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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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Diagnosis, Clinical Presentations, and Outcomes of *Nocardia* Endophthalmitis

EDITOR:

WE READ WITH INTEREST THE RECENT EXCELLENT ARTICLE by Dave and associates describing clinical features and outcomes of eyes with *Nocardia* endophthalmitis.[1] The authors noted that, similar to another large series from India, the majority of cases occurred soon after cataract extraction in immunocompetent patients who presented with extensive anterior chamber inflammation. These postoperative virulent presentations are to be contrasted with the indolent cases we and other groups have previously described associated with endogenous spread and choroidal abscesses in immunocompromised patients.[2,3] Although the causative organism is the same, there is a clear difference in presentation, diagnosis, and rate of positive culture from anterior chamber or vitreous tap alone between the postcataract extraction and endogenous cases. We humbly suggest that these should be treated and discussed as 2 distinct pathologic entities.

To further elucidate this difference it would be valuable to know the specific presentation of the 3 endogenous eyes in the current series and whether speciation from these cases was achieved via in-office vitreous tap or vitrectomy aspirate; in our prior series 3 of 5 eyes had no growth on cultures of vitreous sample. Those 3 eyes ultimately required subretinal biopsy to achieve speciation, reflecting the fact that the fastidious nature of these organisms requires a sufficiently large sample for culture growth.[4]

Although the presentation between postcataract and endogenous cases appears to be distinct, antibiotic sensitivities appear to be similar. All 25 eyes reported by Dave and associates were sensitive to amikacin, matching prior reports. We agree that this should be the first-line intravitreal agent for *Nocardia* endophthalmitis, with consideration for postinjection head positioning upright to minimize macular aminoglycoside-related toxicity.[5]

All in all, we would like to congratulate and thank the authors for contributing more to our understanding of this rare endophthalmitis entity, and we hope that further similar reports will allow a better differentiation of the 2 main subtypes of *Nocardia* endophthalmitis.

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