocular surgery ≤6 months before FAc implant injection; and 4) uncontrolled glaucoma, defined as intraocular pressure above target despite maximal anti-glaucoma treatment in the study eye. In patients with bilateral DME, both eyes were included in the study if all the inclusion and exclusion criteria were fulfilled.

Demographic data (age, gender, and race), detailed medical history (duration and type of DM, glycated hemoglobin), and ophthalmologic history (stage of nonproliferative diabetic retinopathy or proliferative diabetic retinopathy,[22] duration of DME, and previous treatments) were collected at baseline. Patients were followed every 2 months after FAc implant injection up to 12 months, and then every 4 months thereafter. At each visit, patients underwent best-corrected visual acuity (BCVA) measurement on Early Treatment Diabetic Retinopathy Study chart, biomicroscopy, intraocular pressure measured by Goldmann applanation tonometry, dilated fundus examination, and spectral-domain optical coherence tomography on Spectralis HRA (Heidelberg Engineering; Heidelberg, Germany). Central macular thickness (CMT) was automatically obtained through a 19-line horizontal raster centered on the fovea.

At baseline, the horizontal B-scan passing through the fovea was evaluated for the following features: 1) disruption of the ellipsoid zone (EZ) or external limiting membrane (ELM); 2) presence of disorganization of the inner retinal layers; 3) presence of epiretinal membrane; 4) presence and number of hyperreflective intraretinal spots (HRSs); and 5) presence of subfoveal fluid. EZ and ELM were defined as disrupted or absent if they were partially or completely interrupted, respectively.[23] HRSs were manually counted. Two readers (M.V.C., L.C.) analyzed the images; in case of disagreement, a third ophthalmologist (R.L.) was asked.

In case of persistent (residual intraretinal or subfoveal fluid) or recurrent (new intraretinal or subfoveal fluid) DME, anti-VEGF agents were prescribed starting from 4 months after FAc injection. All patients received 0.5 mg/0.05 mL of ranibizumab (Lucentis; Novartis Pharma AG, Basel, Switzerland, and Genentech Inc, South San Francisco, California, USA) or 2 mg/0.05 mL of aflibercept (Eylea, VEGF Trap-Eye; Regeneron Inc, New York, New York, USA), according to the preference of the physician treating the patient. Appropriate sterile draping, periocular surface disinfection with 10% povidone-iodine, and conjunctival disinfection with 5% povidone-iodine were performed in a major or minor operating room. Perception of hand motion was checked at the end of the procedure. Patients were re-evaluated 4 weeks after each anti-VEGF treatment. Repeated anti-VEGF administration was driven by the persistence of DME on spectral-domain optical coherence tomography. If multiple anti-VEGF injections were administered, the number of anti-VEGF injections was recorded.

• **STATISTICAL ANALYSIS:** Statistical calculations were performed with the open-source programming language R.[24] Descriptive statistics were reported as the mean ± standard deviation (SD) or frequency and proportions for continuous or categorical variables, respectively. Visual acuity was converted to logarithm of minimal angle of resolution. The last observation carried forward method was used to impute missing data during the follow-up.

The primary goal of this study was to compare the baseline characteristics between patients with persistent or recurrent DME who received anti-VEGF in the first year after FAc implant and those who had a sustained response to FAc and did not require additional treatments. Linear and logistic regression models were respectively used to compare continuous and categorical variables between the 2 groups.

The visual acuity and CMT changes between eyes receiving additional treatment and those not receiving additional treatments over the follow-up were visually inspected with spaghetti plots and then formally tested with a linear mixed model. Within the model, the various time points and group effect (additional vs nonadditional treatments) were the fixed factors, and the random effect

TABLE 1. Baseline Demographic and Clinical Characteristics of Included Patients and Comparison Between Eyes Receiving Additional Anti–Vascular Endothelial Growth Factor Injections and Those Who Did Not Receive Any Additional Treatment

	All	No Additional Anti-VEGF	Additional Anti-VEGF	*P* Value
No. of eyes (no. of patients)	94 (66)	76 (53)	18 (13)	
Age, years, mean ± SD	68.4 ± 9.4	67.6 ± 9.8	71.4 ± 5.6	.03[a]
Gender, n (%)				.4
Male	58 (61.7)	49 (64.5)	9 (50)	
Female	59 (38.3)	9 (35.5)	9 (50)	
Ethnicity, n (%)				
Caucasian	94 (100)			
Type of diabetes mellitus, n (%)				.5
Type 1	29 (30.9)	25 (32.9)	4 (22.2)	
Type 2	65 (69.1)	51 (67.1)	14 (77.8)	
Duration of DM, years, mean ± SD	21.7 ± 12.6	21.8 ± 13.4	21.5 ± 8.5	.9
Duration of DME, n (%)				.9
<3 years	27 (28.7)	22 (28.9)	5 (27.8)	
≥3 years	67 (71.3)	54 (71.1)	13 (72.2)	
HbA1c, %, mean ± SD	7 ± 0.9	6.9 ± 0.8	7.2 ± 1.1	.4
Stage of DR, n (%)				.2
NPDR	64 (68.1)	49 (64.5)	15 (83.3)	
PDR	30 (31.9)	27 (35.5)	3 (16.7)	
Previous vitrectomy, n (%)	13 (13.8)	10 (13.2)	3 (16.7)	.9
Previous PRP, n (%)	47 (50.5)	42 (56)	5 (27.8)	.04[a]
Previous DME treatments, n (%)				
Anti-VEGF	75 (79.8)	63 (82.9)	12 (66.7)	.2
DEX implant	85 (90.4)	67 (88.2)	18 (100)	.2
Focal/grid laser	42 (44.7)	31 (40.8)	11 (61.1)	.2
No. of previous anti-VEGF, mean ± SD	7.4 ± 7.4	7.4 ± 7.8	6.9 ± 4.6	.8
No. of previous DEX implants, mean ± SD	4.3 ± 3.6	4.2 ± 3.7	4.7 ± 3.5	.6
OCT features, n (%)				
Hyperreflective spots >20	74 (78.7)	58 (76.3)	16 (88.9)	.1
Epiretinal membrane	36 (38.3)	27 (35.5)	9 (50)	.7
DRIL	7 (7.4)	6 (7.9)	1 (5.6)	.9
Subretinal fluid	15 (16)	11 (14.5)	3 (16.7)	.8
EZ/ELM disruption, n (%)				.7
Disrupted	45 (47.9)	36 (47.4)	9 (50)	
Absent	14 (14.9)	10 (13.2)	4 (22.2)	

CI = confidence interval; CMT = central macular thickness; DEX = dexamethasone; DM = diabetes mellitus; DME = diabetic macular edema; DR = diabetic retinopathy; DRIL = disorganization of the inner retinal layer; EZ/ELM = ellipsoid zone/external limiting membrane; HbA1c = glycated; HR = hazard ratio; logMAR = logarithm of minimal angle of resolution; N/A = not applicable (all the patients who underwent additional anti-VEGF received previous DEX); NPDR = nonproliferative diabetic retinopathy; OCT = optical coherence tomography; PDR = proliferative diabetic retinopathy; PRP = panretinal photocoagulation; TPPV = trans pars plana vitrectomy.

[a]Statistically significant.

had a nested structure and included the patient and eye identification numbers to account for within-patient and within-eye correlations, respectively. Pairwise comparisons for BCVA or CMT at each time point (0, 2, 4, 6, 8, 10, and 12 months) stratified as a function of the treatment status (additional anti-VEGF vs no additional anti-VEGF) were investigated with the Tukey test. To investigate the fluctuation over time, BCVA and CMT amplitude changes were calculated as the averaged differences between BCVA and CMT values at successive visits, respectively.[25]

Three outcomes were explored: 1) risk factors for administration of additional anti-VEGF agents, 2) interval from FAc to the first anti-VEGF injection, and 3) number of anti-VEGF doses required to maintain regression of DME and interval between consecutive anti-VEGF injections. For outcome 1, the variables associated with the risk of administration of additional anti-VEGF agents were investigated using univariable and multivariable mixed-effect Cox proportional hazard regression models. For each variable, hazard ratios (HRs) and 95% confidence intervals

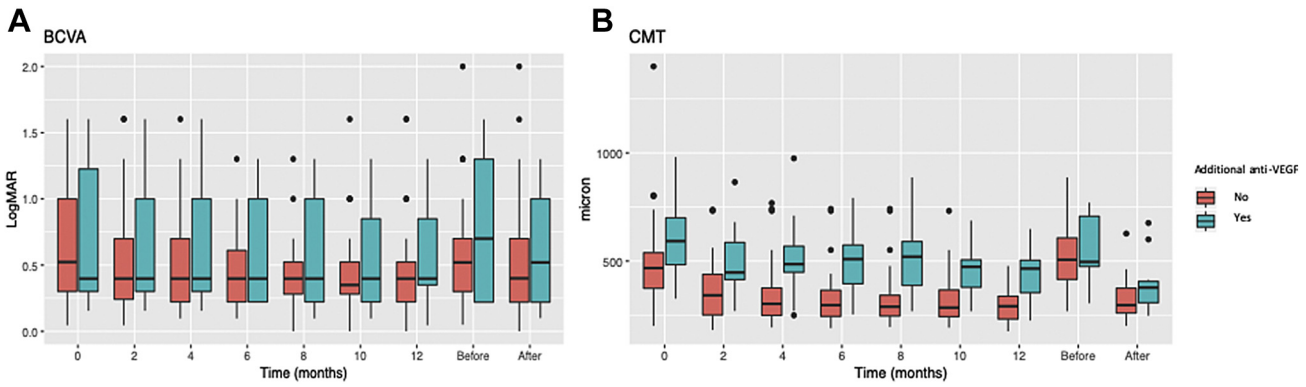

FIGURE 1. Best-corrected visual acuity (BCVA) (A) and central macular thickness (CMT) (B) at the time of fluocinolone acetonide 0.19 mg implant injection (time 0) and throughout 12 months of follow-up. Patients are stratified according to the occurrence of additional anti–vascular endothelial growth factor (VEGF) injections. The bolded horizontal line inside the boxplot represents the median value. Pooled BCVA and CMT before and 1 month after intravitreal injection of anti-VEGF agents are also shown.

(CIs) were reported. For significant risk factors, Kaplan-Meier curves for receiving additional anti-VEGF after FAc implant were generated, and differences between the curves were tested with the log -rank test.

Age, gender, systemic hypertension, type and duration of DM, glycated hemoglobin, stage of diabetic retinopathy, duration of DME (<3 years/≥3years), history of vitrectomy, presence of panretinal photocoagulation (PRP), the nature and the number of previous DME treatments (ie, intravitreal DEX and/or anti-VEGF or macular grid/focal laser), baseline BCVA, and baseline CMT were included as fixed factors. Morphologic optical coherence tomography features were also considered as fixed factors: HRS >20, presence of epiretinal membrane, presence of disorganization of the inner retinal layers, ELM/EZ status (normal/interrupted/absent), and presence of subfoveal fluid. Factors with a P value ≤.05 at the univariable analysis were included in a multivariable model.

A linear mixed model was used for outcomes 2 and 3. Age, gender, systemic hypertension, type and duration of DM, glycated hemoglobin, stage of diabetic retinopathy, duration of DME (<3 years/≥3years), history of vitrectomy, presence of PRP, the nature and the number of previous DME treatments (ie, intravitreal DEX and/or anti-VEGF or macular grid/focal laser), baseline BCVA, baseline CMT, duration of follow-up, HRS >20, presence of epiretinal membrane, presence of disorganization of the inner retinal layers, ELM/EZ status (normal/interrupted/absent), and presence of subfoveal fluid were included as fixed factors. The patient identification number was included as the random effect to account for within-subject correlations because of the inclusion of both eyes of the same patients. Factors with a P value ≤.05 at the univariable analysis were included in a multivariable model.

The cutoff point for statistical significance was set at $P < .05$.

RESULTS

• **BASELINE CHARACTERISTICS:** A total of 94 eyes of 66 patients were enrolled; the mean follow-up was 12.4 ± 2.2 months. Main demographic and baseline clinical features are listed in Table 1. Overall, 18 eyes (19.1%) of 13 patients received additional anti-VEGF injections. No patients had retreatment with the FAc implant, and no adverse events related to anti-VEGF injections were recorded over the follow-up. The subjects undergoing retreatment were significantly older ($P = .03$) and a lower number of them had received PRP before receiving the FAc implant with respect to those not receiving additional anti-VEGF ($P = .04$).

• **VISUAL AND MORPHOLOGIC RESPONSE TO FAC DURING THE FOLLOW-UP:** Overall, both BCVA and CMT significantly improved during the first 12 months (Supplemental Table 1A). There was a significant reduction in the amplitude of CMT changes across the follow-up (Supplemental Table 1A).

The BCVA at baseline and over 12 months after FAc implant was similar among patients who received additional anti-VEGF and those who did not receive extra treatments (Supplemental Table 1B, Figure 1A). Patients undergoing additional anti-VEGF had a significantly thicker CMT at baseline and over the entire follow-up (Supplemental Table 1C, Figure 1B).

Patients who did not receive extra DME treatments showed a persistently low CMT from month 2 to month 12; fluctuation in CMT was low (Figure 2A). Conversely, patients receiving additional anti-VEGF showed a heterogeneous behavior. In some eyes, the CMT was persistently high after FAc implant, with a certain degree of fluctuation over time. The remaining eyes displayed an initial decrease in CMT and a subsequent rebound edema (Figure 2B).

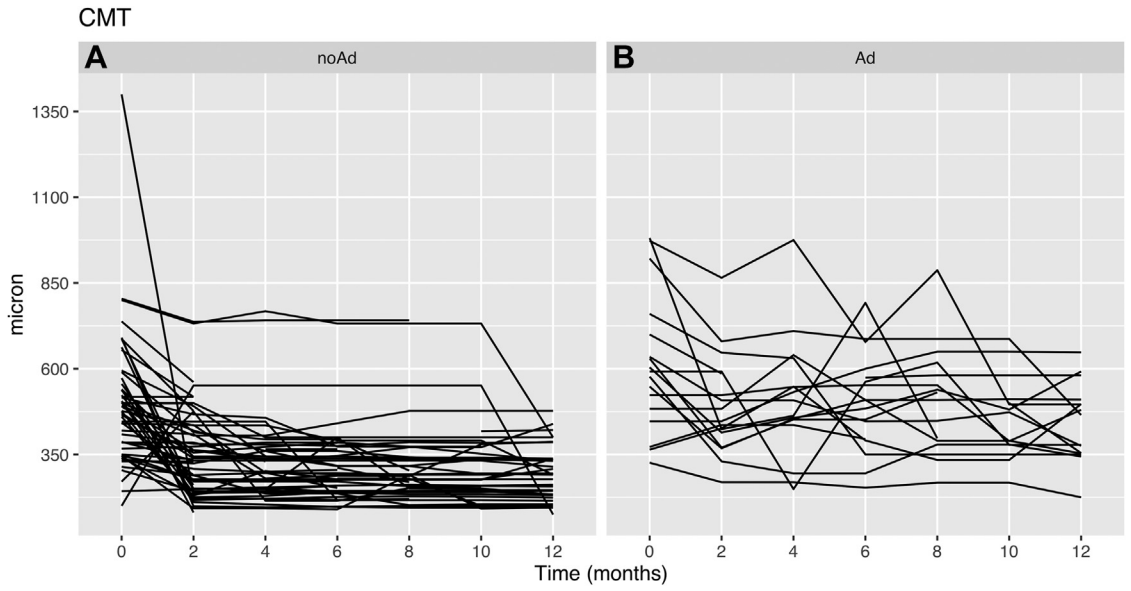

FIGURE 2. Spaghetti plot exploring the longitudinal changes in central macular thickness (CMT) after receiving the fluocinolone acetonide implant. Patients were divided into (A) those not receiving additional anti–vascular endothelial growth factor agents (noAd) and (B) those receiving anti–vascular endothelial growth factor injections (Ad).

Overall, BCVA significantly improved (0.6 ± 0.4 vs 0.5 ± 0.4, $P = .02$) and CMT significantly decreased (539.2 ± 147 vs 419 ± 100.2, $P = .002$) 4 weeks after anti-VEGF administration (Figure 1A, B).

• **OUTCOME 1: RISK OF ADMINISTRATION OF ADDITIONAL ANTI-VEGF AGENTS:** Eyes without pre-existent PRP had a higher risk to undergo supplemental anti-VEGF treatments (HR 1.5 [95% CI 1.1-2.5], $P = .03$, Figure 3A). Higher CMT at the time of FAc implant administration was also a significant risk factor of the need for extra treatment for DME (HR 1.7 [95% CI 1.1-3], $P = .04$, Figure 3B). None of the baseline optical coherence tomography features investigated was associated with the probability to receive additional treatments (Table 2).

• **OUTCOME 2: INTERVAL FROM FAC TO THE FIRST ANTI-VEGF INJECTION:** The mean interval between FAc implant administration and the first anti-VEGF was 7.9 ± 2.3 months (range 4-18 months). A higher number of previous DEX received before FAc implant and a history of type 1 DM were associated with a longer interval between FAc and need for additional treatment ($P = .04$; Table 3).

The interval between FAc implant and the first anti-VEGF had a strong linear positive relationship with the number of DEX implant injections experienced before FAc implant ($P = .002$, $R^2 = 0.47$, Supplemental Figure 1). Eyes that had undergone macular laser treatment before FAc administration received additional treatments for DME after a significantly longer time compared with those who had never undergone macular laser treatment ($P = .02$, Supplemental Figure 1).

• **OUTCOME 3: NUMBER OF ANTI-VEGF DOSES ADMINISTERED AFTER FAC:** Patients with residual/recurrent DME underwent a mean number of injections of 1.3 ± 0.6 (Figure 4); 14 eyes (78%) received 1 injection, 2 eyes (11%) received 2 injections, and 2 eyes received 3 injections (11%). The mean interval between consecutive anti-VEGF injection was 91.3 ± 37.8 days. No association was found between baseline factors and the number of injections given.

DISCUSSION

IN THIS STUDY, WE EVALUATED THE OUTCOMES OF FAC IN A cohort of patients with refractory DME and explored factors associated with the risk of undergoing supplemental treatments in addition to FAc. We found that eyes without pre-existent PRP and those with a higher CMT at the time of FAc administration had a higher risk to undergo supplemental treatments over the follow-up. Anti-VEGF was as an efficient treatment in residual/recurrent DME, leading to both visual and morphologic improvement. The more DEX injections received before FAc the longer the interval between FAc and the need for additional treatments for DME.

To the best of our knowledge, this is the first study focusing on patients with persistent or recurrent DME in the first year after FAc. Focal/grid laser treatment was the

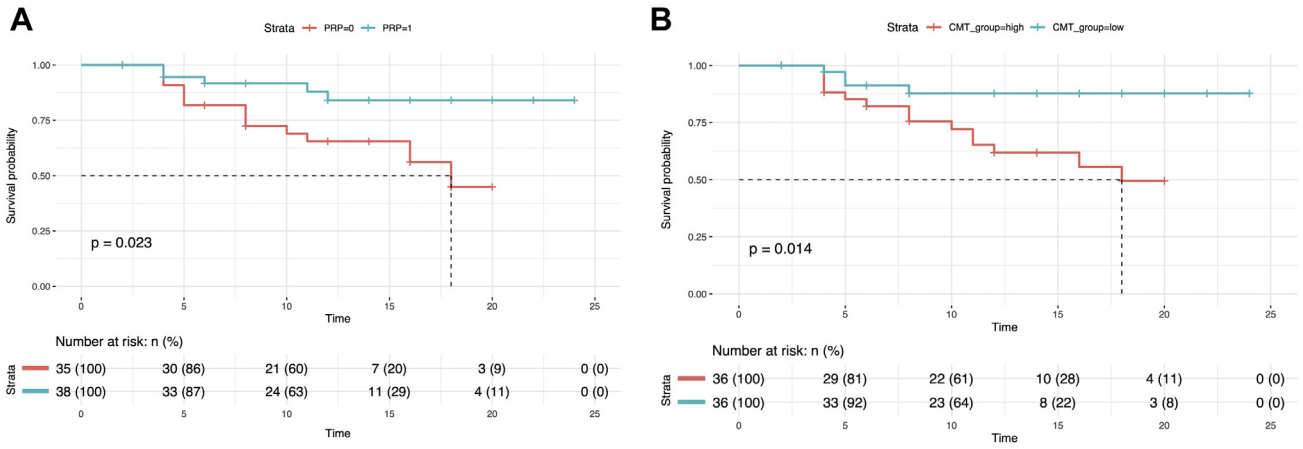

FIGURE 3. Risk factors for additional diabetic macular edema treatment and correlation between dexamethasone implant injections before fluocinolone acetonide implant. (A) Kaplan-Meier plot of probability to receive additional anti–vascular endothelial growth factor injections after fluocinolone acetonide implant according to the presence of panretinal photocoagulation (PRP). Log-rank test *P* value is presented. Time is expressed in months. (B) Kaplan-Meier plot of probability to receive additional anti–vascular endothelial growth factor injections after fluocinolone acetonide implant according to the baseline central macular thickness (CMT), stratified according to the median value (476.5 mm). Log-rank test *P* value is presented. Time is expressed in months.

only allowed rescue treatment in the FAME study; however, 15.2% and 16.3% of patients in the low- and high-dose FAc arms, respectively, underwent off-protocol anti-VEGF injections during the trial.[12] Real-life registries report a rate of retreatment for DME after FAc of 30%-37%,[15–18,20] which is slightly higher than our cohort (19.1%): this disparity might be related to the different duration of follow-up (minimum 24 months in the published studies). Nevertheless, none of these authors have further investigated the baseline characteristics predictive for additional treatments to control DME.

We found that patients receiving additional anti-VEGF injections were significantly older than those who did not require extra anti-DME therapies. Older patients have a poorer response to both anti-VEGF agents[26] and corticosteroids[27]; according to the published studies, older people had an inferior visual gain and a worse final BCVA with respect to younger ones, irrespective of the duration of diabetes or the chronicity of DME.[26,27]

The risk of additional treatments for DME was not influenced by the chronicity of DME. This might be in contrast with the open-label study extension of the RISE/RIDE studies, according to which patients with a longer duration of DME at baseline required more anti-VEGF injections during the study period.[28] Nevertheless, it may also suggest that the duration of DME is not the primary drive in the response to FAc.[16,18,29,30] Future analysis with a longer follow-up will help to clarify the exact relationship between DME duration and clinical response to FAc implant.

A smaller number of eyes in the additional treatment group had received PRP before FAc implant. The role of nonperfused or underperfused hypoxic retina in upregulating the hypoxia-inducible factor transcriptional cascade, leading to secretion of vasoactive cytokines and, ultimately, sustaining chronic DME is well-known.[31] Indeed, many authors have proposed that PRP may aid in lessening the burden of anti-VEGF injections for DME control, with various outcomes.[32–35] A quantitative evaluation of the extent of retinal nonperfusion in patients undergoing additional DME treatment after FAc implant would help in confirming our preliminary results.

Patients who underwent additional treatments after FAc had a significantly thicker macula at the baseline and subsequent follow-up visits; patients with a high CMT at FAc administration should be properly counseled about the potential need for additional treatment over the first year. The visual function was similar between the 2 groups throughout all visits, as previously reported.[16] This finding confirms that visual acuity does not strictly correlate with the macular thickness[36,37] and shows that residual or recurrent DME after FAc administration does not threaten the final visual outcome on long-term follow-up.

Both DEX and FAc steroid implants have shown efficacy in lowering CMT, which is considered the most clinically reliable anatomic parameter for monitoring DME.[36] However, the peculiar pharmacokinetics of the FAc implant seems to be more suitable for chronic DME with respect to the short-term, pulsed kinetics of DEX implant.[38] According to the current concepts in the pathophysiology of the disease, diabetic maculopathy occurs once the concentration of inflammatory cytokines goes beyond a certain threshold of local tolerance.[39] Over this threshold, the inflammatory microenvironment induces a series of clinical events, including intraretinal and subretinal fluid

TABLE 2. Results of Univariable and Multivariable Cox Regression Analysis for Factors Associated with the Risk to Receive Additional Anti–Vascular Endothelial Growth Factor for Residual or Recurrent Diabetic Macular Edema After Fluocinolone Acetonide 0.19 mg Implant

	Univariable		Multivariable	
Variable	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age, years	1.1 (1-1.1)	.2		
Gender, male	0.9 (0.6-1.5)	.7		
Hypertension	0.7 (0.5-1.3)	.3		
HbA1c, %	1.16 (0.7-2)	.6		
DM type 1	0.7 (0.4-1.3)	.3		
DM duration, years	1.4 (0.8-2.6)	.2		
DR type, NPDR	1.7 (0.9-3.1)	.1		
Duration of DME >3 years	1.2 (0.7-2)	.5		
Previous anti-VEGF exposure	1.6 (1-2.7)	.05		
No. of previous anti-VEGF	1 (0.6-1.8)	.9		
Previous DEX exposure	N/A			
No. of previous DEX	1.1 (0.7-1.7)	.7		
Previous macular laser	0.8 (0.5-1.3)	.3		
Previous TPPV	0.8 (0.4-1.4)	.4		
Previous PRP	1.8 (1.1-3)	.03[a]	1.5 (1.1-2.5)	.03[a]
Baseline BCVA, logMAR	1 (0.9-0.6)	.9		
Baseline CMT, mm	5.7 (1.2-25.9)	.02[a]	6 (1.04-34.5)	.04[a]
OCT features				
Hyperreflective spots >20	1.1 (0.5-2.3)	.8		
Epiretinal membrane	0.8 (0.5-1.2)	.2		
DRIL	1.3 (0.5-3.5)	.7		
ELM/EZ status, normal				
Disrupted	0.9 (0.4-1.8)	.7		
Absent	1 (0.5-1.8)	.9		
Subretinal fluid	0.8 (0.4-1.4)	.4		

CI = confidence interval; CMT = central macular thickness; DEX = dexamethasone; DM = diabetes mellitus; DME = diabetic macular edema; DR = diabetic retinopathy; DRIL = disorganization of the inner retinal layer; EZ/ELM = ellipsoid zone/external limiting membrane; HbA1c = glycated; HR = hazard ratio; logMAR = logarithm of minimal angle of resolution; N/A = not applicable (all the patients who underwent additional anti-VEGF received previous DEX); NPDR = nonproliferative diabetic retinopathy; OCT = optical coherence tomography; PDR = proliferative diabetic retinopathy; PRP = panretinal photocoagulation; TPPV = trans pars plana vitrectomy.

[a]Statistically significant.

accumulation, neuronal dysfunction, and microglia activation, which eventually leads to irreversible photoreceptor damage and visual loss.[40,41]

FAc implant exhibits zero-order drug release kinetics with a blunted drug peak and lower steady-state concentration, which can keep the local inflammatory response continuously in a "safe," subclinical range. The molecular bases of FAc implant clinically translate into a significantly decrease in CMT fluctuation[25] compared with the peculiar saw-tooth pattern of treatment effect observed after consecutive DEX injections.[42] Although we did not measure the area under the curve over the first-year of follow-up, our data showed stabilization of macular thickness over successive time points, as noticeable from a constant, progressive reduction in the data dispersion (Supplemental Table 1A, Figure 1B). This trend was noticeable in the overall cohort and the single groups (ie, eyes receiving additional anti-VEGF and those not receiving additional treatments), even though patients receiving additional anti-VEGF showed a higher degree of fluctuation over time. We speculate that the decreased oscillations in the amount of macular edema have a positive effect on photoreceptor function over time.

The interval between FAc implant and the first anti-VEGF injection correlated with the number of previous steroids intravitreal implants; we speculate that repeated DEX implant injections leads to sustained suppression of inflammatory cytokines and significant delay in DME recurrence.[43,44] In a parallel fashion, a recent comparison between DME patients directly shifted from anti-VEGF to FAc and those undergoing DEX implant before FAc administration has shown that eyes previously treated with DEX had a lower and deferred BCVA decline after FAc with respect to eyes never treated with DEX.[30]

TABLE 3. Results of Univariable and Multivariable Linear Regression Analysis for Factors Associated with the Interval Between Fluocinolone Acetonide 0.19 mg Implant and First Anti–Vascular Endothelial Growth Factor Injection for Residual or Recurrent Diabetic Macular Edema

	Univariable		Multivariable	
Variable	Estimate (SE)	*P* Value	Estimate (SE)	*P* Value
Age, years	−3.4 (0.03)	.6		
Gender, male	66.8 (66.1)	.3		
Hypertension	−121.6 (70.1)	.1		
HbA1c, %	−32.6 (32)	.9		
Diabetes mellitus type 1	−178.5 (69.8)	.02[a]	−120.8 (52.8)	.04[a]
Diabetes mellitus duration, years	5.2 (4)	.2		
DR type, NPDR	−69.4 (93.1)	.5		
Duration of DME >3 years	106.2 (69.7)	.2		
Previous anti-VEGF exposure	−78.3 (56.2)	.2		
No. of previous anti-VEGF	−8.8 (7.8)	.5		
Previous DEX exposure	N/A			
No. of previous DEX	25.5 (6.8)	.02[a]	20.2 (6.5)	.04[a]
Previous macular laser	121.7 (61.1)	.07		
Previous TPPV	−67.9 (93.1)	.6		
Previous PRP	−17.8 (75.7)	.8		
Baseline BCVA, logMAR	22.4 (62.2)	.7		
Baseline CMT, mm	165.4 (165.2)	.3		
Length of follow-up, months	24.5 (3.4)	.2		
OCT features				
Hyperreflective spots >20	125.4 (78.4)	.2		
Epiretinal membrane	0.9 (62.8)	.9		
DRIL	3.4 (141.1)	.9		
ELM/EZ status, normal				
Disrupted	87.3 (71)	.3		
Absent	158.1 (83.2)	.2		
Subretinal fluid	134 (58)	.08		

CI = confidence interval; CMT = central macular thickness; DEX = dexamethasone; DM = diabetes mellitus; DME = diabetic macular edema; DR = diabetic retinopathy; DRIL = disorganization of the inner retinal layer; EZ/ELM = ellipsoid zone/external limiting membrane; HbA1c = glycated; HR = hazard ratio; logMAR = logarithm of minimal angle of resolution; N/A = not applicable (all the patients who underwent additional anti-VEGF received previous DEX); NPDR = nonproliferative diabetic retinopathy; OCT = optical coherence tomography; PDR = proliferative diabetic retinopathy; PRP = panretinal photocoagulation; TPPV = trans pars plana vitrectomy.

Estimates for continuous variables are reported for each 1-unit increase unless specified otherwise.

[a]Statistically significant.

The mean number of anti-VEGF injections performed in the first year was similar to the cohort of Fusi-Rubiano and associates,[15] but inferior to the numbers reported in both randomized and real-life studies on anti-VEGF treatment alone.[45–47] These results are in line with the recent pharmacoeconomic evaluations, which support the cost effectiveness of FAc implant in DME.[48,49] FAc implant has been also associated with significant decrease in treatment frequency (from 1 treatment every 2.7 months to 1 treatment every 6 months, $P = .009$), even in the occurrence of residual or recurrent DME.[50] Despite the paucity of eyes receiving >1 anti-VEGF injection in our cohort in the first year of follow-up, the mean interval between consecutive anti-VEGF injections was longer (1 treatment every 3 months) than reported on anti-VEGF–only regimen. This finding may further indicate that continuous proangiogenic cytokine suppression is an effective strategy in lowering the burden of DME.

Because of the uncontrolled nature of our study, we cannot separately establish the role of anti-VEGF agents in the maintenance of visual acuity over the follow-up. The improvement in BCVA after anti-VEGF administration could be also related to a delayed response to FAc or a spontaneous fluctuation in the visual function (regression to the mean). Persistence of macular edema over the follow-up has been recognized as a negative prognostic factor for long-term visual acuity improvement after anti-VEGF therapy.[51] A longer follow-up analysis is needed to assess the influence of residual or recurrent DME on visual acuity after FAc.

In conclusion, a considerable number of patients needed additional treatments in the first year after receiving FAc

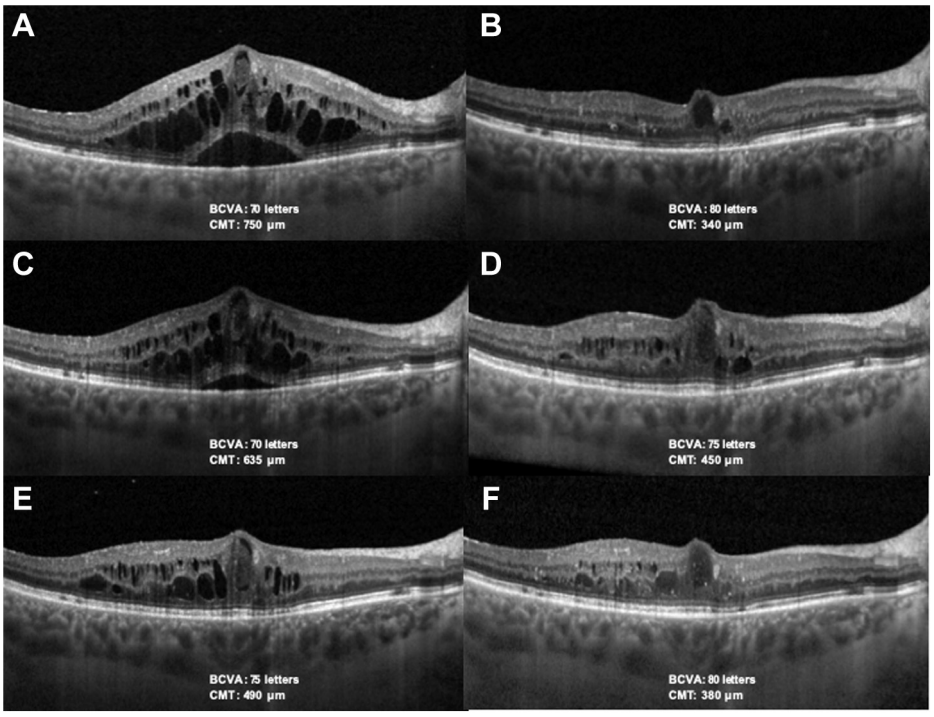

FIGURE 4. Sequential optical coherence tomography (OCT) scans of a 61-year-old pseudophakic woman suffering with type 2 diabetes mellitus for 15 years, complicated by nonproliferative diabetic retinopathy and a 7-year history of diabetic macular edema in both eyes. The right eye underwent 11 injections of anti–vascular endothelial growth factor (VEGF) agents, 6 dexamethasone (DEX) implants, and focal laser treatment before receiving fluocinolone acetonide (FAc) implant. For each time point, best-corrected visual acuity (BCVA) in Early Treatment Diabetic Retinopathy Study letters and central macular thickness (CMT) is shown. (A) OCT scan 30 days after the eleventh injection of anti-VEGF. The patient is unresponsive to antiangiogenic treatment alone. (B) OCT scan 2 months after the sixth injection of DEX implant. The response to DEX is good, but not sustained; repetitive treatments are needed to control diabetic macular edema. (C) OCT scan 5 months after the sixth injection of DEX implant; to reduce the burden of the treatment, the patient is shifted to FAc implant. (D) OCT scan 4 months after FAc implant. The visual acuity improved, with a good anatomic response. (E) OCT scan 8 months after FAc implant. A few new intraretinal cysts are noticeable, with a slightly increased CMT. The patient is scheduled for 1 injection of anti-VEGF. (F) OCT scan 12 months after FAc implant and 45 days after anti-VEGF treatment. The CMT significantly reduced with 1-line letter gain in visual acuity.

implant; nevertheless, their final visual acuity was similar to those who did not require rescue anti-VEGF injections over the follow-up. Patients with higher CMT at baseline and with no history of PRP should be advised for the potential need of additional treatments to control DME. Eyes previously treated with DEX should expect a longer interval free from DME after FAc, with a direct correlation to the number of injections received.

ALL AUTHORS HAVE COMPLETED AND SUBMITTED THE ICMJE FORM FOR DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST. Funding/Support: The authors indicate no financial support. Financial Disclosures: Dr Bandello is a consultant for Allergan Inc, Bayer Shering-Pharma, Hoffmann-La-Roche, Novartis, Sanofi-Aventis, Thrombogenics, Zeiss, Boehringer-Ingelheim, Fidia Sooft, Ntc Pharma, and Sifi. Drs Cicinelli, Capone, Zollet, Rabiolo, and Lattanzio have no financial disclosures. Conceptualization (M.V.C.); Writing - original draft (M.V.C.); Methodology (A.R.); Writing - review and editing (A.R., R.L.); Visualization (P.Z., L.C.); Data curation (P.Z., L.C.); Supervision (R.L., F.B.); Project administration, F.B.). All authors attest that they meet the current ICMJE criteria for authorship.

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