Editorial

Hidden messages in optical coherence tomography: looking beyond fluid

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The outlook for patients with neovascular age-related macular degeneration (AMD) has significantly improved since the advent of anti-vascular endothelial growth factor (anti-VEGF) therapy. Numerous clinical trials have demonstrated favorable visual and anatomical response up to 2 years. However, longer-term results have been variable. Some of this difference has been suggested to be due to difference in treatment exposure after patients exit from randomized control trial (RCT) to real world setting. For example, in the SEVEN-UP study, patients received only an average of 1.6 injections/year during the 5 years after exit from the trial, and the mean visual acuity (VA) declined by 19.8 letters to a level of 8.6 letters loss since their enrollment in the initial trial (1). However, differences in macular morphology may also explain some of the variations in long-term visual outcomes. In the SEVEN-UP study, macular atrophy was significantly associated with poor visual outcome. Several other groups have previously reported the prognostic value, and functional importance of individual morphological features, such as drusen subtypes, outer retinal tubulation (2,3), intraretinal cysts (4-7), pigment epithelial detachment (4-6), outer retina/photoreceptor integrity (8,9), subretinal hyper-reflective material (10) and macular atrophy (9-12). Most of these studies have reported visual outcomes up to 1–2 years. It is important to understand whether these predictive values continue to be significant with longer follow-up period.

The CATT 5-year follow-up study included patients who had previously received ranibizumab or bevacizumab monthly or PRN during the 2-year CATT study period. After releasing from the clinical trial, patients continued to receive anti-VEGF therapy (aflibercept, ranibizumab, or bevacizumab) according to standard of care, and were assessed at a single visit on average 5.5 years after enrollment into the CATT trial. At the 5-year visit, improvements in VA during the first 2 years were not maintained, with the mean VA dropping on average 11 letters from the end of year 2 to a level 3 letters below baseline vision (13).

Recently, Jaffe *et al.* evaluated the associations of morphologic features with the 5-year visual outcome in these patients (4). In particular, they evaluated the impact of fluid, subretinal hyper-reflective material as well as atrophy on visual outcome. The adverse pathological features in the study were defined as those statistically significantly associated with a 3-line VA worsening on multivariate analysis from year 2 to year 5. These features included foveal geographic atrophy (GA), fibrotic atrophy, choroidal neovascularization (CNV), foveal subretinal hyperreflective material (SHRM), foveal intraretinal fluid (IRF), retinal thinning and increased CNV lesion size more than 5 mm^2, or increased GA area >2 mm^2. In addition, decline in VA was associated with greater number of new adverse pathological features occurred at all time points throughout the study. These adverse features mostly indicate the formation of scar and/or atrophy, which cannot be treated by anti-VEGF monotherapy. Therefore, other new strategies of treatment need to be developed in the future, such as neuroprotective

agents.

Presence or absence of fluid, and the location of fluid is an important indicator of disease activity. At year 2 in the CATT study, eyes with IRF in the foveal center had worse mean VA than eyes without IRF (59.9 *vs.* 70.9 letters; P<0.0001), while eyes with subretinal fluid (SRF) in the foveal center had better mean VA than eyes with no SRF (72.8 *vs.* 66.6 letters; P=0.006) (14). At 5-years of the CATT follow-up, there were a higher proportion of eyes with IRF, increasing from 50% at year 2 to 61% at year 5 (13). Furthermore, there was a stronger negative correlation between IRF and VA compared to the initial two years, VA differences between eyes without and with IRF in the foveal center increased from 11 letters at year 2 (75 letters without IRF *vs.* 64 letters with IRF) to 24 letters at year 5 (68 letters without IRF *vs.* 44 letters with IRF). Paradoxically, the authors also noted an increased proportion of eyes with retinal thinning at year 5 (36% at year 5 compared to 22% at year 2), and suggested a possible explanation could be the 'IRF' detected as hypo reflective cystoid space by optical coherence tomography (OCT), may actually represent tissue loss rather than true fluid that leaked from CNV. On the contrary, the presence of foveal SRF and sub-retinal pigment epithelium (sub-RPE) fluid was associated with better mean VA compared to those without on univariate analysis. However, the beneficial effect of SRF on VA disappeared when adjusted for IRF, SHRM, and total CNV lesion size, indicating that SRF might be associated with at least one of these factors.

Among the many adverse pathological features, foveal SHRM was associated with the worst VA, particularly if it involved the foveal center (41 for foveal SHRM, 63 for extrafoveal SHRM and 72 letters for no SHRM) However, SHRM is an OCT feature and can result from a variety of lesion components, including blood, exudation or fibrosis. Specifically, the authors observed that VA was much better if SHRM resolved by year 2 than those in whom it persisted. Therefore, it is important to understand the heterogeneity of SHRM, and potentially different impact on visual outcome based on the underlying lesion component. To help further understand the functional impact of SHRM, Casalino *et al.* reported that location and morphology of SHRM changed after anti-VEGF treatment (15). In particular, undefined SHRM was frequently replaced by the well-defined variety, and most of the SHRM observed had well-defined boundaries with increased reflectivity after anti-VEGF treatment, which strongly suggested a fibrotic scar formation and/or mature neovascular complexes. Hence, treatment strategy focus on blockage of fibrosis and scar formation might be a future hope.

Macular atrophy or GA is another lesion that has been associated with long term visual loss in anti-VEGF treated eyes. Previously, the CATT 5-year follow-up study had reported that the proportion of eyes with abnormally thin retina increased from 22% at year 2 to 36% at 5 years, along with 20% GA at 2 years increased to 41% at 5 years (13). The current study further observed that although eyes with GA at year 5 had worse VA at baseline, years 1 and 2 compared to eyes without GA by year 5, the VA difference at year 5 widened markedly. The development of GA accelerates VA loss, and once GA is formed, it is unlikely to reverse.

These findings are important in helping us understand the unmet clinical needs beyond anti-VEGF therapy. Furthermore, in Asian populations, there is a high prevalence of polypoidal choroidal vasculopathy (PCV). Several characteristics have been reported to differ between eyes with PCV compared to eyes with CNV-AMD. Eyes with PCV have been associated with thicker subfoveal choroid, a relative paucity of subretinal fibrosis and disciform scarring, and have been reported to have a more favorable visual outcome (16-18). However, to-date, there are limited detailed evaluations of macular morphological features to the same rigor as in the CATT study. Further studies of imaging biomarkers in PCV will be needed to understand if findings from the CATT 5-year are applicable to this population.

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Footnote

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