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REPLY

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We read with interest the thoughtful letter from Shanmugam et al, and thank them for their interest in our study. The issues raised are important, and we welcome the opportunity to address them.

First, the authors state correctly that our study did not categorize eyes as having focal or diffuse diabetic macular edema (DME). The Diabetic Retinopathy Clinical Research Network (DRCR.net) addressed this issue in a 2008 review and found that the terms are defined inconsistently.[1] In addition, there is little evidence in the literature to support that treatment response or vision outcomes vary according to the type of DME. Despite the poorly defined classification, DRCR.net did report from a randomized clinical trial in 338 eyes treated with ranibizumab (Protocol I)[2] that no differences could be detected in visual acuity changes or central subfield thickness changes among eyes characterized by clinicians as predominantly focal, predominantly diffuse, or neither predominantly focal or diffuse.[3] The reference the authors cite claiming that response varies according to optical coherence tomography (OCT) features, such as cystoid abnormalities or subretinal fluid, is limited in that the retrospective series of 143 eyes treated with a single injection of bevacizumab and then followed with serial OCTs for 12 weeks. It is difficult to make comparisons or conclusions from such limited follow-up of a single injection over that time, particularly compared with the 2 years of our study where eyes received a median of 15 to 16 injections. However, we agree with the authors that the randomization of the 660 eyes in our study likely would result in a balance of these OCT features across the 3 treatment arms.

Second, it is true that the DRCR.net study did not obtain fluorescein angiograms and that worsening of macular ischemia could result in worsening of vision. Again, we believe that the randomization of the eyes to the 3 treatment arms makes it unlikely that this had an effect on the differences in vision outcomes among the 3 groups. In addition, because <5% of eyes lost ≥15 letters (3 lines) of vision from baseline to 2 years, even if macular ischemia did worsen and cause worsening of visual acuity, the frequency of such an event was relatively small.

Third, history of prior laser for DME was balanced across the 3 treatment arms and the study results suggest that the treatment response was similar irrespective of whether prior laser had

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been received (i.e., there was no significant interaction of prior laser on the changes in visual acuity or central subfield thickness among the 3 groups).[4] In DRCR.net protocol I, the response to ranibizumab was similar in eyes with and without prior focal laser.[2]

Last, we do not believe there is convincing evidence to support the suggestion that results in the ranibizumab group would have been better if the 0.5-mg dose had been used rather than the 0.3-mg dose. In the RISE/RIDE studies comparing the doses, no significant difference in vision results was found[5]; within the first 6 months of monthly treatment, the average changes in visual acuity from baseline with 0.5- and 0.3-mg ranibizumab were similar in both RISE/RIDE trials. Within the first 6 months of the DRCR.net trial, when most study participants were given injections every 6 months, differences between aflibercept and ranibizumab 0.3 mg already were apparent.

We believe our results have very broad clinical utility and disagree that the factors the authors raise impose limitations. We do agree that OCT segmentation is an important area for further study and might provide data that would better predict the response to treatment of DME with anti-vascular endothelial growth factor therapy, although such studies need to take into account the baseline visual acuity, which at this time is the predominant factor in predicting treatment response across these 3 agents. The DRCR.net is evaluating our OCT data for this purpose.

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