Optical Coherence Tomography, Fluorescein Angiography, and the Management of Neovascular Age-Related Macular Degeneration

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In the article by Castillo et al1 (http://www.aaojournal.org/article/S0161-6420(14)00728-3/fulltext), the authors provide a thoughtful review of “the accuracy of optical coherence tomography (OCT) [compared] with alternative tests for monitoring neovascular age-related macular degeneration (nAMD) and detecting disease activity among eyes previously treated for this condition.” The topic is important. The article focuses mainly on whether OCT can replace fluorescein angiography (FA) because OCT is safer, more convenient, and less costly. Their conclusion is that OCT cannot replace FA: “There is a substantial disagreement between OCT and FA findings in detecting active disease in patients with nAMD who are being monitored. Both modalities may be needed to comprehensively monitor patients with nAMD.”

This conclusion may surprise many who increasingly rely on OCT to diagnose and monitor treatment. The use of FA in the management of choroidal neovascularization (CNV) has decreased, whereas the use of OCT has increased dramatically over the past decade. There are 2 primary situations in which OCT may be used: (1) the diagnosis of recent-onset nAMD and (2) the management of ongoing anti–vascular endothelial growth factor therapy for nAMD. An important question is whether FA is needed and to what extent can OCT replace FA in these situations. Castillo et al1 found both time-domain and spectral-domain OCT to be relatively sensitive (85%) at detecting nAMD, but not very specific (48%) overall. Spectral-domain OCT now is used by most clinicians to image nAMD and actually was less specific than time-domain OCT because of false-positive results such as fluid overlying areas of atrophy or stable disciform scars. The exact role of other testing such as indocyanine green angiography, Amsler grid, and preferential hyperacuity perimetry in the management of nAMD also remains uncertain.

In the anti–vascular endothelial growth factor era, standard of care comprises at least 3 reasonable and appropriate treatment strategies: (1) monthly treatment, (2) pro re nata (PRN) treatment, and (3) treat and extend treatment, all of which have been validated by clinical trials such as the registration trials for ranibizumab2,3 and aflibercept4 and the various ranibizumab versus bevazucimab studies, starting with the Comparison of Age-related Macular Degeneration Treatments Trials (CATT),5 IVAN,6 and others, and most recently, the treat-and-extend LUCAS trial.7

The use of FA and OCT is determined in part by the treatment strategy used. This raises the question of when eyes with nAMD should be treated. The evidence is strongest for a treatment benefit for active nAMD. Evidence of disease activity was an inclusion criterion for most of the trials. ANCHOR allowed immediate treatment because eyes with predominately classic CNV already were known to be extremely likely to progress without treatment, but MARINA required evidence of disease activity before enrollment because it was known that approximately one third of eyes with occult CNV do not progress for 2 years.8 Why inject monthly for patients who may be stable without injections? Also, by requiring activity (which equates to selecting eyes likely to progress), there will be more events in the control arm and therefore a smaller sample size will be needed to prove the benefit of treatment. The use of FA at baseline is needed to determine if there is occult or classic CNV, because we may use a different treatment and monitoring regimen based on the type of nAMD. Eyes with occult nAMD often show slower deterioration without treatment than eyes with classic nAMD, but eyes with occult nAMD also may be more resistant to anti–vascular endothelial growth factor therapy. If one is observing patients with new occult CNV and treating only when there is active or progressive occult disease, then the definition of active occult CNV in MARINA is “[the presence of any of] observable blood, recent vision loss, or a recent increase in a lesion’s greatest linear diameter of 10% or more.” The last criterion would require FA for identification. The activity definition in CATT was slightly different: “the presence of leakage, as seen on fluorescein angiography, and fluid, as seen on time-domain optical coherence tomography (OCT), located either within or below the retina or below the retinal pigment epithelium.” This again requires FA as well as OCT for identification.

The next issue to address after nAMD is diagnosed is when to treat during follow-up. If you are a monthly treater, theoretically no testing is needed, but over time, some eyes demonstrate decreased visual acuity or increased fluid, necessitating a re-evaluation with OCT and possibly FA to try to determine why the treatment is working less effectively. For those who use a PRN strategy, the indication for repeat treatment in the CATT was based on activity defined as “fluid on OCT, new or persistent hemorrhage, decreased visual acuity as compared with the previous examination, or
dye leakage or increased lesion size on fluorescein angiography... Fluorescein angiography was performed at the discretion of the ophthalmologist to aid in retreatment decisions.\textsuperscript{7} Retreatment was based on evidence of CNV activity, primarily the presence of fluid on OCT. Other reasons were allowed but rarely invoked; more than 95% of treatment decisions were based on OCT findings. The treatment decision relied on OCT and occasionally FA. For the treat-and-extend advocates, the LUCAS investigators also relied on a CATT-like decision approach: “The decision about eligibility and treatment was made on the basis of the ophthalmologist’s interpretations of OCT, FA and clinical examination including slit lamp biomicroscopy... Recurrent disease was defined as any fluid on OCT, new or persistent hemorrhage or dye leakage, or increased lesion size on FA. Decreased BCVA [best-corrected visual acuity] was not defined as a recurrence but FA was allowed to aid in retreatment decisions.”\textsuperscript{7} So, again, there is reliance on OCT, and FA is allowed, but not required.

With respect to high-risk nonneovascular eyes and fellow eyes when there is CNV in the first eye, it is well known that eyes with large drusen and pigment are at high risk of CNV developing,\textsuperscript{2} and when a fellow eye is at risk, the 5-year rate of development of CNV in these eyes is approximately 50%. The recently reported incidence of nAMD in fellow eyes from the CATT was 18.6% over a period of 2 years.\textsuperscript{10} Frequent OCT imaging is warranted, and perhaps even daily checks with a home testing system are as well.\textsuperscript{11} Most clinicians seem to favor a treat-and-extend or PRN approach, so OCT would be indicated on each visit. Because of the relatively high incidence of new-onset nAMD in the fellow eye (and because the test is paid as a bilateral test in the United States), examination and imaging of the fellow eye frequently is recommended, especially when symptoms are present. Typically, the fellow eye should be evaluated during the evaluation and treatment of the active eye.

In conclusion, Castillo et al offer important details on OCT, time-domain OCT, spectral-domain OCT, FA, and other testing, and we encourage you to read and learn from their study. Using our “keep it simple” approach, we remind readers to frame your questions carefully. Do you want to know if there is new nAMD or active or progressive nAMD, new disease in the fellow eye, or nAMD for which you will advise treatment? Based on how closely you adhere to clinical trial protocols and the study inclusion and exclusion criteria to guide your care, you may choose to carry out FA and OCT examinations at baseline, to perform monthly OCT examinations for PRN treatment, and to perform OCT examinations at each visit for treat-and-extend care. Fluorescein angiography may be added when there is a change in the clinical status that is not explained by the OCT result. The 2011 American Academy of Ophthalmology AMD Preferred Practice Pattern states, “Intravenous fundus fluorescein angiography is indicated when the patient complains of new metamorphopsia or has unexplained blurred vision, and/or when clinical examination reveals elevation of the RPE or retina, subretinal blood, hard exudates, or subretinal fibrosis and in the following situations... To detect the presence of and determine the extent, type, size, and location of CNV... To detect persistent or recurrent CNV following treatment... To assist in determining the cause of visual loss that is not explained by the clinical examination.” We anticipate the 2014 version of the Age-Related Macular Degeneration Preferred Practice Pattern will contain similar recommendations, reafﬁrming the role of FA in the diagnosis and management of nAMD. Regular OCT testing also is indicated when fellow eyes are at increased risk, and detection may be enhanced with Amsler grid or preferential hyperacuity perimetry testing at home.

References

Footnotes and Financial Disclosures

J.T.: Consultant — Kaleidoscope (unrelated to manuscript topic).