Correlation Between Changes in OCT and Visual Acuity in the Management of Neovascular AMD

Does subretinal fluid matter?

BY DAVID M. BROWN, MD

Optical coherence tomography (OCT) is widely used in the follow-up and management of patients with neovascular age-related macular degeneration (AMD). OCT measurements help clinicians to determine the presence of patterns of disease activity on OCT images of the retina: diffuse edema in the neurosensory retina, intraretinal cysts, subretinal fluid, and sub-retinal pigment epithelium (RPE) fluid. Serial OCT images allow clinicians to follow patients’ progress over time and recognize the appearance of new signs.

OCT has been invaluable in the management of wet AMD since the early investigations of anti-VEGF intravitreal injections, although OCT assessment was only an exploratory analysis in pivotal trials such as ANCHOR and MARINA.1,2

Shortly after those studies were published, as the clinical paradigm was rapidly shifting from the study-based monthly paradigms to less-than-monthly treatment of wet AMD with anti-VEGF agents, Carl Regillo and I wrote a paper examining the factors involved in making these treatment and retreatment decisions.3 That is, if patients were not going to be treated on a monthly basis, we wanted to know what anatomic characteristics could guide the decision of whether or not to treat. After reviewing the literature, evidence from ongoing clinical trials, and the types of clinical assessments available to clinicians, we concluded that...
a combination of clinical examination and qualitative OCT assessment should be used in guiding as-needed (prn) treatment decisions or the decision whether to extend intervals in a treat-and-extend paradigm.

In a nutshell, our conclusion was that fluid is trouble, and ideally treatment should keep that trouble away and try to make the retina flat. That concept is still controversial 5 years after the article was published, and this article presents some of the reasons supporting our conclusions.

**WHY FLUID MATTERS**

A post-hoc analysis of data from the PIER study was performed to investigate whether anatomic characteristics of eyes receiving ranibizumab (Lucentis, Genentech) therapy in that trial were predictive of best corrected visual acuity (BCVA) outcomes. I presented this work at the Macula Society meeting in 2010, and it was published earlier this year.

In PIER, patients in the treatment arms were given 3 monthly ranibizumab injections followed by a quarterly injection schedule. Treated patients initially experienced gains in BCVA analogous to MARINA and ANCHOR, but by the end of 1 year the mean BCVA in the treatment groups had returned to baseline.

However, although the mean BCVA returned to baseline at month 12, individual patients in PIER gained and lost vision during the trial. In an effort to determine whether OCT signs could provide clues as to which patients would gain and which would lose BCVA, I reviewed all the OCTs and fluorescein angiographs (FAs) from the trial and graded them in a masked fashion. My hypothesis in performing this post-hoc analysis was that recurrent edema would be associated with loss of BCVA, and maintaining a dry macula would be associated with a positive visual outcome.

The analysis showed that eyes with no activity (no evidence of disease activity) on qualitative OCT at months 5 and 8 or on fundus fluorescein angiography at months 3 and 5 experienced gain in BCVA from baseline to month 24, while those with evidence of leakage not only lost initial BCVA gains but had net BCVA losses from baseline to month 24.

Based on the findings in this work, we went on to examine anatomic factors as predictors of visual acuity (VA) in the HARBOR study.

HARBOR evaluated the efficacy and safety of 2.0 mg vs 0.5 mg ranibizumab in patients with wet AMD, dosed monthly or prn after 3 loading doses. At 1 year, there was clinically meaningful improvement in VA and anatomic outcomes in all 4 treatment groups, but the trial did not demonstrate superiority of 2.0 mg over 0.5 mg ranibizumab, and the prn groups failed to meet the criteria for noninferiority to ranibizumab 0.5 mg monthly.

The purpose of our subanalysis of HARBOR was to evaluate the association between anatomic measures at months 3, 6, 9, and 12 and VA outcomes at month 12.

We analyzed the associations between mean VA change at month 12 and a number of anatomic measures at months 3, 6, 9, and 12, including overall wet or dry status as defined in HARBOR; the presence (wet) or absence (dry) of cystoid spaces on spectral domain OCT (SD-OCT); and central foveal thickness (CFT) greater than (wet) or less than (dry) 270 µm.

Results were analyzed in numerous ways, and detailed publication of the results will be forthcoming. For the purposes of this article, however, the bottom line is that absence of cystoid spaces on SD-OCT and central foveal thickness (CFT) less than 270 µm at months 6, 9, and 12 was associated with a greater increase in mean VA change. Other anatomic definitions of dry status did not show a consistent association with mean VA change.
Our conclusion from this subanalysis was that HARBOR patients experienced improvements in VA at month 12 regardless of their wet or dry status on SD-OCT. However, patients with dry SD-OCT status (CFT <270 µm and no intraretinal cysts) had better VA outcomes at month 12 when compared with patients with wet SD-OCT status.

CONCLUSIONS

The real-world lesson from the results of these sub-analyses is that some clinicians may be taking the wrong approach when basing retreatment decisions on OCT images. Most of us treat when we see subretinal fluid, and we may be less inclined to treat when we see small intraretinal cysts, thinking they are not significant. Our analyses found that absence of subretinal fluid was not associated with VA change in the first year, but the presence of cysts was. So these little cysts may mean more than many of us have thought (Figures 1 and 2).

These analyses also leave us with a number of questions. Why did subretinal fluid not affect VA change in these studies? Will 24-month results demonstrate further deterioration in eyes with intraretinal cysts? And what will 24-month VA outcomes tell us about the continued safety and efficacy of 0.5 vs 2.0 mg ranibizumab and prn therapy? The answers to these questions are still to come.

Finally, it is my belief that subretinal and sub-RPE fluid has to be searched for diligently in every crevice, and eliminated, if we want our patients with neovascular AMD to achieve the best VA results.

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6. Suner IJ, Yau L, Lai P. HARBOR Study: One-Year Results of Efficacy and Safety of 2.0 mg versus 0.5 mg Ranibizumab in Patients with Subfoveal Choroidal Neovascularization Secondary to Age-Related Macular Degeneration. Paper presented at: Association for Research in Vision and Ophthalmology, May 08, 2012, Fort Lauderdale, FL.