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Effect of Vitreomacular Adhesion on Treatment Outcomes in the Ranibizumab for Edema of the Macula in Diabetes (READ-3) Study

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Purpose: To assess the role of vitreomacular adhesion (VMA) in visual and anatomic outcomes in patients with diabetic macular edema (DME).

Design: Retrospective cohort study.

Participants: Data from patients enrolled in the Ranibizumab for Edema of the Macula in Diabetes: Protocol 3 with High Dose (READ-3) study were analyzed.

Methods: In the READ-3 study, patients with DME received monthly intravitreal injections of either 0.5 or 2.0 mg ranibizumab. Optical coherence tomography images from patients who completed the month 6 visit of the study were analyzed at the baseline visit to identify the presence (VMA+) or absence (VMA−) of VMA. Patients with any degree of vitreomacular traction were excluded from the analysis. Two independent graders graded all images. Vitreomacular adhesion was classified by size of adhesion into either focal (<1500 μm) or broad (≥1500 μm).

Main Outcome Measures: Mean changes in best-corrected visual acuity (BCVA) and central retinal thickness (CRT) at month 6 and incidence of posterior vitreous detachment (PVD).

Results: One hundred fifty-two eyes (152 patients) were randomized in the READ-3 study. One hundred twenty-four eyes (124 patients) were eligible for the study based on study criteria. Twenty-eight eyes did not meet study criteria and were excluded from the study. At baseline, 26 patients were classified as VMA+ and 98 patients were classified as VMA−. The distribution of the 2 doses of ranibizumab (0.5 and 2.0 mg) in the 2 groups was similar. At month 6, the mean improvement in BCVA was 11.31±6.67 and 6.86±7.58 letters in the VMA+ and VMA− groups, respectively ($P = 0.007$). Mean improvement in CRT was −173.81±132.31 and −161.84±131.34 μm in the VMA+ and VMA− groups, respectively ($P = 0.681$). At month 6, among the 26 VMA+ eyes (at baseline), 7 eyes demonstrated PVD, 17 eyes showed no change in VMA status, and 2 eyes were not gradable and were excluded.

Conclusions: Diabetic macular edema patients with VMA have a greater potential for improvement in visual outcomes with anti−vascular endothelial growth factor therapy. Therefore, the presence of VMA should not preclude patients with DME from receiving treatment. *Ophthalmology 2016;123:324-329 © 2016 by the American Academy of Ophthalmology.*

Vascular endothelial growth factor (VEGF) plays a critical role in the pathogenesis of diabetic macular edema (DME), with studies reporting elevated levels of VEGF in the retina and vitreous in eyes with DME.[1] Results from phase 3 clinical trials that evaluated the role of one such VEGF antagonist (ranibizumab) in the treatment of patients with DME[2–4] has led to the approval of the 0.3-mg dose of ranibizumab by the United States Food and Drug Administration.

Although more than half of the participants in these trials demonstrated a visual gain of 10 letters or more, a subset of patients did not show similar gains. Such variation in response to therapy may occur for several reasons, including, but not limited to, variance in genetic makeup, severity of disease, concomitant comorbidities, and environmental factors. Lower mean baseline best-corrected visual acuity (BCVA), uncontrolled edema, foveal atrophy, and focal laser photocoagulation in close proximity to the fovea already have been reported as possible factors leading to poor visual outcomes in patients being treated with ranibizumab for DME.[5] However, Bressler et al[6] reported that in patients with DME, younger age, lower grade of retinopathy, absence of surface wrinkling retinopathy, and presence of hard exudates in the macula at the time of treatment initiation resulted in favorable visual outcomes.

Vitreomacular interface diseases have been reported to occur in up to 7% to 16% of eyes with DME, with an annual incidence as high as 4.5%.[7,8] These anomalies include

http://dx.doi.org/10.1016/j.ophtha.2015.09.032
ISSN 0161-6420/15

vitreomacular traction (VMT), epiretinal membrane (ERM) and vitreomacular adhesion (VMA). The role of VMT and the ERM in affecting treatment outcomes of patients with DME has been reported previously[6]; however, there are no reports in the literature regarding the role of VMA in this patient population. In the index study, we assessed the role of VMA as a possible prognostic factor in patients receiving anti-VEGF therapy for DME. We also assessed the rates of posterior vitreous detachment (PVD) after monthly intravitreal injections of ranibizumab in patients with VMA and DME.

Methods

Data from the Ranibizumab for Edema of the Macula in Diabetes: Protocol 3 with High Doses (READ-3) clinical trial were used for this study. The study was approved by local institutional review boards for selected sites and by the Western Institutional Review Board for others, and it was conducted in compliance with the Declaration of Helsinki, the United States Code of Federal Regulations Title 21, and the Harmonized Tripartite Guidelines for Good Clinical Practice (1996). Written informed consent was obtained from all participants of the study.

The READ-3 is a phase II, randomized, multicenter clinical trial that was designed to evaluate and compare the effects of 2 doses of ranibizumab (0.5 and 2.0 mg) in eyes with DME. Patients in both groups received an intravitreal injection of ranibizumab at baseline and months 1, 2, 3, 4, and 5. Month 6 was the primary end point of the study. The study is registered at www.clinicaltrials.gov under the identifier NCT01077401.

For this substudy, the 2 study groups from the READ-3 data set were combined and categorized into groups based on the presence (VMA+) or absence (VMA−) of VMA. Outcome measures that were assessed in the study included mean changes in BCVA, mean changes in central retinal thickness (CRT) at month 6, and incidence of PVD.

Inclusion and Exclusion Criteria

Patients were included in the study if they met the following criteria: (1) participation in the READ-3 trial and completion of the month 6 visit, and (2) availability of spectral-domain (SD) optical coherence tomography (OCT) images (Spectralis; Heidelberg Engineering, Heidelberg, Germany) of sufficient quality for grading. Patients with any degree of VMT, as defined in the published literature, were excluded from the analysis. The READ-3 protocol excluded enrollment of subjects with VMT at baseline. Careful review of all images revealed only 1 eye with a finding of VMT as defined by the International Vitreomacular Traction Study,[9] and the eye was excluded. Inclusion and exclusion criteria of the READ-3 study have been published previously.[10]

Detection of Vitreomacular Adhesion Using Spectral-Domain Optical Coherence Tomography

Using SD OCT images, VMA status was assessed for patients at the baseline visit. Images were graded by 2 independent graders (M.A.S. and M.K.S.) using defined criteria and classified into either VMA+ or VMA−. Presence of VMA was defined as an elevation of the perifoveal vitreous cortex from the retinal surface along with attachment of the vitreous cortex at the center of the fovea and no secondary detectable changes in foveal contour or underlying retinal tissues. The VMA was classified by size of adhesion into either focal (<1500 μm) or broad (≥1500 μm; Fig 1). Images were analyzed carefully to exclude patients with VMT, which was defined as evidence of perifoveal vitreous cortex detachment from the retinal surface; attachment of the vitreous cortex at the center of the fovea; and association of the attachment with distortion of the foveal surface, intraretinal structural changes, elevation of the fovea above the retinal pigment epithelium, or a combination thereof, but no full-thickness interruption of all retinal layers. The International Vitreomacular Traction Study group previously defined these criteria.[9] Vitreomacular adhesion status also was evaluated at the month 6 visit for all patients.

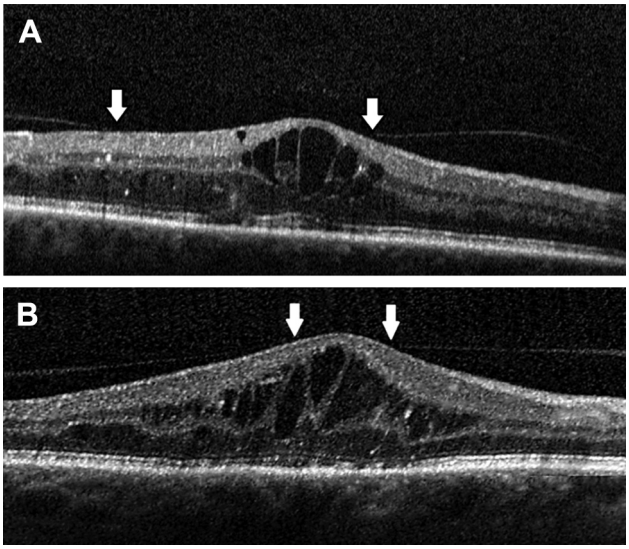

Figure 1. Spectral-domain optical coherence tomography images showing (**A**) broad vitreomacular adhesion (≥1500 μm) and (**B**) focal vitreomacular adhesion (<1500 μm). Arrows indicate vitreous adhesion to the central macula.

Outcome Measures

Outcome measures assessed in the study included (1) mean change in CRT from baseline to month 6, CRT was defined as the thickness of the central 1 mm of the retina on the SD OCT retinal thickness map; and (2) mean change in BCVA from baseline to month 6, BCVA was reported as the number of Early Treatment Diabetic Retinopathy Study letters read at 4 m.

Statistical Analysis

Statistical analysis was performed using GraphPad Prism software version 6 (GraphPad Software, Inc., La Jolla, CA). Frequencies were compared using the chi-square test and the Fisher exact test. The Mann−Whitney *U* test was used to assess the mean difference in BCVA and CRT between the 2 groups at month 6. The Wilcoxon signed-rank test was used to assess the difference in BCVA and CRT between baseline and month 6 for both groups.

Results

One hundred fifty-two eyes (152 patients) were randomized in the READ-3 study. Of 152 eyes, 124 eyes were eligible for this substudy based on the inclusion and exclusion criteria. Twenty-eight eyes did not meet study criteria and were excluded from the study: 17 eyes were found to have ungradable images, 10 patients