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NOVEL TREATMENT STRATEGIES

for Macular Edema Associated With Noninfectious Uveitis

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Novel Treatment Strategies for Macular Edema Associated With Noninfectious Uveitis

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CONTENT SOURCE

This continuing medical education (CME) activity captures content from a roundtable discussion.

ACTIVITY DESCRIPTION

In the following roundtable, experts in retina and uveitis discuss the risk of vision loss associated with each type of uveitis, evaluate the safety and efficacy of different treatment modalities for noninfectious posterior uveitis, including corticosteroids, sustained-release implants, immunomodulatory agents, and biologics, and discuss the potential advantages of steroid administration to the suprachoroidal space.

TARGET AUDIENCE

This certified CME activity is designed for anterior segment specialists, general ophthalmologists, and other eye care practitioners involved in the management of noninfectious uveitis.

LEARNING OBJECTIVES

Upon completion of this activity, the participant should be able to:

- **Describe** the risk of vision loss associated with each type of uveitis.
- **Evaluate** the safety and efficacy of different treatment modalities for noninfectious posterior uveitis, including corticosteroids, sustained release implants, immunomodulatory/immunosuppressive agents, and biologics.
- **Discuss** the potential advantages of steroid administration to the suprachoroidal space.

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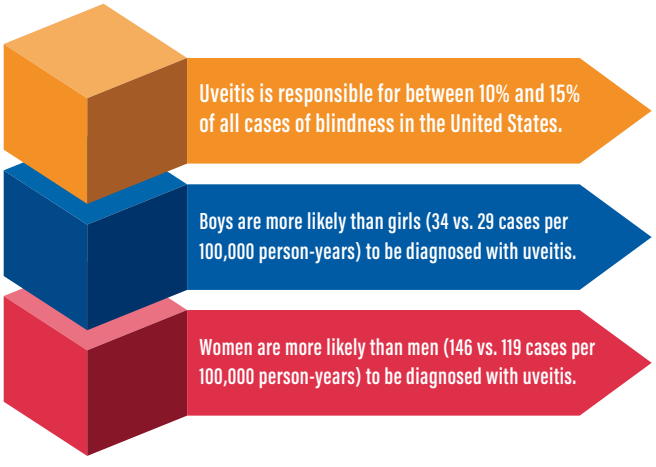
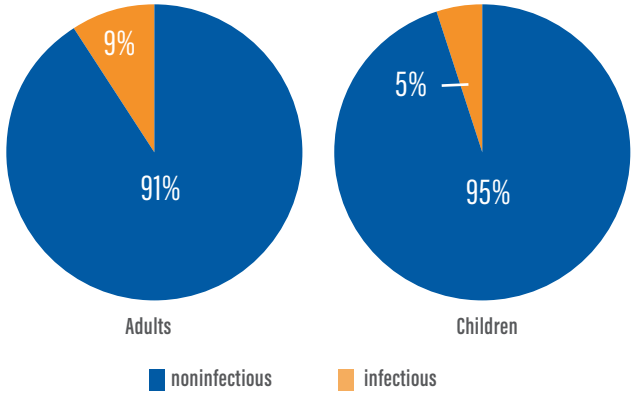
Novel Treatmenta Strategies for Macular Edema Associated With Noninfectious Uveitis

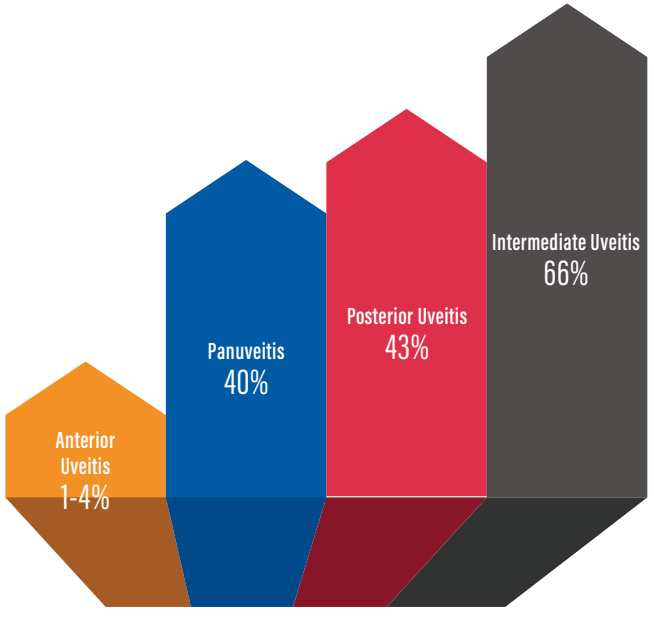
Uveitis is intraocular inflammation, predominantly in the uveal tract or the vascular tissue between the retina and sclera (See a snapshot of uveitis in Figure 1).[1-5] *Uveitis causes up to 15% of blindness in the United States*[6] *Uveitis is often associated with systemic disease, which is critical to identify in order to properly treat and manage patients. Vision loss is dependent on the location of the inflammation, and retina specialists must be able to properly identify the location. Uveitis must be identified and treated early in order to prevent irreversible vision loss. In the following roundtable, experts in retina and uveitis discuss the risk of vision loss associated with each type of uveitis, evaluate the safety and efficacy of different treatment modalities for noninfectious posterior uveitis, including corticosteroids, sustained-release implants, immunomodulatory agents, and biologics, and discuss the potential advantages of steroid administration to the suprachoroidal space.*

—Thomas Albini, MD, Moderator



Noninfectious and Infectious Uveitis Cases in Adults vs. Children





Percentage of Uveitis Patients with 25% Visual Acuity Loss by Anatomic Location[21,22]

Figure 1. Snapshot of uveitis, percentage by type of uveitis, and percentage of patients with vision loss by anatomic location.[1-5] **Graphs originally published in "Uveitis Crash Course,"** ***Retina Today*****. October 2017.**

DIAGNOSING UVEITIS

Q | THOMAS ALBINI, MD: A patient presents in your office with posterior segment uveitis. What are your first steps? What questions do you ask the patient regarding their medical history before you even begin to evaluate them?

"When diagnosing uveitis, it is important to look at multiple modalities of imaging in order to identify the extent of the inflammation...You have to assess whether it involves the vessels or just the leakage in the macula with cystoid macular edema and what pattern you are seeing. For each patient I see, I want to assess anterior chamber cell, vitritis, chorioretinal lesions, cystoid macular edema, and retinal vasculitis. These last three clinical inflammatory manifestations are best evaluated with multimodal imaging."

—Thomas Albini, MD

STEVEN YEH, MD: It is important to think about their ophthalmic history but also their systemic diagnosis as well. I would want to know whether they have a history of systemic autoimmune disease conditions or associated etiologies, such as sarcoidosis, multiple sclerosis, and anything that potentially can contribute to ocular inflammation. From an ophthalmic standpoint, I want to know how long they have had this inflammation. How long have they had symptoms of their disease? Finally, I also would like to explore any therapies they are currently on for uveitis and whether those therapies are topical, local, or systemic. Figure 1[1-5] provides a simplistic overview of the state of this disease.

DR. ALBINI: Is there anything in the patient's history that would lead you to believe this is an infectious case versus a noninfectious case of uveitis?

DR. YEH: Clinicians must take infectious or noninfectious disease into consideration when evaluating patients. For instance, if the patient has had a history of systemic immunosuppression for a rheumatologic condition or for cancer therapy, then I am automatically considering infectious diseases that could lead to uveitis, such as cytomegalovirus retinitis. If the patient has had a history of a vaccination with live virus for shingles, then I think about acute retinal necrosis. These are some considerations that would lead me to consider an infectious process compared to a noninfectious condition.

DR. ALBINI: What kind of imaging would you obtain in a posterior segment inflammatory case?

DIANA V. DO, MD: Clinical exams are extremely important in these cases. A complete eye exam should include dilating the pupils to look at the posterior segment. Does the uveitis involve one eye or both eyes? Which part of the eye has the inflammation? Is it sequestered in the anterior segment, or does it involve the posterior segment as well? In addition to a careful exam, I find that multimodal imaging helps to evaluate the extent of the involvement and assist in the diagnosis and management.

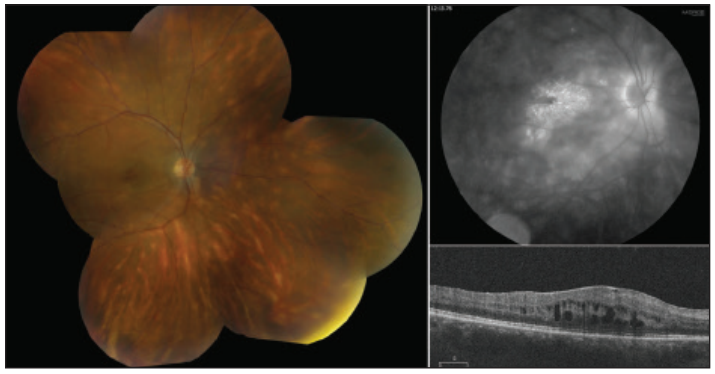
DR. ALBINI: Do you obtain OCT or fluorescein angiograms (FAs) during your exam?

CHARLES C. WYKOFF, MD, PHD, FACS: I agree with Dr. Do that a complete, bilateral ocular examination is the starting point. In the setting of uveitis with posterior-segment involvement, I will obtain OCT and ultrawide-field fundus photographs, and I have a low-threshold to obtain ultrawide-field angiography.

DR. ALBINI: When diagnosing uveitis, it is important to look at multiple modalities of imaging in order to identify the extent of the inflammation. Figure 2 demonstrates a few examples of various imaging. You have to assess whether it involves the vessels or just the leakage in the macula with cystoid macular edema (CME) and what pattern you are seeing. For each patient I see, I want to assess anterior chamber cell, vitritis, chorioretinal lesions, CME, and retinal vasculitis. These last three clinical inflammatory manifestations are best evaluated with multimodal imaging. OCT for CME, FA for vasculitis, and fundus photography, fundus autofluoresence, and both FA and indocyanine angiography (ICGA) for chorioretinal lesions. These images can help you determine, for example, sarcoidosis by picking up chrorioretinal lesions or inflammatory lesions with overlying vitritis that might suggest a toxoplasmosis. You want to appreciate very early on that this could be an infectious case.

DR. YEH: There are some disease-specific findings that will consider when I am examining images. It is important to obtain these diagnostic tests, but you also need to look at the imaging specific findings of a disease condition. For example, birdshot retinochoroidopathy is a rare form of posterior uveitis that mainly affects the retina and choroid, primarily white patients aged 30 to 60 years. The precise trigger of the disease is unknown, but this is a fascinating condition where you will have optic disc leakage that may be out of proportion to what you see clinically. In my observation, it sometimes suggests that there is choroidal-based inflammation as well, which you will pick up on ICGA in the form of hypocyanescent lesions. The FA shows this characteristic pattern of segmental periphlebitis, which is quite characteristic of birdshot retinochoroidopathy. These findings on FA may also lead you to obtain the ICGA because you see this characteristic vasculitis. Figure 2 shows how birdshot choroiditis may present.

I believe that we will see the field moving towards these disease-



Courtesy of Steven Yeh, MD; and Jessica G. Shantha, MD.

Figure 2. Fundus photo montage shows multiple oval, cream-colored lesions within the choroid in the right eye consistent with birdshot choroiditis (A). A venous phase FA shows petalloid leakage and optic disc hyperfluorescence (B). OCT shows macular edema (ME) greater nasally leading to decreased VA to 20/40 in the right eye (C). Photos originally published in "The Burden of Noninfectious Uveitis of the Posterior Segment: A Review," *Retina Today*. July/August 2016.

specific outcomes. From a clinical trial standpoint, we combined many of these heterogeneous conditions into a noninfectious uveitis category when, in reality, these conditions are very different. If you have a patient with vasculitis versus a patient with choroidopathy or choroiditis, how you evaluate their response to therapy will vary. I always tell our residents and fellows that even if they think the other eye looks quiet clinically, it is important to consider diagnostic imaging with FA and to image both eyes. It is very easy to miss vasculitis in the asymptomatic, and sometimes less severely affected, eye.

DR. ALBINI: What laboratory testing do you order to facilitate ruling out other infectious diseases?

DR. YEH: The two infectious entities that I consider, at least from a serologists standpoint, are tuberculosis and syphilis. For tuberculosis, I will order a QuantiFERON-TB Gold test (Qiagen), which is highly specific and sensitive.[7] For syphilis testing, I will do a syphilis Immunoglobulin G, followed by a reflex rapid plasma regain if it comes back positive. I will also consider ordering ionized calcium for sarcoidosis.[8] If my clinical suspicion is there, then I will also order an HLA-A29 for posterior uveitis that is consistent with birdshot.

DR. DO: I also evaluate for viral retinitis and, specifically, herpes as a possible cause of the inflammation. In diagnostic dilemmas, I will start the patient on an empiric therapy, but if they are not responding adequately, I will obtain aqueous fluid and send for polymerase chain reaction testing to determine the possible culprit.

DR. ALBINI: Risk factors for endogenous endophthalmitis are often overlooked in these patients. Common risk factors for endogenous endophthalmitis are a recent hospitalization, diabetes, a urinary tract infection, and immunosuppression associated with cancer, neutropenia, and HIV.[9] Therefore, it is important to ask patients about recent hospitalizations and nonocular surgeries because the risk of developing endogenous endophthalmitis increases the longer someone has been in an intensive care unit. It is also important to get a complete medical history in these patients. While treating patients who are immunocompromised or patients who have an HIV infection, for example, I am quicker to perform a diagnostic vitrectomy to rule out infectious causes before I prescribe local or systemic steroids, which have the potential to endanger the health of those patients.

MANAGING UVEITIS: LOCAL VERSUS SYSTEMIC THERAPY

Q | **DR. ALBINI:** What is your first-line approach for controlling inflammation in patients with noninfectious uveitis?

DR. DO: It depends on whether both eyes are involved or if the inflammation is isolated to one eye. In cases of noninfectious, unilateral posterior uveitis, I will discuss the risk and benefits of local versus systemic treatment with patients. In many of those patients with unilateral uveitis, without systemic involvement, I will most likely recommend a local therapy, such as intraocular steroids, to suppress the local immune system. Intravitreal steroids have been proven to be effective in reducing posterior segment inflammation. However, prolonged use of intraocular steroids can be associated with elevated eye pressure and cataract progression. In patients with bilateral non-infectious uveitis, I discuss both local treatment and systemic treatment. Often, these patients will need systemic immune modulatory agents to control their eye disease. If systemic treatment is necessary, I will start with high dose oral steroids (with subsequent tapering of the steroid) and a steroid sparing agent, such as mycophenolate mofetil. Systemic immunosuppression can be very effective in controlling bilateral uveitis and the MUST study has demonstrated that systemic therapy can be safe.[10,11] However, systemic immunomodulatory agents can be associated with side effects,[10,11] such as nausea, vomiting, and reduction in certain blood cell counts.

DR. WYKOFF: I am comfortable using local therapies to manage my noninfectious uveitis patients. Often, such local therapy involves use of steroids: topical, periocular, and/or intravitreal. I am also comfortable prescribing oral prednisone for up to 3 months. I do not routinely prescribe systemic immunosuppression beyond prednisone. If a patient needs more than local therapy and/or infrequent, short-term courses of oral prednisone, I will treat them in combination with a rheumatologist or refer them to a focused uveitis specialist who is comfortable prescribing systemic immunosuppression.

DR. ALBINI: How do you approach a patient with a history of ocular hypertension related to steroid use?

DR. WYKOFF: I approach that patient cautiously. In my hands, local steroid delivery in the form of an intravitreal or periocular injection will result in a clinically meaningful elevation in IOP in about a third of patients and leads to cataract acceleration in nearly all patients if the patient is followed long enough. So, I make sure patients are aware of these risks, and I ensure that our conversation

is well documented. If we proceed with steroid treatment, then I follow the patient closely. In the context of baseline glaucoma with significant nerve damage, depending on the level of disease control, I would be particularly cautious before using local steroids.

DR. ALBINI: What do you think about using local steroids in young patients, in terms of cataract progression?

DR. YEH: I completely agree with Dr. Wykoff that we want to be very cautious with systemic immunosuppression in any patient, regardless of their age. The things that I think about are if they have a history of hyperglycemia, diabetes, or hypertension because there are side effects to this therapy. Patients may have mood swings, weight gain, and hypertension.

In regard to local therapy, there is very real risk of developing cataract and glaucoma. Cataract is a very common complication of chronic or recurrent uveitis, leading up to 40% of the VA loss in these patients.[12] One study found that 40% of patients with uveitis will experience raised IOP, and about 30% of those patients will need glaucoma treatment.[13] This can be especially important in younger, phakic patients, and we should try to limit how much local corticosteroid we administer, at least with the currently available injectable corticosteroids. There is a high rate of these side effects, particularly with repeated injections. However, as discussed, sometimes there are factors that preclude systemic therapy.

DR. ALBINI: Do you feel that patients who have these types of inflammatory problems sometimes have a predisposed prejudice to one type of therapy—local versus systemic? Do you find that some patients select the therapy themselves? Or are most of your patients at ease with either type of treatment option as you are discussing it with them?

DR. DO: When a patient first develops uveitis, and you discuss local versus systemic therapy, they are concerned about the risk and benefits of either of those approaches. They tend to be anxious about systemic immunosuppression. Take the MUST study, for example, which looked at systemic therapy randomized against the fluocinolone acetonide intravitreal implant (Retisert, Bausch + Lomb).[10] MUST enrolled 255 patients (481 eyes with uveitis), over 3 years. Half of the eyes with uveitis had a BCVA worse than 20/40, and 16% had a BCVA worse than 20/200 at baseline. Lens opacities, ME, and epiretinal membrane were common. Systemic immunosuppression was found to be relatively safe up to 5 years of follow-up.[11] Based on these data, I can reassure patients that if we do choose systemic immunosuppression, there is a good chance that they won't have any serious adverse events if we monitor them closely.

In pediatric populations where you are afraid about the side effects of intraocular steroids, therapies such as adalimumab (Humira, AbbVie), which is approved for children older than age 4, are useful. The incidence of uveitis in this population is not insignificant. Uveitis will develop in 12% to 38% of patients with juvenile idiopathic arthritis, the most common rheumatic disease in pediatric patients.[14,15] Adalimumab has been proven to be effective in young patients with uveitis, significantly delaying the time to treatment failure.[16-18] Side effects, such as minor infections, respiratory disorders, and gastrointestinal disorders, do occur, however. I recommend comanaging these patients with a rheumatologist.

DR. ALBINI: There are some cases where it is much easier to go with local therapy, such as in women who are contemplating pregnancy or who are pregnant. The data on corticosteroids during pregnancy are inconsistent, although it is likely safe. For example, one study found that prednisone increases the risk of oral cleft by more than three fold, but a later study found no data showing an association between corticosteroid use during pregnancy and oral cleft.[19,20] Most patients don't want to take that risk.

Adalimumab is a Category B drug with regard to pregnancy, so we could go forward with it if needed. Obviously, this would be a discussion to have with the patients' obstetrician to try to decide how exactly we are going to manage the patient. As clinicians, there is an appeal for local therapy in that it can put the patients' mind at ease, so she knows she is doing everything she can to have a safe and healthy pregnancy.

Unfortunately, I see a large number of patients who require multiple agents to bring the inflammation under control. These patients aren't responding to one or two drugs and need a three-drug regimen. You can sometimes get away with a local therapy in those patients, but I have found that the fluocinolone acetonide intravitreal implant works particularly well in these scenarios. Sometimes you can have a systemic therapy, like a metabolite, that is well tolerated and add a local therapy, such as a dexamethasone injection (Ozurdex, Allergan), and achieve optimal control. Are there any particular types of inflammatory changes that would push you toward local therapy?

DR. YEH: ME is one of the key components that pushes me toward local therapy. While systemic therapies are helpful for inflammation, they don't necessarily control the ME, and this does not happen immediately.

The Systemic Immunosuppressive Therapy for Eye Diseases Cohort Study (SITE) was a large retrospective cohort study of nearly 8,000 patients with noninfectious ocular inflammatory diseases treated at five tertiary-care centers from 1979 to 2005 that looked at systemic immunosuppression.[21] SITE found that the rate of steroid-sparing success with immunosuppression approximated 60% to 70% with antimetabolites, such as methotrexate.[21] Therefore, we know that one in three of these patients are going to need something else. And, that being said, for the patients who are controlled, I find that some of those patients still may not have the ME resolved.

DR. ALBINI: Dr. Wykoff, how aggressively do you treat ME with these patients?

DR. WYKOFF: If a patient with uveitis has symptomatic ME, I typically treat them with intravitreal or periocular steroid delivery.

In the absence of symptoms or in the presence of noncenter-involved ME, I may observe closely and consider initial topical steroid treatment.

DR. ALBINI: How important is ME for patients with different types of inflammation, such as retina vasculitis, anterior chamber cell, and vitreous cell?

DR. DO: Treating ME is very important because there is a correlation between ME and visual symptoms.[22] The degree of vision loss depends on the location, severity, and duration of the ME, but ME can lead to chronic vision loss if left untreated. Patients with posterior, non-infectious uveitis can develop ME as a manifestation of their inflammation.[23] If I see ME in a patient with uveitis, I treat it aggressively. If I select local therapy for the ME, I can consider intravitreal steroids or intravitreal anti-VEGF agents. If the patient is on systemic therapy, sometimes the ME can persist, and I will add a local intraocular agent, such as steroids, to address the ME. I don't want the retina to stay swollen, which can lead to photoreceptor damage.

CLINICAL TRIALS IN UVEITIS

Q | DR. ALBINI: One of the interesting things about the PEACHTREE study[24] is that the researchers really targeted ME as a major inflammatory component. What were the take-home messages from these data?

DR. YEH: The PEACHTREE study was a randomized, multicenter phase 3 clinical trial that evaluated the safety and efficacy of suprachoroidal-delivered corticosteroid triamcinolone acetonide (CLS-TA) for ME due to noninfectious uveitis.[24] The study included all anatomic classifications of uveitis, including anterior intermediate, posterior, and panuveitis, and patients had ME greater than 300 µm. Suprachoroidal CLS-TA met the primary study endpoint, with 47% of patients who were treated with CLS-TA with two injections at enrollment achieving a 15-letter gain in VA at week 12. This was not seen in the sham arm. In addition, the other major take-home point is that suprachoroidal injection was well-tolerated with no serious adverse events reported attributable to the study treatment. CLS-TA significantly improved ME in uveitis patients, had a very low rate of elevation in IOP, as well as a low rate of cataract formation, which was comparable to the sham group. The elevated rate of IOP for the CLS-TA arm was 11.5% occuring in 15.6% of patients for the sham arm through the 24-week trial. The majority of patients in the CLS-TA arm did not require rescue therapy during study. However, among the patients who did receive corticosteroid rescue medication, 26.3% in the sham arm experienced elevated IOP-adverse events.

DR. DO: The PEACHTREE study provides important new data on a treatment for uveitic ME. This randomized trial demonstrates that suprachoroidal-delivered steroids can be effective and safe in the treatment of ME.[24] This treatment modality is an exciting option for eyes with ME.

"Treating ME is very important because there is a correlation between ME and visual symptoms. The degree of vision loss depends on the location, severity, and duration of the ME, but ME can lead to chronic vision loss if left untreated."

—Diana V. Do, MD

DR. ALBINI: We now have an immense amount of 7-year data from the MUST study.[25] What did MUST tell us about how to manage patients with uveitis?

DR. DO: First, the MUST study was sponsored by the National Eye Institute, making it a highly important clinical trial. It gave us long-term data on systemic immunosuppression for noninfectious uveitis. Patients were randomly assigned either to the systemic therapy or to the fluocinolone acetonide intravitreal implant, which is active for about 2 years in an eye. The study showed that with appropriate monitoring, people who are on immunosuppressive agents can have a safe outcome with no significant risk of adverse events. It also showed that the fluocinolone acetonide implant can be effective for keeping the posterior segment inflammation quiescent. However, as we all know, intraocular steroids have side effects, so we were not surprised to see the significant risk for elevated IOP and cataract progression in eyes that received the fluocinolone acetonide implant.

DR. ALBINI: We had close to 80% of patients requiring topical medications to lower pressure and 30% of patients requiring incisional surgery to control the pressure. But the upside of that was that the implant worked just as well as standard systemic medication over the first 4.5 years.

DR. DO: Both treatments were equivalent. In fact, inflammatory control was better at all time points with the implant. In the last 2 years, the effect wore off, and there was a low reimplantation rate for reasons that aren't clear. Systemic therapy added about a line of vision more than the implant at that long-term time point.

DR. YEH: I agree with Drs. Do and Albini that the 2-year data showed comparable VA results between corticosteroid-sparing immunosuppression and the corticosteroid implant. It is notable, as Dr. Do mentioned, that patients on systemic therapy showed

an approximate 1-line better VA at long-term 7-year follow-up compared to implant.[26] I think this underscores the importance of assessing the long-term outcomes of our treatments, given the risk of disease recurrence and potential for chronic disease requiring monitoring treatment in all of our patients.

DR. ALBINI: What did SAKURA 1 tell us about the treatment of uveitis?

DR. YEH: SAKURA 1 looked at intravitreal sirolimus for the treatment of noninfectious uveitis of the posterior segment (posterior, intermediate, or panuveitis), with vitreous haze reduction as the primary efficacy outcome.[27] The primary endpoint was assessed at month 5. The study randomly assigned 347 patients into three arms at a 1:1:1 ratio to receive intravitreal sirolimus 44 µg (active control), 440 µg, and 880 µg at baseline, month 2, and month 4, respectively. The study showed that there is a significantly greater reduction of vitreous haze in patients who received up to a 440-µg dose when compared to active comparator (about 10% of the dose or 44 µg). At month 5, 23% of patients in the 440-µg group, 16% in the 880-µg group, and 10% in the 44-µg group achieved the primary endpoint. VA was maintained or improved in 80%, 80%, and 79% of patients in the 440-µg, 880-µg, and 44-µg groups, respectively.

What was interesting is that we didn't see an improved dose response with the 880-µg group for reasons that are unclear. In addition, intravitreal sirolimus was well-tolerated from the standpoint of ocular hypertension, and cataract was comparable between groups. The secondary endpoint did show that patients who received the 440-µg dose were able to go off corticosteroids without the need for rescue therapy. That is encouraging. This is a different mechanism of action altogether compared to corticosteroid. The SAKURA 2 study has enrolled 245 patients to double-masked injections of intravitreal sirolimus at the same dose levels as SAKURA 1 every other month for 6 months. Results from that trial are pending.

DR. ALBINI: One of the things that was remarkable to me about the SAKURA 1 trial was the safety side. They demonstrated that there was no significant pressure changes and no cataract progression with local therapy. However, as you said, we don't have the all the data yet from the full SAKURA program. But from what we have seen, the safety profile looked remarkably good.

DR. WYKOFF: As someone heavily involved in clinical trials, I found the control arm in this trial fascinating and confusing. Patients in the control arm received the same pharmaceutical as was given to the active treatment arms, just at a much lower dose, and the rationale behind this is not intuitively obvious to me. Do you think the efficacy data may have been different if the control arm had been a true placebo arm?

DR. YEH: Yes, I do think the efficacy data would have been different in a true placebo arm. When you have a control arm with some medication, then it seems likely you will see some benefit.

DR. ALBINI: A treated control arm also makes it harder to interpret the data. The researchers discussed including a true placebo arm but decided that, for ethical reasons, they couldn't treat patients with nothing. So, they wanted to treat the control arm with a dose they determined would be minimally effective.

Let's move on to the HURON study, which looked at a single injection of dexamethasone.[28] Dexamethasone is a biodegradable, intravitreal implant that is given through a 23.5-gauge needle in the clinic. The study looked at the injection in active cases versus placebo with vitreous haze. Its primary outcome was a two-step reduction of vitreous haze. Although this was a short study of only 26 weeks, researchers also looked at the safety profile of the implant, including ocular hypertension, incisional glaucoma surgery, and cataract progression. The study had a large preponderance of about 80% of patients with intermediate uveitis. Patients responded quite well and demonstrated a very nice reduction in vitreous haze. The proportion of eyes with a vitreous haze score of 0 at week 8 was 47% with the 0.7 mg dexamethasone implant, 36% with the 0.35 mg dexamethasone implant, and 12% with the sham ($P < 0.001$). This improvement was maintained through week 26. Significantly more patients who received the implant achieved a gain of 15 or more letters from baseline BCVA compared to the sham group.

Researchers also showed that there was a significant amount of ocular hypertension requiring drops, but it was well controlled on topical medication, which is a stark contrast to the MUST study and the effects of the fluocinolone acetonide intravitreal implant. The percentage of eyes with IOP of 25 mm Hg or more peaked at 7.1% for the 0.7 mg dexamethasone implant, 8.7% for the 0.35 mg dexamethasone implant, and 4.2% for the sham group ($P > 0.05$). Zero incisional glaucoma procedures were performed in the HURON trial, with the caveat being that the follow-up was brief, and it was only a single-injection study. The incidence of cataract reported in the phakic eyes was 15% with the 0.7 mg implant, 12% with the 0.35 mg implant, and 7% with the sham ($P > 0.05$).

DR. ALBINI: If we extrapolate from the MEAD study, for example, which had 3 years of dexamethasone with repeat injections, we know that dexamethasone maintained a much lower level of ocular hypertension controlled with drops than the fluocinolone acetonide intravitreal implant.[29,30] There were some instances of incisional surgery, although the numbers were very low in MEAD as well; only two patients (0.6%) in the 0.7 mg dexamethasone group and one patient (0.3%) in the 0.35 mg dexamethasone group required trabeculectomy. Now, of course, uveitis patients have a much higher rate of developing glaucoma. So, in addition to the steroid response, they have a multimechanism uveitic glaucoma at play. We therefore know that those numbers would be higher, but the numbers for the fluocinolone acetonide intravitreal implant shouldn't be as high as they are in the MUST study.

The first systemic medication for uveitis was approved more than 1 year ago . Can you tell us about the VISUAL I and VISUAL II studies?

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DR. YEH: VISUAL I and VISUAL II looked at the efficacy of adalimumab for the treatment of noninfectious uveitis.[31,32] VISUAL I enrolled patients with active noninfectious intermediate uveitis, posterior uveitis, or panuveitis despite having received prednisone treatment for 2 or more weeks. VISUAL II enrolled patients with inactive, noninfectious intermediate, posterior, or panuveitic uveitis controlled by 10 mg to 35 mg/day of prednisone.

The percentage of patients who actually recurred during the 6-month period was far less than patients who were treated with adalimumab versus sham. About 70% of patients treated with sham developed recurrences. In VISUAL I, the median time to treatment failure was 24 weeks in the adalimumab group and 13 weeks in the placebo group. The patients in the intention-to-treat population who received adalimumab were less likely than those in the placebo group to have treatment failure. Patients in the adalimumab group did experience more frequent adverse events.

In VISUAL II, treatment failure occurred in 55% of patients in the placebo group compared with 39% of patients in the adalimumab group. Further, time to treatment failure was significantly improved in the adalimumab group compared with the placebo group (median not estimated [> 18 months] vs 8.3 months; HR 0.57, 95% CI 0.39-0.84; $P = 0.004$).

One thing that I do think is interesting is that while the efficacy signals were shown at 6 months, patients who were on treatment still developed recurrences. It may be that this is a heterogeneous group of conditions and that, although the majority of patients who were treated responded to therapy, there is still a group of patients who will need different therapy. Regardless, this was a significant milestone for the treatment of uveitis. These multicenter, randomized trials led to the US FDA approval of adalimumab for noninfectious uveitis.

DR. ALBINI: It is interesting that in uveitis, unlike a lot of other posterior segment conditions, we are still struggling to find the best primary outcome for these studies. We have talked about a number of studies now with primary outcomes ranging from VA in MUST, vitreous haze in HURON, time to recurrence in VISUAL I and VISUAL II, and VA in PEACHTREE. What are the relative strengths and weaknesses of those different primary outcomes and study designs? How can clinicians better interpret these data when the designs and primary outcomes vary?

DR. WYKOFF: When designing clinical trials, there are two concepts to keep in mind: approvability and applicability to clinical practice. Approvability is probably the most important from an industry perspective. You have to make sure the agencies that regulate your drug will view your endpoint as approvable. Once the drug is approved, ideally the data used to obtain approval can be used to guide real-world clinical practice. This is often where a disconnect can occur. In the context of uveitis, the concept of measuring vitreous haze as a trial endpoint is largely meaningless in my clinic. I currently have no objective way to document vitreous haze levels on a day-to-day patient basis.

Vision is a common endpoint that is both approvable and largely applicable to clinical practice. But, even more relevant to current retinal practice strategies, at least for diseases that affect the macula, are anatomic endpoints, such as OCT. Hopefully going forward, we, as a field, can identify more anatomic endpoints that can be correlated strongly enough with vision to be approvable endpoints.

DR. ALBINI: I think many uveitis specialists would echo your sentiments about vitreous haze. It is a point of frustration for many physicians. VA is directly translatable to the patient, but it has been difficult to measure in uveitis because sometimes we are looking for inflammatory control, and sometimes the vision just doesn't get better. Some patients with end-stage uveitis or complicating factors, like glaucoma or cataracts, will not see visual improvements. We saw this in the long-term results from the MUST study,[25] for example. Even though there was successful inflammatory control, the vision improvement was flat. If vision improved at all, it was less than a line or just a couple of letters across the board.

The PEACHTREE study,[24] however, had a novel study design in that it used VA and gave us a sense of how many letters the patients gained. They were able to do so by focusing on the subset of uveitis patients that had CME. Now, people might say PEACHTREE data are not applicable to other types of uveitis, although their secondary outcomes showed benefit even in anterior chamber cells and flare. To me, PEACHTREE had a novel study design that allowed us to maximize the use of OCT for documenting the ME.

DR. YEH: The secondary outcome measures in PEACHTREE, for instance anterior chamber and vitreous haze, are very good because it actually directs you to where the antiinflammatory effect is taking place.

DR. DO: The PEACHTREE study was also novel because it examined a delivery of steroid to a new part of the eye that we have never

"Delivery into the suprachoroidal space requires new methodology. Uveitis is the first therapeutic area to have completed phase 3 trial data, and it appears exceptionally positive. It is a very exciting time to explore a whole new way of delivering pharmacotherapies for vitreoretinal diseases."

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utilized before, the suprachoroidal space. PEACHTREE showed, for the first time, that drug delivery can be effective in this area.[24] It may open doors for other drugs to be delivered there in the future.

DR. WYKOFF: I agree with Dr. Do. Most retina specialists are comfortable giving intravitreal and periocular injections. Delivery into the suprachoroidal space requires new methodology. Uveitis is the first therapeutic area to have completed phase 3 trial data, and it appears exceptionally positive. It is a very exciting time to explore a whole new way of delivering pharmacotherapies for vitreoretinal diseases.

That said, there is still much to learn about the suprachoroidal space. First, the injection procedure is substantially different than a standard intravitreal injection, and I believe the slope of the learning curve is more gradual than the learning curve for performing intravitreal injections. Second, intravitreal and periocular steroids are well known to accelerate cataract progression and cause elevated IOP in about a third of patients. In comparison, one of the interesting and promising aspects of suprachoroidal delivery of steroids is that this route of delivery may have a different side-effect profile. There appears to be a signal from PEACHTREE that we are seeing less IOP elevation. More complete data and longer-term data is needed to better understand the risks associated with steroids delivered into the suprachoroidal space.

By expansion of the suprachoroidal potential space into a real space following drug delivery, we now may have the opportunity to physically measure its volume in vivo. If one performs an anterior segment OCT following a suprachoroidal injection, one can often detect and measure expansion of the suprachoroidal space.[33] Going forward, I believe we are going to learn more about how these drugs distribute in a human eye, along with how the volume of the drug that we visualize may correlate with clinical outcomes and durability measurements. We may have a biomarker that we have never had using an intravitreal delivery system.

DR. ALBINI: When you obtain these anterior chamber OCTs on the patient, do you see that space expand only in the area where you have given the injection? Or does it expand all the way around the limbus?

DR. WYKOFF: We need to evaluate more patients to have a more complete answer to that important question. Currently, we have a limited dataset of imaged eyes. In the patients that we have imaged, we typically see the greatest expansion of the suprachoroidal space in the quadrant of the injection, and this expansion tapers off as imaging moves further from the site of injection. In the eyes that we have imaged, we have found that the real space created following suprachoroidal delivery returns to a potential space over time. So, we don't see lasting changes in the suprachoroidal space, at least anteriorly, following injection once the drug has dissipated from the suprachoroidal space.

DR. ALBINI: Do you know what the expected duration of maintaining drug in the suprachoroidal space is following a single injection?

DR. WYKOFF: From my understanding, animal models suggest at least a 3-month timeframe.

DR. DO: In the PEACHTREE data, the OCT curves show that it may be durable longer than 3 months. The study design required a mandatory second injection, but when we look at the mean change in OCT, it did not seem to drop significantly before 3 months. So, many of those patients could have not needed treatment at month 3. The drug could perhaps last beyond 4 or 5 months in some patients.

DR. ALBINI: How would you compare this injection delivery to sub-Tenon's and the intravitreal injection, in terms of the ease of administering the injection and patient perception?

DR. DO: As Dr. Wykoff mentioned, intravitreal injection has become very easy for vitreoretinal specialists to perform, and we are very accustomed to it. I would say the majority of vitreoretinal specialists do not perform sub-Tenon's injections. So, if there was posterior segment disease, we would either choose intravitreal or, with proper education and training, perhaps the suprachoroidal route. With the evidence from PEACHTREE, we know that a suprachoroidal injection can be effective and safe. This could be a possible new route of administration in the near future.

That said, training at the beginning is important because it is a new procedure that we have not encountered before. It can be a very simple office-based procedure, but the treating physician needs to know the proper technique in order to make it a streamlined approach that is effective, but I think it can be done.

DR. ALBINI: What do you think about the injector that they developed for the delivery of the medicine?

DR. YEH: The injector has a unique design with engineering to achieve consistent delivery of medication to the suprachoroidal

space. The manufacturer worked on trying to make a delivery approach that was amenable to taking advantage of the loss of resistance that we encounter when we are in the sclera. After you pass the sclera and enter the suprachoroidal space, there is a loss of resistance that we can feel that will allow the medication to enter the suprachoroidal space.

However, there is a learning curve associated with it where physicians will need to be trained. In addition to measuring where you are going to put the injection, there is a certain tactile feel that physicians will need to experience and adapt to. It is understanding that the angle of the needle is perpendicular and also the feel of loss of resistance when the medication enters the suprachoroidal space. Vitreoretinal surgeons and uveitis specialists are constantly evolving. It is a technique that can be readily learned, and there is promising efficacy data that shows that it can have efficacy with favorable safety signals as well.

DR. WYKOFF: I also experienced a clear learning curve. A critical part of the learning curve is understanding how to give the injection in a way that minimizes patient discomfort. Rapid injection, in my experience, is more likely to cause local discomfort than very slow delivery. Mechanically, this may be explained by the fact that a real space is being created from a potential space. Suprachoroidal space expansion requires that tissue be displaced, and this displacement can lead to pain. If the suprachoroidal space is expanded slowly, patients are much less likely to feel discomfort. Second, in order to minimize patient discomfort, it is critical that the medication be delivered into the suprachoroidal space; forcing delivery while not in the correct anatomic space could potentially create a cleft within the layers of the sclera. When performing an injection, it is imperative to create a dimple of the external ocular layers, remain perpendicular to the ocular surface, and wait for that sense of tactile release of resistance before you deliver the entire bolus. I think we, as a field, will improve at doing these injections, and we will improve at teaching other physicians how to do them as we gain more experience through the multiple, ongoing study programs employing suprachoroidal steroid delivery.

DR. ALBINI: Thank you all for your comments and insights. We are at an exciting time for the management of patients with noninfectious uveitis. ■

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NOVEL TREATMENT STRATEGIES
for Macular Edema Associated With Noninfectious Uveitis

Release Date: October 2018
Expiration Date: October 2019

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DEMOGRAPHIC INFORMATION

Profession
___ MD/DO
___ NP
___ Nurse/APN
___ PA
___ Other

Years in Practice
___ >20
___ 11-20
___ 6-10
___ 1-5
___ <1

Patients Seen Per Week (with the disease targeted in this educational activity)
___ 0
___ 1-5
___ 6-10
___ 11-15
___ 15-20
___ 20+

Region
___ Northeast
___ Northwest
___ Midwest
___ Southeast
___ Southwest

Setting
___ Solo Practice
___ Community Hospital
___ Government or VA
___ Group Practice
___ Other
___ I do not actively practice

Models of Care
___ Fee for Service
___ ACO
___ Patient-Centered Medical Home
___ Capitation
___ Bundled Payments
___ Other

Training of Fellows ___ Yes ___ No

LEARNING OBJECTIVES

DID THE PROGRAM MEET THE FOLLOWING EDUCATIONAL OBJECTIVES?	AGREE	NEUTRAL	DISAGREE
Describe the risk of vision loss associated with each type of uveitis.	_____	_____	_____
Evaluate the safety and efficacy of different treatment modalities for noninfectious posterior uveitis, including corticosteroids, sustained release implants, immunomodulatory/immunosuppressive agents, and biologics.	_____	_____	_____
Discuss the potential advantages of steroid administration to the suprachoroidal space.	_____	_____	_____

POST TEST QUESTIONS

1. **PLEASE RATE YOUR CONFIDENCE IN YOUR ABILITY TO APPLY UPDATES IN DIAGNOSING AND MANAGING UVEITIS IN THE CLINIC BASED ON THIS ACTIVITY (BASED ON A SCALE OF 1 TO 5, WITH 1 BEING NOT AT ALL CONFIDENT AND 5 BEING EXTREMELY CONFIDENT).**
   a. 1
   b. 2
   c. 3
   d. 4
   e. 5

2. **PLEASE RATE HOW OFTEN YOU INTEND TO APPLY UPDATES IN DIAGNOSING AND MANAGING UVEITIS TO "REAL-WORLD" PATIENT MANAGEMENT (BASED ON A SCALE OF 1 TO 5, WITH 1 BEING NEVER AND 5 BEING ALWAYS).**
   a. 1
   b. 2
   c. 3
   d. 4
   e. 5

3. **APPROXIMATELY WHAT PERCENTAGE OF PATIENTS WITH UVEITIS WILL DEVELOP A CLINICALLY MEANINGFUL INCREASE IN IOP LEADING TO GLAUCOMA TREATMENT?**
   a. 10%
   b. 20%
   c. 30%
   d. 40%

4. **WHAT IS THE RECOMMENDED TREATMENT FOR PEDIATRIC PATIENTS WITH UVEITIS?**
   a. Adalimumab
   b. Systemic prednisone
   c. Posterior sub-Tenon's steroid injection
   d. Dexamethasone implant

5. **THE PHASE 3 _____ STUDY ILLUSTRATED THE SAFETY AND EFFICACY OF SUPRACHOROIDAL-DELIVERED CORTICOSTEROID TRIAMCINOLONE ACETONIDE FOR THE TREATMENT OF UVEITIS.**
   a. MUST
   b. PEACHTREE
   c. SITE
   d. SAKURA 1

6. **WHAT IS THE PROVEN DURATION OF MAINTAINING A DRUG IN THE SUPRACHOROIDAL SPACE FOLLOWING A SINGLE INJECTION?**
   a. Two months
   b. Three months
   c. Four months
   d. Five months

7. **ADALIMUMAB WAS APPROVED BY THE FDA FOR THE TREATMENT OF NONINFECTIOUS UVEITIS, BASED ON WHICH STUDY(IES)?**
   a. SAKURA 1
   b. HURON
   c. MEAD
   d. VISUAL I/II

8. **WHAT PARTS OF A PATIENT'S MEDICAL HISTORY SHOULD LEAD A CLINICIAN TOWARDS AN INDICATION OF AN INFECTIOUS CASE OF UVEITIS? SELECT ALL THAT APPLY.**
   a. Cancer therapy
   b. Birdshot retinochoroidopathy
   c. Recent hospitalization
   d. Juvenile idiopathic arthritis

9. **WHAT IS THE MOST APPROPRIATE FIRST-LINE APPROACH FOR CONTROLLING INFLAMMATION IN PATIENTS WITH UNILATERAL NONINFECTIOUS UVEITIS?**
   a. Whole-body immunosuppression
   b. Systemic prednisone
   c. Fluocinolone acetonide intravitreal implant
   d. Intraocular steroids

10. **BASED ON THE ROUNDTABLE PARTICIPANTS, _____ IS A VIABLE RESEARCH END POINT IN NONINFECTIOUS UVEITIS, BUT IT DOES NOT NECESSARILY TRANSLATE WELL INTO CLINICAL PRACTICE.**
    a. VA
    b. Vitreous haze
    c. IOP spikes
    d. Anatomic improvements

ACTIVITY EVALUATION/SATISFACTION MEASURES

Your responses to the questions below will help us evaluate this continuing medical education (CME) activity. They will provide us with evidence that improvements were made in patient care as a result of this activity as required by the Accreditation Council for Continuing Medical Education (ACCME).

Rate your knowledge/skill level prior to participating in this course: 5 = High, 1 = Low _____

Rate your knowledge/skill level after participating in this course: 5 = High, 1 = Low _____

This activity improved my competence in managing patients with this disease/condition/symptom. _____ Yes _____ No

I plan to make changes to my practice based on this activity. _____ Yes _____ No

Please identify any barriers to change (check all that apply):

_____ Cost
_____ Lack of consensus or professional guidelines
_____ Lack of administrative support
_____ Lack of experience
_____ Lack of time to assess/counsel patients
_____ Lack of opportunity (patients)
_____ Reimbursement/insurance issues
_____ Lack of resources (equipment)
_____ Patient compliance issues
_____ No barriers
Other. Please specify: _____
_____
_____
_____

The design of the program was effective for the content conveyed. ___ Yes ___ No

The content supported the identified learning objectives. ___ Yes ___ No

The content was free of commercial bias. ___ Yes ___ No

The content was relative to your practice. ___ Yes ___ No

The faculty was effective. ___ Yes ___ No

You were satisfied overall with the activity. ___ Yes ___ No

Would you recommend this program to your colleagues? ___ Yes ___ No

Please check the Core Competencies (as defined by the Accreditation Council for Graduate Medical Education) that were enhanced through your participation in this activity:

_____ Patient Care
_____ Practice-Based Learning and Improvement
_____ Professionalism
_____ Medical Knowledge
_____ Interpersonal and Communication Skills
_____ System-Based Practice

Additional comments:

_____

_____ I certify that I have participated in this entire activity.

This information will help evaluate this CME activity; may we contact you by email in 3 months to see if you have made this change? If so, please provide your email address below.

_____


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