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Correlation between Deep Capillary Plexus Perfusion and Long-Term Photoreceptor Recovery after Diabetic Macular Edema Treatment

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Purpose: To determine the association between baseline deep capillary plexus (DCP) integrity and long-term photoreceptor recovery as well as visual outcome after treatment in patients with diabetic macular edema (DME).

Design: Retrospective, interventional case series.

Participants: Sixty-seven eyes with DME that resolved successfully with initial treatment (baseline) and that remained edema free for 12 months after the initial DME resolution.

Methods: Best-corrected visual acuity (BCVA), spectral-domain (SD) OCT, and OCT angiography findings were collected at baseline and at 6 and 12 months after baseline. Correlations were analyzed between DCP integrity parameters (vascular flow density [VD] and area of the foveal avascular zone [FAZ]) and photoreceptor integrity parameters (ellipsoid zone [EZ] and external limiting membrane [ELM] integrity). Multivariate linear regression analysis was conducted to identify the baseline predictors for photoreceptor recovery and visual improvement.

Main Outcome Measures: The association between baseline DCP integrity and recovery of photoreceptor integrity over 12 months.

Results: At baseline, the mean central retinal thickness was 306.1±51.8 μm. The mean baseline DCP VD and FAZ were 14.4±5.2% and 0.71±0.36 mm^2, and the mean baseline EZ and ELM integrity were 57.2±26.1% and 76.4±19.8%, respectively. Ellipsoid zone and ELM integrity recovered significantly at 12 months from baseline (both $P < 0.001$). The degree of EZ and ELM integrity recovery was well correlated with the baseline DCP VD ($P = 0.004$ and $P = 0.009$, respectively) and DCP FAZ ($P = 0.007$ and $P = 0.009$, respectively). Moreover, the mean change in BCVA from baseline to 12 months was significantly greater with higher baseline DCP VD ($P = 0.003$) and smaller DCP FAZ ($P = 0.042$). Compared with anti−vascular endothelial growth factor (VEGF) nonresponders, anti-VEGF responders had higher baseline DCP integrity and a significantly greater degree of photoreceptor recovery at 12 months.

Conclusions: The degree of DCP preservation at the time of initial DME resolution is correlated closely with long-term recovery of photoreceptor integrity and visual outcome in patients with resolved DME. *Ophthalmology Retina 2017;■:1−9 © 2017 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

Supplemental material is available at www.ophthalmologyretina.org.

Diabetic macular edema (DME) is a major cause of visual loss in diabetic patients[1] and affects up to 21 million of 93 million patients with diabetic retinopathy (DR) worldwide.[2] Anti−vascular endothelial growth factor (VEGF) agents currently are the primary treatment option for DME,[3−5] and corticosteroid agents also are used in some DME eyes that are resistant to anti-VEGF or are pseudophakic.[6−8] Nevertheless, refractory cases require repeated intravitreal injections, which place physical and financial burdens on patients[9]; moreover, delayed resolution of macular edema also can lead to irreversible photoreceptor damage.[10,11] Hence, it is important to identify factors that allow for prediction of treatment response and visual outcome after DME treatment.

Macular ischemia confirmed by fluorescein angiography is known to be associated with poor visual outcomes after DME treatment.[12,13] After the advances in spectral-domain (SD) OCT, several investigators have attempted to identify the correlation between structural changes observed in SD OCT and visual prognosis in patients with DME.[14−18] However, results of these studies remain controversial. Disruptions of ellipsoid zone (EZ) and external limiting membrane (ELM) as evaluated by SD OCT also are known to be associated with visual acuity in DME and other retinal diseases.[19−24] However, the evaluation of photoreceptor integrity may be difficult and inaccurate in cases in which the macula is edematous because of intraretinal fluid collection; therefore, DME should be resolved effectively before photoreceptor integrity can be measured accurately.

The recent development of OCT angiography (OCTA) has enabled closer observation of blood flow through each

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retinal capillary plexus without the need for intravenous dye injection, a parameter that could not be evaluated previously with fluorescein angiography or SD OCT.[25] Several studies have shown that deep capillary plexus (DCP) loss is more prominent than superficial capillary plexus (SCP) loss in eyes with DR or DME,[26–30] thus highlighting the importance of DCP evaluation.

We previously reported that in DCP, anti-VEGF nonresponder DME eyes had significantly lower vascular flow density (VD) and larger areas of foveal avascular zone (FAZ) than did anti-VEGF responder eyes.[31] Furthermore, patients who were resistant to initial anti-VEGF treatments experienced significant visual loss, even though they were treated successfully with subsequent intravitreal steroid administration or vitrectomy surgery. In the present study, we examined long-term visual recovery after successful treatment of DME over 12 months and assessed the association between the extent of baseline DCP loss (recorded immediately after initial DME resolution) and final photoreceptor recovery.

Methods

Patients and Ophthalmologic Examinations

This retrospective interventional case series included the eyes of DME patients who exhibited an edema-free macula for 12 months after initial resolution of DME, regardless of their initial anti-VEGF responsiveness or types of additional treatments received. This study was performed in accordance with the tenets of the 1975 Declaration of Helsinki and its 1983 revision and was approved by the institutional review board of Asan Medical Center, Seoul, Korea. We recorded treatment patterns and outcomes in these cases during the following 12 months. To avoid potential bias, we excluded eyes that underwent cataract extraction or vitrectomy during the follow-up period. We also excluded eyes that could not be scanned using SD OCT or those with poor OCTA images with a signal strength index of less than 50 resulting from media opacity or with significant motion artifacts because of poor patient cooperation.

In our previous study, an anti-VEGF responder was defined as an eye showing a reduction of more than 50 μm in central retinal thickness (CRT) after 3 consecutive anti-VEGF injections, and a nonresponder was defined as an eye showing no reduction, a reduction less than 50 μm, or an increase in CRT after 3 consecutive anti-VEGF injections. Among a total of 83 DME eyes (32 responders and 51 nonresponders) from the study, 32 responder eyes and 35 nonresponder eyes (64 bevacizumab-treated eyes, 2 aflibercept-treated eyes, and 1 ranibizumab-treated eye) that were treated with additional dexamethasone implants showed resolution of DME over the subsequent 12 months. Thus, 67 DME eyes from 47 consecutive patients who showed resolved macular edema were included in this study. To analyze the recovery of photoreceptor integrity and visual outcome, we defined the baseline time point of initial DME resolution as 1 month after the last intravitreal injection of anti-VEGF or dexamethasone implant, depending on the anti-VEGF responsiveness (Fig 1). At this baseline time point, OCTA was performed to minimize the segmentation error associated with the presence of cystoid space, intraretinal fluid, or subretinal fluid.

We reviewed the clinical characteristics of patients, including diabetes duration, DR duration, presence of hypertension, and glycosylated hemoglobin levels, within the preceding 3 months. Moreover, best-corrected visual acuity (BCVA) measurement using a Snellen chart, fundus photography, and SD OCT were performed at each follow-up visit. We recorded the following data at baseline and after 6 and 12 months: BCVA, CRT, and photoreceptor status based on the integrity of EZ and ELM layers. The OCTA images at baseline and after 12 months also were collected. We permitted a variation of 1 week for the follow-up interval.

Image Analysis

OCT angiography (AngioVue; Optovue, Inc., Fremont, CA) was used to obtain split-spectrum amplitude-decorrelation angiography images, as previously described.[25] The scanning area was captured in 3 × 3-mm sections and was centered at the fovea. We used autosegmentation software, wherein the en face image was segmented with an inner boundary of 15 μm beneath the inner plexiform layer and an outer boundary of 70 μm beneath the inner plexiform layer, to obtain images of DCP. In eyes with incorrect segmentation, we manually adjusted the offset value of the inner

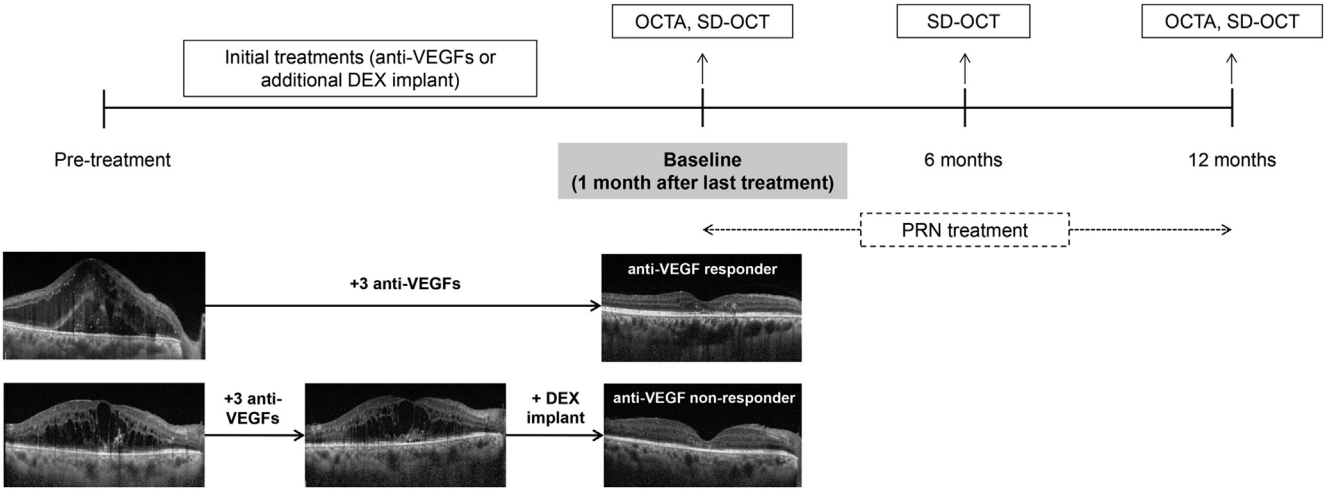

Figure 1. Diagram showing analyzed study visit and ophthalmologic examinations after treatment for diabetic macular edema (DME). The baseline time point was defined as 1 month after the last intravitreal injection (anti–vascular endothelial growth factor [VEGF]) or dexamethasone (DEX) implant. Eyes with resolved DME that were followed up for at least 12 months with pro re nata (PRN) treatment were included in the analysis. OCTA = OCT angiography; SD = spectral-domain.