Letter to the Editor: Ranibizumab 0.3 mg for Persistent Diabetic Macular Edema After Recent, Frequent, and Chronic Bevacizumab: The ROTATE Trial

Dear Editor,

We would like to address several challenges that have arisen from the study by Fechter et al.,1 which can be specifically summarized below.

In this study, there was a selection bias attributable to the inclusion of eyes that had received various treatments before enrollment, namely focal laser therapy (FLT), panretinal photocoagulation (PRP), and intravitreal bevacizumab (Avastin; Genentech, South San Francisco, CA). Moreover, this study allowed for the inclusion of eyes with epiretinal membranes (ERMs) and vitreomacular adhesions (VMAs) per investigator discretion.

The following relevant data are missing from the study: the anatomic types of macular edema (cystic changes within neurosensory retina/subretinal fluid/mixed type) at baseline and month 12; the proportion of eyes with ERM and VMA at month 12; the qualitative status of the four outer retinal layers (disruption and absence) at enrollment and month 12; the proportion of the eyes with retinal dryness at month 12; and the duration of diabetic macular edema (DME) at entry into the study.

Initially, a comparison had to be carried out between the two groups of patients to establish whether they were comparable. Accordingly, this comparison should have been conducted only if there were no significant differences between the baseline ocular characteristics — namely, previously received anti-vascular endothelial growth factor (VEGF) injections, FLT, or PRP; insulin dependency; and the type of diabetic retinopathy (proliferative or nonproliferative). These characteristics exhibited evident differences.

The final results of this series were unsatisfactory. Thus, the central subfield thickness (CST) decreased significantly to 324.15 µm, a value that is more than that of the cutoff for the upper level of normal CST,2 revealing unresolved macular edema, and two-thirds of all eyes failed to demonstrate improvement in macular fluorescein angiography leakage. In addition, the proportion of patients with significant systemic events was quite large in this study, which had a relatively small sample size.

The effectiveness of ranibizumab (Lucentis; Genentech, South San Francisco, CA) therapy cannot be evaluated definitely because the study design lacked a real washout period between the prior treatments and the first ranibizumab injection. This washout period is essential between the two periods of treatments in terms of aliased effects. Thus, the impact of the significant carryover effects of the laser/bevacizumab pretreatment may be confounded with direct ranibizumab treatment effects because these effects could not be estimated separately. Therefore, carryover effects may bias the interpretation of the data analysis.

Altogether, specific anti-VEGF drugs represent the front-line therapy for the treatment of DME, but VEGF inhibition alone may not be sufficient to decrease the inflammatory response. Therefore, the addition of a nonspecific anti-VEGF substance, (eg, a dexamethasone implant [Ozurdex; Allergan, Irvine, CA]) is mandatory. Regardless of the anti-VEGF agents employed (bevacizumab/ranibizumab/dexamethasone implant), the efficacy of the therapy primarily depends on the promptness of the therapy after DME diagnosis.3,4,5

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Reply to Letter to the Editor: Ranibizumab 0.3 mg for Persistent DME After Recent, Frequent, and Chronic Bevacizumab: The ROTATE Trial

Thank you to the authors for their letter and concerns. They raise concern for selection bias with inclusion of epiretinal membrane (ERM), vitreomacular adhesion (VMA), and prior laser and injection therapies. Inclusion criteria in our trial required eyes with chronic diabetic macular edema (DME) to have had frequent and recent bevacizumab (Avastin; Genentech, South San Francisco, CA) (six injections during the previous 9 months, two injections during the previous 2 months). Our eyes represent real-world eyes with chronic DME that have persistent DME after recent bevacizumab. Our aim was to prospectively report the anatomic and visual results when such eyes are switched to ranibizumab (Lucentis; Genentech, South San Francisco, CA).

Although we acknowledge inherent limitations of a 30-eye study without a control group continuing bevacizumab, we do not believe a selection bias exists by including eyes with ERM, VMA, or previous therapies such as laser. We acknowledge in our manuscript that ERM is usually excluded from larger trials evaluating anti-vascular endothelial growth factor (VEGF) therapies for DME. However, our data indicate that baseline ERM and VMA did not inhibit improvement after switching to ranibizumab. We acknowledge in our manuscript the limitations based on our small numbers with regard to further interpretation. In fact, at least for ERM, our results were contrary to a potential bias for a lack of improvement in eyes with pre-existing ERM. With regard to VMA, we also discuss that the READ 3 DME Study with 2 mg ranibizumab similarly noted that VMA may in fact be a favorable baseline characteristic for potential improvement after ranibizumab DME therapy.

In response to other concerns above, we did not feel it significant or necessary in a small study to subgroup to anatomic optical coherence tomography (OCT) types of macular edema and note the long duration of diabetic macular edema at study entry. It is also difficult in a small trial to differentiate any significant differences between varying baseline characteristics by performing multiple multivariable analyses.

We agree with our colleagues that the persistence of OCT thickness and angiographic leakage requires better therapies for DME. However, DRCR Protocols I and T established that visual acuity (VA) is maintained or improved with persistent anti-vascular endothelial growth factor (VEGF) therapy for eyes with persistent DME despite 24 weeks of anti-VEGF therapy. With regard to the concerns of a lack of washout period between prior treatments and first ranibizumab injection, we disagree. In fact, a study design with an anti-VEGF washout period enhances bias for improvement when switching to a different anti-VEGF agent. We eliminated a bevacizumab washout period to avoid such bias. Despite the inherent bias of a small study without a control group including continuation of bevacizumab and the possibility of regression to the mean, our study is unique in that we prospectively demonstrate VA improvement after switching from bevacizumab to ranibizumab.

Finally, we disagree with the notion “that a nonspecific anti-VEGF substance would be mandatory” for eyes with persistent DME. The DRCR protocol U demonstrates no evidence for VA improvement with the addition of dexamethasone implant to anti-VEGF in eyes with persistent DME.

There remains few large-scale, prospective, randomized studies regarding the appropriate therapy for persistent DME after anti-VEGF therapy. We demonstrate evidence of VA improvement and OCT thinning after a switch to ranibizumab from bevacizumab, but realize our study limitations. We hope that our prospective analysis can help guide clinicians in deciding whether to continue the same anti-VEGF agent, switch to a different anti-VEGF agent, or switch to laser or steroid therapy. Other larger trials such as DRCR Protocol AC will further help to delineate management of eyes with persistent DME after bevacizumab.

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