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CME Activity

Noninfectious Posterior Uveitis: The Rationale for Steroid Use

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TARGET AUDIENCE

The target audience for this program is retina specialists and general ophthalmologists specializing in the treatment of retina disease.

LEARNING OBJECTIVES

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

- Describe key factors in the differential diagnosis of noninfectious posterior uveitis
- Discuss current treatment guidelines and the side effects associated with them
- Evaluate the safety and efficacy of different treatment modalities for noninfectious posterior uveitis, including corticosteroids, sustained release implants, immunomodulatory/immunosuppressive agents, and biologics
- Assess clinical trial data pertaining to new therapies, including steroid-sparing treatments

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Noninfectious Posterior Uveitis: The Rationale for Steroid Use

Uveitis is a leading cause of vision loss in the developed world¹ and is responsible for about 20% of all cases of bilateral blindness.^{2,3} Complications of uveitis may include cataracts, neovascularization, scarring, cystoid macular edema, hypertension and glaucoma, and retinal detachment.⁴ Macular edema is commonly a feature, and when it is present can cause significant vision impairment and eventual blindness.

Up to 50% of uveitis cases have no extraocular associated disease.³ However, uveitis is commonly associated with systemic disease, either infectious or autoimmune in nature. Because uveitis is often a consequence of systemic disease but has potentially dire ocular manifestations, treatment is often a challenging balancing act. Immunomodulatory agents usually play a central role in attempting to achieve long-term quiescence of the inflammation, yet local anti-inflammatory agents are often called on to treat the vision-threatening sequelae.

Fortunately for uveitis patients, there has been a spate of recent research activity in this complex disease, thus expanding the treatment options and increasing the odds of helping patients achieve durable steroid-free remission. In this roundtable, experts in the field of uveitis have gathered to discuss the latest treatment paradigms and to offer insights on the evolving treatment landscape.

—Thomas Albini, MD, moderator

DIAGNOSIS, EVALUATION, AND THE CLINICAL WORKUP OF POSTERIOR INFLAMMATION

Thomas Albini, MD: What do you include in the differential diagnosis when evaluating an eye with potential noninfectious posterior uveitis, and how do you narrow it down to make a definitive diagnosis?

Nisha Acharya, MD: The first step is understanding what anatomical locations are involved, which means dilating the pupil to fully appreciate the location and extent of inflammation. Inflammation is characterized as anterior, intermediate, posterior, or panuveitis, and care must be taken to differentiate noninfectious from infectious etiologies. These can look very similar but they require different treatment approaches and have different implications. When I am evaluating cases that involve the posterior segment I maintain a high index of suspicion for prominent infectious entities, such as syphilis, tuberculosis, and herpetic disease, until I am able to definitively eliminate them as potential causes.

Quan Dong Nguyen, MD, MSc: Validated questionnaires are a helpful clinical adjunct and can add to the impressions gleaned

from taking a history and the patient interview. Taking a generic history is often insufficient to understand the potential causes. It is necessary to tailor the questions to the particular patient to understand gender, sexual behavior, and potential exposure sources, including sexual partners and animal exposures. Ethnicity may be important, as is recent travel history. If a patient tells me about recent travel to India, I might consider tuberculosis as a potential cause, whereas if he or she recently visited Brazil, toxoplasmosis may be of higher concern.

Endogenous endophthalmitis is a relevant concern among individuals who are intravenous drug users or who recently underwent mitral valve replacement who are presenting with fever and blurry vision. Rashes and joint pain are other indices of systemic inflammation or autoimmune disease that may be playing a role.

Steven Yeh, MD: There are a number of considerations for the clinical examination. In addition to the suggestions made by Drs. Acharya and Nguyen, I also think dermatologic, rheumatologic, musculoskeletal, and pulmonary findings can be useful for determining the cause of posterior inflammation. During the ocular examination, the anatomic location of the uveitis is important, as are the presence of a hypopyon and endogenous endophthalmitis.

Both immunologic and noninfectious factors can lead to hypopyon. Moving from the front to the back of the eye, posterior synechiae and cataract can indicate disease chronicity, as well cystoid macular edema (CME). If an epiretinal membrane is present, then that requires treatment for multiple reasons.

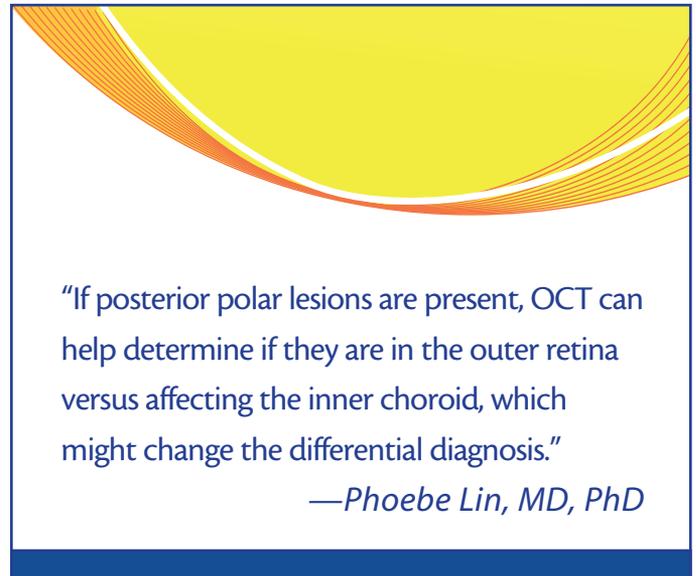
Dr. Albini: What is the role of multimodal imaging to characterize the uveitis? How do we use imaging either for diagnosis or to observe patients over time?

Phoebe Lin, MD, PhD: Imaging is useful in the assessment of uveitis and adds to the evaluation of the posterior segment. For example, ultra-widefield imaging is not as dramatically affected by mild degrees of media opacity, and it is particularly useful for objectively recording the number of chorioretinal lesions or extent of vascular sheathing, at least within the field of view. Autofluorescence is also helpful in the setting of chorioretinal lesions, specifically affecting the outer retina and/or retinal pigment epithelium, some of which may not be as easily identified on examination. Fluorescein angiogram (FA) can reveal several pathognomonic signs, oftentimes even in the presence of mild to moderate media haze. Retinal vascular leakage, optic disc leakage, and peripheral vascular leakage on ultra-widefield FA may be present in posterior uveitis, although there is not complete understanding of the clinical significance of isolated peripheral vascular leakage. Retinal neovascularization is a potentially important sign of severity. Other signs can potentially aid in making a differential diagnosis. For example, venular leakage, indicative of periphlebitis, can narrow the differential to certain types of noninfectious uveitis, such as sarcoidosis or multiple sclerosis-associated intermediate uveitis.

Optical coherence tomography (OCT), even if it is prone to image acquisition errors in eyes with media opacities, can provide important information. OCT is the best tool to assess for CME. If posterior polar lesions are present, OCT can help determine if they are in the outer retina versus affecting the inner choroid, which might change the differential diagnosis. Full thickness retinal involvement may indicate an infectious cause, because not many immune-mediated causes lead to a full-thickness retinal necrosis. Outer retinal lesions can be either infectious or noninfectious, but there might be certain entities that are more likely to look like one pattern or another.

Dr. Albini: Generally speaking, how helpful is laboratory testing in making a diagnosis?

Dr. Nguyen: In general, yes, there are certain laboratory tests that all uveitis patients should have, such as testing for syphilis. There are others that may be added based on the patient history and interview. There is also potential for positive results to act as red herrings, either because the result was false positive, or because the result is an incidental and isolated finding that may not be so



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—Phoebe Lin, MD, PhD

meaningful. For example, positive antinuclear antibody result is one criterion for the diagnosis of systemic lupus, but unless other diagnostic signs are present, the result of a positive antinuclear antibody, with positive antidouble stranded DNA and other finding such as proteinuria, will not be so helpful and contributory to the overall process of making a diagnosis.

Dr. Albini: What laboratory testing do you consider to be essential?

Dr. Nguyen: The three I would consider as almost mandatory include evaluation for syphilis; chest X-ray, to look for disease that is often manifested in the chest and to screen for any gross abnormality in the lung before starting systemic therapy; and testing for sarcoidosis, because it can masquerade as a number of other entities. Serologic testing can be nonspecific, for example ELISA, but it should be paired with other systemic findings.

Dr. Albini: There may be an argument that the most important testing we can do is to rule out the prominent infectious etiologies, including syphilis and tuberculosis, but the latter may be a complex discussion.

Dr. Nguyen: Understanding serologic tuberculosis reactivity may be more important than is currently appreciated. As global travel becomes easier and more prominent, the spread of infectious entities that we often consider to be issues exclusive to the developing world become more likely. For example, I practice in the Midwest, and the number of cases I see in my clinic that involve tuberculosis surprises me.

Dr. Acharya: HLA testing is used a lot in working up patients with uveitis, although some discretion should be used for interpretation of

results. For instance, type B-5 and B-51 mutations are more prevalent in patients with Behçet disease; however, the allele for this mutation is independently present in several ethnic populations and it may not necessarily result in phenotypic expression of Behçet disease. The results of HLA testing, then, may be racially dependent, and using HLA testing to rule in/rule out patients may be problematic. On the other hand, among patients with birdshot chorioretinopathy, HLA-A29 testing may be warranted if the clinical examination reveals findings such as ovoid lesions in the right patient profile and vascular leakage or disc edema, especially in older female patients. In that setting, HLA-A29 testing can confirm the clinical impression.

TREATMENT APPROACHES IN UVEITIS

Dr. Albini: Uveitis is a complex heterogeneous group of diseases. It is beyond the scope of this conversation to discuss specific treatment approaches for every disease entity that can cause inflammation in the eye. However, are there fundamental principles for management of uveitis that are applicable across the spectrum of uveitic conditions?

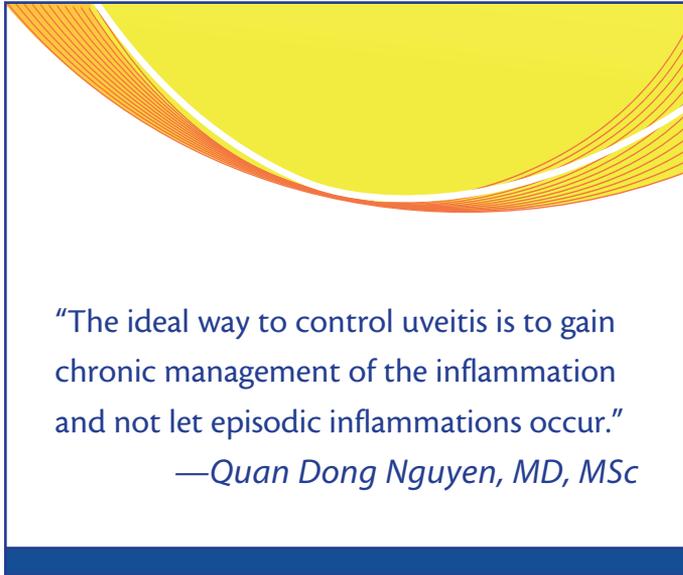
Dr. Nguyen: The ideal way to control uveitis is to gain chronic management of the inflammation and not let episodic inflammations occur. Local corticosteroid is usually not sufficient for primary treatment, but it can be an appropriate supplement to systemic therapy. For example, if I had a patient with systemic sarcoidosis who has ocular involvement, the goal would be to gain control of the systemic disease. Let us say the patient had a local flare-up while the systemic disease was well controlled. In that scenario, instead of increasing systemic control, I would consider a steroid sustained-release device such as a dexamethasone implant to provide management of inflammation at its source.

Dr. Albini: Are steroids reasonable in the acute phase while systemic steroid-sparing therapy is brought on board?

Dr. Yeh: If there is macular edema, certainly a corticosteroid should be considered. Edema is a feature in about 40% to 60% of all patients with uveitis,⁵ and is the leading cause of vision impairment in patients with uveitis.⁶

Dr. Acharya: I believe it is important to present the various options to the patient and have a conversation about the approach to therapy. I use steroids to address acute inflammation in intermediate, posterior, and panuveitis, but it is really patient and disease dependent. For example, in unilateral disease, I might consider a local injection. There could be numerous reasons to avoid systemic therapy, including osteoporosis, poorly controlled diabetes, a past history of steroid intolerance, and pediatric patients, to name a few. The lens status is also important, as is any past history of IOP elevation.

I find that a local steroid may be useful to gain rapid control when a systemic immunomodulatory agent or a biologic is



“The ideal way to control uveitis is to gain chronic management of the inflammation and not let episodic inflammations occur.”

—Quan Dong Nguyen, MD, MSc

initiated, as these are slower acting agents. As Dr. Nguyen alluded to, steroids are also useful for an acute flare-up in the patient who is getting less than ideal control on existing treatment. I also agree with Dr. Yeh, in that local corticosteroid therapy is the best option for macular edema.

Dr. Albini: What are the options for patients experiencing an acute flare-up but who are not good candidates for steroid therapy?

Dr. Nguyen: It will depend on the situation. For the patient with severe retinal vasculitis, for example, a TNF-alpha inhibitor would likely be of benefit. For a patient with severe ocular inflammation and renal involvement that needs immediate control, an alkylating agent, such as cyclophosphamide, can be considered.

Dr. Lin: I had a patient recently who fit this scenario. She had an acute-on-chronic retinal vasculitis, and a history of bilateral bullous serous retinal detachments affecting the macula when she was on steroids in the past due to multifocal central serous retinopathy. She was already on an antimetabolite that was not adequately controlling inflammation, and other systemic agents were not tolerated, so we used intravenous cyclophosphamide. Treatment was ultimately successful.

CONSIDERATIONS FOR SYSTEMIC AGENTS

Dr. Albini: What factors are important when choosing a systemic agent? The main factors I consider are side effects, safety data, and ease of access for a particular patient, including price and insurance coverage. Unfortunately, comparative efficacy data among these agents is lacking. What is clear is that no single agent works in every case. All therapies have side effects—for example, antimetabolites are contraindicated in patients with liver disease and anti-TNF agents are contraindicated in patients

with multiple sclerosis. We still have longer safety data on anti-metabolites than we have for anti-TNF agents, so I still prefer antimetabolites to anti-TNF agents as first-line agents. It is not always trivial to get coverage for mycophenolate mofetil for a patient, and it is prohibitively expensive for most patients to buy out of pocket. Methotrexate is much more economical. Anti-TNF agents are even more expensive, but will likely be used more often now that adalimumab has recently gained approval for use in uveitis. How does this approval affect treatment?

Dr. Lin: When transitioning off of systemic corticosteroids to another immunosuppressive agent, I consider the etiology of disease; patient factors including preferences, lifestyle, other medications, medical problems, prior toxicity, and/or prior efficacy; and unfortunately, the cost to the patient in terms of what can be covered by the patient's insurance company. If a patient has sarcoid uveitis, I am highly inclined to initiate methotrexate, which has shown to be quite effective for this entity, whereas, if they have Behçet's uveitis, I would try to initiate infliximab or adalimumab as quickly as possible. Patient factors such as renal disease, baseline state of immunosuppression, and alcohol consumption, for instance, might also change both the choice of systemic agent as well as the dosing.

Dr. Nguyen: In many western countries (certainly, we must also consider other countries where infection is prevalent), the majority of uveitis cases are autoimmune in nature, and about 20% of those are associated with a systemic disease process.^{7,8} When we think about the autoimmune etiologies, TNF-alpha cytokines are very active in the inflammatory cascade.⁸ Thus, these biologics have a very strong rationale for therapy. The phase 3 VISUAL 1 and VISUAL 2 studies, which were the basis for the adalimumab approval, demonstrated that adalimumab extended time to treatment failure compared with placebo—the study's primary endpoint—and yielded superior outcomes with respect to secondary measures, such as anterior cell grade, vitreous haze, and BCVA.⁹ Adverse event rates were similar for the two groups and align with what we know about adalimumab.

Dr. Albini: There are actually a number of anti-TNF-alpha agents that have either been studied or proposed for uveitis. Are there discernable differences within the drug class in either safety or efficacy?

Dr. Nguyen: It has been my experience that infliximab may have a faster onset and may quiet the inflammation a little quicker than adalimumab. That is based on my experience, and I do not believe there are any studies looking at that specifically.

Dr. Acharya: I have seen this, as well, where a patient may respond a bit better to one particular biologic versus another. It may be related to the dosing, such as with infliximab where there is a large range of doses and frequency of infusions.

“Patient factors such as renal disease, baseline state of immunosuppression, and alcohol consumption, for instance, might also change both the choice of systemic agent as well as the dosing.”

—Phoebe Lin, MD, PhD

Dr. Albini: There is at least one study comparing the two from the French Uveitis Network.³ It does not speak to the question of onset of action, but the study did find comparable efficacy, with a 93% response rate and a 28% 12-month response rate, among 160 patients with refractory uveitis.

Dr. Lin: I wonder if patients receiving one medication over the other might be more prone to develop antidrug antibodies or if there are, in fact, differences in efficacy between the two drugs regardless of the development of these antibodies.

Dr. Nguyen: There is some emerging evidence that patients can develop antidrug antibodies.¹⁰ There have been some case reports and some smaller studies in the systemic literature suggesting this effect where patients have to be switched to another biologic after developing antibodies against their therapy.

Dr. Albini: Are there other anti-TNFs that can be used in situations where either adalimumab or infliximab are unsuccessful?

Dr. Acharya: I have a handful of patients on certolizumab or golimumab, but I do not think there is a lot of experience using these drugs for treatment of uveitis. Much of the rationale for their use is based on case reports and limited information. Theoretically, though, these are monoclonal antibodies, and they are chemically different than fusion proteins, such as etanercept, which is not that effective for uveitis. Moreover, certolizumab is pegylated, so it should not cross the placenta, and so theoretically that should be a good option in patients who are pregnant or breast-feeding.

Dr. Albini: What are the nonbiologic steroid-sparing options for chronic posterior segment disease? How would you describe your frequency of using the different options that are available?

Dr. Yeh: Taking into account that there are differences in which agent is used depending on the disease state, I would estimate I use about 70% mycophenolate and about 30% methotrexate.

Dr. Albini: And how do you decide between the two?

Dr. Yeh: The decision will be based on a mixture of disease and patient factors. For a patient with rheumatoid arthritis, for instance, if there is any concern about liver toxicity, I will choose methotrexate. Mycophenolate is well tolerated, so it is a good option for younger individuals and patients with birdshot chorioretinopathy. On the other hand, some patients will prefer an agent like methotrexate once a week rather than daily mycophenolate. Dr. Acharya is leading a study now that will hopefully answer some of these questions.

Dr. Acharya: The retrospective SITE study does provide some insights on the relative efficacy of these agents. Keeping in mind the limitations of the retrospective nature of the study, mycophenolate mofetil may look like it was a little bit more successful in achieving steroid-sparing control of inflammation, azathioprine a little bit less so, and methotrexate somewhere in the middle.

Collaborating with Aravind Eye Hospital in India, I implemented an 80-patient prospective randomized trial comparing methotrexate, 25 mg weekly, orally, with 2 g daily mycophenolate mofetil in subjects with intermediate, posterior, or panuveitis.¹¹ Patients had active inflammation at the time of enrollment and were started on concomitant immunosuppressant and corticosteroid therapy, which was tapered according to the SUN guidelines. We found that about 69% of patients receiving methotrexate achieved treatment success compared with 47% on mycophenolate. There was not a statistically significant difference, however. We are currently conducting a larger trial that is funded by the National Eye Institute to compare these two medications.

OPTIONS FOR LOCAL THERAPY

Dr. Albini: The emergence of biologics has added a new dimension to uveitis treatment, and overall, there is a trend to less use of T-cell inhibitors and alkylating agents. Overall, we have several options at our disposal for chronic control of the system. As we have noted already, however, there may be situations that call for a local anti-inflammatory. What are the options for local therapy?

Dr. Acharya: The nonbiologic drugs, such as methotrexate and mycophenolate mofetil, are only effective for steroid-sparing control in about 40% to 60% of cases. In the MUST study, fewer than 20% of subjects were controlled off steroids.¹² What these numbers tell us is that a lot of patients are likely going to require adjunctive therapy to achieve long-term control. The question becomes, do you increase the systemic therapy or do you use low-dose corticosteroids knowing the potential for side effects?

Dr. Albini: Is monotherapy with low-dose systemic steroids an option for patients with chronic posterior segment uveitis?

Dr. Yeh: There are occasional patients who require use of chronic low-dose corticosteroid, but there is an appreciable risk of side effects. There are varying opinions in the literature about what constitutes a low dose. It used to be that 10 mg was the limit, but now the preference is to get the dose below 7.5 mg—and even at that dose, side effects are a concern. As a general rule, if patients are started at a higher therapeutic dose, it is preferable to get them below 7.5 mg by about 3 months. However, research by Dr. Nguyen has shown that physicians may use higher doses of corticosteroids for longer periods of time than currently recommended.¹³

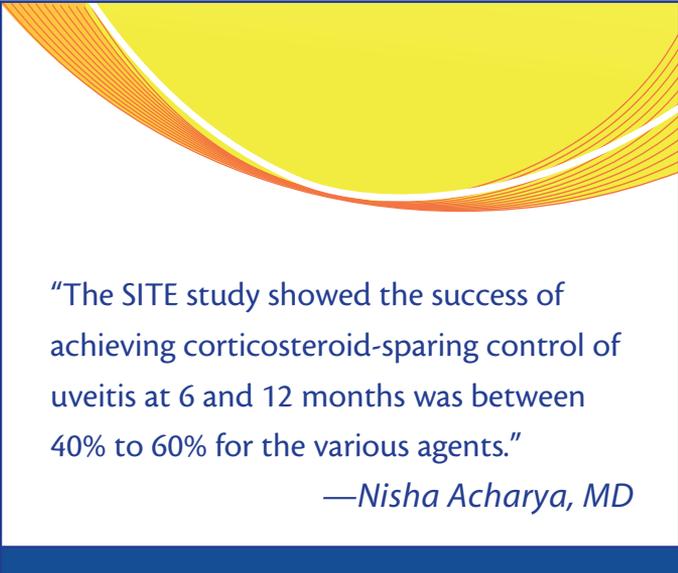
Dr. Albini: What about the route of administration? Is the route as important as the agent in terms of safety and efficacy?

Dr. Nguyen: In the past, I used to perform a lot of transeptal or sub-Tenon triamcinolone injections, but I no longer use it as frequently, and I avoid it if at all possible. If I am going to perform a local steroid injection, I feel more comfortable with the intravitreal route because it has a rapid onset of action. There is concern about pressure elevations with intravitreal injections,^{14,15} however, that might suggest a larger role for either a short-acting dexamethasone implant or a longer-acting fluocinolone implant.

Dr. Albini: Do you use local steroid therapy as monotherapy or is that typically used as an adjunct to systemic immunosuppression?

Dr. Yeh: I think it depends on the disease state in terms of whether a local steroid can be used as monotherapy. One situation that comes to mind is a pseudophakic patient with unilateral intermediate uveitis with vitreous opacity as the major finding. Another patient, who, for example, has CME that recurs every 2 to 3 years may not need repeat corticosteroid therapy. I think it may come down to whether the patient has ongoing retinal pathology, like a smoldering case of birdshot or someone with sarcoidosis, where there is a build-up of CME every 6 months. That patient would need local corticosteroids as an adjunctive agent.

Dr. Acharya: I agree. Ongoing active disease requires an agent for sustained control, and that is hard to accomplish with repeated steroid injections that wear off. The peak and trough of active drug can be disastrous for the inflammation. That said, patient preference can be an important factor. I have one patient with active vascular leakage secondary to birdshot chorioretinopathy who failed on mycophenolate, TNF-alpha inhibitors, and who tried both adalimumab and infliximab. She did not want to try any more systemic therapy options so we tried the dexamethasone implant. We are now using repeated implants as monotherapy with good success. That is not my typical treatment schema for



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—*Nisha Acharya, MD*

birdshot, but the case demonstrates that patient preference can shape the treatment approach.

Dr. Albini: How do you determine the timing for reinjection?

Dr. Acharya: That is something that is specific to each patient, and the duration of effect is longer with dexamethasone implant compared with intravitreal triamcinolone, but it is usually not more than 3 months in patients who need chronic treatment.

Dr. Nguyen: There are also fewer concerns about elevated pressure with the dexamethasone implant. One can get intraocular hypertension with just one injection of triamcinolone.

Dr. Acharya: That is true, although the risk is not negligible with the dexamethasone implant. I recently had a patient who required glaucoma surgery after one injection of the dexamethasone implant.

Dr. Lin: In terms of duration, I am not convinced there is much difference between intravitreal triamcinolone and the dexamethasone implant unless it is after a vitrectomy, in which case an intravitreal injection would only last a couple days.

Dr. Albini: Where does the fluocinolone acetonide 0.59 mg implant fit into treatment?

Dr. Nguyen: I think the fluocinolone acetonide 0.59 mg implant has a very definitive role with two important caveats. First, it will almost always lead to cataract formation. Second, if pressure elevation occurs, it will more than likely require surgery. That said, it can be a good option for patients with very active inflammation, such as in birdshot chorioretinopathy. Patients

with vascular leakage may also benefit from the long-acting implant. There may be other scenarios, such as the patient with unilateral disease who cannot tolerate systemic treatment.

RECENT STUDY DATA

Dr. Albini: What have we learned from the work by the SITE study group?

Dr. Acharya: The SITE study showed the success of achieving corticosteroid-sparing control of uveitis at 6 and 12 months was between 40% to 60% for the various agents.¹⁶⁻²⁰ That gives us a rough idea of the efficacy of these agents. There was also reassuring data in terms of cancer rates in this study: for most of the drugs studied there were no signals detected of increased cancer or increased death rates. However, the data was conflicting among the biologics, and specifically the TNF-alpha inhibitors. There may in fact be an increased risk of cancer among those taking TNF-alpha inhibitors. There is an ongoing study to look specifically at the biologic drugs in uveitis patients and whether there is an increased risk of cancer.²¹

Dr. Lin: There are large longitudinal studies in patients with rheumatoid arthritis that do not show an increased cancer risk with TNF-alpha inhibitors,²² but that is in a population with a significantly higher rate of mortality compared to uveitis. At least theoretically, TNF-alpha blockers may accelerate the growth of pre-existing cancer cells, but they may not cause de novo cancer.

Dr. Albini: Does the SITE data reveal anything else that can help us in the clinic?

Dr. Lin: About 60% of patients developed elevated IOP over 35 mm Hg over 10 years, which could be useful for counseling patients about their disease. One of the potential risk factors identified was systemic hypertension, but the caveat with these data are that rather than measuring blood pressure, this was determined based on the use of systemic antihypertensive therapy. There were also higher rates in individuals with unilateral uveitis, although it was not clear if those patients were on local therapy that might have contributed to an increased risk. Patients who had a vitrectomy were also at a higher risk.

Dr. Nguyen: These are interesting findings, but I think it is important to remind ourselves about the SITE study, and that these are all observations based on retrospective review.

Dr. Lin: That is correct. All of these signals are interesting questions at this point and will require additional study.

Dr. Albini: Turning to the MUST study,¹² what did we learn about systemic therapy and the potential role of the 0.59 mg fluocinolone implant?

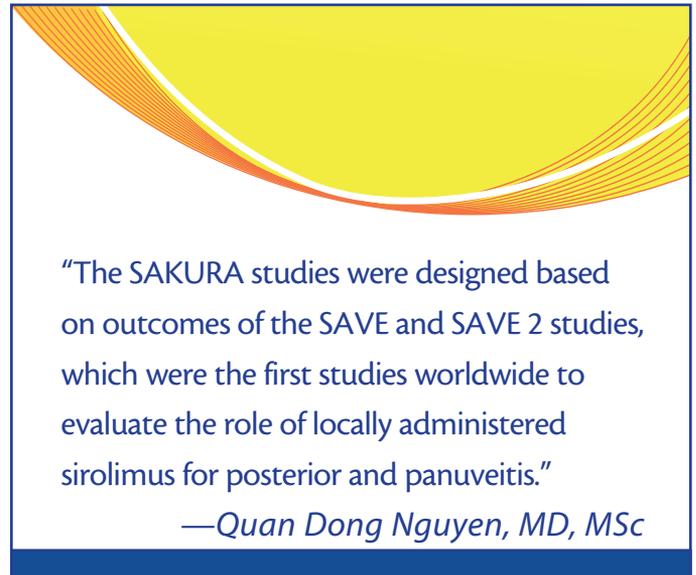
Dr. Yeh: The visual acuity results were comparable between the systemic treatment and fluocinolone acetonide implant groups at 2 years. There was also a small but statistically significant improvement in the vitreous inflammation when comparing the benefit with the implant versus systemic medications. Overall, systemic medications were well tolerated; there was a higher rate of prescriptions for infections, but nothing requiring hospitalization. It was not clear whether this was due to bias because of the fact that they were on systemic immunosuppression. On the other hand, although there were benefits from quality-of-life perspective²³ with the local implant, there was a higher risk of cataract and 25% risk of glaucoma requiring filtration surgery at 2 years. The bottom line is that each of these approaches, local steroid implant and systemic therapy, are reasonable alternatives for noninfectious uveitis.

Dr. Lin: Results from the MUST study at 54 months of follow-up were also very interesting. There was very similar crossover in each group, with about 17% of patients going from implant to systemic treatment, and 20% from the systemic treatment to implant group. The reasons for crossover were also informative; in the immunosuppression group, crossover to the implant was usually due to suboptimal control of ocular inflammation, whereas, in the implant group, crossover to systemic treatment was usually due to systemic inflammation. These findings suggest that there was probably a slight underestimation of the efficacy of the implant.

Dr. Acharya: The data on macular edema from MUST may be informative for clinical practice as well. Although there were no differences between the implant and systemic therapy in terms of resolution of edema or rates of 20% decrease in macular thickness, there were significant differences favoring the implant in terms of actual change in thickness or decrease in thickness from baseline. In addition, a large proportion of patients in the systemic arm required adjunctive steroid injections to attain control. This was an intent-to-treat analysis, and so subjects were counted in the systemic arm even if they received adjunctive steroid injections, and the implant arm still showed significantly greater decrease in macular thickness. The sum total of these findings is that local corticosteroids are a good option for control of macular edema in uveitis.

Dr. Albini: The SAKURA 1 study looked at a novel nonsteroidal local therapy.²⁴ Dr. Nguyen, what is important to know about this study?

Dr. Nguyen: The SAKURA studies were designed based on outcomes of the SAVE and SAVE 2 studies, which were the first studies worldwide to evaluate the role of locally administered sirolimus for posterior and panuveitis.²⁵⁻²⁷ In the SAVE studies, adverse events associated with sirolimus were considered rare, with vitreous floaters as the most commonly reported event. Other events included single instances of blurred vision,



postinjection subconjunctival hemorrhage, forehead rash above the study eye, ocular pain and redness, and progression of pre-existing cataract and glaucoma. There were reports of ocular pain and redness associated with the injection. However, there were no serious adverse events, and no systemic events were related to the study drug. In the SAKURA 1 study, sirolimus, which is a locally administered mTOR inhibiting immunosuppressive agent that was dosed every 2 months, provided good control in terms of decreasing vitreous haze, which was the primary endpoint. All the secondary endpoints were also met. Based on these findings, sirolimus would appear to be a good option for primary treatment or as adjunctive therapy. In the study, a majority of patients were not on a corticosteroid at the time of enrollment, and if they were, they were immediately tapered down. That demonstrates the potential role of the drug as primary therapy. In terms of adjunctive therapy, sirolimus would be a good option to avoid the use of steroids, and, therefore, the risk of cataract or elevated IOP. The SAKURA 2 study is ongoing, and so far, the data are very consistent between the two studies.

THE UVEITIS PIPELINE

Dr. Albini: Are there any other agents in the pipeline that we should keep an eye on?

Dr. Lin: The final results of the phase 3 trial of the fluocinolone acetonide 0.18 mg implant could be interesting.²⁸ We know that fluocinolone acetonide is an effective agent, but this particular implant would offer a nonsurgical option with a lower dose than the current on-the-market product. The company recently announced 12-month results, which confirmed a lot of findings from 6 months of follow-up. Notably, there was much higher recurrence of uveitis in the sham group compared to the treatment arm (85.7% vs 26.4%) and visual acuity improved by 15 or

more letters from baseline in 22.9% versus 11.9% in the treatment versus sham group. Of patients who started the study on immunosuppressant therapy, 18.2% and 52.4% in the treatment and control groups, respectively, were still using them at 12 months. As far as safety, there was an average 1.3 mm Hg elevation in IOP in treated eyes compared with a 0.7 mm Hg increase in control eyes. Among phakic eyes, 45.2% and 9.5% of treated and control patients, respectively, required cataract surgery.²⁹

Dr. Yeh: Suprachoroidal corticosteroid delivery is a potentially interesting option as well. Phase 2 results of a study looking at suprachoroidal injection of triamcinolone demonstrated a definite

treatment effect with a very good safety profile.³⁰ There was almost no effect on pressure in the trial and no cataract development. Granted, this was a small study, but it provides a proof of concept of a novel drug delivery mechanism for local treatment of macular edema associated with uveitis. The phase 3 PEACHTREE study³¹ is underway and will evaluate whether corticosteroid delivery in that compartment offers any efficacy advantages while potential improving the safety profile. We may not know where all these agents will fit in, but it is nevertheless encouraging to see so much development in uveitis, because within the heterogeneous family of uveitic diseases, it's entirely plausible that different medical approaches will be important for the different conditions.

Study Overviews

SITE

The Systemic Immunosuppressive Therapy for Eye Diseases (SITE) consortium is a collaboration of academic ocular inflammation practices in the United States who have undertaken a retrospective cohort study primarily to investigate long-term adverse events occurring in patients on systemic therapies for ocular inflammatory disease. Although it was not the primary goal of this collaboration, the group has already published several retrospective reviews of treatment outcomes after administration of methotrexate, cyclosporine, azathioprine, cyclophosphamide, and mycophenolate mofetil. The SITE investigators have an ongoing study that intends to determine whether therapy that suppresses the immune system given to treat inflammatory diseases of the eye is associated with a greater risk of death and/or cancer.¹ The study will also look for signals indicating short-term complications associated with immunosuppressive therapy.

For the study, medical charts of 10,000 to 15,000 patients will be collected and reviewed in a retrospective cohort design. Charts of patients treated with immunosuppressive therapy will be compared with (1) the general US population and (2) a group of patients with the same inflammatory eye diseases who did not receive immunosuppression. The primary outcomes are incidence of cancer, with secondary measures including control of the eye disease, visual sharpness, changes in the use of corticosteroids, and rates of remission—when disease symptoms are lessened.

Major inclusion criteria will include individuals who started treatment between ages 18 and 29 for anterior uveitis; intermediate uveitis; posterior uveitis or panuveitis; scleritis; mucous membrane pemphigoid; or other noninfectious ocular inflammatory disease. Exclusion criteria include no ocular inflammatory disease or infectious ocular inflammatory disease.

MUST

The MUST study² is a randomized controlled clinical trial comparing local therapy with fluocinolone acetonide intraocular implant 0.59 mg versus systemic corticosteroid therapy supplemented, when

indicated, by corticosteroid-sparing potent immunomodulator therapy. At least 250 patients age 13 or older will be randomized in a 1:1 double-blind fashion. The primary outcome of the study is change in BCVA from baseline to 24 months, with a highly clinically meaningful change defined as a change of 7.5 letters on the ETDRS chart.

The study will also measure a number of secondary outcomes, including:

- Macular edema ≥ 240 μm assessed on optical coherence tomography at 24 months as graded by a central reading center
- Uveitis activity determined by clinician assessment at each study visit
- Intraocular pressure:
 - ≥ 30 mm Hg at 24 months
 - ≥ 24 mm Hg at 24 months
 - ≥ 10 mm Hg above baseline at 24 months
- Glaucoma incidence within 24 months
- Requirement for IOP-lowering medication during study duration
- Requirement for IOP-lowering surgery during study duration
- Cataract incidence during study duration
- Change in self-reported vision-related function as measured by the National Eye Institute 25-item Visual Function Questionnaire (NEI-VFQ 25)
- Vision targeted composite score from baseline to 24 months
- Change in SF-36 mental component score from baseline to 24 months
- Change in SF-36 physical component score from baseline to 24 months
- Hyperlipidemia incidence during study duration
- Hypertension diagnosis requiring treatment during study duration
- Onset of diabetes mellitus during study duration
- Mortality

(Continued on page 12)

Dr. Acharya: The MUST network is conducting two trials right now, POINT³² and MERIT,³³ that are not looking at novel agents, but they could provide critically important information that is applicable to everyday clinical practice. POINT is looking at periocular triamcinolone versus intravitreal triamcinolone versus dexamethasone implant injection in a three-armed comparative study. Meanwhile, MERIT is designed to study intravitreal methotrexate, intravitreal ranibizumab, and the intravitreal dexamethasone implant for the treatment of persistent uveitic macular edema. Following up on the point that Dr. Yeh just made, these kinds of studies may help us figure out where these options fit in treating patients with uveitis.

Dr. Nguyen: It is further down the pipeline, but there is important work being done with IL-6 inhibition that appears promising. There are two approaches in early stage development, one that is intravenously and one that is injected subcutaneously. In addition, based on the clinical results thus far, both approaches can provide control of uveitic macular edema.

CONCLUSION

Dr. Albini: I want to thank all the participants for their input. There is a wealth of ongoing research to try and gain a better understanding of where the various treatment options fit in, even as new therapeutic modalities come through the pipeline. Uveitis

(Continued from page 11)

SAKURA

The SAKURA study was a phase 3, multinational, multicenter, randomized, double-masked study for the treatment of active, noninfectious uveitis comparing DE-109, a locally administered mTOR-inhibiting immunosuppressive agent dosed every 2 months, in three dose strengths.³ The study enrolled 600 patients, with vitreous haze score at 5 months as the primary outcome. The study employed an active comparator model, with intent to demonstrate differences between active treatment arms of differing dosage strengths.

The sponsor also initiated a phase 3b extension study to evaluate the long-term safety of treatment with DE-109 (440 µg) in 200 subjects with posterior noninfectious uveitis who participated in the SAKURA development program.⁴ Per the protocol, subjects in the first phase of the study who received at least two injections of DE-109 and demonstrated clinical benefit were considered for enrollment in this portion of the study for treatment under a prn protocol using the 440-µg dose.

PEACHTREE

PEACHTREE⁵ is a phase 3 study designed to evaluate the safety and efficacy of suprachoroidally administered triamcinolone acetonide (4 mg dose) in individuals with macular edema associated with noninfectious uveitis. Safety and efficacy will be compared to sham injection. At least 150 individuals with noninfectious pan-, anterior, intermediate, and posterior uveitis will be enrolled and randomized in a 1:1 fashion. Treatment, whether sham or active, will be administered twice, 12 weeks apart, and patients will be observed for 24 weeks from the time of the first injection.

The primary outcome measure is the proportion of individuals with a change from baseline of ≥ 15 letters in ETDRS BCVA at 24 weeks. Secondary measures include change in macular edema at 24 weeks (mean change from baseline in central subfield thickness) and adverse events as measured at 24 weeks.

FAI INSERT

This is a phase 3 multinational, multicenter, randomized, masked, controlled study designed to evaluate the safety and efficacy of an injectable fluocinolone acetonide 0.18 mg compared with a sham injection in patients with chronic noninfectious uveitis affecting the posterior segment of the eye.⁶ At least 150 patients will be enrolled and randomized in a 1:1 fashion. The primary endpoint of the study is reduction in recurrence of uveitis in study eye within 6 months. The secondary endpoint is reduction in recurrence of uveitis in the study eye within 3 years. Other outcome measures include recurrence of uveitis in the fellow eye within 1 year and recurrence of uveitis in the fellow eye within 3 years.

Major inclusion criteria for the study are (1) one or both eyes having a history of recurrent noninfectious uveitis affecting the posterior segment of the eye with or without anterior uveitis > 1 year duration; (2) study eye with < 10 anterior chamber cells and a vitreous haze \leq grade 2 at the time of enrollment; (3) visual acuity of at least 15 letters on the ETDRS chart; and (4) during the 12 months prior to enrollment, the study eye has either received either systemic corticosteroid or other systemic therapies given for at least 3 months, and/or at least 2 intra- or periocular administrations of corticosteroid for management of uveitis. Enrollment can also commence if the study eye has experienced at least two separate recurrences of uveitis requiring systemic, intra-, or periocular injection of a corticosteroid agent.

1. ClinicalTrials.gov. Systemic immunosuppressive therapy for eye diseases (SITE) cohort study. <https://clinicaltrials.gov/ct2/show/NCT00116090>. Updated September 26, 2015. Accessed September 13, 2016.

2. Tomkins-Netzer O, Lightman S, Drye L, et al; Multicenter Uveitis Steroid Treatment Trial Research Group. Outcome of treatment of uveitic macular edema: The Multicenter Uveitis Steroid Treatment Trial 2-year results. *Ophthalmology*. 2015;122(11):2351-2359.

3. ClinicalTrials.gov. Study assessing double-masked uveitis treatment (SAKURA). <https://clinicaltrials.gov/ct2/show/NCT01358266>. Updated January 21, 2015. Accessed September 13, 2016.

4. ClinicalTrials.gov. A phase IIIb, multinational, multicenter, open-label extension study assessing the long-term safety of prn intravitreal injections of DE-109 in subjects with non-infectious uveitis of the posterior segment of the eye who have participated in the SAKURA development program (32-009). <https://clinicaltrials.gov/ct2/show/NCT02251938>. Updated August 31, 2016. Accessed September 13, 2016.

5. ClinicalTrials.gov. Suprachoroidal injection of CLS-TA in subjects with macular edema associated with non-infectious uveitis (PEACHTREE). <https://clinicaltrials.gov/ct2/show/NCT02595398>. Updated July 14, 2016. Accessed September 12, 2016.

6. ClinicalTrials.gov. Safety and efficacy study of a fluocinolone acetonide intravitreal (FAI) insert in subjects with chronic non-infectious posterior uveitis. <https://clinicaltrials.gov/ct2/show/NCT02746991>. Updated April 20, 2016. Accessed September 12, 2016.

is a challenging entity to diagnose and treat to remission. Yet, the emergence of biologics and the potential addition of intriguing new local therapies add to the robust armamentarium of options to help patients achieve long-term control of their disease. We look forward to the completion of several phase 3 treatment trials that will hopefully provide us even more interventions while also unveiling new understandings of uveitis. ■

1. Karim R, Sykakis E, Lightman S, Fraser-Bell S. Interventions for the treatment of uveitic macular edema: a systematic review and meta-analysis. *Clin Ophthalmol*. 2013;7:1109–1144.
2. De Smet MD, Taylor SRJ, Bodaghi B, et al. Understanding uveitis: the impact of research on visual outcomes. *Prog Retin Eye Res*. 2011;30:452–470.
3. Vallet H, Seve P, Biard L, et al. Infliximab versus adalimumab in the treatment of refractory inflammatory uveitis. *Arthritis Rheumatol*. 2016;68(6):1522–1530.
4. Prete M, Guerriero S, Dammacco R, et al. Autoimmune uveitis: a retrospective analysis of 104 patients from a tertiary reference center. *J Ophthalmic Inflamm Infect*. 2014;4:17.
5. Lardenoye CWTA, van Kooij B, Rothova A. Impact of macular edema on visual acuity in uveitis. *Ophthalmology*. 2006; 113(8):1446–1449.
6. Dick AD. The treatment of chronic uveitic macular oedema. *Br J Ophthalmol*. 1994;78(1):1–2.
7. Barisani-Asenbauer T, Maca SM, Mejdoubi L, et al. Uveitis—a rare disease often associated with systemic diseases and infections—a systematic review of 2619 patients. *Orphanet J Rare Diseases*. 2012;7:57.
8. Prete M, Dammacco R, Fatone MC, Racanelli V. Autoimmune uveitis: clinical, pathogenetic, and therapeutic features. *Clin Exp Med*. 2016;16(2):125–136.
9. Jaffe GJ, Thorne JE, Scales D, et al. SAT0523 Adalimumab in patients with active, non-infectious uveitis requiring high-dose corticosteroids: the Visual-1 Trial. *Ann Rheum Dis*. 2015;74:849–850.
10. Vincent FB, Morand EF, Murphy K, et al. Antidrug antibodies (ADAb) to tumour necrosis factor (TNF)-specific neutralising agents in chronic inflammatory diseases: a real issue, a clinical perspective. *Ann Rheum Dis*. 2013;72(2):165–178.
11. Rathinam SR, Babu M, Thundikandy R, et al. A randomized clinical trial comparing methotrexate and mycophenolate mofetil for noninfectious uveitis. *Ophthalmology*. 2014;121(10):1863–1070.
12. Tomkins-Netzer O, Lightman S, Drye L, et al; Multicenter Uveitis Steroid Treatment Trial Research Group. Outcome of treatment of uveitic macular edema: The Multicenter Uveitis Steroid Treatment Trial 2-year results. *Ophthalmology*. 2015;122(11):2351–2359.
13. Nguyen QD, Hatf E, Kayen B, et al. A cross-sectional study of the current treatment patterns in noninfectious uveitis among specialists in the United States. *Ophthalmology*. 2011;118(1):184–190.
14. Razaqhejaja MR et al. Steroid-induced iatrogenic glaucoma. *Ophthalmic Res*. 2012;47(2):66–80.
15. Becker B. Intraocular pressure response to topical corticosteroids. *Invest Ophthalmol*. 1965;4:198–205.
16. Gangaputra S, Newcomb CW, Liesegang TL, et al. Methotrexate for ocular inflammatory diseases. *Ophthalmology*. 2009;116:2188–2198.
17. Kacmaz RO, Kempen JH, Newcomb C, et al. Cyclosporine for ocular inflammatory diseases. *Ophthalmology*. 2010;117:576–584.
18. Pasadhika S, Kempen JH, Newcomb CW, et al. Azathioprine for ocular inflammatory diseases. *Am J Ophthalmol*. 2009;148:500–509.
19. Pujari SS, Kempen JH, Newcomb CW, et al. Cyclophosphamide for ocular inflammatory diseases. *Ophthalmology*. 2010;117:356–365.
20. Thorne JE, Jabs DA, Qazi FA, et al. Mycophenolate mofetil therapy for inflammatory eye disease. *Ophthalmology*. 2005;112:1472–1477.
21. Kempen JH, Daniel E, Dunn JP, et al. Overall and cancer related mortality among patients with ocular inflammation treated with immunosuppressive drugs: retrospective cohort study. *BMJ*. 2009;339:b2480.
22. Chen Y, Sun J, Yang Y, et al. Malignancy risk of anti-tumor necrosis factor alpha blockers: an overview of systematic reviews and meta-analyses. *Clin Rheumatol*. 2016;35(1):1–18.
23. Multicenter Uveitis Steroid Treatment (MUST) Trial Follow-up Study Research Group. Quality of life and risks associated with systemic anti-inflammatory therapy versus fluocinolone acetonide intraocular implant for intermediate uveitis, posterior uveitis, or panuveitis: fifty-four-month results of the Multicenter Uveitis Steroid Treatment Trial and Follow-up Study. *Ophthalmology*. 2015;122(10):1976–1986.
24. Merrill P, Nguyen QD, Clark LW; SAKURA Study Group. The SAKURA study, a phase III, multicenter, randomized, double-masked, study of intravitreal injections of DE-109 for the treatment of active, noninfectious uveitis of the posterior segment: baseline ocular disease characteristics. Presented at: 2014 annual meeting of the Association for Research in Vision and Ophthalmology; May 4–8, 2014; Orlando, FL.
25. Nguyen QD, Ibrahim MA, Watters A, et al. Ocular tolerability and efficacy of intravitreal and subconjunctival injections of sirolimus in patients with non-infectious uveitis: primary 6-month results of the SAVE Study. *J Ophthalmic Inflamm Infect*. 2013;3(1):32.
26. Ibrahim MA, Sepah YJ, Watters A, et al. One-year outcomes of the SAVE study: sirolimus as a therapeutic approach for uveitis. *Transl Vis Sci Technol*. 2015;4(2):4.
27. Vigil EM, Sepah YJ, Watters AL, et al. Assessment of changes in quality of life among patients in the SAVE study—sirolimus as therapeutic approach to uveitis: a randomized study to assess the safety and bioactivity of intravitreal and subconjunctival injections of sirolimus in patients with non-infectious uveitis. *J Ophthalmic Inflamm Infect*. 2015;5:13.
28. ClinicalTrials.gov. Safety and efficacy study of a fluocinolone acetonide intravitreal (FAI) insert in subjects with chronic non-infectious posterior uveitis. <https://clinicaltrials.gov/ct2/show/NCT02746991>. Updated April 20, 2016. Accessed September 12, 2016.
29. pSivida's medidur maintains same high statistical significance in primary endpoint through 12 months in first phase 3 trial (p less than 0.00000001). psdv.client.shareholder.com. <http://psdv.client.shareholder.com/releasedetail.cfm?ReleaseID=981381>. Published July 27, 2016. Accessed August 1, 2016.
30. Yeh S. Suprachoroidal administration of triamcinolone acetonide: results of a phase 2 study of patients with non-infectious uveitis. Presented at: American Society of Retina Surgeons; August 14, 2016; San Francisco, CA.
31. ClinicalTrials.gov. Suprachoroidal injection of CLS-TA in subjects with macular edema associated with non-infectious uveitis (PEACHTREE). <https://clinicaltrials.gov/ct2/show/NCT02595398>. Updated July 14, 2016. Accessed September 12, 2016.
32. ClinicalTrials.gov. Periocular and intravitreal corticosteroids for uveitic macular edema trial (POINT). <https://clinicaltrials.gov/ct2/show/NCT02374060>. Updated October 2, 2015. Accessed September 12, 2016.
33. ClinicalTrials.gov. Macular edema ranibizumab v. intravitreal anti-inflammatory therapy trial (MERIT). <https://clinicaltrials.gov/ct2/show/NCT02623426>. Updated December 4, 2015. Accessed September 12, 2016.

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NONINFECTIOUS POSTERIOR UVEITIS: THE RATIONALE FOR STEROID USE CME QUESTIONS

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1. Approximately what percentage of uveitis cases have no systemic involvement (ie, signs and symptoms are confined to the eye)?

- a. Fewer than 10%
- b. About 25%
- c. About 50%
- d. About 75%

2. Macular edema is a feature of uveitis in approximately how many cases?

- a. 10% to 30%
- b. 20% to 40%
- c. 30% to 50%
- d. 40% to 60%

3. Although anti-TNF-alpha agents have been studied in the treatment of uveitis, there are currently no such agents approved specifically for the treatment of uveitis.

- a. True
- b. False

4. According to the panel, what is the potential role for a locally administered anti-inflammatory agent in an eye with macular edema secondary to uveitis?

- a. Local anti-inflammatories may be used while systemic therapy is initiated, as systemic agents may take longer to have onset of action
- b. While the goal of uveitis treatment is to achieve long-term, steroid-free remission, local anti-inflammatory agents, even corticosteroids, may be appropriate to address any macular edema
- c. Local anti-inflammatory agents may be useful for acute inflammatory flare-ups that may occur in patients being treated with systemic agents
- d. All of the above

5. Although not definitive, there is suggestive evidence in published literature indicating that patients can develop antibodies against biologic agents, thus rendering their use less than optimally effective.

- a. True
- b. False

6. In the multicenter, randomized MUST study, approximately what percentage of patients achieved complete remission while on systemic therapy without the need for a locally administered corticosteroid?

- a. 10%
- b. 15%
- c. 20%
- d. 25%

7. According to the retrospective SITE studies, when data for methotrexate, cyclosporine, azathioprine, cyclophosphamide, and mycophenolate mofetil are considered together, approximately what percentage of patients achieve corticosteroid-sparing control of uveitis at 6 and 12 months?

- a. 20% to 40%
- b. 30% to 50%
- c. 40% to 60%
- d. 50% to 70%

8. What is the panel's consensus on the role of HLA testing in the workup of a patient with suspected uveitis?

- a. Because of its close association with uveitis, HLA-A29 testing should be performed in all patients with suspected uveitis
- b. Because demographic studies indicate varying degrees of prevalence in different ethnic populations that may or may not lead to inflammatory eye disease, discretion should be applied in HLA testing and interpretation of results
- c. Because there is an indefinite link between uveitis and HLA-A29 in some cases, testing should not be performed in the workup of patients with suspected uveitis
- d. Because HLA-A29 is highly prevalent in populations with birdshot chorioretinopathy, laboratory testing for HLA-A29 should only be performed in these patients

9. Which of the following are recognized as potential causes of uveitis?

- a. Systemic causes, such as an autoimmune disease, an inflammatory condition, or cancer affecting the eye
- b. Infection, including bacterial, viral, or fungal
- c. Idiopathic
- d. All of the above

10. According to the panel, there is no real difference in the treatment of uveitis due to infectious or noninfectious etiologies.

- a. True
- b. False

ACTIVITY EVALUATION

Did the program meet the following educational objectives?

Agree Neutral Disagree

Describe key factors in the differential diagnosis of noninfectious posterior uveitis

Discuss current treatment guidelines and the side effects associated with them

Evaluate the safety and efficacy of different treatment modalities for noninfectious posterior uveitis, including corticosteroids, sustained release implants, immunomodulatory/immunosuppressive agents, and biologics

Assess clinical trial data pertaining to new therapies, including steroid-sparing treatments

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Name and email _____

Do you feel the program was educationally sound and commercially balanced? Yes No

Comments regarding commercial bias:

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 _____

Would you recommend this program to a colleague? Yes No

Do you feel the information presented will change your patient care? Yes No

Please identify how you will improve/change: _____

Change the management and/or treatment of patients. Please specify

Create/revise protocols, policies, and/or procedures. Please specify

Please identify the barriers to change.

____ 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: _____

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