Correspondence

Anti–Vascular Endothelial Growth Factor Treatment for Diabetic Macular Edema in a Real-World Clinical Setting

EDITOR:

I READ THE CONCLUSION OF THE ARTICLE BY MAGGIO AND colleagues[1] with great interest. They suggest an early switch to other treatment where anti–vascular endothelial growth factor (VEGF) therapy is ineffective for diabetic macular edema (DME).[1] Their impression resonates with experience elsewhere in the world.

A sizeable share of patients respond poorly or are resistant to anti-VEGF therapy. The cysts of DME persist and, over a course of time, the ongoing anatomical damage leads to visual loss. Therefore the improvement of macular anatomy is a key goal. DME has different pathophysiology in the nonchronic and chronic states.[2] With increasing duration of DME there are changes in the retinal bioenvironment. Inflammation ensues, and cytokines arise within DME tissue. In the inflammatory chronic state the DME responds well to steroid therapy. By contrast, in the earlier, nonchronic stage, DME is driven by VEGF and accordingly anti-VEGF injections are effective.

From the response to anti-VEGF therapy it can be inferred which of the 2 mechanisms (VEGF or cytokines) is driving the DME. A short course of anti-VEGF therapy can be sufficiently informative. The EARLY analysis of trial data stated that poor responders can be identified after 3 anti-VEGF injections.[3] Another group has reported that the response to a single intravitreal dose of anti-VEGF can predict the later responsiveness to anti-VEGF therapy.[4]

Recognizing chronic diffuse DME, an advanced stage of disease, a clinician knows that a single dose of anti-VEGF is unlikely to provide a clear response. A run of 3 treatments, however, generates a dose-response timeline. It shows the extent to which DME is sensitive to anti-VEGF therapy. The sensitivity itself is an indicator of the underlying pathophysiology in the macula. With a nonresponse the clinician can infer that the DME pivots on inflammatory cytokines (rather than on VEGF). Logically, intravitreal steroid is commenced, and has the added benefit of being longer-acting than anti-VEGF therapy. The aim is effective suppression of DME along a long clinical course, with the treatment of any steroid side-effects viewed as an integral part of the overall care.

For chronic diffuse DME (with its inflammatory milieu), anti-VEGF injections can have limited or no therapeutic effect. A high frequency of injections can be needed to obtain a clinical response, and compliance with follow-up is a distinct problem in this particular group of patients. Formerly, on countless occasions, I have seen that where anti-VEGF injections have failed an intravitreal dose of triamcinolone can dry out the macula. In the eye with DME, a dose of triamcinolone alters the inflammatory cytokine profile when compared with an anti-VEGF medication like bevacizumab.[5] Moreover, the steroid exerts a slight anti-VEGF effect.

In DME management the chronicity of the disease is a primary factor to consider. Others are the area of macula affected, thickness of edema, laterality, and metabolic control. These factors must be noted at the outset during individualized care. The seasoned clinician can then hazard a guess as to whether anti-VEGF therapy will prove effective. Therefore, I agree with Maggio and colleagues that, where a short course of anti-VEGF is not having a useful effect, there should be a prompt switch to pharmacotherapy that more accurately treats the pathophysiology active within the diabetic macula.

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REPLY

WE THANK DR. GANDHI FOR THE INTEREST IN OUR WORK and for the valuable observation regarding the management of refractory diabetic macular edema (DME).[1]

In our retrospective study, a good long-term response to anti–vascular endothelial growth factor (VEGF) treatment for DME was found in a real-world population, supporting this treatment in similar settings. However, a subgroup of eyes (26%) exhibited a suboptimal response. In these eyes, the addition of subsequent alternative therapeutic options, including intravitreal injection of dexamethasone and vitrectomy, resulted in better visual outcomes when applied early.

Patients with persistent DME despite regular anti-VEGF therapy represent a management challenge. Although previous studies suggested that a short course of anti-VEGF could sufficiently identify eyes with suboptimal responses,[2] there is still no consensus regarding the proper timing for discontinuing anti-VEGF treatment in favor of alternative strategies. Previous authors[3] have observed that a limited initial response to anti-VEGF does not entirely preclude the possibility of a more complete future response, although the reason for this delayed improvement in some eyes, but not in others, is unclear. In addition, findings from recent trials[4,5] suggest caution when considering changing therapies early, considering resulting visual improvements from continued treatment despite the persistent DME. However, as discussed in our article, it should be considered that real-world settings do not always permit continued, intensive treatment protocols like those used in the trials. Real-world restrictions may result in a lower number of injections than what would be required for visual improvement in these eyes. In our population, eyes with no initial response showed the same chance to improve with repeated injections (33 of 65 eyes demonstrated a late response). Therefore, it remains to be clarified whether these cases would be best managed by an early change of therapy to reduce the risk of nonresponse. In fact, in eyes undergoing subsequent alternative therapeutic options, visual outcomes improved when alternative strategies were applied early. Speculatively, the reason may be related to the development of photoreceptor damage and atrophic changes that limited the potential for visual recovery in eyes with chronic disease. As mentioned in our article, these findings support an early change of the treatment strategy for eyes that are unresponsive to anti-VEGF treatment.

The incomplete response to anti-VEGF therapy reflects the complex and multifactorial pathophysiology of DME. As pointed out by Dr. Gandhi, the pathophysiological mechanisms underlying the disease may differ considerably between chronic and nonchronic DME. This would support switching therapies in eyes with chronic disease. In fact, the role of inflammation might be prevalent in these cases. However, the best strategy for eyes with nonchronic disease that do not show an early response to anti-VEGF therapy remains to be clarified. In fact, previous studies have reported a percentage of patients with naïve, recent-onset DME experiencing unsatisfactory anatomical and functional response to anti-VEGF treatment. These are the cases in which management is more challenging. Moreover, preventing chronicity in these eyes is crucial.

Persistent DME may cause irreversible visual impairment and limit any subsequent potential for vision recovery because of long-lasting ultrastructural changes, disruption of retinal architecture, and chronic tissue stress ultimately resulting in photoreceptor loss. Therefore, a better comprehension of the mechanisms underlying the refractory disease, as well as identifying the best timing for switching therapies, is strongly needed to optimize management.

Although our study suggests the opportunity for an early change of treatment strategy, it should be considered that a real-life study does not allow to draw any definitive conclusions about the management of refractory DME. Trials comparing eyes undergoing early switching to eyes continuing treatment with anti-VEGF could provide useful information. In conclusion, additional prospective multicentric studies are required to clarify the best management for DME in eyes that are responding suboptimally to anti-VEGF therapy.

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