

Letter to the Editor: Short-Term Outcomes of Aflibercept Therapy for Diabetic Macular Edema in Patients With Incomplete Response to Ranibizumab and/or Bevacizumab

Dear Editor,

The study by Wood et al.¹ has several shortcomings that prevent the validation and extrapolation of their results and that can be specifically summarized as follows:

1. The authors concluded that at 1 month after the first injection of aflibercept (Eylea; Regeneron, Tarrytown, NY), central subfield foveal thickness (CSFT) decreased significantly from 421 μm to 325 μm .¹ Importantly, these values are more than the cutoff (315.2 μm) for the upper level of normal foveal thickness (270.2 $\mu\text{m} \pm 22.5 \mu\text{m}$)² +2 standard deviations. We believe that persistence of high CSFT values highlights unresolved macular edema and indicates that the disease process is still active and progressive, requiring further treatment with anti-angiogenic agents.

2. There were no data on the anatomical types of macular edema (subretinal fluid/cystic changes), nor were there details regarding vitreoretinal interface abnormalities (vitreomacular adhesion/traction, epiretinal membrane) before and after conversion to aflibercept. Nothing was stated referring to the duration of diabetes or diabetic macular edema (DME).

3. There were three eyes (eyes 2,10, and 13) with CSFT under the cutoff for the upper level of normal foveal thickness² (eg, 290 μm , 299 μm , and 277 μm , respectively) before aflibercept injection. We wondered why they had to be converted to aflibercept.

4. The number of bevacizumab (Avastin; Genentech, South San Francisco, CA)/ranibizumab (Lucentis; Genentech, South San Francisco, CA) injections was between three and 15, with most (78.5%) being six or fewer (11 eyes). This number of injections was too small to label the eyes as incomplete responders/nonresponders requiring conversion to aflibercept.

5. The presumed pharmacological advantages of aflibercept over bevacizumab or ranibizumab — namely, a higher binding affinity for vascular endothelial growth factor (VEGF)-A and activity against

VEGF-B and placental-derived growth factor^{3,4} — were not confirmed by the poor results of this series. Thus, there was persistent macular edema (CSFT $\geq 320 \mu\text{m}$) in seven eyes (50%) (eyes 1, 3, 4, 5, 6, 9, and 12 with CSFT values of 343 μm , 341 μm , 551 μm , 378 μm , 424 μm , 378 μm , and 324 μm , respectively) and a loss in visual acuity (one line) in three eyes (eyes 6, 12, and 13) after aflibercept injection.

Altogether, regardless of the anti-VEGF agents used (bevacizumab/ranibizumab/aflibercept), the efficacy of therapy depends primarily on the precociousness of the therapy after DME diagnosis. Therefore, therapy with anti-angiogenic agents has to be promptly applied as soon as possible after DME onset. Every delay of therapy adversely influences the deterioration of visual functions, which is difficult to restore even with subsequent treatment.

Dan Călugăru, MD, PhD

Mihai Călugăru, MD, PhD

Department of Ophthalmology, University of Medicine, Cluj-Napoca, Romania

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Mihai Călugăru, MD, PhD, can be reached at Strada Brâncoveanu 11, 3400 Cluj-Napoca/Romania; email: mihai.calugaru@mail.dntcj.ro.

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Reply to Letter to the Editor: Short-Term Outcomes of Aflibercept Therapy for Diabetic Macular Edema in Patients With Incomplete Response to Ranibizumab and/or Bevacizumab

We appreciate the letter writers' comments, as they may represent areas for clarification from many readers of our recent manuscript.¹ We agree with the letter writers' conclusion that a reduction from 421 μm to 325 μm does not represent resolution



Darius M. Moshfeghi

of diabetic macular edema (DME), and that the disease process was still active and required continued therapy. However, we believe the letter writers did not appreciate the purpose of our report, which was to describe the "short-term" outcomes (ie, after a single intravitreal injection [IVI]) of aflibercept (Eylea; Regeneron, Tarrytown, NY) therapy. The

purpose of our paper was not to describe long-term outcomes or report on outcomes of aflibercept after more than one IVI. Those very important points could be the focus of a future manuscript.

In our study, patients were defined as having an "incomplete response" to bevacizumab (Avastin; Genentech, South San Francisco, CA) and/or ranibizumab (Lucentis; Genentech, South San Francisco, CA) if there was persistent intraretinal fluid (IRF) or subretinal fluid (SRF) after a minimum of three IVIs. The central subfield thickness (CST) measurements were not taken into consideration for the inclusion criteria. As the letter writers state, some of the eyes included in our switch to aflibercept had CSTs in the "normal range" but were still deemed as incomplete responders given the persistence of

IRF or SRF after at least three IVIs with other anti-vascular endothelial growth factor (VEGF) agents.

The letter writers are correct in stating that after one IVI of aflibercept, there was persistent IRF and SRF in many eyes, as well as a CST outside the normal range. Again, our manuscript did not make a claim that one IVI of aflibercept would completely resolve DME eyes that were incomplete responders to other anti-VEGF agents. Our purpose was to report on the short-term outcomes after one IVI of aflibercept. Many eyes continued to have aflibercept IVIs after the data were collected to treat their ongoing DME. Lastly, there were some eyes that did better than others, with regard to both fluid status and visual acuity. There were not enough eyes enrolled to perform a multivariate analysis to determine what factors may have contributed to those outcomes. If we decide to perform that type of analysis in a future study, then reporting on the duration of diabetes, the anatomic types of DME, and the details regarding vitreoretinal interface abnormalities would certainly be interesting variates to consider.

Darius M. Moshfeghi, MD

Byers Eye Institute,
Stanford University of School of Medicine

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Darius M. Moshfeghi, MD, can be reached at Byers Eye Institute, 2452 Watson Ct, Palo Alto, CA 94303; email: dariusm@stanford.edu.

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