Letter to the Editor: Aflibercept For Diabetic Macular Edema in Eyes Previously Treated With Ranibizumab And/Or Bevacizumab May Further Improve Macular Thickness

Dear Editor,

We would like to address several challenges that have arisen from the study by Shah and Heier,[1] which can be specifically summarized below.

The study was retrospectively conducted with the existence of a selection bias attributable to the various treatments and nonstandardized treatment algorithms applied prior to switching to aflibercept (Eylea; Regeneron, Tarrytown, NY) — namely, eyes received an average of six bevacizumab (Avastin; Genentech, South San Francisco, CA) injections, 10 ranibizumab (Lucentis; Genentech, South San Francisco, CA) injections, and 0.7 triamcinolone injections. Six eyes were treated on a pro re nata basis based on visual acuity (VA), macular appearance, and physician and patient preference, and the remaining 24 eyes were treated regularly since presentation. Additionally, 10 eyes had prior focal laser.

The following critical data are missing from the study: The duration of the diabetic macular edema (DME) before entering the study; the anatomic types of DME (subretinal fluid, cystic changes, mixed type) at presentation, before and after switching; the proportion of eyes considered "dry" as per the criterion of central subfield macular thickness (CST) less than 320 µm[2] at the end of the study; vitreoretinal interface abnormalities (vitreomacular adhesion, traction, epiretinal membranes) at presentation, before and after switching; and the mean washout period after prior focal laser.

A mean washout period of 39 days prior to switching seems to be too short in terms of aliased effects for patients who have been treated with a mean of 16 bevacizumab and/or ranibizumab injections. Thus, the impact of the significant carryover effects of the bevacizumab/ranibizumab/focal laser treatment may be confounded in this study with direct effects of the aflibercept because these effects could not be estimated separately; carryover effects may bias the interpretation of data analysis.

The presumed pharmacological advantages of aflibercept over bevacizumab or ranibizumab — for example, a higher binding affinity for vascular endothelial growth factor (VEGF)-A and activity against VEGF-B and placental-derived growth factor, as well as a longer duration of effect[3] — were not confirmed by the unsatisfactory results of this series. Thus, the VA gains were approximately two Early Treatment Diabetic Retinopathy Study (ETDRS) letters and the CST decreased significantly to 332 µm after switching, a value that was more than the cutoff (315.2 µm) of the upper level of the normal foveal thickness plus two standard deviations.[2] We believe that persistence of high values of the CST highlights unresolved macular edema and indicates that the disease process is still active and progressive, requiring further treatment with anti-angiogenic agents.

Altogether, regardless of the anti-VEGF agents employed (bevacizumab/ranibizumab/aflibercept), the efficacy of therapy depends primarily on the promptness of the therapy after DME diagnosis.[4,5]

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Reply to Letter to the Editor: Aflibercept For Diabetic Macular Edema in Eyes Previously Treated With Ranibizumab And/Or Bevacizumab May Further Improve Macular Thickness

Dear Editor,

The authors of the letter to the editor raise several important and valid challenges facing our small exploratory study, as well as retrospective studies, in general. In an effort to address some of these limitations, we required three ranibizumab (Lucentis; Genentech, South San Francisco, CA) or bevacizumab (Avastin; Genentech, South San Francisco, CA) injections at a fixed interval prior to conversion to aflibercept (Eylea; Regeneron, Tarrytown, NY). Further, we required the follow-up interval after switching to aflibercept (43 days) to be equal to or longer than the interval prior to switching (39 days); this aimed to eliminate the potential bias of documenting of a better response from a shorter follow-up interval. Our study was intended to be hypothesis-generating, and several other studies have reported similar results.[1-5] We hope future prospective studies will evaluate switching to aflibercept in a stepwise fashion, given the clinical observations noted by retrospective studies.

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