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Macular Thickness Fluctuation and Visual Outcome in Diabetic Macular Edema Treated With Dexamethasone Intravitreal Implant

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Abstract

Objective: Assess variability in central retinal thickness (CRT) on long-term visual acuity in patients with diabetic macular edema (DME) receiving dexamethasone intravitreal (DEX) implant.

Methods: Best-corrected visual acuity (BCVA) and CRT data from patients treated with DEX 0.7 mg were pooled from two 3-year randomized trials. Primary outcome measures were CRT variability (CRT standard deviation [CRT-SD] and average change from baseline in BCVA over 39 months.

Results: Comparison of BCVA average change in study eyes categorized by CRT variability indicated diminishing BCVA improvement with increasing CRT variability (least squares mean change +6.54, +4.66, +3.10, and –0.34 letters in Quartiles 1, 2, 3, and 4, respectively; P<.001). Regression analysis demonstrated a significant negative association between BCVA average change over 3 years and CRT variability (r^2=0.1756, P≤.001), with increasing CRT-SD (estimate –0.044, P<.001) and higher baseline BCVA (estimate –0.264, P<.001) adversely affecting BCVA response. Among study eyes with retinal edema (CRT ≥300 µm) during follow-up, BCVA average improvement diminished with long-lasting (>1 year) edema (least squares mean change +5.92, +6.86, and +0.83 letters in eyes with edema for ≤6, >6 to ≤12, and >12 months, respectively). For study eyes without edema (CRT <300 µm) during follow-up, BCVA average improvement increased with variability (SD) of time with CRT <300 µm (least square mean change +3.24, +3.25, +4.97, and +6.48 letters in Quartiles 1, 2, 3, and 4, respectively).

Conclusions: In DME, long-term visual acuity with DEX implant 0.7 mg treatment is negatively affected by CRT variability and persistent retinal edema.

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Introduction

Diabetic retinopathy is the leading cause of visual disability among adults of working age, affecting an estimated 103 million people worldwide [1]. Diabetic macular edema (DME), characterized by breakdown of the inner blood-retinal barrier, microvascular leakage, and accumulation of fluid in the subretinal or intraretinal spaces [2-5], is the most common form of vision-threatening diabetic retinopathy [1,6,7].

Approved pharmacological treatment options for DME include intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents and intravitreal corticosteroids. Anti-VEGF therapy has demonstrated superior visual acuity outcomes and acceptable risks compared with focal or macular grid laser [8]; nevertheless, up to 40% of patients with DME show incomplete visual or anatomical response to anti-VEGF agents [9,10]. Intravitreal corticosteroids (e.g., dexamethasone, fluocinolone acetonide, and triamcinolone acetonide) provide an alternative treatment option for patients who are considered insufficiently responsive to, or unsuitable for, anti-VEGF therapy. The phase 3 MEAD clinical studies of dexamethasone intravitreal (DEX) implant, administered at ≥6-month intervals, demonstrated sustained improvements in both visual and anatomic outcomes over a 3-year treatment period among treatment-naïve patients with DME and those previously treated with anti-VEGF agents or laser [11].

Central subfield retinal thickness (CRT; central 1-mm macular subfield) is the preferred optical coherence tomography (OCT) measure of macula edema, as it offers high reproducibility and good correlation with other measurements of the central macula [12]. However, clinical studies indicate only modest correlation at best between changes in CRT and changes in best corrected visual acuity (BCVA) in response to focal/grid laser [13], anti-VEGF [14-18], and corticosteroid [19] therapy in patients with center-involved DME. A possible explanation for the disconnect between CRT and visual outcome in DME is that macular thickness does not take into consideration OCT-derived ultrastructural features, such as disorganization of the retinal inner layers, loss of the ellipsoid zone, and disturbance of foveal photoreceptor integrity, that may be more directly related to visual function in DME [20-25]. Moreover, a single CRT measurement provides no indication of the dynamics of CRT variability over time. In vitro studies suggest that cyclical mechanical stress on retinal pigment epithelium cells induces retinal pigment epithelium damage [26], leading to photoreceptor loss and retinal degeneration [27]. Recent clinical studies indicate that larger fluctuations of CRT are associated with poorer visual outcomes in patients receiving anti-VEGF or corticosteroid therapy for macular edema secondary to diabetes [28-30] and retinal vein occlusion [31,32], and for neovascular age-related macular degeneration [33-36].

Information on the effects of CRT variability on vision outcomes in patients receiving intravitreal corticosteroid treatment for DME is limited [37]. This retrospective analysis of data from the phase 3 MEAD clinical trials was undertaken to assess the effect of CRT variability on long-term (3-year) BCVA outcome in patients with DME treated with DEX implant.

Methods

The MEAD study comprised 2 phase 3 multicenter, masked, sham-controlled clinical trials of identical design (registered at www.clinicaltrials.gov; NCT00168337 and NCT00168389) that investigated the long-term efficacy and safety of DEX implant in the treatment of DME; data from the 2 trials were subsequently pooled for this and other restrospective analyses [11]. Each clinical site's respective institutional review board/ethics committee approved the study. All patients provided written informed consent before enrollment. Both studies were carried out in compliance with the ethical guidelines of the Declaration of Helsinki and the Health Insurance Portability and Accountability Act.

In brief, 1048 patients aged ≥18 years with DME, BCVA of 20/50 to 20/200 Snellen, and CRT of >300 µm were enrolled and randomized (1:1:1) to treatment with DEX implant 0.35 mg (n=347), DEX implant 0.7 mg (n=351), or sham procedure (n=350), and followed for either 36 or 39 months. Study visits were scheduled every 6 weeks during the first year of the study, and every 12 weeks during the second and third years. Patients who met the retreatment eligibility criteria – i.e., evidence of residual edema, with CRT >225 µm (subsequently revised to CRT >175 µm) – could be retreated with DEX implant at intervals of ≥6 months, up to a maximum of 7 treatments over 3 years. After a study protocol amendment (May 2010) patients who had not yet completed the study and who met the retreatment eligibility criteria were retreated with DEX implant at month 36 and received an additional study visit at month 39. Patients requiring adjunctive or other treatment for macular edema were withdrawn from the study prior to its administration. The present retrospective analysis was confined to those MEAD study patients undergoing treatment with DEX implant 0.7 mg.

Measures of CRT variability

In the MEAD study, following initiation of study treatment, retinal thickness in the central 1-mm macular subfield of the study eye was measured by time-domain OCT (Stratus OCT3 or OCT2, Carl Zeiss Meditec Inc., Dublin, CA, USA) at regular 3-month intervals for the duration of follow-up. Average change in CRT from baseline during the course of the study was calculated on the basis of observed CRT measurements, using the area under the curve (AUC) approach to provide an integrated estimate of overall parameter change over the specified time period [38]. For the present analysis, missing CRT measurements in the MEAD dataset were imputed using the last observation carried forward (LOCF) method, and CRT variability was expressed in terms of the standard deviation of all CRT measurements (CRT-SD; observed and imputed) for the patient's study eye over 39 months. Based on these measurements, study eyes were categorized according to quartile of CRT-SD, namely Quartile 1 (minimum to 25th percentile), Quartile 2 (25th to 50th percentile), Quartile 3 (50th to 75th percentile), and Quartile 4 (75th percentile to maximum), and BCVA outcomes were compared across quartiles.

Measures of visual outcome

In the MEAD study, BCVA was measured every 6 weeks (year 1) or 12 weeks (years 2 and 3) using Early Treatment Diabetic Retinopathy Study (ETDRS) methodology. The primary visual outcome in the present analysis was the average change from baseline in BCVA over 39 months, as determined using the AUC approach. For this calculation, missing BCVA readings in the MEAD dataset were imputed using the LOCF method. Secondary outcomes of interest included average change from baseline in BCVA at month 39.

Statistics

Interquartile comparisons of baseline demographic and clinical characteristics were performed with analysis of variance (continuous variables) and logistic regression analysis (categorical variable). Average change from baseline in BCVA over the study period (AUC approach) was expressed for each quartile as the least square mean (LSM) value with 95% confidence interval (CI). Interquartile comparisons of LSM values of average change in BCVA over the study period were performed using an analysis of covariance model, with CRT-SD quartile as the factor variable and baseline BCVA as a covariate. Following analysis of variance/analysis of covariance, the Tukey-Kramer test was used to perform multiple pairwise interquartile comparisons, allowing compensation for type 1 error inflation. Missing BCVA and CRT data were imputed with the LOCF hod. Regression analysis, based on an analysis of covariance model with CRT-SD and baseline BCVA as covariates was used to assess the association between CRT-SD and BCVA average change over the 3-year study period. All analyses were performed using SAS version 9.4.

Results

Post hoc analysis population

In total, 351 patients (intention-to-treat population) were enrolled and randomized to treatment with DEX implant 0.7 mg in the MEAD study, of whom 330 (94.0%), 292 (83.2%), 254 (72.4%), and 225 (64.1%) patients completed 6, 12, 24, and 36/39 months, respectively, of follow-up. Baseline BCVA and CRT measurements were obtained from 351 and 348 patients, respectively, in the DEX 0.7 mg treatment arm of the MEAD study. The intention-to-treat population for the present analysis comprised the 349 patients in the DEX implant 0.7 mg treatment arm who had ≥1 post-baseline CRT measurement(s). Among this population, the minimum CRT-SD value during follow-up was 0 µm, the 25th percentile was 37.7 µm, the 50th percentile was 73.8 µm, the 75th percentile was 122.1 µm, and the maximum was 348.7 µm.

On categorization of patients by quartile of CRT variability during follow-up, no significant interquartile differences were noted regard to age or sex, or baseline clinical characteristics of glycemic control, Diabetic Retinopathy Severity score, duration of DME, and lens status of the study eye. However, study eyes in Quartile 4 had significantly (*P*<.05) lower baseline BCVA and significantly higher baseline CRT than those in the other quartiles (Table 1).

Effect of CRT variability on BCVA average change during the study

Study eyes in Q1, Q2, Q3, and Q4 received a mean of 2.6, 4.2, 4.7, and 5.0 DEX implant injections, respectively, over the 3-year study period. Average change from baseline in BCVA over the 3-year study period, expressed as the LSM (95% CI) value, was +6.54 (4.84, 8.24) letters in Quartile 1, +4.66 (2.98, 6.35) letters in Quartile 2, +3.10 (1.40, 4.79) letters in Quartile 3, and -0.34 (–2.06, 1.38) letters in Quartile 4 (*P*<.001 for overall cross-cohort comparison). Interquartile comparisons indicated that LSM values of BCVA average change over the study period were significantly larger in Quartiles 1, 2, and 3 relative to Quartile 4, and also significantly larger in Quartile 1 relative to Quartile 3 (Table 2).

A similar pattern of diminishing response across quartiles of CRT variability was obtained with respect to BCVA change from baseline at study end (month 39), with interquartile comparisons indicating significantly larger treatment effects in Quartiles 1 and 2 compared with Quartile 4 (Supplementary Table S1).

Effect of duration of retinal edema on BCVA average change during the study

Of the analysis subpopulation demonstrating retinal edema (CRT ≥300 µm) in the study eye during follow-up (n=294), 45 patients had CRT ≥300 µm for ≤6 months (Group A), 44 patients had CRT ≥300 µm for >6 to ≤12 months (Group B), and 205 patients had CRT ≥300 µm for >12 months (Group C). The average change from baseline in BCVA over 39 months, expressed as the LSM (95% CI) value, was +5.92 (3.63, 8.22) letters in Group A, 6.86 (4.54, 9.19) letters in Group B, and 0.83 (–0.24, 1.91) letters in Group C. Intercohort comparisons indicated that the LSM change in average BCVA over the 3 years of follow-up was significantly larger in Group A and Group B compared with Group C (Table 3).

Conversely, for the analysis subpopulation demonstrating retinal dryness (CRT <300 µm) in the study eye during follow-up (n=289), visual acuity was assessed in terms of the variability in time with retinal dryness. On stratification of patients into quartiles according to the standard deviation of time with CRT <300 µm in the study eye (0th, 25th, 50th, 75th, and 100th percentile values of 0, 4.7, 9.6, 11.4, and 17.7 months, respectively), the average change from baseline in BCVA over 39 months, expressed as the LSM (95% CI) value, was +3.24 (1.34, 5.14) letters in Quartile 1, +3.25 (1.35, 5.15) letters in Quartile 2, +4.97 (3.07, 6.87) letters in Quartile 3, and 6.48 (4.59, 8.37) letters in Quartile 4. Interquartile comparisons indicated that the LSM value of BCVA average change over the study period was significantly larger in Quartile 4 relative to Quartile 1 (Supplementary Table S2).

Association between CRT variability and BCVA average change

Regression analysis indicated that, among study eyes treated with DEX implant 0.7 mg, CRT variability was significantly and negatively associated (r^2=0.1756, *P*≤.001) with BCVA average change (improvement) over the 3-year study period (Figure 1). BCVA improvement over the study period was adversely impacted both by increasing CRT-SD (estimate –0.044, standard error 0.005, *P*<.001) and by higher baseline BCVA (estimate –0.264, standard error 0.033, *P*<.001) (Table 4).

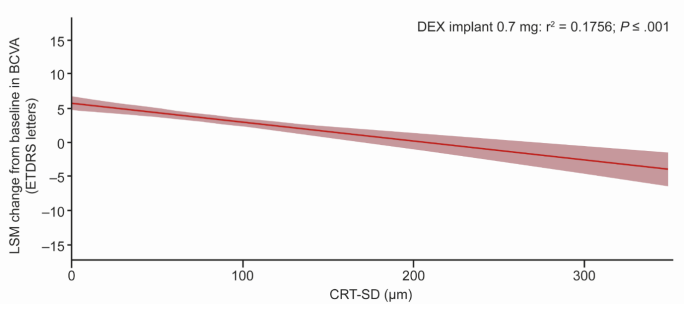

Figure 1: Average change from baseline in BCVA over study period as a function of variability in CRT. The shaded zone above and below the regression line represents the 95% confidence interval. Based on analysis of covariance model with change from baseline in BCVA average change (area under the curve approach) as the response, race, sex, and number of treatments as factors, and CRT-SD, age, and baseline BCVA as covariates. BCVA: Best Corrected Visual Acuity; CRT-SD: Standard Deviation of Central Retinal Thickness; DEX: Dexamethasone Intravitreal; EDTRS: Early Treatment Diabetic Retinopathy Study; LSM: Least Squares Mean.

Table 1: Baseline Patient and Study Eye Characteristics by CRT-SD Quartile.

Characteristic	Quartile 1 (n=87)	Quartile 2 (n=88)	Quartile 3 (n=86)	Quartile 4 (n = 88)	Across-Quartile Comparison
Age, mean (SD), years	62.4 (9.1)	63.4 (8.2)	62.0 (8.5)	62.2 (7.6)	*P*= .7183
Sex, n (%) Male Female	47 (54.0) 40 (46.0)	51 (58.0) 37 (42.0)	60 (69.8) 26 (30.2)	53 (60.2) 35 (39.8)	*P*= .183
HbA1c (%), mean (SD)	7.52 (1.18)	7.54 (1.14)	7.57 (1.13)	7.68 (1.17)	*P*= .7990
DR severity score, mean (SD)	5.4 (1.7)	5.7 (1.3)	5.5 (1.5)	5.7 (1.4)	*P*= .5573
Duration of ME, mean (SD), months	25.5 (29.8)	24.9 (26.0)	19.3 (22.5)	24.3 (24.8)	*P*= .3758
Lens status, n (%) Phakic Pseudophakic	 64 (73.6) 23 (26.4)	 61 (69.3) 27 (30.7)	 64 (74.4) 22 (25.6)	 74 (84.1) 14 (15.9)	*P*= .137
BCVA, mean (SD), ETDRS letters	58.5 (9.8)	58.3 (8.7)	55.7 (8.8)	51.9 (10.8)	*P*<. 0001
CRT, mean (SD), µm	398.7 (130.3)	415.6 (131.6)	472.6 (145.6)	564.0 (164.3)	*P*<. 0001

BCVA: Best-Corrected Visual Acuity; CRT: Central Retinal Thickness; CRT-SD: Standard Deviation of Central Subfield Retinal Thickness; DR: Diabetic Retinopathy; ETDRS: Early Treatment Diabetic Retinopathy Study; HbA1c: Glycated Hemoglobin; ME: Macular Edema; SD: Standard Deviation.

Table 2: DEX Implant Treatment and Average Change From Baseline in BCVA Over Study Period, Categorized by Quartile of CRT-SD.

Parameter	Quartile 1 (n=87)	Quartile 2 (n=88)	Quartile 3 (n=86)	Quartile 4 (n=88)
No. of DEX implant injections, mean (SD)	2.6 (1.76)	4.2 (1.88)	4.7 (1.85)	5.0 (1.49)
Baseline BCVA (ETDRS letters), mean (SD)	58.5 (9.8)	58.3 (8.7)	55.7 (8.8)	51.9 (10.8)
Average BCVA during study (ETDRS letters), mean (SD)	64.5 (11.6)	62.5 (11.6)	58.9 (10.2)	52.5 (10.3)
BCVA average change from baseline (ETDRS letters), LSM (95% CI)	6.54 (4.84, 8.24)	4.66 (2.98, 6.35)	3.10 (1.40, 4.79)	–0.34 (–2.06, 1.38)
Difference in BCVA average change (ETDRS letters), LSM (95% CI); *P* value[a]				
Q4 vs Q 1	–6.9 (– 9.3, –4.4); *P*<.001			
Q3 vs Q1	–3.4 (–5.8, –1.1); *P*=.026			
Q2 vs Q1	–1.9 (–4.3, 0.5); *P*=.407			
Q3 vs Q4	3.4 (1.0, 5.8); *P*=.027			
Q2 vs Q4	5.0 (2.6, 7.4); *P*<.001			
Q2 vs Q3	1.6 (–0.8, 4.0); *P*=.573			

BCVA: Best-Corrected Visual Acuity; CI: Confidence Interval; CRT: Central Retinal Thickness; CRT-SD: Standard Deviation of Central Retinal Thickness; ETDRS: Early Treatment Diabetic Retinopathy Study; LSM: Least Squares Mean; Q: Quartile; SD: Standard Deviation.

[a]Intergroup comparison of LSM average change in BCVA during the study period, based on analysis of covariance model with CRT-SD quartile as factor and baseline BCVA as covariate.

Table 3: Average Change From Baseline in BCVA Over Study Period, Categorized by Duration of Retinal Edema.

Parameter	Group A CRT ≥300 µm for ≤6 months (n=45)	Group B CRT ≥300 µm for >6 to ≤12 months (n=44)	Group C CRT ≥300 µm for >12 months (n=205)
Baseline BCVA (ETDRS letters), mean (SD)	56.0 (9.8)	57.2 (8.6)	55.8 (10.1)
Average BCVA during study (ETDRS letters), mean (SD)	61.9 (10.2)	63.8 (9.6)	56.7 (11.8)
BCVA average change from baseline (ETDRS letters), LSM (95% CI)	5.92 (3.63, 8.22)	6.86 (4.54, 9.19)	0.83 (–0.24, 1.91)
Difference in BCVA average change (ETDRS letters), LSM (95% CI); *P* value[a]			
Group B vs Group A	0.9 (–2.3, 4.2); *P*=.570		
Group C vs Group A	– 5.1 (–7.6, -2.6); *P*<.0001		
Group C vs Group B	– 6.0 (–8.6, –3.5); *P*<.0001		

BCVA: Best Corrected Visual Acuity; CI: Confidence Interval; CRT: Central Retinal Thickness; ETDRS: Early Treatment Diabetic Retinopathy Study; LSM: Least Squares Mean; SD: Standard Deviation.

[a]Intergroup comparison of LSM average change in BCVA during the study period, based on analysis of covariance model with duration of retinal edema as factor and baseline BCVA as covariate.

Table 4: Regression Analysis of Average Change From Baseline in BCVA Over Study Period (AUC Approach) With CRT-SD as Predictor.

Effect	Estimate	Standard Error	*P* Value
Intercept	30.729	3.879	<.001
CRT-SD	–0.044	0.005	<.001
Age	–0.11	0.037	.003
Sex			
Female	–2.1	0.631	<.001
Male	0		
Race			
Asian	2.007	1.874	.284
Black	2.923	2.238	.192
Caucasian	1.191	1.766	.500
Hispanic	2.602	1.987	.191
Japanese	–3.559	5.917	.548
Other	0		
Number of treatments			
1	–4.463	1.389	.001
2	–3.949	1.316	.003
3	0.86	1.371	.531
4	–2.451	1.342	.068
5	–3.608	1.313	.006
6	–2.078	1.182	.079
7	0		
Baseline BCVA	–0.264	0.033	<.001

AUC: Area Under the Curve; BCVA: Best Corrected Visual Acuity; CRT-SD: Standard Deviation of Central Retinal Thickness.

Discussion

This post hoc analysis of anatomical and functional data from MEAD study eyes undergoing intravitreal treatment with DEX implant 0.7 mg for DME indicates that CRT variability, as determined by OCT, is significantly and negatively associated with long-term BCVA improvement. On stratification of eyes according to their CRT variability (CRT-SD) over the 3-year treatment period, there was a difference of 6.9 ETDRS letters in BCVA average change over this period, and a difference of 9.8 letters in BCVA change at month 39 in favor of the least variable quartile relative to the most variable quartile. Likewise, when study eyes were categorized by their duration of exposure to retinal edema (defined as CRT ≥300 µm), significantly greater average improvements in BCVA over 3 years were shown by eyes with shorter-lasting (<6 months or 6-12 months) versus longer-lasting (>12 months) retinal edema.

These findings are consistent with and corroborate earlier reports linking repeated fluctuations in CRT with inferior visual outcomes in patients receiving intravitreal anti-VEGF (bevacizumab, ranibizumab, or aflibercept) and corticosteroid (fluocinolone) therapy for center-involved DME [28-30]. A post hoc analysis of data from the Diabetic Retinopathy Clinical Research Protocol T and Protocol V trials [10,39], which stratified study eyes (n=1,179) by CRT-SD quartile while adjusting for baseline BCVA, CRT, lens status, and treatment arm, reported significantly better improvements in BCVA outcomes at 12 and 24 months in the least variable quartile (Quartile 1) relative to the most variable quartile (Quartile 4) [28]. A retrospective study of electronic medical records from DME patients (n=266) receiving anti-VEGF therapy in clinical practice, which used mixed-effects linear regression to control for baseline, demographic, and treatment variables, reported CRT-SD to be an independent predictor of visual acuity, with a 100 µm reduction in CRT-SD translating into a mean improvement of 6.9 ETDRS letters at 12 months [29]. Stratification of study eyes by CRT variability (CRT-SD) over 12 months revealed a difference in visual acuity at 12 months of 9.7 ETDRS letters between the least and most variable quartiles. Furthermore, a post hoc analysis of real-world data from the US Retrospective Chart Review in Patients Receiving Iluvien (USER) study [40] revealed a modest but statistically significant correlation (r^2=0.1526, *P*<.0001) between CRT-SD and the last observed visual acuity measurement in study eyes (n=120) receiving fluocinolone acetonide implant for DME [30]. In the present study, we choose to analyze CRT fluctuations but other parameters such as macular volume fluctuations could have been used instead. Anatomical findings from the MEAD study indicated that dexamethasone implant-treated eyes experienced greater reductions in macular volume than sham-treated eyes [41]. However, the association between macular volume fluctuations and visual outcome does not appear to have been explored in DME. Measuring changes in the various retinal tissue compartments is hugely time consuming if performed manually, and analysis of OCT cube scans from multiple visits would require the development and validation of an Artificial Intelligence (AI) software algorithm applicable to DME. This type of machine-learning technology is currently in its infancy but holds the promise of identifying OCT volumetric biomarkers that could be used to individualize treatment decisions in DME [42-44].

In the MEAD study, administration of DEX implant at ≥6-month intervals (a median of 4 to 5 injections were given over the 3-year study period) resulted in a saw-tooth pattern of CRT oscillation over time, with the duration of each cycle of CRT reduction and rebound approximating to the dosing interval [41]. Accordingly, a shorter retreatment interval (<6 months) might be anticipated to decrease the amplitude of CRT fluctuation with DEX implant and thereby improve visual outcomes. Consistent with previous studies indicating that the effect of DEX implant on CRT peaks at approximately 1 to 3 months before gradually declining [45-47], real-world data suggest that anatomic recurrence of DME generally occurs between months 4 and 5, preceding functional recurrence by approximately 2 weeks [48]. Several randomized studies employing shorter (4- or 5-month) treatment intervals have demonstrated clinical benefits with DEX implant [49,50]. Given these findings, it is possible that the patients in this study were undertreated. These findings therefore would favor a strategy of early retreatment with DEX implant to limit CRT fluctuation as well as chronic alterations to the retina associated with DME recurrence [51,52].

Strengths of this analysis include its use of prospectively gathered data from a controlled clinical trial employing a standardized OCT scanning protocol, and a regular schedule of clinic visits over 3 years of follow-up. A weakness of this analysis is its retrospective nature, which prevents inference of causality between anatomical and functional outcomes. A further limitation of the analysis is its heavy reliance on LOCF for imputation of incomplete CRT and BCVA data occasioned by patient attrition (by the time of the final study visit at month 39 over one-third of the original patient cohort had discontinued or been lost to follow-up). The LOCF technique for replacing missing longitudinal data assumes that patient dropout is random and unrelated to the outcome being measured (e.g., it is not due to lack of treatment efficacy), and that for those patients who drop out, their observations would not have changed if they had remained in the study [53]. For the present analysis, these assumptions are

unrealistic, and generalizing available BCVA and CRT data in this way introduces potential survival bias by underestimating the true variability in these parameters.

In conclusion, CRT variability may provide a reliable predictive marker of visual outcome, when used in association with CRT measurements and other qualitative OCT biomarkers (e.g., disorganization of the retinal inner layers, loss of ellipsoid zone, and disturbance of foveal photoreceptor integrity), in patients with DME. Mitigating the frequency and persistency of fluctuations in macular thickness in DME may translate into beneficial effects on visual outcomes.

Author declarations

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Data sharing statement

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual, and trial-level data (analysis data sets), as well as other information (eg, protocols, clinical study reports, or analysis plans), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications.

These clinical trial data can be requested by any qualified researchers who engage in rigorous, independent, scientific research, and will be provided following review and approval of a research proposal, Statistical Analysis Plan (SAP), and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time after approval in the US and Europe and after acceptance of this manuscript for publication. The data will be accessible for 12 months, with possible extensions considered. For more information on the process or to submit a request, visit the following link: https://vivli.org/ourmember/abbvie/ then select “Home”.

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Conflict of interest

Thibaud Mathis reports consultancy fees from AbbVie, Bayer, Horus, Novartis, and Roche. Franck Fajnkuchen reports consultancy fees from AbbVie, Bayer, Horus, and Novartis. Audrey Giocanti-Aurégan reports consultancy fees from AbbVie, Apellis, Bayer, Horus, Novartis, Roche, and Thea. Desiree Owen, Hongxin Lai, and Julien Bruban are employees of AbbVie and may hold AbbVie stock and/or stock options.

Abbreviations and acronyms: AI: Artificial Intelligence; Anti-VEGF: Anti-Vascular Endothelial Growth Factor; AUC: Area Under The Curve; BCVA: Best Corrected Visual Acuity; CI: Confidence Interval; CRT: Central Retinal Thickness; CRT-SD: Standard Deviation of Central Retinal Thickness; DME: Diabetic Macular Edema; DEX: Dexamethasone Intravitreal; ETDRS: Early Treatment Diabetic Retinopathy Study; LOCF: Last Observation Carried Forward; LSM: Least Square Mean; OCT: Optical Coherence Tomography.

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Sup Table 1: Change From Baseline in BCVA at Month 39, Categorized by Quartile of CRT-SD.

Parameter	Quartile 1 (n=87)	Quartile 2 (n=88)	Quartile 3 (n=86)	Quartile 4 (n=88)
Baseline BCVA (ETDRS letters), mean (SD)	58.5 (9.8)	58.3 (8.7)	55.7 (8.8)	51.9 (10.8)
BCVA at month 39 (ETDRS letters), mean (SD)	64.8 (14.4)	61.9 (17.3)	57.8 (16.9)	50.5 (17.7)
BCVA change from baseline at month 39 (ETDRS letters), LSM (95% CI)	7.08 (3.84, 10.33)	4.34 (1.12, 7.57)	1.95 (–1.30, 5.19)	–2.76 (–6.04, 0.52)
Difference in BCVA change (ETDRS letters), LSM (95% CI); *P* value[a]				
Q4 vs Q1	–9.8 (–14.5, –5.2); *P*<.001			
Q3 vs Q1	–5.1 (–9.7, –0.6); *P*=.125			
Q2 vs Q1	–2.7 (–7.3, 1.8); *P*=.636			
Q3 vs Q4	4.7 (0.1, 9.3); *P*=.186			
Q2 vs Q4	7.1 (2.5, 11.7); *P*=.015			
Q2 vs Q3	2.4 (–2.2, 7.0); *P*=.731			

BCVA: Best-Corrected Visual Acuity; CI: Confidence Interval; CRT: Central Retinal Thickness; CRT-SD: Standard Deviation of Central Retinal Thickness; ETDRS: Early Treatment Diabetic Retinopathy Study; LSM: Least Squares Mean; Q: Quartile; SD: Standard Deviation.
[a]Intergroup comparison of LSM change in BCVA at month 39, based on analysis of covariance model with CRT-SD quartile as factor and baseline BCVA as covariate.

Sup Table 2: Average Change From Baseline in BCVA Over Study Period, Categorized by SD-Time with CRT <300 µm.

Parameter	Quartile 1 (n=72)	Quartile 2 (n=72)	Quartile 3 (n=72)	Quartile 4 (n=73)
Baseline BCVA (ETDRS letters), mean (SD)	54.1 (10.1)	56.4 (9.2)	56.8 (9.7)	57.3 (9.1)
Average BCVA during study (ETDRS letters), mean (SD)	57.3 (11.8)	59.7 (12.0)	61.8 (11.1)	63.8 (10.1)
BCVA average change from baseline (ETDRS letters), LSM (95% CI)	3.24 (1.34, 5.14)	3.25 (1.35, 5.15)	4.97 (3.07, 6.87)	6.48 (4.59, 8.37)
Difference in BCVA average change (ETDRS letters), LSM (95% CI); *P* value[a]				
Q4 vs Q1	3.2 (0.6, 5.9); *P*=0.018			
Q3 vs Q1	1.7 (–1.0, 4.4); *P*=.207			
Q2 vs Q1	0.01 (–2.7, 2.7); *P*=.995			

BCVA: Best-Corrected Visual Acuity; CI: Confidence Interval; CRT: Central Retinal Thickness; ETDRS: Early Treatment Diabetic Retinopathy Study; LSM: Least Squares Mean; Q: Quartile; SD: Standard Deviation; SD-time: Standard Deviation of Time.
[a]Intergroup comparison of LSM average change in BCVA during the study period, based on analysis of covariance model with SD-time with CRT <300 µm quartile as factor and baseline BCVA as covariate.