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Efficacy of Ranibizumab in Eyes with Diabetic Macular Edema and Macular Nonperfusion in RIDE and RISE

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Purpose: To determine whether there are baseline characteristics that distinguish patients with diabetic macular edema (DME) with coexisting macular nonperfusion (MNP) at baseline and assess these patients' potential to achieve favorable visual acuity (VA), anatomic, and diabetic retinopathy (DR) outcomes over 24 months.

Design: Post hoc analysis of RIDE/RISE, 2 phase 3, parallel, randomized, multicenter, double-masked trials (ClinicalTrials.gov: NCT00473382; NCT00473330).

Participants: Study eyes with best-corrected VA (BCVA)/fluorescein angiogram (FA) data at baseline.

Methods: To measure MNP, the Early Treatment for Diabetic Retinopathy Study (ETDRS) grid was overlaid on FAs of the macula. The MNP area was calculated by estimating the percentage of capillary loss in the central, inner, and outer subfields and converting into disc areas (DAs) using a software algorithm. Summary statistics and *P* values, respectively, were provided for all outcomes and comparisons of interest.

Main Outcome Measures: Baseline characteristics; MNP area, BCVA, and central subfield thickness (CST) at months 12 and 24; and incidence of study eyes with ≥2-step DR improvement at months 3, 6, 12, 18, and 24.

Results: Baseline MNP was detected in 28.2%, 25.8%, and 26.3% of study eyes in the ranibizumab 0.3 mg (n = 213), ranibizumab 0.5 mg (n = 225), and sham (n = 228) arms, respectively. At baseline, patients with MNP were younger and had shorter diabetes duration, worse vision, increased CST, and worse DR severity (*P* values < 0.01 vs. those without MNP). In the ranibizumab 0.3 mg arm, eyes with baseline MNP had lower mean baseline BCVA (53.4 vs. 57.2 ETDRS letters for those without baseline MNP; *P* = 0.05), but mean BCVA gain at month 24 was comparable (+15.6 vs. +13.4 ETDRS letters, respectively; *P* = 0.2). Eyes with baseline MNP had increased CST at baseline, but experienced a greater decrease in CST by month 24. The proportion of eyes with ≥2-step DR improvement was greater for eyes with versus without baseline MNP in each ranibizumab arm.

Conclusions: Despite having worse vision/increased CST versus those without baseline MNP, eyes with concurrent DME and baseline MNP entering RIDE/RISE experienced robust VA and anatomic improvement with ranibizumab and therefore should not be excluded from therapy. *Ophthalmology 2018;■:1–7 © 2018 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/).*

Diabetic retinopathy (DR) and diabetic macular edema (DME) are major causes of visual impairment affecting millions of people worldwide, causing significant morbidity and affecting their quality of life. The advent of anti–vascular endothelial growth factor (VEGF) agents has improved treatment of diabetic eye disease and visual results.[1,2] Despite therapeutic advances, prognostic information has been lacking regarding the treatment of DME in eyes with coexisting macular nonperfusion (MNP). Although animal studies have demonstrated a dose-dependent relationship between increasing levels of VEGF and retinal vascular nonperfusion mediated by leukostasis,[3,4] clinical insights from human data have been lacking. In the absence of supporting evidence, a general understanding has developed in the retina community that increased VEGF expression in the setting of MNP in DME was a compensatory mechanism designed to potentially help to restore perfusion within the macula. Subsequently, a hypothesis developed that VEGF blockade through intravitreal anti-VEGF therapy may result in an increase of the severity or extension of the nonperfusion with consequent adverse visual sequelae to the patient. Although physiologically appealing as a theory, little was known about this complex interrelation and true long-term consequences of VEGF inhibition in the setting of MNP.

In RIDE and RISE (ClinicalTrials.gov identifiers: NCT00473382; NCT00473330), which were 2 phase 3, parallel, randomized, multicenter, double-masked trials, patients with DME received monthly intravitreal ranibizumab (RBZ) (0.3 or 0.5 mg) or sham injections for 24 months.[5] In this post hoc analysis, we evaluated the patients with baseline MNP based on fluorescein angiogram (FA). Previously, 2 publications[6,7] explored MNP in patients with DME from RIDE and RISE. Campochiaro et al[6] examined the effect of VEGF inhibition with monthly RBZ on posterior retinal

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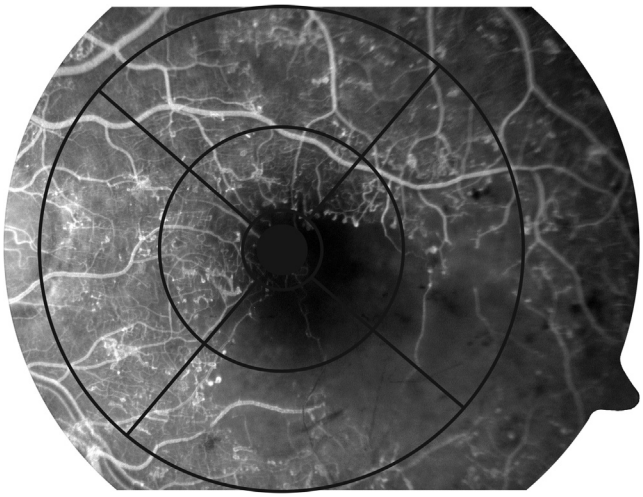


Figure 1. Illustration of Early Treatment for Diabetic Retinopathy Study (ETDRS) grid overlaid on fluorescein angiograms (FAs) of the macula to measure macular nonperfusion (MNP) using a RIDE/RISE patient eye as example. All images were evaluated by trained and certified graders at the Fundus Photograph Reading Center, Madison, Wisconsin. Black fill on image indicates area not measured for nonperfusion. To measure MNP, the ETDRS grid was overlaid on FA images and the percentage of capillary loss was estimated for each subfield. Then, the percentages were converted into disc areas (DAs). Based on DA results, change in MNP status was categorized as worsening (increase in MNP area), no change, or improvement (decrease in MNP area).

nonperfusion and observed that RBZ reduced the progression of MNP over 24 months compared with sham, irrespective of MNP status at baseline. Ip et al[7] assessed DR severity in patients receiving RBZ for up to 3 years and identified baseline patient characteristics associated with the development of proliferative DR. This study found that MNP in the central subfield measured on FA at baseline was a prognostic factor for DR severity worsening, but did not negatively affect vision gains in the RBZ arm.

This post hoc analysis focuses on eyes presenting at baseline with DME and concurrent MNP before the initiation of RBZ therapy. We hope to address whether the vision and anatomic improvements observed with RBZ treatment in the overall RIDE and RISE population were also observed in the subset of study eyes with concurrent MNP at baseline to provide a more complete understanding of this patient population and identify any distinguishing features. Accordingly, the objectives of this analysis of patients with DME in RIDE and RISE were 2-fold: first, to assess potential differences in baseline characteristics between study eyes with and without MNP at baseline and second, to examine and compare the potential of study eyes with and without MNP at baseline to achieve favorable visual acuity (VA), anatomic, and DR severity outcomes after 24 months of RBZ therapy.

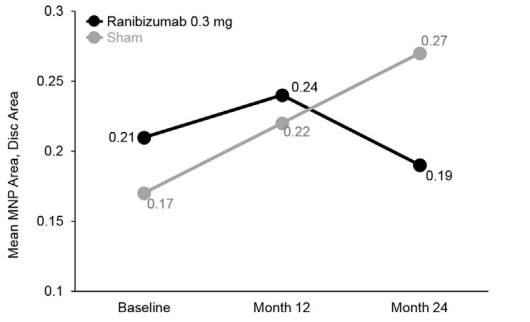
Methods

The methods of RIDE and RISE have been described in detail.[5,8] These trials were compliant with the Health Insurance Portability and Accountability Act and Declaration of Helsinki. Protocols were approved by institutional review boards or ethics committees. All patients provided written informed consent before enrolling in the study.

Presence and area of MNP were evaluated in study eyes (intention-to-treat population) using FA data. All images were evaluated by trained and certified graders at the Fundus Photograph Reading Center, Madison, Wisconsin. To measure MNP, the Early Treatment for Diabetic Retinopathy Study (ETDRS) grid was overlaid on FAs of the macula (field 2 of 7-field fundus photographs) (Fig 1). In each image, the percentage of capillary loss within each specified subfield was estimated, and these percentages were converted into disc areas (DAs) using a software algorithm applied by the reading center. The MNP area was calculated as total DAs of capillary loss on the central, inner, and outer subfields of the ETDRS grid. Additional details of this method of measuring MNP have been described.[6] Change in MNP status from baseline compared the total DAs of capillary loss at baseline and each specified time point. A difference of >0 in DAs of capillary loss compared with baseline was categorized as MNP worsening, a difference of <0 compared with baseline was categorized as MNP improvement, and no difference was categorized as no change.

Baseline characteristics for overall patients with versus without MNP were summarized. The MNP area for the 3 treatment arms (RBZ 0.3 mg, RBZ 0.5 mg, sham) at baseline, month 12, and month 24 were summarized. Mean best-corrected visual acuity (BCVA; ETDRS letters) and central subfield thickness (CST; by time-domain OCT) at months 12 and 24 and the proportion of patients with $\geq$2-step DR improvement at months 3, 6, 12, 18, and 24 were evaluated for patients with versus without MNP at baseline by treatment arm. Change in BCVA at months 12 and 24 was summarized by change in MNP status (worsening, no change, or improvement). Although the following results focus on the RBZ 0.3 mg arm, which is the approved dosage for treatment of DME in the United States, the RBZ 0.5 mg data are included in figures 2 and 3 for completeness.

Summary statistics (N, mean [standard deviation] for continuous variables, n [%] or n/N [%] for categoric variables) were provided for all outcomes of interest. *P* values were provided for comparisons of interest. For baseline characteristics and BCVA or CST outcomes, a 2-group *t* test based on the Satterthwaite method was used for continuous variables, and a 2-sided Fisher exact test was used for categoric variables to compare patients with versus without MNP at baseline. The proportion of patients with $\geq$2-step



Mean (SD) MNP Area, Disc Areas			
Ranibizumab 0.3 mg	0.21 (0.72)	0.24 (1.06)	0.19 (0.81)
Ranibizumab 0.5 mg	0.25 (0.78)	0.10 (0.50)	0.17 (0.58)
Sham	0.17 (0.43)	0.22 (0.63)	0.27 (0.59)

Figure 2. Mean area of macular nonperfusion (MNP) over time for the RIDE and RISE treatment arms; SD = standard deviation.