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CORRESPONDENCE

Sir,
Aflibercept in diabetic macular edema: evaluating efficacy as a primary and secondary therapeutic option

We would like to address several challenges arising from the article by Ashraf *et al*[1] regarding the alternative roles for aflibercept (Eylea, Regeneron Pharmaceuticals, Tarrytown, NY, USA) in the management of eyes with non-naive diabetic macular edema (DME).

1. We do not agree the authors'assertion that switching to aflibercept may be a valid option for patients being treated with alternate anti-vascular endothelial growth factor (VEGF) agents. The presumed pharmacologic advantages of aflibercept over bevacizumab (Avastin, Genentech, South San Francisco, CA, USA) or ranibizumab (Lucentis, Genentech) (for example, a higher binding affinity for VEGF-A and activity against VEGF-B, and placental-derived growth factor) were not confirmed by the poor results of the latest publications. Thus, Wood *et al*[2] reported persistent macular edema in 50% of the eyes and a loss in visual acuity (1 line) in 21.4% of the eyes after aflibercept injection. Rahimy *et al*[3] displayed incomplete resolution of the DME (significant decrease of foveal thickness to 348.7 μm, a value that was more than the cutoff for the upper level of normal foveal thickness[4]), increase in the number of eyes with epiretinal membranes from 18 to 20, and of those with vitreomacular traction from 2 to 4 after switching to aflibercept.

2. VEGF is one contributor to macular edema in patients with diabetic retinopathy. Besides, a panoply of proinflammatory and proangiogenic cytokines, chemokines, and growth factors may be associated with pathophysiology of DME. They are maximally expressed in the ischemic lesions of the long-standing DME and exacerbate the deterioration primarily caused by VEGF in the initially damaged macular ganglion cell complex.

3. The specific anti-VEGF drugs represent the frontline therapy for the treatment of DME, but only the VEGF inhibition may not be sufficient to decrease inflammatory response. Therefore, addition of a non-specific anti-VEGF substance, that is, a corticosteroid injection, is mandatory.

Altogether, regardless of the intravitreal pharmacotherapy chosen, namely, specific (bevacizumab/ranibizumab/aflibercept) or nonspecific (corticosteroid implant) anti-VEGF agents, the efficacy of the treatment depends primarily on the promptness of the therapy after DME onset. Both groups of anti-VEGF substances provide similar rates of vision improvement, but with superior anatomic outcomes and fewer injections in the corticosteroid implant-treated eyes. However, more patients receiving the corticosteroid implant lose vision mainly due to cataract.[5]

Conflict of interest

The authors declare no conflict of interest.

Author contributions

Both the authors (DC and MC) were involved in design and conduct of the study; collection, management, analysis and interpretation of the data; and preparation, review or approval of the manuscript.

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D Călugăru[1] and M Călugăru[2]

[1]Department of Ophthalmology, University of Medicine Grigore T Popa, Iaşi, Romania
[2]Department of Ophthalmology, University of Medicine, Cluj-Napoca, Romania
E-mail: mihai.calugaru@mail.dntcj.ro

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We thank Dan Călugăru and Mihai Călugăru for their insight into our publication; however, we disagree with several of the points they made.

There is no clear data showing the greater efficacy of switching to steroids versus aflibercept in cases of chronic DME refractory to bevacizumab/ranibizumab therapy (Table 1). In addition, steroids are known to cause complications such as elevated IOP as well as cataracts which is a limitation to their use particularly in phakic patients. The exact timing of this switch is particularly important because as suggested by the FAME study, chronic edema is estimated to begin 1.73 years post the start of edema.[1] Patients treated with steroids in the FAME study who had edema <3 years failed to show anatomic or visual gains compared with the sham group. Only patients who had edema >3 years responded significantly. If we were to consider the definition suggested, patients are expected to have received at least 19 prior injections before steroids would be a valid option. In the study by Rahimy *et al*[2] patients had a previous median of 13 injections which would fall within the predicted margin of non-chronic edema. Therefore, it is