New Modalities for Treating Diseases of the Choroid and Retina

Highlights from a roundtable discussion held during the 2014 meeting of the Association for Research in Vision and Ophthalmology.

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MODERATOR
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PANELISTS
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Steven Yeh, MD, is a vitreoretinal and uveitis specialist at the Emory Eye Center in Atlanta, where he is an assistant professor of ophthalmology. Dr. Yeh is a consultant to Bausch + Lomb and Clearside Biomedical. He may be reached at steven.yeh@emory.edu.

Retina specialists are experiencing an ongoing paradigm shift in the treatment of diseases of the choroid and retina. Although current first-line therapy in most cases is an anti-VEGF agent, physicians are often faced with a suboptimal response and must weigh the pros and cons of adjunctive or replacement therapy. Fortunately, new pharmacologic therapies and alternative methods of drug delivery will expand the options to target specific pathologies and achieve better outcomes.

—David S. Boyer, MD

CURRENT THERAPIES
Retinal Vein Occlusion
David S. Boyer, MD: What is your current treatment regimen for retinal vein occlusions?

Mark S. Humayun, MD, PhD: Anti-VEGF agents are my first line of treatment for branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO).

Giovanni Staurenghi, MD: For BRVO, I choose a therapy based on the location of the occlusion and the patient’s age. I may use laser, an anti-VEGF agent, or an intravitreal corticosteroid. For CRVO, I use either an anti-VEGF agent or a corticosteroid.

Dr. Boyer: Dr. Yeh, what is your usual workup if you suspect CRVO?

Steven Yeh, MD: I assess the patient’s systemic risk factors to determine if he or she is vasculopathic, specifically emphasizing hypertension, particularly if he or she is poorly controlled. I also will note a history of glaucoma, which may be a risk factor for vein occlusive disease. I use widefield angiography and spectral domain optical coherence tomography (OCT) to determine the extent of peripheral ischemia and macular edema.

Dr. Boyer: Would you alter your treatment plan based on the amount of ischemia?
Dr. Yeh: I would not necessarily change what I do at the initial evaluation, unless some neovascularization is evident, because I usually start with anti-VEGF therapy, which has been shown to decrease the risk of neovascularization to less than 5% with any intravitreal anti-VEGF agent used.2,4

Dr. Boyer: That is an important point. If a significant amount of macular nonperfusion is present in the periphery and the patient has been treated aggressively with an anti-VEGF agent, once you stop anti-VEGF therapy, the clock begins again, and glaucoma or ruberosis may occur. I would likely treat with an anti-VEGF agent at least 3 times, and if the response is suboptimal, I may add a steroid. Dr. Yeh, what do you do when the response to therapy is unsatisfactory?

Dr. Yeh: I consider a corticosteroid injection, after weighing the potential concomitant risks of cataract development and elevated intraocular pressure (IOP) and development of glaucoma. (See also The Effects of Long-term VEGF Suppression on page 4.)

Diabetic Macular Edema

Dr. Boyer: What is your approach to diagnosis and treatment of diabetic macular edema (DME)?

Dr. Humayun: At the initial visit, I perform fluorescein angiography and OCT, and I treat with an anti-VEGF agent. On subsequent visits, I perform OCT only and treat with an anti-VEGF agent.

Dr. Staurenghi: Typically, I use an anti-VEGF agent and/or laser. As a second choice, I may use a corticosteroid. If a patient does not respond to my first-line approach, I may perform vitrectomy.

Dr. Yeh: From an imaging standpoint, I assess the degree of foveal perfusion and the peripheral perfusion status in terms of what is driving the macular edema. What is clear from studies looking at inflammatory chemokines and cytokines is that this complex process is partly VEGF-driven, and other factors play a role.5 Based on data from the DRCR.net studies, patients with center-involved DME seem to derive visual acuity benefits from anti-VEGF therapy. Whether laser is administered promptly or is deferred in some patients is not so important.5

For center-involved DME with clinically significant macular edema, I typically use anti-VEGF therapy. If the DME is not center-involved, I may consider focal laser. Sometimes I use a combination of these 2 therapies, depending on whether or not there are good microaneurysm targets.

“There is quite a demand, at least in DME, for the use of steroids in combination with anti-VEGF therapy. It would be beneficial to have other methods for delivering steroids that would not cause cataract.”

—David S. Boyer, MD

Dr. Boyer: How do you monitor patients, and what prompts you to switch treatments?

Dr. Yeh: I monitor patients on a monthly basis. I typically administer at least 3 anti-VEGF injections. I have seen some patients have minimal to no response after 1 injection, but respond after a second injection. For that reason, I usually do not switch therapy after just 1 injection. If the disease is not responding after 3 injections, or if the response is incomplete, I consider other treatment modalities.

Dr. Boyer: Dr. Humayun, if initial anti-VEGF therapy does not produce the expected response, do you switch to a different anti-VEGF agent, do you switch to a steroid, or do you add laser therapy?

Dr. Humayun: If the patient demonstrates a poor or partial response, I switch to a different anti-VEGF agent, and if this has no effect, I use an intraocular steroid, such as dexamethasone intravitreal implant (Ozurdex, Allergan).

Dr. Yeh: I, too, will consider switching to a different anti-VEGF agent before treating with a corticosteroid, mainly because of the risks associated with steroids. Most patients with DME are young and phakic, and they will require more injections, which carries a risk of cataract development.

Dr. Boyer: Dr. Yeh brings up some good points. Steroids as we administer them today carry a significant risk for cataracts. After multiple injections, most patients develop a cataract. I tend to be conservative in my use of steroids for this reason. Fortunately, cataract surgery is highly successful, but if we cannot dry the retina, patients eventually lose vision. There is quite a demand, at least in DME, for the use of steroids in some patients in combination with anti-VEGF therapy. It would be beneficial
to have other methods for delivering steroids that would not cause cataract.

Age-related Macular Degeneration

Dr. Boyer: What is your usual approach to diagnosis and treatment of age-related macular degeneration (AMD)?

Dr. Staurenghi: First, I differentiate pure choroidal neovascularization from specific types of lesions, such as polypoidal choroidal vasculopathy (PCV) and retinal angiomatous proliferation (RAP), because I have a different approach for each disease state. For PCV, for example, anti-VEGF therapy is not the first choice, and follow-up is not so frequent. For RAP lesions, anti-VEGF treatment is the first choice with frequent follow-up and attention to the second eye, because of the high risk of both eyes becoming involved in 3 years.6

Dr. Boyer: What are the typical signs of PCV? Do you change your approach with that diagnosis?

Dr. Yeh: Sometimes polyps are clinically identifiable, but in my experience, that is rare. I look for signs, such as significant bleeding that seems out of proportion to the lesion. People of Asian or African descent are at risk for PCV.7

Dr. Boyer: How do you treat these patients?

Dr. Yeh: I typically administer an anti-VEGF agent initially, but from a prognostic standpoint, I know these patients may require a different form of therapy, possibly focal laser, photodynamic therapy with verteporfin (Visudyne, Valeant Pharmaceuticals, Inc.), or corticosteroids.

Dr. Boyer: How do you manage patients with AMD who are not responding to anti-VEGF therapy?

Dr. Yeh: If I started treating with bevacizumab (Avastin, Genentech), I may switch to ranibizumab (Lucentis, Genentech) or aflibercept (Eylea, Regeneron). I may choose ranibizumab, because of its increased binding affinity to VEGF when com-

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pared with bevacizumab, or I may choose aflibercept, because a number of studies have shown that a proportion of patients can respond, at least anatomically, to aflibercept therapy.  

Dr. Boyer: Are enhanced-depth imaging OCT and indocyanine green angiography important for identifying non-VEGF-related conditions in patients who do not respond to initial therapy? (See also Integral Imaging Tools on page 7.)

Dr. Yeh: Yes. Some patients may actually have central serous retinopathy (CSR) or something that appears to be a CSR-like form of AMD, with increased choroidal thickness and persistent fluid. These patients may respond to photodynamic therapy.

Uveitis

Dr. Boyer: Dr. Yeh, you are a uveitis specialist. In addition to the usual medical and ocular history and review of systems and risk factors, what does your typical workup for uveitis include?

Dr. Yeh: Patients with uveitis warrant a serologic workup to detect autoimmune or infectious etiologies. For instance, I practice in the southeastern United States, which has a high population of black patients who have sarcoidosis, which is very common. I also try to exclude an infectious process prior to treating with a corticosteroid. The incidence of syphilis has been increasing and is endemic in our area. Therefore, I typically test for serologic evidence of syphilis as well as tuberculosis. I want to make sure that any antiinflammatory medications used will not worsen the patient’s condition. If characteristic lesions of posterior uveitis, such as birdshot retinochoroidopathy, are present, I may order human leukocyte antigen (HLA)-A29 tissue typing. I may test for Lyme disease if the patient has a history of a tick bite, although this is uncommon in our area.

Dr. Boyer: Do you stage uveitis?

Dr. Yeh: I categorize uveitis as anterior, intermediate, posterior, and panuveitis, according to the standardization of uveitis nomenclature guidelines.  

Dr. Boyer: How do you choose a treatment regimen?

Dr. Yeh: When I choose an antiinflammatory medication for noninfectious uveitis, I consider several factors, including whether the disease is unilateral or bilateral, and if systemic comorbidities contraindicate systemic corticosteroids. I also consider the patient’s phakic status, history of glaucoma, and the presence of macular edema, which responds well to locally administered corticosteroids.

Dr. Boyer: How do you treat posterior uveitis with moderate vitreous haze and cystoid macular edema?

Dr. Yeh: If the disease is bilateral and there are no contraindications, I discuss oral, periocular, and intravitreal corticosteroids with the patient. If a patient has unilateral, intermediate uveitis with cystoid macular edema that has not demonstrated significant chronicity, I consider a local corticosteroid injection.

In my experience, patients who have bilateral disease, particularly severe bilateral inflammatory disease, sarcoidosis, or collagen vascular disease with associated vasculitis, respond well to corticosteroids. If a patient has a systemic autoimmune condition, his or her rheumatologist is usually happy to help with immunosuppressive measures, which may be what the patient needs in addition to local therapy.

If a patient has significant anterior uveitis, topical corticosteroids are effective. From a vision standpoint, however, by the time most of these patients arrive in a vitreoretinal practice, they need something more. We must determine how often they will need therapy and if they will need long-term therapy.

STEROID CONSIDERATIONS

Dr. Boyer: Often, retina specialists hesitate to use intra-vitreal steroids because of the complications of cataract development and increased IOP. Dr. Staurenghi, are you comfortable using steroids in most patient populations?

Dr. Staurenghi: My decision whether or not to use a steroid depends on the patient’s age, cataract status, and the risk for or presence of glaucoma. If a patient is pseudophakic, for example, I am comfortable using a steroid.

Dr. Boyer: If the incidence of increased IOP and cataracts associated with steroid use can be dramatically
reduced, would steroids retain a role in treating posterior segment diseases?

Dr. Humayun: Yes. In addition to fewer side effects, the duration of action and the level of visual acuity gain should also be considered. A new, more effective steroid with fewer side effects that would require less frequent treatment would be appealing.

Dr. Yeh: Route of administration and side-effect profile are important. Currently, we administer many intravitreal injections, but the side effects may be just as visually concerning as the diseases we are treating, particularly in younger phakic patients. Sometimes, they require cataract surgery as result of steroid therapy, and cataract surgery is not trivial in these patients, because of the concomitant severe inflammation.

If a sustained-release corticosteroid or other anti-inflammatory agent could be delivered into a different compartment of the eye, I believe that would be advantageous.

NEW DRUG DELIVERY OPTIONS

Dr. Boyer: Drug delivery is one of the most exciting areas of research today. Although intravitreal injection of anti-VEGF agents is a mainstay of therapy, the frequency and chronicity of injections required, as well as the sometimes unpredictable outcomes, are drawbacks. Corticosteroids are effective in addressing the inflammatory component of retinal disease, but they may cause complications. Dr. Humayun, what impact will drug delivery have on future treatment of diseases of the choroid and retina?

Dr. Humayun: Drug delivery will have an enormous impact in the future. Local delivery of a drug to the posterior segment of the eye is especially attractive, as it avoids systemic side effects. Suprachoroidal and intravit-
real implants are very appealing. These implants would have to deliver the most effective drugs with the fewest side effects.

**Dr. Yeh:** A medication that could last longer inside the eye would also be advantageous to reduce the treatment burden for our patients and our clinics.

Thinking about available treatments for uveitis from a drug delivery standpoint, I believe the flucinolone acetonide intravitreal implant (Retisert, Bausch + Lomb) has changed our ability to deliver medications, and it is a surgical device that allows patients to avoid repeated injections. At the same time, however, there is the concomitant risk that 90% of patients may require cataract surgery within 2 years, and 25% to 40% may require glaucoma filtration surgery.¹⁰⁻¹²

**Dr. Boyer:** How do you compare Retisert to the long-acting dexamethasone implant?

**Dr. Yeh:** I think both implants have a place in our armamentarium. The dexamethasone implant is an effective treatment for macular edema, but it does not last quite as long as the flucinolone implant. I believe the dexamethasone implant can be appropriate for uveitis patients who do not have a chronic retinal degenerative component to their uveitis. Patients who require repeated intravitreal or perioperative corticosteroid injections, regardless of the device used, must be monitored closely for signs of retinal degeneration. We do not have definitive evidence, for instance, regarding the toll on photoreceptor loss with recurrent cystoid macular edema. In addition, patients with birdshot retinochoroidopathy may develop peripheral visual field loss if they are not monitored closely.

**Dr. Boyer:** Several new drug delivery devices and systems are currently under development. A device by Neurotech, NT-501 (Renexus), consists of encapsulated human cells genetically modified to secrete ciliary neurotrophic factor (CNTF) to treat geographic atrophy and retinitis pigmentosa. This treatment seemed to show some biologic effect in a clinical trial, but because the control group did well, it did not reach statistical significance.¹³ Another version of this device, NT-503, secretes an anti-VEGF drug for long-term chronic suppression.

ForSight Vision4, Inc., is working with Genentech to develop a port delivery system in which a refillable device is placed in the eye through a scleral incision.

Exclusive of devices and implants, drug delivery via the suprachoroidal space appears to be an ideal method for getting drugs directly to the choroid and retina. I know work is currently being conducted by Clearside Biomedical. Dr. Humayun, please describe Clearside’s approach to drug delivery. In what stage of development is the company?

**Dr. Boyer:** Not all drug delivery research is focused on devices. Utah-based Aciont, Inc., is working on a noninvasive technique called iontophoresis that uses electrical current to drive drugs in the form of ions into and through tissue.

Several companies are working on nanoparticle technology, which will be instrumental in developing sustained-release formulas of various drugs. Coupled with a microinjection platform, this technology will enable delivery of drugs to the suprachoroidal space.
I believe the idea of delivering drugs to the suprachoroidal space is a valid one, with the potential to reduce the side-effect profile of the drugs. If we can reduce the risk of cataract and glaucoma, this may become the preferred method for administering this type of drug.

Dr. Yeh: I completely agree that when we think about medications such as corticosteroids, which have demonstrated efficacy for short-term treatment of DME and uveitis, we cannot ignore that they are fraught with other issues from a side-effect standpoint. If there is a way of delivering this medication closer to the targeted area and with a lasting effect requiring fewer injections, I think that it would be desirable.

Dr. Boyer: The ideal drug delivery system could be performed in the office rather than in an OR. How would that fit into your paradigm of treatments?

Dr. Staurenghi: I completely agree that it would be advantageous to have a treatment that could be performed in the office.

Dr. Humayun: The ideal drug delivery system should be first and foremost safe and effective. Hence, if it requires a simple procedure even in the OR, this would be acceptable, provided the system would then function for multiple years.

Dr. Boyer: What new drug delivery systems seem to be safe, easy to use, and hold the greatest promise?

Dr. Humayun: The suprachoroidal delivery of drugs is a new delivery method that if safe and effective has the advantage of not injecting drugs into the vitreous cavity.

Dr. Boyer: Hopefully, advances in drug delivery will make it safer for us to use steroids. Reducing the treatment burden is also key, especially if lampalizumab (anti-factor D, Roche) is approved as a treatment for geographic atrophy. We cannot sustain a schedule of monthly or every-6-week injections indefinitely. These are patients who will live a long time (see also Managing the Increasing Number of Injections on page 6.)

CONCLUSION

Dr. Boyer: The panel today has elucidated the treatment paradigms for a variety of retinal conditions including AMD, retinal vein occlusion, uveitis, and diabetes. Future drug delivery systems will help reduce the treatment burden and hopefully reduce the potential side effects of our current treatments, making them much more effective and safer.