



Long term outcome after anti-VEGF treatment—what do we know about the impact of morphological parameters?

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Despite the initial positive effect of anti-VEGF treatment in eyes with neovascular AMD (nAMD), long-term results still remain un-satisfying (1-3). Five-year outcomes from the CATT study showed a mean decline of 11 letters from the 2-year follow-up visit, and 3 letters compared to the original baseline (3). This is similar to the long-term results from an observational study reported by Gillies *et al.* demonstrating a 2.6 letter loss of visual acuity (VA) at 7 years compared to baseline (2), as well as the results from the SEVEN-UP study which showed an even more dramatic 8.6 letter loss relative to baseline 7 years after the initiation of anti-VEGF therapy (1). Several explanations for these suboptimal lower outcomes may be considered, including undertreatment in a real-world environment leading to progressive exudation and scarring, as well as the development of retinal pigment epithelial (RPE) atrophy—both of which yielding progressive photoreceptor dysfunction and loss (1,4,5). However, the relationship between these various morphological parameters evident over time in eyes with nAMD and VA are not yet fully understood.

In their manuscript “*Macular Morphology and Visual Acuity in Year Five of the Comparison of Age-related Macular Degeneration Treatments Trials (CATT)*”, the authors report on a detailed analysis of morphological parameters and their association with VA in 523 patients with available morphological and VA data 5 years after entry into the CATT study (6). The results of this analysis indicate that the development of a new foveal scar, CNV, intraretinal fluid (IRF), subretinal hyperreflective material (SHRM)

and retinal thinning, development or worsening of foveal geographic atrophy (GA), and an increase in lesion size during follow-up are important contributors to the VA decline observed from year 2 to 5. Foveal SHRM demonstrated the biggest impact on VA, presumably due to overlying photoreceptor damage. This finding is in line with earlier reports (7,8) which highlighted the functional importance of SHRM. SHRM in the setting of AMD may correlate with CNV, fibrin, hemorrhage, pseudovitelliform material, or fibrotic scar; however, persistent SHRM during long-term follow-up after anti-VEGF therapy most likely represents scarred fibrovascular tissue. Although a higher proportion of eyes demonstrated retinal thinning at year 5 (36%) compared to year 1 (21%) and 2 (22%), the proportion of eyes with IRF increased steadily during follow-up and foveal IRF was associated with worse VA over the entire study duration. These findings support the hypothesis that IRF that persists despite anti-VEGF therapy may represent “cystoid degeneration” from tissue loss rather than a manifestation of active exudation.

Recently, subretinal hyporeflective fluid (SRF) has been associated with less atrophy and better VA outcomes (9). The underlying mechanism for this effect and the therapeutic relevance of this observation remains unknown. In the CATT study, foveal SRF was associated with better VA at both 2 and 5 years follow-up. However, this apparent positive effect was no longer observed on multivariate analysis at year 5 adjusting for IRF, SHRM and total CNV lesion size, indicating that other factors may be more

relevant than SRF itself for the observed outcomes. It is also worth pointing out that in studies in which SRF was associated with better vision or less atrophy, patients with SRF were still being treated with anti-VEGF therapy (9). Thus, there is no evidence that not treating eyes with SRF leads to better outcomes, whereas there is ample evidence that leaving active exudation untreated leads to vision loss (10). It is possible that a small amount of SRF may represent a CNV membrane that is largely controlled, though not eliminated. Such a “controlled” CNV membrane, if confined below an intact RPE, may potentially have positive effects (11), though this needs to be confirmed in future studies. Regardless, treatment of active exudation remains the priority.

In conclusion, several morphological parameters could be identified that help to better understand the long-term results of anti-VEGF therapy in nAMD. The impact and therapeutic relevance of various parameters, in particular SRF, are not yet fully understood and warrant further investigation. There remains a significant unmet need to develop therapies that limit scar formation as well as the development and progression of atrophy.

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