2013 Macula Society Musings

BY NIKOLAS LONDON, MD

Editor's note: This blog was posted on April 24, 2013, to www.eyetube.net. Occasionally, we will be featuring content from our bloggers for retina in Retina Today. *Nikolas London, MD, contributed the following, which details his experience at the 2013 Macula Society meeting.*

In late February of this year, I was lucky enough to ride the coattails of Paul Tornambe, MD, to the Macula Society meeting in Dana Point, CA. For my first blog entry for *Retina Today*, I provide a summary.

ADVANCED IMAGING MODALITIES

For me, retinal imaging is beautiful and one of the most rewarding parts of the retina subspecialty. I am still excited by the array of modalities to evaluate the function and anatomy of the retina, and I particularly enjoy using these images to show my patients exactly what is happening to them and why, as well as how they are responding to treatment. Despite huge advances over the past decade, the envelope is still being pushed, and I pay particular attention to such talks at ophthalmology conferences.

Richard Rosen, MD (New York Eye and Ear Institute), presented a novel technique called fluoro-microangiography, which is fluorescein angiography (FA) using an adaptive optics scanning laser ophthalmoscope (AO SLO). FA has been the gold standard for decades for evaluating the retinal vasculature and integrity of the blood-retinal barrier. AO SLO enables a much higher resolution assessment of the living retina at a cellular level. Dr. Rosen presented examples showing ultrastructural features of microaneurysms, beautiful images from normal subjects, as well as extended widefield imaging of the retinal periphery. Mark Pennesi, MD (Oregon Health and Science University), presented retinal imaging using flood-illuminated AO, which provided unprecedented resolution and detail of retinal structures, including the ability to calculate the density of cones in the perifoveal retina (ranges from 1300 to 1700 cones/degree^2 in normal subjects). He illustrated how perifoveal cone density decreases slightly with age and drastically in diseases such as retinitis pigmentosa or Stargardt disease. These advances make the retina field particularly exciting for those of us dazzled by technology and hold the promise of improving our ability to care for our patients.

Using less novel technology (but with no less interesting results), other talks focused on enhanced understanding of subtle symptoms of early age-related macular degeneration (AMD). Catherine Cukras, MD (National Eye Institute), presented data showing deficits in rod-mediated dark adaptation in non-advanced AMD. Moreover, Karl Csaky, MD (Texas Retina Associates), presented electroretinogram data demonstrating a progressive loss of rod sensitivity with advancing AMD. These studies provide some confirmation of patients' subjective difficulties with dark adaptation.

AMD

Genetics

The genetics of macular degeneration is a particularly hot field, holding promise to better define the risk for AMD progression and to illustrate potential therapeutic targets in the complicated cascade of events that contribute to advanced AMD. Numerous disease-associated single-nucleotide polymorphisms (SNPs) have been identified, including protective and detrimental markers. These include ARMS2, CHF, C2, C3, H3, and CFB.

Nancy Holekamp, MD (Pepose Vision Institute), presented a comparison of 2 commercially available genetic tests for AMD, Sequenom's RetnaGene and Arctic's Macula Risk. She found that they were discordant 60% of the time, with RetnaGene typically predicting the higher risk. On subsequent analysis, she noted that Macula Risk did not identify a moderate risk allele and appeared to misidentify it as a protective allele. It is important to note that this study was done on first-generation tests, while both companies have gone on to develop improved tests. In practice these tests can play a role in certain circum-

stances. For some patients it is useful to tailor their follow-up schedule and self-testing according to their likelihood of developing advanced AMD. For example, results from the AREDS tells us that a patient with a simple severity score of 4 (a phenotypic categorization) has about a 60% risk of developing advanced AMD within 10 years. Adding genetic information to this can refine this risk to between 30% and 80% depending on the SNPs discovered. Of note, the American Academy of Ophthalmology's Task Force on Genetic Testing recommends against routine use of these tests for AMD management, particularly for patients with early AMD, and genetic testing is not advised for patients with only a family history of AMD without any AMD themselves.

Franco Recchia, MD (Tennessee Retina), discussed this further, noting that the integration of phenotypic and genotypic features improves the sensitivity to predict AMD progression by 15%, equating to identifying an additional 1 million people at risk for visual debilitation. Again, we have little to offer now other than reinforced emphasis on lifestyle changes and tightened surveillance. But the field is rapidly expanding, future preventative strategies and therapies may change this, and it is important to foster this knowledge.

Treatment options for nonexudative AMD

Although wet AMD receives well-deserved attention and an exciting buzz at these meetings, we still have a dearth of treatment options for advanced dry AMD, namely geographic atrophy (GA). Currently, we are left to simply counsel patients on the finding and prognosis and can only observe its progression over time and hope that it never involves the fovea. Fortunately, treatment options for GA are being explored. Philip J. Rosenfeld, MD, PhD (Bascom Palmer Eye Institute), presented data on the progression of GA in the COMPLETE study, in which patients with eyes containing GA were randomized 1:1:1 to receive intravenous eculizumab (Soliris, Alexion Pharmaceuticals Inc.) at a high dose (900 mg/wk for 4 weeks, then 1200 mg every 2 weeks), eculizumab at a low dose (600 mg/wk for 4 weeks, then 900 mg every 2 weeks), or placebo. Eculizumab is a humanized monoclonal antibody complement inhibitor, approved for the treatment of paroxysmal nocturnal hemoglobinuria (PNH). Patients were followed with spectral-domain optical coherence tomography (SD-OCT) monthly for 6 months and then every 3 months. At the 6- and 12-month endpoints there was no difference in the growth rates of GA between the groups. However, useful data were found. SD-OCT was able to classify lesion subtypes and demonstrate that outer photoreceptor disruption precedes the appearance of GA. Of note, eculizumab is extremely expensive, costing up to $400 000 per year for patients with PNH who have a dosing regimen very similar to those in the COMPLETE study ($5000 per 300 mg vial). This raises the question of practicality even if the medication were found to be effective.

Treatment options for exudative AMD

Allen Ho, MD (Mid Atlantic Retina, Wills Eye Institute), presented the 2-year results of the HARBOR study, which evaluated the efficacy and safety of 0.5 mg and 2.0 mg ranibizumab (Lucentis, Genentech) dosed as-needed (prn) or monthly in patients with wet AMD. All 4 groups had significant and clinically meaningful BCVA improvements, and the higher, 2.0 mg dose was not shown to be superior. Moreover, the prn group appeared to achieve similar results to monthly regimens. These data add to our understanding that monthly injections might not be necessary. On the other hand, several studies indicate a slight benefit in those who receive more frequent injections. A treat-and-extend regimen might optimize these endpoints, maximizing visual outcomes while minimizing injections, but this has not yet been rigorously evaluated.

Paul Tornambe, MD (Retina Consultants San Diego), presented a subanalysis of the HARBOR study. Dr. Tornambe showed impressive angiographic regression of choroidal neovascular membranes in eyes treated with monthly or as-needed ranibizumab. Notably, both classic and occult lesions responded, despite the notion that occult membranes are more mature and should not regress with anti-VEGF therapy alone. It remains to be seen whether this represents true regression of the membranes or simply suppression, subject to reactivation if ignored.

Anthony Adamis, MD (Genentech), discussed the association of baseline-lesion size with BCVA at month 12 in the ranibizumab studies. In both classic and occult lesions, patients with smaller baseline membranes did better than patients with larger lesions, with better visual acuity outcomes. This is important and reinforces the idea of identifying patients early. We are finding that we often identify patients very early and can start treatment with very small lesions.

Eduardo Novais, MD (Vision Institute, Federal University, Brazil) presented an interesting study in which he performed daily OCT scans of 5 treatment-naïve eyes following the first anti-VEGF injection. Although the minimum central retinal thickness (CRT) was observed at the end of the 30-day period, there was a tendency for an increase in CRT at day 17. This illustrates an important concept for patients who appear to respond suboptimally to treatment. They may actually have a response, but we miss the effect by only examining them 30 days later. I often ask these patients to return for a scan 2 weeks after the injection to see if there is any response at that time. If so, they may need more

frequent injections, or need to be switched to a potentially longer-acting agent such as aflibercept (Eyelea, Regeneron).

We have a relative wealth of choices now for initial management of wet AMD, providing options for the treatment of cases that are not responding as robustly to treatment as we would like or are recalcitrant altogether. John Loewenstein, MD (Massachusetts Eye and Ear Infirmary), presented data suggesting that, in general, suboptimal responders switched from bevacizumab or ranibizumab to aflibercept experienced stabilized vision, improved anatomic outcomes, and an ability to extend the time interval between injections.

It is an exciting time for the treatment of AMD with multiple medications in the research phase that promise to improve outcomes and decrease the treatment burden on our patients. One of these is the anti-VEGF DARPin, which Allergan is studying in phase 2 trials. The agent appears to be safe and well-tolerated and may extend the dosing interval up to 16 weeks.

Fovista is an anti-platelet-derived growth factor (PDGF) agent being studied by Ophthotech as an intravitreal adjunctive therapy with anti-VEGF injections. Pravin Dugel, MD (Retinal Consultants of Arizona), presented the 24-month results, which showed a statistically significant higher letter gain in combination-treated patients compared with those who received ranibizumab monotherapy (10.6 letters vs 6.5 letters). Another potential adjunctive treatment option is iSONEP (Lpath, Pfizer), an anti-sphingosine-1-phosphate (S1P), which is administered as an intravenous infusion and may be adjunctive to anti-VEGF therapy. This is also being studied as a standalone option. Pazopanib is a tyrosine kinase inhibitor being developed by GlaxoSmithKline that inhibits multiple pro-angiogenic factors including VEGF, PDGF, and the stem cell factor receptor. It is being explored as an adjunctive, topical eyedrop for wet AMD with favorable early results. Pazopanib is not alone. Squalamine is another eyedrop in phase 2 trials, being evaluated by Ohr Pharmaceutical.

Eugene de Juan Jr., MD (ForSight Labs), presented a surgically implanted, refillable drug delivery system that attempts sustained release of ranibizumab. The device is interesting and holds promise. However, the valid point was brought up that we should be wary of converting the treatment of AMD from an office-based procedure to 1 for which surgery is required.

DIABETIC MACULAR EDEMA

Michael Elman, MD (Elman Retina Group), presented the 3-year results of a large study evaluating ranibizumab for center-involving diabetic macular edema (DME) with prompt vs deferred macular laser treatment. The data showed a slight advantage (3 letters at 3 years) to those in the deferred laser group. This suggests that macular laser at the initiation of ranibizumab treatment is no better than deferring laser treatment for 6 months or more and may be detrimental for visual outcomes. On the other hand, the difference was slight, and laser-treated patients received fewer injections over the course of the study.

Susan Bressler, MD (Wilmer Eye Institute), presented data showing a sustained benefit to visual function through 36 months for patients with DME participating in the RESTORE Extension study. Personally, I am not a believer in anti-VEGF injections ad nauseum for patients with DME. I typically start with a series of monthly anti-VEGF injections to reduce the edema, and I obtain a widefield fluorescein angiogram to look for peripheral nonperfusion, which is a driver of vascular incompetence in the macula through the release of VEGF and inflammatory factor. Targeted panretinal photocoagulation to these areas of nonperfusion, if present, can provide sustained relief of DME, while minimizing the potentially vision-threatening side effects of macular laser and anti-VEGF injections. I use macular laser in selected patients with persistent leakage if I think that it will help wean them from anti-VEGF injections.

TAKE-HOME MESSAGE

The 2013 Macula Society meeting is a forum for some of the most intelligent and creative minds in our field to get together and converse about their thoughts and ideas. The meeting brings the best in retina together for a few days, and I have no doubt that it sparks the ideas of tomorrow, be it inspiration struck from a particularly outstanding presentation, or the product of a late-night discussion over a few drinks. Needless to say, I felt a bit like a fish out of water, or, better yet, a middle-school kid at a college party. Regardless, I had a wonderful time and am grateful for the experience.

My favorite moment? It had to be my chance to sit down with one of my heros and a true gentleman of our field, Wayne Fung, MD (Pacific Eye Associates), for several hours over dinner. We talked about the history of the field, his mentors, and his mentees. He told me how much he enjoyed being a retina surgeon and what a satisfying, fulfilling career it has been. This was wonderful to hear, and if my very early career is any indication, I will surely be telling the same story myself 1 day. Attending the Macula Society meeting reminded me how proud I am to be a retina surgeon, and how excited I am for the next 50 years. ■

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