RE: Adrean et al.: Consistent long-term therapy of neovascular age-related macular degeneration managed by 50 or more anti-VEGF injections using a treat-extend-stop protocol (Ophthalmology. 2018;125:1047-1053)

TO THE EDITOR. We read with interest the report by Adrean et al regarding the treat-extend-stop (TES) protocol for the long-term treatment of neovascular age-related macular degeneration (nAMD). Based on their results, the authors conclude that the TES protocol is likely to maintain or improve vision in eyes requiring long-term intravitreal anti-vascular endothelial growth factor therapy. However, we believe that clinicians should consider certain methodologic aspects of their study design before accepting its conclusions and applying this regimen in their own practices.

The authors’ decision to analyze only eyes that had received ≥50 injections may have inadvertently created a selection bias toward eyes with better visual outcomes. This concern is supported by their data; at a mean follow-up of 8 years, 90% of eyes studied maintained visual acuity of ≥20/100. In a recent analysis of 8-year follow-up of nAMD managed with a treat-and-extend regimen (TER), Berg et al noted that >50% of eyes initiating this regimen discontinued within the first 2 years, often owing to poor vision. By 8 years, only 26% of eyes remained on the TER.

An important and highly probable confounder with both the TER and as-needed dosing is that eyes reaching ≥50 injections will be those retaining better central vision. Eyes with poor vision owing to central scarring or macular atrophy would likely receive fewer treatments, because they are more likely to be transitioned to as-needed dosing owing to a perception that continued injections may be of limited further benefit. Similarly, patients with poor visual outcomes are more likely to be lost to follow-up, particularly if they perceive no further benefit of ongoing examinations or if they seek treatment elsewhere.

Adrean et al also did not report the baseline neovascular lesion characteristics for their cohort. Previously published long-term retrospective studies with fixed dosing or a TER have demonstrated that, after initially successful anti-vascular endothelial growth factor therapy, most eyes show decreased acuity over time. There are also some nAMD subtypes that maintain better long-term vision. Mrejen et al showed that the baseline lesion composition of treatment-naïve nAMD significantly influenced long-term visual outcomes with a TER. Eyes with type 1 (subretinal pigment epithelium) lesions had the best long-term visual outcomes as compared with those with other lesion subtypes. Berg et al demonstrated that the negative impact on visual acuity was more pronounced in eyes with classic and retinal angiomatous proliferation lesions compared with occult and mixed choroidal neovascularization subtypes.

Similarly, a retrospective analysis of 5 year follow-up data from the CATT group demonstrated that retinal angiomatous proliferation was associated with a higher risk of developing geographic atrophy (GA) and poor vision, whereas neither occult lesions nor subretinal pigment epithelium lesions had an overall worse vision. Adrean et al noted only 4 eyes with central GA limiting their vision. A possible explanation for the low number of eyes with central GA in their study could be the inclusion of eyes with predominantly type 1 lesions at baseline. These eyes seem to be less susceptible to GA and thereby maintain better long-term vision on a TER, despite requiring more frequent injections than eyes with other neovascular subtypes.

Interestingly, although intended as a report of the TES protocol, on close inspection, only 4 of 67 eyes (6%) in the study by Adrean et al had stopped treatment at the last examination. One should then be cautious before assuming similar visual outcomes would be achieved for eyes meeting the TES protocol’s guidelines for discontinuation of injections and subsequent extension of follow-up to quarterly visits.

Without further understanding of the baseline lesions and characteristics of the eyes selected in this current study, it is difficult for clinicians to properly use the recommended TES protocol. Further baseline information about these eyes may help readers understand the complex nAMD disease responses to different anti-vascular endothelial growth factor treatment regimens.

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References


