Invited Commentary

Treating Neovascular Age-Related Macular Degeneration—So Much More to Learn

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Anti-vascular endothelial growth factor (VEGF) treatment for neovascular age-related macular degeneration (nAMD) has been a resounding success and a breakthrough in the treatment for a disease complication that can devastate lives. As a group, patients do very well, at least for the first few years, if treated sufficiently often to control neovascular activity. However, even when treatments are delivered with appropriate, protocol-directed treatment frequencies, with time, atrophy and fibrosis affect the outcomes and can be associated with loss of visual acuity.[1] Understanding the drivers and risk factors for the development of these late complications, which can limit visual acuity outcomes despite successful suppression of the VEGF drive, is critical if we are to limit their effects in an attempt to maintain early visual acuity gains in the long term.

Related article

In an article by Evans et al[2] in this issue of *JAMA Ophthalmology*, the authors explore the association of fluctuations in retinal thickness on visual acuity and the anatomic outcomes of atrophy and fibrosis in cases of nAMD being treated with anti-VEGF.[2] Fluctuation in central retinal thickness could be an important variable as we move to individualize treatments that maximize visual acuity outcomes but minimize treatment visits. With this in mind, we are seeing protocols, such as treat and extend, which can allow longer intervals between injections provided that lesions are considered inactive. Where initially we had assumed that our end goal should be a completely dry retina, using fluid as a surrogate for neovascular activity, there is now an active debate around the need to be completely intolerant of fluid, particularly subretinal fluid (SRF), when considering extending treatment intervals. Emerging evidence suggests that it may be possible to tolerate some SRF, with no close correlation between visual acuity outcomes and a dry retina.[3-5] Indeed, it has been suggested that tolerating some SRF may protect the retina from atrophy.[6] However, both increasing treatment intervals and tolerating SRF are likely to lead to greater fluctuations in retinal thickness than monthly or treat-until-dry protocols.

To investigate the outcome of fluctuating central retinal thickness, the authors[2] conducted a post hoc analysis of 1731 participants in the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT) and the Alternative Treatments to Inhibit VEGF in Age-Related Choroidal Neovascularization (IVAN) Trial. The authors measured the foveal centerpoint thickness and its standard deviation (FCPTSD) and determined the associations between FCPTSD quartiles and 2-year outcomes, such as best-corrected visual acuity (BCVA), development of fibrosis, and macular atrophy.

The authors[2] found that eyes with greater fluctuation in retinal thickness had significantly worse BCVAs at 2 years (adjusted for baseline BCVA) and were more likely to develop fibrosis and geographic atrophy than eyes that had less fluctuation. Of note, the protocols in CATT and IVAN looked at 2 drugs, bevacizumab and ranibizumab. Both protocols randomly assigned participants to either monthly treatment or pro ne rata treatment, in which treatment was withheld if the lesions were quiescent, largely based on the absence of fluid. It might be argued that the cohorts receiving pro ne rata treatment were undertreated using this reactive protocol strategy. However, the authors report that the same associations of thickness fluctuations with worse BCVA, fibrosis, and atrophy were also seen in the monthly treatment groups, implying that fluctuations in fluid, not undertreatment, were the reason for the poorer outcomes. Over the 2 years of follow-up, there was a staggering increase in the number of eyes that developed fibrosis associated with increasing variation in FCPTSD; the odds of developing fibrosis increased from 7.8% to 58.7%. A similar but less striking increased risk was found for geographic atrophy, which rose from 9.0% at baseline to 30.2% at year 2.

Thus, we have reports suggesting that some SRF might be desirable and appear to protect from atrophy, but that fluctuations in fluid are associated with the development of atrophy or fibrosis. Evans et al[2] provide some biological rationale, citing evidence from other tissue types that intermittent stretching leads to the recruitment of macrophages, which triggers fibrosis. The authors call for anti-VEGF agents with greater treatment durability or sustained release to overcome this issue, but in addition, it may be useful to add compounds that prevent fibrosis and atrophy to our armamentarium.

There is still much more to learn when considering treatment for nAMD. Are fluctuations in thickness the only important variable? Is stable SRF, implying a neovascular lesion that is present but well controlled and potentially providing oxygen to the outer retina, the desirable end goal? Long-term, granular, high-quality, prospective, real-world data collected long after sponsored trials have been completed will be an important source of data to answer many protocol-associated questions, including those around risk factors for atrophy and fibrosis.[7] Such data could be obtained if clinicians routinely recorded disease activity status, based on documented criteria, such as fluid status and visual acuity change, as well as the presence or absence of atrophy and fibrosis. This could be captured on compatible data platforms, generating uniform, large data sets with access to imaging to validate important disease variables. The combined data sets would be immensely valuable to help discover the drivers of visual acuity loss when treating nAMD. Such a rich repository would provide the nuanced data required to further inform us how best to treat nAMD, ensuring the best, sustained, long-term visual health outcomes for patients.

ARTICLE INFORMATION

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