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Optical Coherence Tomography Biomarkers as Functional Outcome Predictors in Diabetic Macular Edema Treated with Dexamethasone Implant

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Purpose: Identification and characterization of patients with diabetic macular edema (DME) are important for individualizing treatment and optimizing outcome. We investigated optical coherence tomography (OCT) biomarkers for DME treated by intravitreal dexamethasone (DEX) implant.

Design: Multicenter, retrospective, observational cohort study.

Participants: A total of 299 eyes from 284 patients treated with DEX implant for DME (naïve, n = 209; refractory, n = 90). Baseline best-corrected visual acuity (BCVA) was between 0.3 and 1.0 on a logarithm of minimum angle of resolution visual chart.

Methods: The OCT scans previous to DEX implants were evaluated for submacular fluid, size and location of cystoid changes, inner segment-outer segment (IS-OS) continuity, quantity and location of hyperreflective foci (HRF), vitreomacular interface abnormalities, and epiretinal membrane. The BCVA and central macular thickness were recorded at baseline and at 1, 2, and 4 months after treatment with DEX implants. Correlations between OCT measures and visual outcome were analyzed using the generalized estimating equations procedure.

Main Outcome Measures: The correlation between spectral-domain (SD) OCT measures at baseline and BCVA response (mean change from baseline; categorized improvement [<5, 5−9, or ≥10; Early Treatment Diabetic Retinopathy Study letters] in BCVA) after treatment with a DEX implant.

Results: The presence of subretinal fluid (odds ratio [OR], 1.98; 95% confidence interval [CI], 1.23−3.20; $P = 0.01$), absence of HRF (OR, 3.66; 95% CI, 1.40−9.62; $P = 0.01$), and integrity of the IS-OS layer (OR, 2.09; 95% CI, 1.30−3.37; $P = 0.003$) were all predictive of better visual outcome after treatment with DEX implants. Although eyes with naïve DME gained more vision than refractory eyes ($P < 0.001$), the predictive value of OCT findings did not differ according to this classification.

Conclusions: Spectral-domain OCT is useful in identifying various imaging findings in DME. Among eyes with DME, those with submacular fluid, no HRF, and a continuous IS-OS layer responded better to DEX implants than those without these features. These findings call for further study of combinations of OCT and metabolic biomarkers. *Ophthalmology 2017;■:1−9 © 2017 by the American Academy of Ophthalmology*

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Vision loss associated with diabetic retinopathy is most commonly caused by diabetic macular edema (DME),[1] which affects approximately 7% of all diabetic patients.[2] Antivascular endothelial growth factor (VEGF) injections are generally considered suitable first-line therapy for center-involved DME and are effective in improving visual acuity (VA), with 10% to 40% of patients achieving significant improvement in best-corrected visual acuity (BCVA) after 1 year of treatment.[3−6] Still, a considerable proportion of patients do not respond satisfactorily to anti-VEGF agents, even with intensive treatment over the first year.[7−9] A recent post hoc analysis of the Diabetic Retinopathy Clinical Research Network's (DRCR.net) Protocol I study revealed that approximately 40% of eyes gain <5 letters after 3 months and approximately 50% of these maintain poorer long-term visual outcomes after 3 years than eyes with favorable early response.[10] Thus, early identification and characterization of patients with DME are critical, as well as the provision of individualized treatment regarding optimal functional outcome and disease management.

The efficacy of dexamethasone (DEX) intravitreal implant 0.7 mg (Ozurdex, Allergan, Inc., Irvine, CA) in DME has been shown by improvement in VA and decrease in retinal thickness,[11,12] even in patients with DME that is refractory to anti-VEGF treatments.[13−15] Corticosteroids and anti-VEGF treatments target different pathways in the pathogenesis of DME.[16]

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Anatomic measures on spectral-domain (SD) optical coherence tomography (OCT), such as precise evaluation of individual layers, quantification of retinal thickness and macular volume, and qualitative assessment of fluid distribution and existence of hyperreflective foci (HRF),[17] could predict treatment success or failure to various therapies. Baseline OCT measures have been investigated regarding their predictive value in patients with DME treated by anti-VEGF therapy.[18–25] We hypothesized that distinct structural changes identifiable on SD OCT could help predict treatment responses to DEX implants, distinct from findings in eyes treated with anti-VEGF treatments. The purpose of this study was to investigate whether characteristics identified on SD OCT may serve as biomarkers and predict treatment response to DEX implants in patients with DME.

Methods

Institutional review board approval was obtained through the individual institutional review boards at the participating institutes for a retrospective consecutive chart review. This international multicenter study included 14 centers (Supplementary Material, available at www.aaojournal.org). The research adhered to the tenets of the Declaration of Helsinki. Patient records from January 1, 2011, to August 1, 2016, were reviewed for cases of DME treated by intravitreal DEX implant.

Study Participants

To be included in the analysis, patients had to fulfill the following criteria: (1) age ≥18 years; (2) type 1 or 2 diabetes mellitus; (3) DME (both naïve and refractory) causing visual loss, with study eye BCVA measuring 0.3 to 1.0 logarithm of the minimum angle of resolution; macular edema defined clinically and by retinal thickness of >250 μm in the central subfield; and intraretinal or subretinal fluid (SRF) seen on SD OCT; (4) treatment with DEX implant. For patients who received bilateral treatment with DEX, both eyes were included. Refractory DME was defined as worsening of BCVA by 2 Early Treatment Diabetic Retinopathy Study lines or reduction of less than 10% of retinal thickness on SD OCT measured 1 month after at least 3 anti-VEGF injections that were given at monthly intervals.[10] Only first treatments with DEX implants were considered for the study. Exclusion criteria were (1) another concomitant ocular disease that causes macular edema (i.e., neovascular age-related macular degeneration or choroidal neovascularization due to other reasons, retinal vein occlusion, uveitis, and recent intraocular surgery possibly causing postsurgical macular edema); (2) another ocular condition that compromises VA, except for the presence of cataract; and (3) previous treatment with intraocular corticosteroids within the 6 months before treatment with the DEX implant.

Patient charts were reviewed for demographic data, hemoglobin A1C (HbA1C) values, type of retinopathy (nonproliferative or proliferative), previous treatments for DME, and BCVA before the DEX implant and at 1, 2 and 4 months after the injection.

Optical Coherence Tomography Analysis

The OCT scans were obtained using SD OCT: Heidelberg Spectralis, Heidelberg, Germany; Optovue Avanti, Fremont, California; Topcon 3D OCT-2000, Tokyo, Japan; and Cirrus, Zeiss, Oberkochen, Germany. Quantitative assessment of DME included central macular thickness (CMT) that was calculated automatically by the instrument and recorded at baseline and at 1, 2, and 4 months after the DEX implant. Qualitative and quantitative evaluations of SD OCT images performed at baseline assessed the presence of several morphologic features (Fig 1), including (1) SRF; (2) cystoid changes in the outer nuclear layer (ONL) and maximal cyst size in the ONL (small <100 μm, large 100–200 μm, 3 = giant >200 μm); (3) presence of cystoid changes in the inner nuclear layer (INL); (4) continuity of the inner segment-outer segment (IS-OS) layer (completely continuous, partly disrupted, completely disrupted); (5) presence of HRF, as well as quantity (few 2–10, moderate 11–20, many >21) and location (between the internal limiting membrane and the INL; between the outer plexiform layer and external limiting membrane; in all retinal layers); (6) status of the vitreomacular interface (detached, vitreomacular adhesion, vitreomacular traction); and (7) presence of an epiretinal membrane. The listed features were evaluated on 3 horizontal OCT scans: 1 b-scan encompassing the fovea, 2 b-scans respectively 500 μm superior and 500 μm inferior to the fovea. Grading of the OCT images was performed by 3 experienced retina specialists (DZ: 109 cases, MI: 100 cases, AI: 90 cases) who were blinded to the functional and anatomic results. Interrater reliability was calculated among 90 cases that were graded by all graders. The CMT was recorded at baseline and at 1, 2, and 4 months after the DEX implant.

Statistical Analysis

Interrater reliability was tested as absolute agreement with a 2-way mixed interclass correlation model. To control for the correlated nature of our data, we used a generalized estimating equation (GEE) procedure. Differences in functional treatment response and OCT baseline measures between naïve and refractory patients were calculated by a GEE model and included baseline BCVA as a covariate. Differences in anatomic outcomes were calculated and include baseline CMT as a covariate.

The GEE models for outcome measures (BCVA response at 2 and 4 months) were run by testing the following predictors at baseline: (1) BCVA; (2) naïve or refractory DME; (3) the presence of SRF; (4) the presence of ONL cysts; (5) ONL cyst size; (6) presence of INL cysts; (7) IS/OS continuity; (8) HRF presence; (9) HRF quantity; (10) HRF location; (11) vitreoretinal interface; and (12) presence of an epiretinal membrane. Predictors were included stepwise in the GEE model and kept in the model if the P value was less than 0.10. The final GEE model was used to calculate the odds ratios (ORs) and their 95% confidence intervals (CIs), with a change of 5 letters in baseline BCVA considered a standard unit of change.

An association of HbA1c levels with baseline and response parameters was examined using a linear GEE model. For BCVA and CMT response after 4 months, baseline levels were included as covariates.

The last observation carried forward method was used to impute missing data. Values are presented as mean ± standard deviation. Statistical analysis was performed with SPSS Statistics 22 (IBM, Armonk, NY).

Results

Study Participants

A total of 299 eyes from 284 patients were included in the analysis. Demographic data are shown in Table 1. In 209 eyes (70%), DME was naïve; 90 cases (30%) were refractory to previous anti-VEGF injections. The mean number of previous anti-VEGF injections was 7.7±8.8. A total of 104 eyes (35%) were previously treated by macular laser. A total of 169 eyes (57%) were phakic, and 130 eyes (43%) were pseudophakic. HbA1c levels were available for 180 patients; the mean value was 8.4%±2.7%.