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CLINICAL EVIDENCE OF THE MULTIFACTORIAL NATURE OF DIABETIC MACULAR EDEMA

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Purpose: To report functional and morphologic outcomes, based on diabetic macular edema (DME) chronicity and baseline best-corrected visual acuity (BCVA), from a subanalysis of the fluocinolone acetonide for macular edema (FAME) trials.

Methods: Patients were categorized by DME duration (nonchronic [ncDME] or chronic [cDME] DME) and three nonexclusive baseline vision strata. Anatomic and visual acuity VA outcomes of these cohorts were compared with treatment assignment.

Results: For all patients with ncDME and cDME who received sham control, 27.8% and 13.4%, respectively, gained ≥15 BCVA letters, whereas 22.3% and 34.0% of 0.2 μg/day fluocinolone acetonide (FAc)-treated patients, respectively, gained ≥15 BCVA letters. Among patients with ncDME who received sham control, as baseline vision decreased, the percentage gaining ≥15 BCVA letters increased; however, among those with cDME, the percentage gaining ≥15 BCVA letters did not change as baseline vision decreased. Conversely, among 0.2 μg/day FAc-treated patients, the percentage gaining ≥15 BCVA letters increased with decreasing baseline vision, regardless of DME chronicity. Anatomical outcomes were similar within treatment arms, regardless of the DME duration.

Conclusion: Patients with cDME and poor baseline vision who were exposed to low-dose FAc experienced BCVA improvements that were not observed in a similar group from the sham-control arm. These data support the multifactorial pathogenesis of cDME.

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Diabetic macular edema (DME) remains a leading cause of vision loss in working-aged adults, despite significantly improved outcomes after the introduction of new therapies such as vascular endothelial growth factor (VEGF) inhibitors.[1–3] However, there is evidence that VEGF is not always the sole pathology-mediating cytokine in DME. A recent study that analyzed the biochemical composition of aqueous humor demonstrated increasing inflammatory cytokine levels, but no change in VEGF content, as the severity of diabetic retinopathy increased.[4] Diabetic macular edema can manifest at any stage of the diabetic retinopathy severity spectrum and before the development of retinal ischemia[5,6]; therefore, its pathogenesis cannot be attributed solely to an increase in VEGF levels. In fact, Phase 3 clinical trial data have demonstrated significantly improved visual acuity associated with intravitreal triamcinolone acetonide and implants releasing dexamethasone and fluocinolone acetonide (FAc) compared with controls.[7–9]

The hypothesis that DME is multifactorial has been supported by clinical trial data. A prespecified subanalysis of the fluocinolone acetonide for macular edema (FAME) trials demonstrated that FAc-treated patients with chronic DME (cDME) achieved a greater visual benefit than patients with nonchronic DME (ncDME).[10,11] Furthermore, recent emerging data suggest that even with VEGF inhibitors, efficacy may be lower when DME is long-standing.[12] Unlike other landmark DME trials that included treatment-naive participants,[8,13,14] the FAME trials had eligibility criteria that required prior focal/grid macular laser.[7] As a consequence, there were no treatment-naive patients in the FAME trials; therefore, the population was enriched with patients with cDME. Thermal laser therapy was permitted as a rescue treatment in the FAME trials. Although nonprotocol treatments were discouraged, both triamcinolone acetonide and bevacizumab, which became the standard of care during this period, were used in all treatment arms at the various clinical sites

of the FAME trials. Thus, the sham-control cohort in the FAME trials, which received intermittent therapy with a variety of agents, can be compared with the cohort that received continuous treatment with the FAc implant.

In this post hoc analysis, we compare the functional outcomes of patients with cDME and ncDME in the sham and 0.2 μg/day FAc-treatment arms based on three nonexclusive baseline visual acuity strata ($\leq$20/100, $\leq$20/80, and $\leq$20/64). These strata evolved as a result of an analysis that was conducted as part of a health technology assessment to evaluate cost-effectiveness. This assessment included an examination of the efficacy of the 0.2 μg/day FAc implant across the three nonexclusive baseline visual acuity strata. Additionally, clinical trials typically enroll patients with a range of visual acuities rather than by specific vision strata; therefore, nonexclusive strata are more representative of how visual acuity groups would be defined in a clinical trial. We hypothesized that because patients within each treatment arm were treated similarly regardless of DME duration, differences in visual acuity response would reflect differences in the retinal microenvironment. We compared the degree of similarity in baseline characteristics between patients with cDME versus those with ncDME in the sham-control and 0.2 μg/day FAc arms and also the change in center point thickness (CPT) and visual acuity over the 36 months of the study by baseline vision strata.

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Methods

FAME Study Design

The study population and design of the FAME trials have been described previously.[7] Briefly, FAME comprised two multicenter, randomized, double-masked, sham-controlled, parallel-group studies performed under a single protocol (C-01-05-001, sponsored by Alimera Sciences, Inc, Alpharetta, GA) that compared FAc intravitreal implants (0.2 or 0.5 μg/day) with sham-control injection (± laser photocoagulation ± nonprotocol therapies [including VEGF inhibitors and triamcinolone acetonide]) in patients with DME. The former provided continuous therapy, whereas the latter was intermittent. Patients were eligible to participate in the FAME trials if they had a foveal CPT $\geq$250 μm despite $\geq$1 prior focal/grid macular photocoagulation treatment and best-corrected visual acuity (BCVA) between 19 and 68 Early Treatment Diabetic Retinopathy Study (ETDRS) letters (Snellen equivalent, 20/50–20/400). Key study assessments included BCVA (measured using ETDRS charts at 4 m or an electronic visual acuity tester at 3 m), foveal CPT (measured using the Fast Macular Scan protocol on a Stratus three optical coherence tomography instrument [Carl Zeiss Meditec, Dublin, CA]), and adverse events (AEs; in the case of glaucomatous change to the optic nerve, the University of Wisconsin Fundus Photograph Reading Center performed optic nerve head grading[15]).

During the trials, patients could be retreated with their assigned study treatment between months 12 and 33 if progression of edema was evident (BCVA loss of $\geq$5 ETDRS letters or an increased foveal thickness of $\geq$50 μm from best reading in previous 12 months) according to the assessing (masked) investigator. At the beginning of week 6, patients were permitted to receive rescue (focal/grid or panretinal photocoagulation) laser

therapy for persistent or recurrent DME. In the FAME trials, patients who received nonprotocol intermittent therapy (triamcinolone acetonide and VEGF inhibitors) were not excluded from statistical analysis.

Subanalysis of the FAME Data

This was a post hoc subanalysis in which patients were grouped by nonexclusive categories based on baseline BCVA. Groups were defined by a difference of 5 ETDRS letters (≤20/100 [≤53 letters], ≤20/80 [≤58 letters], ≤20/64 [≤63 letters]; Figure 1) and were not mutually exclusive.

In the current analysis, DME chronicity (nonchronic vs. chronic) was defined based on the median duration of DME reported by patients at the baseline in the FAME trials (3 years).[10]

The intent-to-treat principle was used for all efficacy analyses. The method of last observation carried forward was used to impute values for all missing data. For analyses of baseline characteristics, the primary efficacy endpoint, and secondary efficacy endpoints based on binary variables, a comparison between treatment arms was made using a Cochran–Mantel–Haenszel Chi-square test. For analysis of baseline characteristics and secondary endpoints that were continuous variables, comparisons between treatment arms were made using an analysis of variance model with treatment arm as fixed effects.

Results

Baseline Characteristics

Baseline characteristics were similar among patients regardless of the treatment arm or DME duration; however, there was a greater percentage of phakic patients among those with ncDME than cDME (Table 1; because patients were categorized by DME duration, the differences in the duration of disease are to be expected). In a subgroup analysis of patients with DME based on the disease duration, the effect of 0.2 μg/day FAc versus sham control was similar between all patients and those who were pseudophakic at the baseline,[11] which suggests that outcomes based on DME duration and baseline vision should not be affected by the baseline lens status.

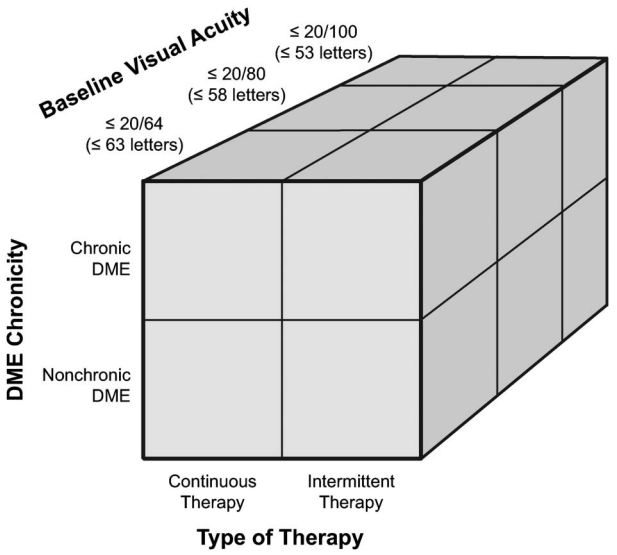

Fig. 1. Study design.

Treatment Usage

Among patients assigned to sham control, retreatment rates were higher in patients with cDME compared with those with ncDME, and this difference reached statistical significance (33.9% vs. 20.5%; $P = 0.039$; Table 2). A similar difference was not observed in the 0.2 μg/day FAc arm. Table 2 also shows that the proportion of patients with cDME who received off-protocol therapies was higher than those with ncDME in the sham-control arm, and this differential was not seen in the FAc arm.

Adverse Events

The incidence of cataract was greater in the 0.2 μg/day FAc arm compared with that in the sham-control arm, with little difference based on DME duration in each arm. Cataract extraction rates were higher among patients with cDME than those with ncDME, regardless of treatment assignment, although the difference in surgery rates was more pronounced in the sham-control arm compared with that in the 0.2 μg/day FAc arm (Table 3).

Within each treatment arm, use of intraocular pressure-lowering medication was similar regardless of DME duration. Only one patient in the sham-control arm required intraocular pressure-lowering surgery, and this was a patient with ncDME. Among patients who received 0.2 μg/day FAc, a similar percentage of patients with cDME and ncDME required intraocular pressure-lowering surgery.

Foveal Center Point Thickness Outcomes and Visual Acuity in Patients who Received Sham Control or 0.2 μg/day Fluocinolone Acetonide: Results Stratified by Diabetic Macular Edema Chronicity

Patients in the sham-control and 0.2 μg/day FAc arms achieved comparable improvements in CPT, regardless of DME chronicity (Figure 2, A and B, respectively). However, among those who received sham contral, a significantly greater percentage of patients with ncDME

Table 1. Baseline Characteristics by Baseline Vision Group Among Patients in the FAME Trials

Characteristic	Sham Control		0.2 μg/day FAc	
	ncDME	cDME	ncDME	cDME
Patients, n (%)				
All patients	72 (100)	112 (100)	166 (100)	209 (100)
≤20/64 (≤63 letters)	52 (72.2)	90 (80.4)	119 (71.7)	161 (77.0)
≤20/80 (≤58 letters)	33 (45.8)	63 (56.3)	83 (50.0)	124 (59.3)
≤20/100 (≤53 letters)	26 (36.1)	48 (42.9)	68 (41.0)	90 (43.1)
BCVA, ETDRS letters, mean (SD)				
All patients	55.7 (11.5)	54.0 (11.2)	54.7 (11.7)	52.2 (13.4)
≤20/64	51.5 (10.9)	50.9 (10.2)	50.2 (10.7)	47.9 (12.3)
≤20/80	45.9 (10.0)	46.5 (9.1)	45.4 (9.5)	44.0 (11.4)
≤20/100	43.0 (9.3)	43.2 (7.9)	43.1 (8.9)	39.5 (10.1)
ETDRS diabetic retinopathy score				
All patients				
n	70	109	158	198
Mean (SD)	6.0 (1.6)	5.8 (1.6)	5.7 (1.6)	5.7 (1.5)
≤20/64				
n	50	88	112	152
Mean (SD)	6.2 (1.7)	5.8 (1.6)	5.8 (1.6)	5.8 (1.6)
≤20/80				
n	31	61	77	115
Mean (SD)	6.4 (1.8)	5.9 (1.6)	5.9 (1.7)	5.9 (1.6)
≤20/100				
n	25	46	63	85
Mean (SD)	6.4 (1.9)	6.1 (1.6)	5.9 (1.7)	6.0 (1.7)
Duration of DME, mean (SD), years				
All patients	1.7 (0.5)	5.4 (4.2)	1.7 (0.5)	5.1 (3.1)
≤20/64	1.7 (0.5)	5.6 (4.6)	1.7 (0.5)	4.9 (3.1)
≤20/80	1.7 (0.5)	5.0 (2.6)	1.7 (0.5)	4.9 (3.1)
≤20/100	1.7 (0.5)	4.8 (2.1)	1.6 (0.5)	4.9 (3.1)
Phakic, n (%)				
All patients	54 (75.0)	66 (58.9)	122 (73.5)	114 (54.5)
≤20/64	41 (78.8)	47 (52.2)	87 (73.1)	91 (56.5)
≤20/80	25 (75.8)	32 (50.8)	59 (71.1)	68 (54.8)
≤20/100	20 (76.9)	26 (54.2)	49 (72.1)	53 (58.9)
HbA_{1c}, mean (SD), %				
All patients	8.1 (1.9)	7.7 (1.5)	7.9 (1.6)	7.8 (1.6)
≤20/64	8.3 (2.1)	7.6 (1.3)	7.9 (1.5)	7.8 (1.6)
≤20/80	8.4 (2.3)	7.8 (1.4)	7.8 (1.3)	7.8 (1.6)
≤20/100	8.5 (2.4)	7.9 (1.5)	7.6 (1.3)	7.9 (1.7)
CPT, mean (SD), μm				
All patients	435.0 (149.1)	461.8 (153.5)	466.6 (152.9)	456.2 (165.9)
≤20/64	451.8 (159.9)	470.5 (160.3)	485.2 (158.4)	478.7 (172.3)
≤20/80	452.7 (168.4)	492.0 (161.0)	509.2 (163.9)	487.5 (177.8)
≤20/100	456.0 (168.6)	509.3 (169.5)	518.9 (162.8)	512.6 (180.2)

HbA_{1c}, glycated hemoglobin.

achieved a ≥15-letter improvement in BCVA compared with patients with cDME (27.8% vs. 13.4%; $P = 0.012$; Figure 2C). This finding was not driven by the frequency of rescue laser treatment or nonprotocol therapies received by the 2 groups, as they were comparable (Table 2). Among those treated with 0.2 μg/day FAc, a significantly greater percentage of patients with cDME achieved a ≥15-letter improvement in BCVA than those with ncDME (34.0% vs. 22.3%; $P = 0.029$; Figure 2D). This finding was not influenced by the frequencies of rescue laser treatment or nonprotocol therapies that were delivered in addition to the FAc as these were similar in the groups with ncDME and cDME (Table 2).

Visual Acuity in Patients who Received Sham Control: Results Stratified by Diabetic Macular Edema Chronicity and Baseline Visual Acuity

In the sham-control arm, a significantly greater percentage of those with ncDME gained ≥15 letters of BCVA compared with those with cDME (Figure 3A). However, the percentages of patients with cDME who

Table 2. Retreatment, Laser, and Off-Protocol Therapies Received by Baseline Vision Group in the FAME Trials

	Sham Control			0.2 μg/day FAc		
	ncDME	cDME	*P**	ncDME	cDME	*P**
Patients receiving >1 study treatments (sham control or 0.2 μg/d FAc), n (%)						
All patients	15 (20.5)	38 (33.9)	0.039	46 (27.7)	50 (23.9)	0.409
≤20/64	10 (19.2)	32 (35.6)	0.033	36 (30.3)	39 (24.2)	0.276
≤20/80	6 (18.2)	19 (30.2)	0.197	22 (26.8)	31 (25.0)	0.775
≤20/100	4 (15.4)	14 (29.2)	0.179	20 (29.9)	25 (27.8)	0.959
Patients receiving any rescue laser treatment, n (%)						
All patients	45 (62.5)	69 (61.6)	0.998	71 (42.8)	85 (40.7)	0.720
≤20/64	35 (67.3)	56 (62.2)	0.621	50 (42.0)	63 (39.1)	0.645
≤20/80	21 (63.6)	40 (63.5)	0.946	34 (41.0)	49 (39.5)	0.846
≤20/100	15 (57.7)	28 (58.3)	0.886	26 (38.2)	35 (38.9)	0.961
Patients receiving panretinal photocoagulation therapy, n (%)						
All patients	20 (27.8)	24 (21.4)	0.305	27 (16.3)	23 (11.0)	0.132
≤20/64	17 (32.7)	17 (18.9)	0.060	19 (16.0)	19 (11.8)	0.310
≤20/80	10 (30.3)	16 (25.4)	0.614	14 (16.9)	15 (12.1)	0.335
≤20/100	9 (34.6)	13 (27.1)	0.542	9 (13.2)	12 (13.3)	0.967
Patients receiving any off-protocol therapy, n (%)						
All patients	22 (30.6)	39 (34.8)	0.582	29 (17.5)	28 (13.4)	0.226
≤20/64	19 (36.5)	35 (38.9)	0.772	22 (18.5)	22 (13.7)	0.232
≤20/80	8 (24.2)	25 (39.7)	0.138	15 (18.1)	16 (12.9)	0.268
≤20/100	5 (19.2)	21 (43.8)	0.039	13 (19.1)	11 (12.2)	0.111

*P value based on a Cochran–Mantel–Haenszel Chi-square test stratified by baseline visual acuity.

gained ≥15 letters of BCVA were similar across baseline visual acuity strata. Within each baseline vision stratum, a significantly greater percentage of patients with ncDME gained ≥15 letters of BCVA compared with those with cDME.

In the sham-control arm, a numerically, but not statistically significant, greater percentage of patients with ncDME achieved ≥20/40 visual acuity versus those with cDME (Figure 3B). The percentages of patients with ncDME who achieved a visual outcome of ≥20/40 were similar in the ≤20/64, ≤20/80, and ≤20/100 strata. However, the percentage of patients with cDME who achieved a visual outcome of ≥20/40 was lower in each successively lower baseline visual acuity stratum, with only 6.3% of patients in the lowest baseline vision stratum achieving ≥20/40 visual acuity. Within each baseline vision stratum, there was no statistically significant difference in the percentage of patients who achieved a visual outcome of ≥20/40 between those with ncDME and cDME.

Visual Acuity After Treatment With 0.2 μg/day Fluocinolone Acetonide: Results Stratified by Diabetic Macular Edema Chronicity and Baseline Visual Acuity

In the 0.2 μg/day FAc arm, a significantly greater percentage of patients with cDME compared with those with ncDME gained ≥15 letters of BCVA (Figure 4A). There was an increased percentage of patients who gained ≥15 letters of BCVA with each successively lower baseline visual acuity stratum, regardless of DME chronicity; however, for each baseline vision stratum, a numerically greater percentage of patients with cDME gained ≥15 letters of BCVA versus those with ncDME.

Among all patients who received 0.2 μg/day FAc, a significantly greater percentage of patients with cDME compared with those with ncDME achieved ≥20/40 visual acuity (Figure 4B). Similar percentages of patients with ncDME in the ≤20/64, ≤20/80, and ≤20/100 strata achieved a visual acuity outcome of ≥20/40; however, with each successively lower baseline visual acuity stratum, fewer patients with cDME achieved a visual outcome of ≥20/40.

Discussion

This post hoc subanalysis of the FAME trials reports the efficacy and safety of 0.2 μg/day FAc (continuous therapy) versus sham control (various intermittent therapies) in patients with ncDME or cDME as a function of the baseline vision status. In this subanalysis, patients in each treatment arm were categorized by disease chronicity and baseline vision. Categorizing

Table 3. Cataract- and Intraocular Pressure-Related Events in Patients With ncDME and cDME by Baseline Vision Group

Adverse Event	Sham Control		0.2 μg/day FAc	
	ncDME	cDME	ncDME	cDME
Cataract adverse event,* n (%)				
All patients	26 (48.1)	34 (51.5)	94 (77.0)	98 (86.0)
≤20/64	21 (51.2)	25 (53.2)	65 (74.7)	78 (85.7)
≤20/80	13 (52.0)	16 (50.0)	45 (76.3)	58 (85.3)
≤20/100	11 (55.0)	15 (57.7)	37 (75.5)	45 (84.9)
Cataract extraction,* n (%)				
All patients	8 (14.8)	24 (36.4)	91 (74.6)	97 (85.1)
≤20/64	8 (19.5)	18 (38.3)	64 (73.6)	79 (86.8)
≤20/80	5 (20.0)	13 (40.6)	46 (78.0)	59 (86.8)
≤20/100	4 (20.0)	12 (46.2)	39 (79.6)	46 (86.8)
Intraocular pressure-lowering medication,† n (%)				
All patients	9 (12.5)	17 (15.2)	69 (41.6)	75 (35.9)
≤20/64	6 (11.5)	16 (17.8)	50 (42.0)	53 (32.9)
≤20/80	2 (6.1)	12 (19.0)	34 (41.0)	43 (34.7)
≤20/100	1 (3.8)	9 (18.8)	27 (39.7)	31 (34.4)
Intraocular pressure-lowering surgery,‡ n (%)				
All patients	1 (1.4)	0	7 (4.2)	11 (5.3)
≤20/64	0	0	4 (3.4)	10 (6.2)
≤20/80	0	0	2 (2.4)	9 (7.3)
≤20/100	0	0	2 (2.9)	8 (8.9)

*Among randomized and treated phakic patients only.
†For a minimum of 7 days.
‡Includes trabeculectomy, glaucoma surgery, and vitrectomy for elevated intraocular pressure.

patients by baseline vision provided a reference point for the visual acuity improvement patterns typically observed in clinical trials. Patients with poor baseline vision generally experience greater visual gains after intervention compared with their counterparts with better vision.[16–18] Patients with better vision at the time of intervention typically experience a treatment "ceiling effect" as a consequence of the limited potential for improvement.[18] In the present report, patients with ncDME in the sham-control arm who were treated with intermittent therapy followed this trend. However, this trend was not observed among patients with cDME in the sham-control arm who were treated with intermittent therapy. By contrast, patients with cDME and poor baseline vision who were treated with continuous 0.2 μg/day FAc did experience improvements in vision in line with those previously observed. Categorizing patients by disease chronicity within each treatment arm allowed for observation of response to therapies with distinct mechanisms of action to support the hypothesis of change within the retina microenvironment associated with disease chronicity. Our findings show that disease chronicity plays an important role in the heterogeneity of functional outcomes in DME and that continuous low-dose corticosteroid therapy is particularly beneficial in patients who would otherwise be refractory to intermittent therapy.

The underlying pathology of an individual patient's DME may be manifested by their response to therapeutic agents with differing mechanisms of action. In the RIDE/RISE trials of patients with DME, those who received ranibizumab 2 years after randomization gained ≈ 2 letters of BCVA over 12 months (compared with an improvement of ≈ 10 letters over 12 months among those who received ranibizumab at randomization).[2] Interestingly, the improvement was small despite an appreciable reduction in central foveal thickness (≈100 μm)[2] suggesting the presence of persistent retinal morphologic abnormalities unrelated to vascular leakage. However, the literature is inconsistent regarding correlations between improved visual acuity and reductions in foveal thickness. The Diabetic Retinopathy Clinical Research Network Protocol A suggested little correlation between improved visual acuity and reduction of CPT.[19] However, in the FAME trials, at 2 years postrandomization, patients who received FAc implants experienced both significant improvements in visual acuity and reductions in foveal thickness.[7] In a previous publication arising out of the FAME trials, a prespecified subanalysis based on DME duration has demonstrated that patients with DME for >1.73 years gained nearly 6 ETDRS letters of BCVA after receiving 0.2 μg/day FAc for 12 months (The aforementioned median DME duration of 3 years

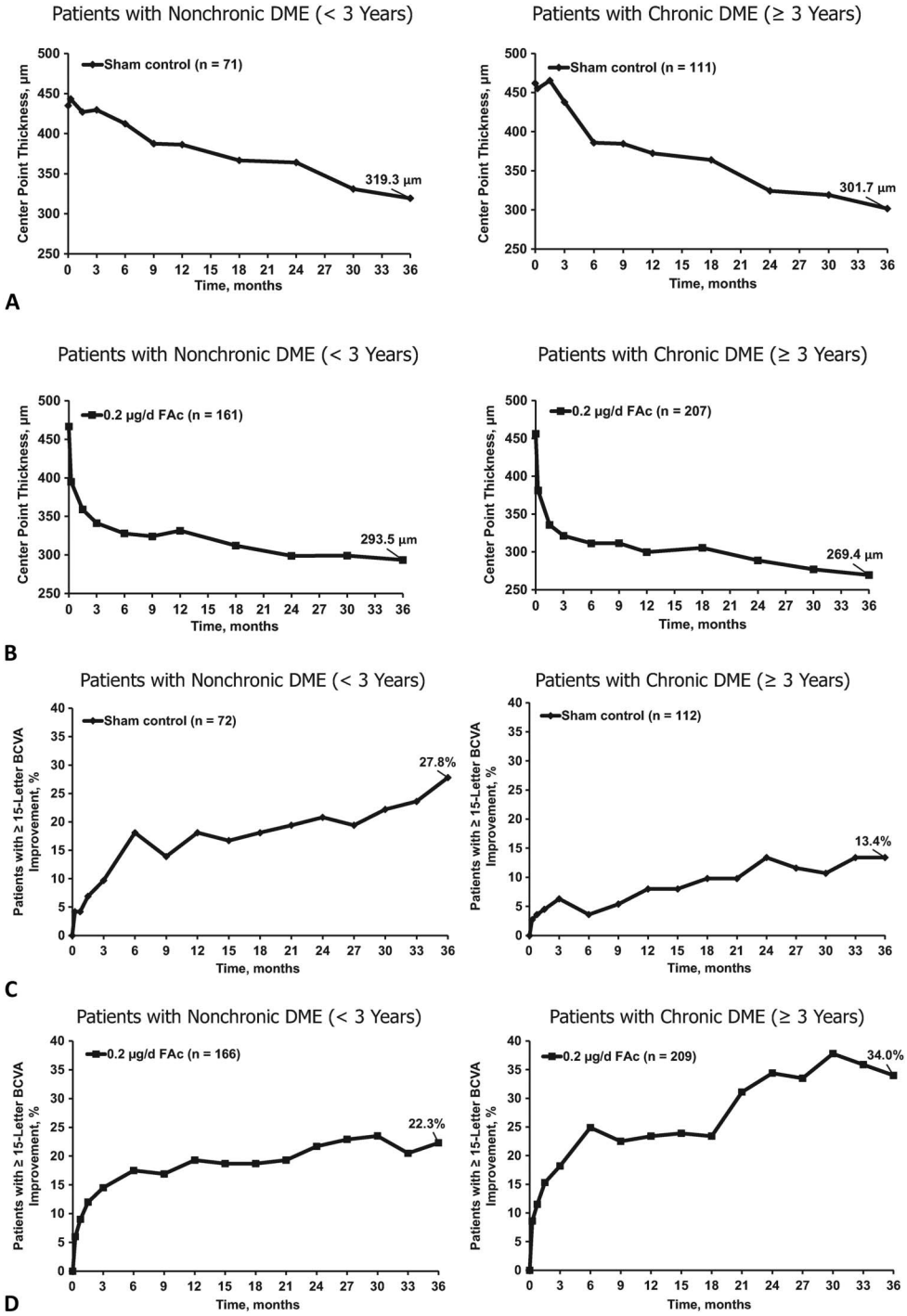

Fig. 2. Center Point Thickness and Visual Acuity Outcomes Among Patients who Received Sham Control (**A** and **B**, respectively) and 0.2 μg/day FAc (**C** and **D**, respectively).

was based on the year of diagnosis.)[11] The median DME duration of 1.73 years is based on the specific day, month, and year of diagnosis with DME. There was a significant concordance in DME chronicity between the 2 algorithms, and $\approx$ 93% of patients retained their original categorization.[11] Our data suggest that a low dose of corticosteroid may act through pathways that are not fully understood to improve functional recovery in chronic disease. Reports of improved vision with corticosteroid use among patients who previously experienced suboptimal results associated with anti-VEGF agents have been published,[20–24] and at least one prospective randomized clinical trial addressing this specific question is ongoing.[25]

The difference in efficacy based on the DME duration and treatment arm suggests a change in

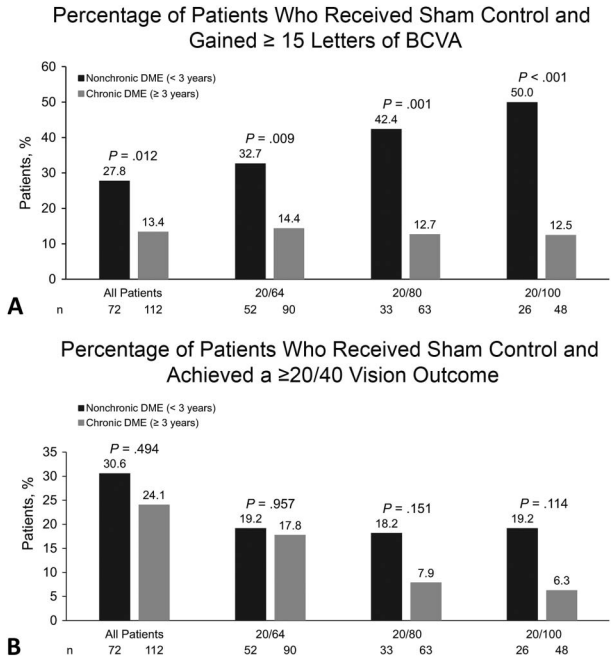

Fig. 3. Visual Acuity Outcomes (percentage of patients who gained ≥ 15 letters of BCVA and percentage of patients who achieved a ≥ 20/40 vision outcome, **A** and **B**, respectively) Among Patients who Received Sham Control: Results Stratified by DME Chronicity and Baseline Vision. *P* values based on a Cochran-Mantel-Haenszel c2 test stratified by baseline visual acuity.

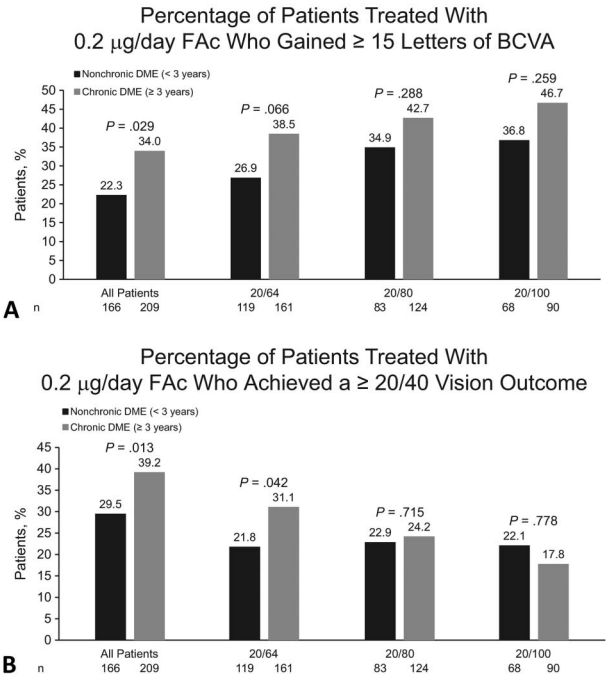

Fig. 4. Visual Acuity Outcomes (percentage of patients who gained ≥ 15 letters of BCVA and percentage of patients who achieved a ≥ 20/40 vision outcome, **A** and **B**, respectively) Among Patients Treated With 0.2 μg/day FAc: Results Stratified by DME Chronicity and Baseline Vision. *P* values based on a Cochran-Mantel-Haenszel c2 test stratified by baseline visual acuity.

cytokine composition within the retina microenvironment. Over the course of the study, the percentage of patients who experienced an improvement in BCVA of ≥15 ETDRS letters among those with ncDME who were treated with continuous 0.2 μg/day FAc therapy increased; however, this effect was significantly greater among patients with cDME. Corticosteroids per se are known to reduce VEGF levels, albeit not to the extent of anti-VEGF agents.[26] Thus, the difference in functional outcomes based on DME duration among patients in the sham-control arm who received laser and intermittent therapy supports the notion that the retinal microenvironment composition varies with the duration of DME, particularly given the similar frequency of laser and nonprotocol therapy use among these patients. The efficacy data presented herein may reflect a disease that is primarily VEGF driven in patients with ncDME; however, as the duration of DME increases, VEGF may no longer be the primary pathological mediator and the corticosteroid effect is greater.

Visual acuity improvement associated with pharmacotherapies as a function of baseline vision has been explored in clinical trials. A subanalysis of the BOLT study, in which patients were treated with bevacizumab, demonstrated a numerically greater change in visual acuity at the study end among those with baseline visual acuity <54 ETDRS letters versus those with baseline visual acuity ≥54 letters.[17] Also, the recently published Diabetic Retinopathy Clinical Research Network Protocol T trial reported numerically greater improvements across all treatment arms in patients with poor baseline vision compared with those who had better baseline vision.[16] Our findings are in agreement with the results of these prior studies, with the exception of results in patients with cDME in the sham-control arm; however, treatment in these patients with continuous 0.2 μg/day FAc restored the expected outcome.

This report provides clinical evidence suggesting that as DME duration increases, the multifactorial nature of the disease becomes more prominent. Among those who received sham control (laser and intermittent therapies), distinct responder types were observed between patients with ncDME and cDME. Treatment patterns were similar among patients who received continuous 0.2 μg/day FAc, although greater efficacy was observed in patients with cDME compared with those with ncDME. In patients with cDME, the likelihood of achieving vision ≥20/40 with treatment diminishes as the vision worsens. Therefore, our findings suggest a need for close monitoring of such patients to avoid significant vision loss and are in accord with the indication approved by the European Medicines Agency for 0.2 μg/day FAc.[27] Thus, 0.2 μg/day FAc

represents a treatment option for patients who are unresponsive to alternative or intermittent therapies.

Key words: baseline visual acuity, best-corrected visual acuity, chronic diabetic macular edema, diabetic macular edema, fluocinolone acetonide, intravitreal corticosteroids, nonbioerodible implants.

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