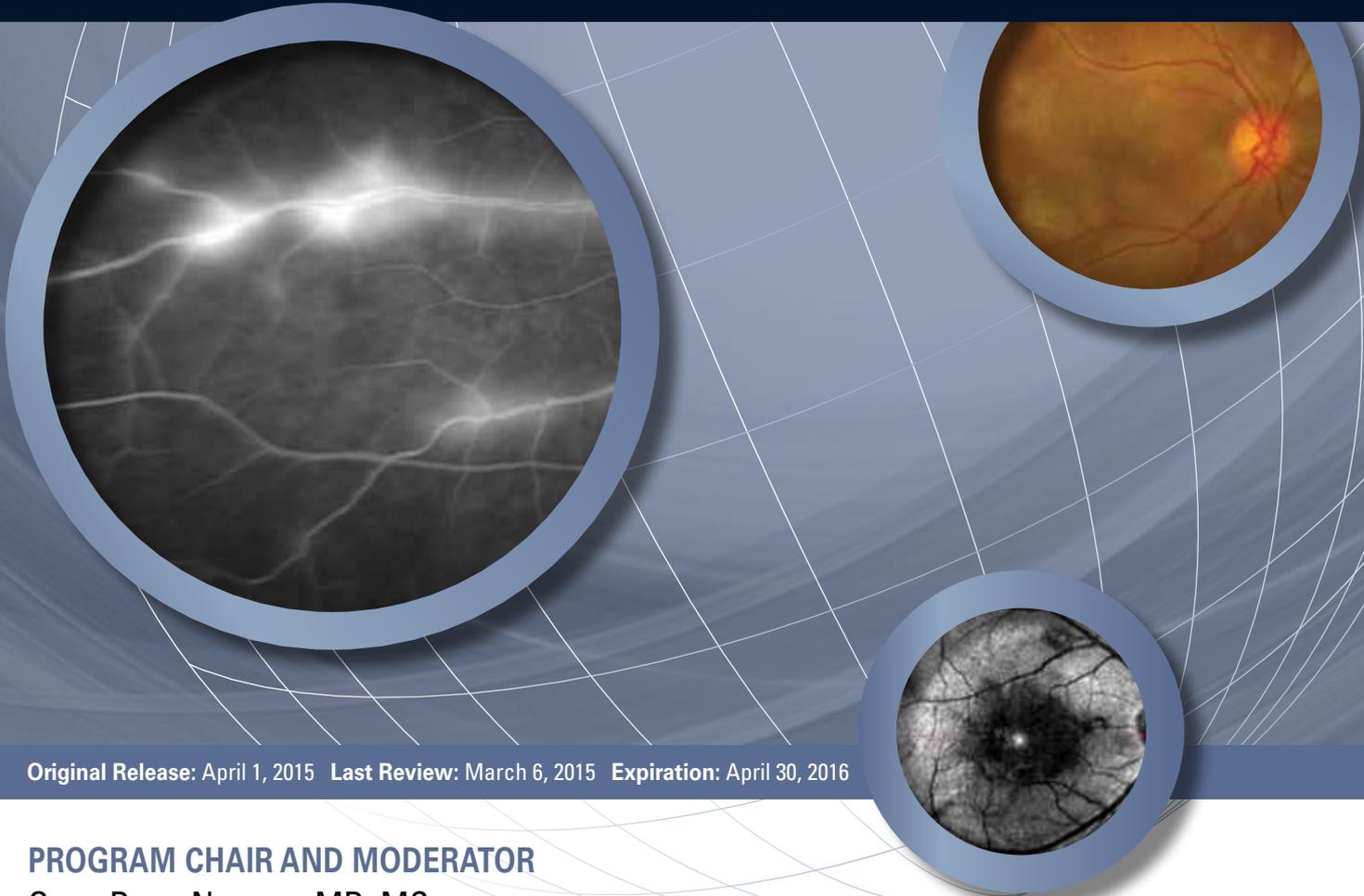


# Global Developments and Approaches in the Treatment of

# CHRONIC NONINFECTIOUS POSTERIOR UVEITIS

## Highlights From an Expert Roundtable Discussion



Original Release: April 1, 2015 Last Review: March 6, 2015 Expiration: April 30, 2016

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This continuing medical education activity is supported through an unrestricted educational grant from Santen Pharmaceutical Co, Ltd.



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## CONTENT SOURCE

This continuing medical education (CME) activity captures content from an expert roundtable discussion held during the American Academy of Ophthalmology Annual Meeting in Chicago, Illinois, on October 19, 2014.

## ACTIVITY DESCRIPTION

Noninfectious posterior uveitis can be challenging to manage and cause irreversible visual impairment. Patients with noninfectious uveitis often have associated systemic disease. Local and systemic corticosteroid therapy is the current mainstay of treatment. Numerous and significant developments for improving uveitis management are under way; many address the drawbacks of side effects, in an effort to improve tolerance to therapy and patient outcomes. Given the global scope of these management challenges, several international faculty have shared research from around the world on uveitis treatment at a recent American Academy of Ophthalmology Uveitis Subspecialty Day meeting as well as at other conferences dedicated to the topic.

## TARGET AUDIENCE

This activity intends to educate US and European retina specialists and other ophthalmologists caring for patients with noninfectious uveitis.

## LEARNING OBJECTIVES

Upon completion of this activity, participants will be better able to:

- Describe key factors in the differential diagnosis of noninfectious uveitis
- Articulate current guidelines pertaining to the treatment of noninfectious uveitis
- Evaluate the safety and efficacy of different immunomodulatory/immunosuppressive agents in the treatment of noninfectious uveitis
- Assess clinical trial data pertaining to new systemic therapies for noninfectious uveitis
- Review the mechanisms for emerging steroid-sparing therapies for noninfectious uveitis

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## Introduction

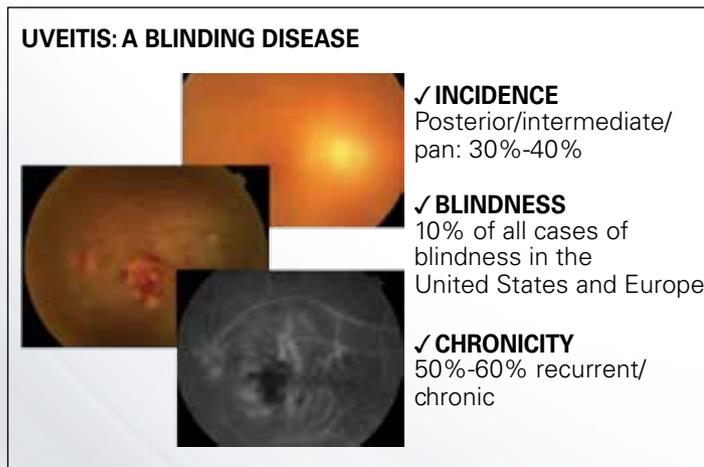
Uveitis of the posterior segment encompasses a variety of diagnostic descriptions, namely intermediate uveitis, posterior uveitis, and panuveitis. Uveitis affecting the posterior segment can be infectious, although most cases are noninfectious.<sup>1</sup> Corticosteroids and immunomodulatory drugs are the cornerstones for treatment of noninfectious uveitis in the posterior segment. Treatment of posterior uveitis generally necessitates the use of intraocular injections/implants or systemic therapies. A panel of uveitis and retina specialists from the United States and Europe met recently to discuss current treatments for noninfectious uveitis of the posterior segment and the roles they play in managing patients with this condition.

The goal of this monograph is to discuss management of noninfectious posterior segment uveitis in the context of a growing number of local therapeutic options. Given that there are a limited number of uveitis specialists available to treat uveitis, retina specialists are providing much of the ophthalmic care that these patients require. Many of the systemic treatments being used today are “off-label” and many have side effects, which can cause retina specialists to be uncomfortable prescribing and employing them. In the near future, we hope to have more options for local delivery of immunomodulatory therapies, such as intravitreal injections.

—Quan Dong Nguyen, MD, MSc

## European Retina Practice

**Prof Bandello:** Approximately 10% of all cases of blindness in Europe and the United States are related to uveitis.<sup>2</sup> (Figure 1) We should not underestimate the importance of this chronic disease, not only for its contribution to blindness but also for the effect it has on quality of life. Further, the cost of treatment and lost productivity for working-age patients add economic components to the consequences of uveitis.



**Figure 1.** Epidemiology of uveitis.

*Photos Courtesy of Francesco Bandello, MD, FEBO*

As a retina specialist treating posterior segment uveitis, my first priority is to try to control inflammation. I want to do this while avoiding complications and preserving as much vision as possible, ultimately hoping to improve patient quality of life. Retina specialists in Europe are comfortable with, and routinely provide, periocular/intraocular and systemic treatments.

Local therapies used in Europe include periocular and intravitreal injections of triamcinolone acetonide or intraocular implants that release fluocinolone acetonide (FA) or dexamethasone over a prolonged period of time. A nonbiodegradable 0.59-mg FA implant that delivers a daily dose of FA for approximately 1000 days has been used,<sup>3</sup> although it is not approved in Europe. The 0.19-mg FA implant delivers a smaller daily dose and is approved in Europe for the treatment of diabetic macular edema (DME).<sup>4</sup> A biodegradable 0.7-mg dexamethasone implant that delivers drug for approximately 3 to 6 months is approved for the treatment of DME.<sup>5</sup> These local treatment options need to be considered in unilateral/asymmetric cases, or when the systemic dose required to manage ophthalmic inflammation is contraindicated. In such cases, it is paramount that infection or masquerade syndromes be ruled out because in these instances, high-dose local corticosteroid therapies can be dangerous.

Oral corticosteroids remain the most common treatment for bilateral cases of posterior segment uveitis. Systemic corticosteroid therapy is particularly useful for patients who have a concomitant systemic disease that is the etiology of the uveitis. Corticosteroids remain the gold standard, providing rapid anti-inflammatory activity. Retina specialists tend to be comfortable using these drugs for short courses of treatment. Because the well-known side effects tend to be associated more with long-term therapy, other—corticosteroid-sparing—treatments are often considered if steroids cannot be discontinued quickly.

In cases involving recalcitrant or severe disease, and in cases involving children or pregnant women, the use of biologics may be necessary. Older drugs such as methotrexate and cyclosporine still tend to be the most commonly used in Europe; however, some of the newer drugs—tumor necrosis factor (TNF)- $\alpha$  blockers, interferon, anti-lymphocytes, anti-interleukins—are gaining popularity. Retina specialists are less comfortable using these biologic drugs for a variety of reasons, among them their off-label use, the need for infusions or injections in some cases, and their side-effect profiles. When use of these drugs becomes necessary, retina specialists often refer patients to uveitis specialists, rheumatologists, or other specialists with more experience managing patients on biologics.

## Retina Practice in the United States

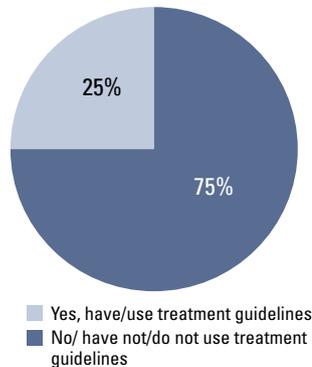
**Prof Do:** The top 3 uveitis treatment choices for retina specialists in the United States are the following: #1 – steroids; #2 – steroids; and #3 – steroids. Why is this? Retina specialists and ophthalmologists who do not specialize in ocular inflammation are more familiar with steroids than with other immunosuppressive agents. Very few departments of ophthalmology in the United States have uveitis fellowship-trained faculty. Therefore, many retina specialists and general ophthalmologists completing their training have never been exposed to the treatment guidelines for uveitis patients who have noninfectious inflammation. (Figure 2)

In 2011, several of our colleagues from the United States and abroad published a seminal paper reporting the results of a cross-sectional study of the current treatment patterns of ophthalmologists in the United States when encountering patients with noninfectious uveitis.<sup>6</sup> The results showed that 62% of these patients received systemic corticosteroids, with a mean initial daily dose of 44 mg tapered to 34 mg as the maintenance dose. This is 3 to 4 times the recommended

## TREATMENT PATTERNS

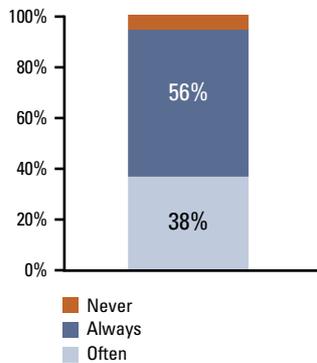
### Treatment Guideline Awareness

The majority (75%) of physicians did not use/ were not aware of treatment guidelines for uveitis



### Treatment Guideline Adherence

Of the physicians who use treatment guidelines (n=16), 94% always/often adhere to the guidelines



**Figure 2.** Adherence to uveitis treatment guidelines among US physicians.<sup>6</sup>

maximum maintenance dosage of less than 10 mg/d.<sup>7</sup> (Figure 3) Among physicians surveyed, 75% did not follow, or were not aware of, treatment guidelines for uveitis.

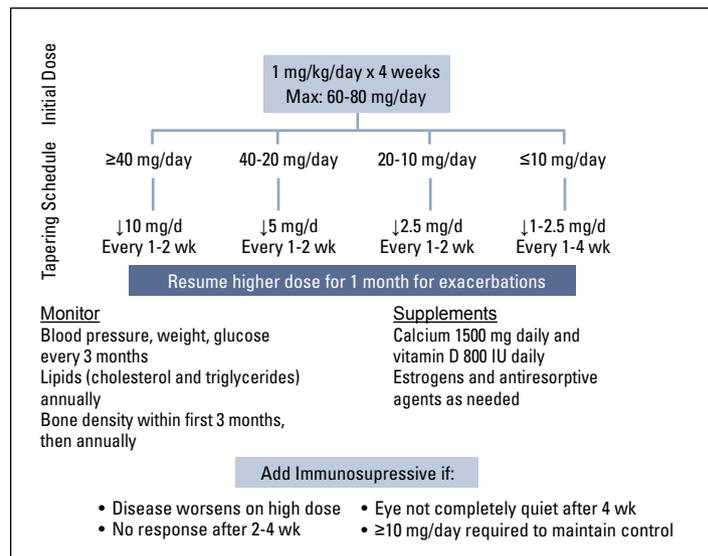
In addition to systemic therapy, many US retina specialists use intraocular triamcinolone acetonide as an off-label use of a formulation approved for systemic use. The dexamethasone intravitreal implant is gaining use in both noninfectious uveitis and retinal vascular diseases such as DME because it is US Food and Drug Administration approved. We also use the FA implant, which is approved in the United States for noninfectious uveitis, although there are some barriers to its use because of the cost and the challenges with insurance reimbursement procedures. These intravitreal options have a well-known side-effect profile that includes cataract formation in phakic patients and intraocular pressure (IOP) elevation.

If there is a diagnostic dilemma or if the clinical course of a patient is not improving, I will refer the patient to a uveitis specialist.

**Prof Nguyen:** If you do not have a uveitis specialist in your practice or university, at what point do you consider referring these patients to another specialist?

**Prof Bandello:** I am reluctant to manage patients for problems that I do not feel I can manage well. When corticosteroids are not enough and when other systemic agents necessitating follow-up for side effects are called for, I prefer to send patients to someone who is able to manage all the different aspects of the therapy, whether a uveitis specialist, rheumatologist, or some other specialist. In other words, whenever I am not concentrating solely on the eye and need to consider evaluations of other parts of the body that I do not know as well, I prefer to delegate someone else.

I am fortunate to work with a group of uveitis specialists in my department and so I typically refer all patients with inflammatory disorders to them, especially when immunomodulatory agents are needed.



**Figure 3:** Oral prednisone uveitis treatment guidelines.<sup>7</sup>

**Prof Do:** I agree. Vitreoretinal surgeons are comfortable inside the eye. I think the majority of retina specialists do not feel comfortable with systemic immunomodulatory therapy, with the exception of short courses of corticosteroids, because they are not familiar with the dosing and potential side effects of nonsteroidal immunosuppressive agents. If a patient is not responding to intraocular treatment and has persistent inflammation and worsening vision, I refer to a uveitis specialist. Retina specialists would be more comfortable managing patients with noninfectious posterior uveitis were there more intraocular therapy options available.

**Prof LeHoang:** This is consistent with what we see in France as well. The retina specialists prefer to refer patients to the uveitis specialist, particularly to a tertiary uveitis center, instead of administering immunomodulatory agents themselves. Even some uveitis specialists prefer to comanage these cases with an internist, rheumatologist, or other specialists, such as a pediatrician.

**Prof Adán:** My personal point of view regarding the management of a patient with posterior uveitis, retinal vasculitis, and the like, is that the retina specialist has to stay very involved. Retina specialists have expertise regarding fluorescein angiography, optical coherence tomography, and surgical management of the posterior segment of the eye. I understand that the retina specialist may be readily familiar with surgical treatments, but he or she has to become more familiar and comfortable with the medical treatments as well. Even when the systemic immunomodulatory drugs are delivered and monitored by another specialist, the retina specialist must stay very involved.

**Dr Srivastava:** This is an excellent discussion and conveys the concept that management of uveitis patients can be very complex and will, at times, necessitate input from a team of caregivers with a broad range of expertise. In our center we have both retina and uveitis specialists. Just as the retina specialist will consult the uveitis specialist in some cases, so will the uveitis specialist consult the retina specialist. Good communication is important for managing any complex case. In my opinion, one does not have to be both retina and uveitis trained to effectively treat these patients. One does, however, need some training in the steps of the treatment paradigm following oral corticosteroids.

**Prof Nguyen:** There seems to be consensus that management of patients with posterior segment uveitis often needs to consist of a partnership between ophthalmologists who specialize in retinal diseases and/or uveitis and others clinicians with immunology experience, such as rheumatologists, oncologists, and internists. The question arises, What about practitioners in small communities without easy access to all those specialists? Prof LeHoang, please share your thoughts about what retina specialists need to know to manage patients with noninfectious posterior uveitis when referral is not possible.

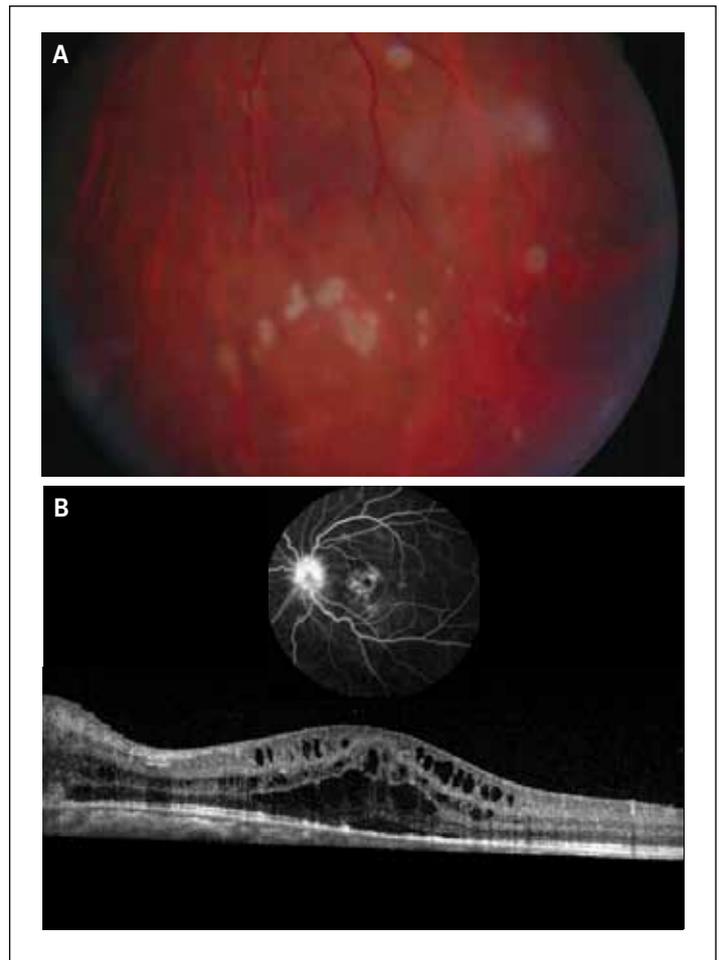
### Uveitis Management by the Retina Specialist

**Prof LeHoang:** First and foremost, the ophthalmologist has to recognize that uveitis is a very severe and sight-threatening disease. Before the start of any treatment, infectious causes and masquerade syndromes or malignancies must be ruled out. An initial step is to consider the patient's age: if he or she is very old, aged older than 70 years, or very young, aged younger than 5 years, one must be very suspicious of infection or malignancy. Noninfectious posterior uveitis may often be asymmetric; but in strictly unilateral disease, infectious origins such as the herpes viruses, tuberculosis (TB), syphilis, Lyme disease, toxoplasmosis, toxocariasis, or others must again be suspected and ruled out. It is best to refer the patient to a uveitis specialist (even if located at a distance of 10 hours' travel time) if you cannot rule out infection or a masquerade syndrome in your own setting, because anti-inflammatory treatments, particularly corticosteroids and immunomodulating agents, are contraindicated in these cases.

The challenge is that posterior segment inflammation can take several forms and the vitreoretinal appearance can be similar for infectious and noninfectious disease. Inflammation, regardless of etiology, can be retinitis with yellowish-white thickening of the retina, secondary hemorrhages and focal ischemia, or choroiditis with patchy yellow-white infiltrates very deep under the retinal pigment epithelium with overlying vitritis, or a combination of both. The term posterior uveitis also includes cases of retinal vasculitis with perivascular cuffing and sheathing. Optic nerve involvement occurs frequently in posterior uveitis, beginning even before there are visible signs of vitritis or vasculitis. Intermediate uveitis also is a posterior chamber uveitic condition. Patients with slowly progressive, painless loss of vision who present with floaters, vitritis, snowballs (Figure 4A), or snowbanking, especially in the presence of cystoid macular edema (CME) (Figure 4B) should be considered intermediate uveitis suspects.

Determining if the disease state is restricted to the eye or is part of a systemic condition is important in guiding treatment decisions. Past medical history can be helpful in making that determination. Although there are many transitional and combined forms of uveitis, you can sometimes differentiate etiology according to granulomatous vs nongranulomatous disease. Behçet disease should be suspected when a patient has noninfectious nongranulomatous posterior chamber uveitis, whereas sarcoidosis is of suspicion when granulomatous disease is seen and infections such as TB and syphilis have been ruled out.

What is the minimal testing needed when a uveitis suspect first presents to the retina specialist? Firstly, I disagree with the textbooks that suggest a thorough systemic workup is not called for at the time of the initial presentation and can be



**Figure 4.** Intermediate uveitis. [A] Snowball; [B] Cystoid macular edema.

*Photos Courtesy of Phuc LeHoang, MD, PhD, FEBO*

reserved until there is evidence of recurrent disease. The initial visit is the only opportunity for you to make an early diagnosis, initiate early treatment, and, potentially, cure the patient. Do not wait for recurrence. Secondly, one must make sure that it is a noninfectious uveitis. The minimum workup should include complete blood cell counts, an erythrocyte sedimentation rate, and a C-reactive protein test. I test all my patients for syphilis. A chest x-ray is mandatory and can exclude TB, sarcoidosis, or malignancy such as lymphoma. A purified protein derivative (PPD) skin test for TB may be useful in the United States, but not in Europe, where many patients were vaccinated during childhood, making 80% of PPD skin tests positive during the adult life. However, a phylctenular PPD skin test may still be informative even in Europe. Now we can use commercially available standardized tests (interferon-gamma release assay tests) to measure the in vitro level of interferon gamma released by the patient's lymphocytes, which will be elevated in the presence of TB antigens. Testing for elevated serum angiotensin-converting enzyme and serum lysozyme levels can help confirm sarcoidosis. Human leukocyte antigen typing is rarely useful for diagnosing the cause of uveitis, except for the HLA-A29 antigen, which is present in nearly 100% of birdshot chorioretinopathy cases.

**Dr Srivastava:** Often I hear colleagues express a concern that they are missing something bad—whether an infectious disease, a masquerade syndrome, or a systemic disease. When retina specialists know that a posterior segment uveitis

is infectious, they are comfortable with treating that patient. When they do not know for sure, or are worried about an undiagnosed systemic problem, is when their concern is raised and comfort level wanes. The Kaiser Permanente Hawaii Pacific Ocular Inflammation Study<sup>8</sup> and the Northern California Epidemiology of Uveitis Study<sup>2</sup> showed that most uveitis is noninfectious, and that it is idiopathic. Knowing that should make retina specialists more comfortable treating this disease. When diagnostic data (including laboratory findings and clinical examination) do not indicate infection or other etiologies, one can assume that the eye disease is idiopathic and proceed to treat it. It is important to follow patients once treatment has been initiated to evaluate their response to therapy. One can then adjust the differential diagnosis according to that response.

**Prof LeHoang:** When you are comfortable that you have ruled out infection, you can initiate high-dose oral or intravenous steroid treatment and plan to taper to a maintenance dose of less than 10 mg/d as soon as possible. I prefer to taper to less than 7 mg/d, but you must refrain from decreasing steroids too quickly in order to avoid a flare-up. If inflammation persists or recurs at intolerable high dose, or if you are unable to reduce the dose without immediate recurrence, then you need to be very careful and suspicious of infection or a masquerade. Do not hesitate to repeat the workup. This is a very, very critical point. If the second or a third workup still does not show any infections or tumors, then proceed with systemic immunomodulatory agents or consider adding local steroid treatment if the lack of sufficient response is limited to the eye.

When adding local steroid treatment, periocular or intravitreal, be aware that such procedures can induce severe ocular complications; it is therefore important to be capable of performing cataract or glaucoma surgery or to collaborate with good ophthalmic surgeons. Surgical management of glaucoma, and even cataracts, in a patient with uveitis often necessitates special protocols to prevent a postoperative flare-up.

Finally, do not forget our nonophthalmology colleagues who can provide very important care of the extraocular manifestations of many of these ocular conditions. Inquire about potential extraocular signs such as oral ulcers, genital ulcers, arthritis, pulmonary symptoms, and so forth, and refer to the internist, rheumatologist, or oncologist, as the case may dictate. In conclusion, my advice is, Be practical. If access to a uveitis specialist is not convenient, it is the ophthalmologist's obligation to exclude infections and masquerade syndromes. Take a good medical history, and orient the workup, treatment, and collaborations accordingly, even for the first episode of posterior segment uveitis.

**Prof Adán:** To manage a patient with uveitis, it is important to know medicine. Some uveitis patients do have idiopathic inflammation that is limited to the back of the eye; they can be managed solely by the ophthalmologist, whether a retina specialist or a general ophthalmologist. But many of these patients have systemic manifestations and require comanagement with rheumatologists, internists, or others; nevertheless, you still have to understand the pharmacologic agents. It is very important that ophthalmologists be knowledgeable about more than just corticosteroids, especially the new biologics, for managing intraocular inflammation.

## Current Treatments for Noninfectious Posterior Uveitis

### Treatment Options in Europe

**Prof Adán:** Because we do not have good multicenter studies to establish treatment protocols for noninfectious posterior uveitis, I will share my personal point of view and experience. Although the situation varies by country, most patients in Europe, rather than being participants in private insurance plans, are part of a public health care system, which I think, in general, makes access to off-label treatments such as biologic drugs easier than in the United States. Comanagement with other specialties, mostly rheumatology, is also common in Europe, although there are no specific treatment guidelines.

Local corticosteroids are used when inflammation, or residual inflammation in the case of a systemically treated patient, is limited to the eye. Subtenon triamcinolone injections are most commonly used in clinical practice. For me the reasons are the low cost and the fact that they are easy to use. As with all treatments, there are some limitations. Clinical experience has shown that a percentage of patients will develop high IOP and/or cataract as a result of these injections, and it is difficult to predict which patients will have that response. A biodegradable dexamethasone intravitreal implant was approved in Europe for use in treating noninfectious uveitis in 2011. This implant is most commonly used in cases with clinically significant CME. Cost, combined with the frequency of injections needed, could limit the use of this implant to mostly adjunctive therapy, but the implant has been shown to be safe and effective. We have recently published results of a multicenter study that showed favorable visual acuity and vitreous haze outcomes, but found that more than 50% of the eyes required more than 1 injection per year.<sup>9</sup> The nonbiodegradable fluocinolone acetonide intravitreal implant has limited use. This 3-year implant is not approved in Europe: the cost of the implant is quite high, and there is a nearly 100% rate of cataract in phakic eyes. Also, 1 in 3 implanted eyes requires IOP-lowering surgery.

As for systemic treatments, corticosteroids are the first-line drug in noninfectious inflammatory conditions, including posterior segment uveitis. When >10 mg/d corticosteroid treatment is needed to keep ocular inflammation controlled, immunomodulatory therapies (IMTs) are used. In Europe, cyclosporine, mycophenolate, azathioprine, and methotrexate are the most common IMTs used for noninfectious posterior segment uveitis. For patients whose uveitis is refractory to traditional immunosuppressants, infliximab and adalimumab are the anti-TNF- $\alpha$  biologics that are most often used. There is evidence that patients with certain systemic etiologies are best treated early with the anti-TNF- $\alpha$  medications.<sup>10</sup> Adamantiades-Behçet disease is believed to respond well to infliximab,<sup>11</sup> and pediatric posterior segment uveitis patients, including those whose condition is associated with juvenile idiopathic arthritis, do well on adalimumab.<sup>12</sup>

Regarding other biologics, interferon and the interleukin-6 inhibitor tocilizumab are beginning to be used more. We recently published the results of a small retrospective cohort study showing success when treating inflammatory macular edema refractory to the anti-TNF- $\alpha$  medications.<sup>13</sup> Interferon is used mostly in Germany and Turkey, mainly in Behçet disease and in cases with macular edema. An advantage of interferon is that when treatment is stopped, a high percentage of patients remain in remission.<sup>14</sup>

**Table 1.** Outcome of Systemic Immunosuppressive Therapy<sup>15</sup>

| Drug          | Success at 1 Year | ≤10 mg Prednisone | Discontinued Within 1 Year |
|---------------|-------------------|-------------------|----------------------------|
| Mycophenolate | 73%               | 55%               | 12%                        |
| Cyclosporine  | 51%               | 36%               | 10%                        |
| Cytoxan       | 76%               | 61%               | 34%                        |
| Methotrexate  | 66%               | 58%               | 15%                        |
| Azathioprine  | 62%               | 47%               | 25%                        |

Surgery, pars plana vitrectomy, still has a role and is used selectively in the treatment of intermediate uveitis, pars planitis, and refractory macular edema.

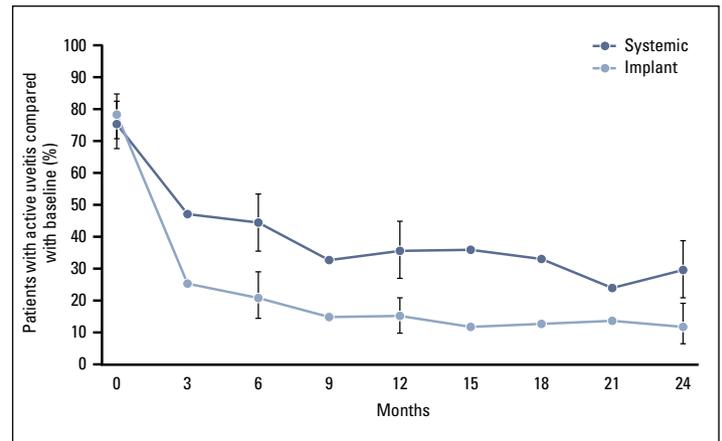
**Prof LeHoang:** Treatments in Europe vary from country to country. Currently in France, we scarcely use cyclosporine as monotherapy. My first-line treatment is oral or intravenous steroids, as is the case with all our colleagues. When dealing with a particularly severe, recalcitrant sight-threatening noninfectious posterior uveitis, it is mandatory to add immunomodulating therapy either immediately, combined with the steroids, or subsequently and rapidly during the steroid tapering phase to help reduce steroid dependence. The order of preference guiding our choice of immunomodulating agents to be combined with oral steroids is as follows: (1) interferon, (2) mycophenolate mofetil, (3) combination of azathioprine + cyclosporine or mycophenolate mofetil + cyclosporine. I feel very safe using interferon because it does not induce severe immunosuppression and has at least 3 modes of action: it is anti-inflammatory, it is antiviral, and it is antitumoral. When interferon is contraindicated, ineffective, or ill-tolerated, the choice among the other alternatives is dependent on the characteristics of the uveitis being treated and the particular patient's general state of health.

**Prof Nguyen:** Some of the drugs we use in the United States are not available elsewhere in the world. On the other hand, some therapeutic agents, for example, interferon, which is quite commonly used in Europe, are not as popular in the United States. Dr Srivastava, please follow up with a US perspective.

### Treatment Options in the United States

**Dr Srivastava:** Treatment in the United States for noninfectious posterior uveitis is generally similar to that in Europe, but with a few differences. The guidelines recommend high-dose corticosteroid treatment first line, with steroid-sparing agents added if inflammation cannot be controlled with ≤10-mg prednisone daily within 3 months. As stated earlier, there is evidence that the average corticosteroid dose being used may be well above that recommended and that only a small proportion of patients receive immunosuppressives.<sup>6</sup>

The general ophthalmologist tends to send a patient to the retina specialist when inflammation involves the posterior segment. The retina specialist, depending on his or her training and geographic location, will give local injections, prescribe oral steroids, or refer to rheumatology or to a uveitis specialist. Uveitis specialists in the United States tend to treat these patients themselves because they are comfortable with immunosuppressant use, or they have very close interactions with rheumatologists.



**Figure 5.** Percentage with active inflammation from baseline to 24 months in eyes with intermediate, posterior, or panuveitis assigned to implant or systemic therapy. At 12 months systemic 40% active; implant 15% active.<sup>17</sup>

The Systemic Immunosuppressive Therapy for Eye Diseases (SITE) Cohort Study<sup>15</sup> has given us some good information regarding outcomes from many treatments. (Table 1) Many of these drugs have response rates as high as 50% to 70%, depending on the criteria used.

One difference between European and US treatment options seems to be the choice of local steroids used. I think there is much more intravitreal use of triamcinolone acetonide injectable suspension 40 mg/mL, or other forms of triamcinolone, in the United States. There is use of the dexamethasone implant, but currently intravitreal therapy is still predominantly triamcinolone. Fluocinolone acetonide implants are also available. Excellent clinical trials support the use of the 0.59-mg FA implant, with reductions in recurrence and reductions in the need for additional therapy. All patients who are phakic require cataract surgery. The filtering surgery rates are approximately 30% to 35%.<sup>16</sup> For patients with ocular disease only or recurrent CME, an argument can be made for using this implant.

The Multicenter Uveitis Steroid Treatment (MUST) Trial was designed to compare outcomes with systemic therapy vs those with the 0.59-mg FA implant.<sup>17</sup> (Figure 5) Patients with active posterior segment uveitis were randomized to either oral prednisone with systemic immunosuppressive agents or to the implant. The exact immunosuppressive agent used was left to the treating physician's discretion. Both groups did well. There was a trend toward better vision in the implant group. The implant group had less active uveitis, less macular edema, better quality of life, but obviously higher risk for cataracts, ocular hypertension, and glaucoma.

Uveitis was controlled more quickly with local therapy, and the control appears to be durable.

I tell all my patients—every single one of them—who are in their 20s or 30s that they are very likely to have this condition for a while. Then I ask them what they would rather do, take oral or systemic immunosuppressives for 40 years, have 13 fluocinolone implants in each eye with cataract surgery and glaucoma surgery, or at least 80 injections of the dexamethasone implant with probable cataract surgery and glaucoma surgery in each eye. I think all of us on the panel would agree that we would like to be able to offer better choices.

**Prof Nguyen:** What would that better choice look like? What would be the ideal agent?

### Future Posterior Segment Uveitis Treatments

**Dr Srivastava:** We want something that would be like “anti-VEGF for uveitis in the eye”—something safe and effective that has changed the retina practice. If you think about uveitis as a retinal disease, an injection-based therapy that has low side effects, and that works well, would make treatment more comfortable for the retina specialist.

**Prof Nguyen:** There are many exciting emerging therapies, of both local and systemic formulation, that will, no doubt, help to resolve many of today’s unmet needs. (Table 2)

Of the emerging therapies, intravitreal sirolimus is the furthest along in development. By inhibiting the mTOR (mammalian target of rapamycin), sirolimus blocks leukocyte activation and the production of inflammatory cytokines. An oral formulation of sirolimus is used for the prophylaxis of organ rejection in adult patients receiving a kidney transplant. When given intravitreally, this formulation of sirolimus forms a slowly dissolving depot in the vitreous humor that is thought to limit the immunosuppressive effects to the eye and to minimize systemic exposure.

In fact, results of the first phase 3 Study Assessing Double-masked Uveitis Treatment (SAKURA) were presented at the 2014 American Academy of Ophthalmology (AAO) Annual Meeting.<sup>26</sup> One hundred three sites in 15 countries randomized 347 patients with active noninfectious uveitis affecting the posterior chamber to treatment with 44-µg, 440-µg, or 880-µg intravitreal injections of sirolimus every 2 months. The primary outcome, reduction of vitreal haze, was met. Vitreal haze was reduced to grade 0.5 or less in more study subjects in the 440-µg treatment group than in other treatment groups, with a statistically significant difference.

If something like intravitreal sirolimus was available, would there be any concerns about overuse of intravitreal injections? We just heard a case presented at AAO 2014 of a patient who has received 128 intravitreal anti-VEGF injections; the eye has maintained its structural integrity.

**Prof LeHoang:** I am going to be provocative and state that I think local treatments should be administered only as adjunct therapy. There is no lymph node in the eye; when you treat locally, the focus is on an established response in the eye to inflammation that was initiated systemically outside the eye. It is important to diminish the ocular inflammation, and even to return immune privilege to the eye, but we have to keep in mind that the lymphocytes present in the eye are coming from extraocular lymphoid organs. What would be nice is to have available local, nonsteroidal treatment, so that we can avoid the steroidal side effects that everyone has mentioned.

**Prof Nguyen:** This is a fair point, but we do see cases, such as the bilateral birdshot chorioretinopathy cases described by Rush and colleagues,<sup>27</sup> in which we can treat each eye locally and attain complete stabilization of the disease. Prof Do, what are your thoughts?

**Prof Do:** If the workup indicates that the inflammation is localized to the eye and that it is not infectious, I would try a local therapy. If the initial agent is not effective, it would be beneficial to have a different local therapy to try. Sometimes a

**Table 2.** Current Clinical Trials of Agents to Treat Uveitis

| Systemic Treatments |        |                                |                     |
|---------------------|--------|--------------------------------|---------------------|
| Monoclonal Antibody | Target | Trial                          | Timeline            |
| Adalimumab          | TNF-α  | VISUAL <sup>18</sup>           | 2015/2016 (phase 3) |
| Tocilizumab         | IL-6   | STOP-UVEITIS <sup>19</sup>     | 2016/2017 (phase 2) |
| Gevokizumab         | IL-1β  | EYEGUARD <sup>20</sup>         | 2016 (phase 3)      |
| Sarilumab           | IL-6   | SARIL-NIU-SATURN <sup>21</sup> | 2017 (phase 2)      |

| Local Treatments                       |                |                       |                    |
|--|----------------|-----------------------|--------------------|
| Drug                                   | Mechanism      | Trial                 | Timeline           |
| Sirolimus                              | mTOR inhibitor | SAVE <sup>22</sup>    | Complete (phase 1) |
|  |                | SAVE-2 <sup>23</sup>  | Ongoing (phase 2)  |
|  |                | SAKURA <sup>24</sup>  | Ongoing (phase 3)  |
| Suprachoroidal Triamcinolone Acetonide | Corticosteroid | DOGWOOD <sup>25</sup> | 2016 (phase 2)     |

IL=interleukin; mTOR=mammalian target of rapamycin; TNF=tumor necrosis factor.

single agent does not work for every case. In a case in which it is not easy to refer to a uveitis specialist, I might try combination local therapy before administering systemic therapy.

**Prof Srivastava:** We have to make a distinction between acute and chronic disease. I think most of us agree that systemic steroids work really well in the acute setting. We have guidelines for how to quiet acute inflammation. If the patient re-flares during tapering, or if high doses are needed, then it is time to start thinking about chronic immunosuppressive therapy. In a patient who has chronic disease and who is on immunosuppressive therapy, it makes sense to give an injection in the eye for a local recurrence in the eye.

**Prof LeHoang:** Local therapies are also very important considerations for the vitreoretinal or cataract surgeon when operating on a uveitic eye for controlling the inflammation flare-up associated with surgical trauma.

**Prof Adán:** Of course, inflammation from surgical trauma is different from posterior uveitis, which, I think, makes a very important point. We cannot treat all patients with inflammation in the posterior segment with the same drugs. We must personalize treatment and continue researching new drugs and alternate routes of administration.

**Prof Nguyen:** Our discussion has been excellent and I am excited about the future of treatment for noninfectious posterior uveitis. We will continue to push for well-controlled, randomized trials evaluating the use of new targeted systemic, and soon local, immunosuppressive therapies.

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## POSTTEST

To obtain *AMA PRA Category 1 Credit™* for this activity, complete the CME Post Test by writing the best answer to each question in the Answer Box located on the Activity Evaluation/Credit Request form on the following page. Alternatively, you can complete the CME Post Test at <http://tinyurl.com/posterioruveitis>.

See detailed instructions at **To Obtain AMA PRA Category 1 Credit™** on page 3.

- Epidemiology studies have shown that most posterior uveitis is:
  - Infectious
  - Idiopathic
  - Blinding
  - Due to sarcoidosis
- Before starting any treatment for posterior segment uveitis, one must rule out:
  - Infectious causes
  - Masquerade syndromes
  - Malignancies
  - All the above
- To which structure/s is the site of inflammation in posterior uveitis limited?
  - Retina
  - Retinal pigment epithelium
  - Choroid
  - Both retina and choroid
- Current guidelines for treating noninfectious posterior uveitis recommend initial treatment with:
  - Intravitreal steroid injections
  - 1 mg/kg/d oral prednisone
  - Topical ophthalmic corticosteroids
  - Referral to a rheumatologist
- The recommended maximum dose of oral prednisone for noninfectious uveitis patients to minimize side effects is:
  - 1 mg/kg/d
  - 34 mg/d
  - 10 mg/d
  - >40 mg/d
- The Systemic Immunosuppressive Therapy for Eye Diseases (SITE) Cohort Study found:
  - High discontinuation rates for interferon
  - 40% of patients treated with anti-VEGF therapies successfully discontinued corticosteroids
  - Response rates of 50% to 70% for the drugs evaluated
  - None of the above
- Which of the following drugs are being evaluated as a systemic treatment for noninfectious uveitis in a phase 3 clinical trial?
  - Triamcinolone acetonide
  - Adalimumab
  - Sarilumab
  - Sirolimus
- Intravitreal sirolimus has been shown to:
  - Inhibit mTOR
  - Activate leukocytes
  - Block cytokine production
  - Both a. and c.
- The phase 3 study SAKURA assessed sirolimus for treatment of noninfectious posterior uveitis. Which of the following statements regarding the study design and results is true?
  - The study was conducted at 103 sites in the United States
  - The primary end point was superiority to triamcinolone acetonide
  - Sirolimus 440 µg was significantly better than the 44-µg or 880-µg dose at reducing vitreal haze
  - Adjunctive therapy with topical NSAIDs was shown to provide significant visual acuity improvement
- To which of the following targets of biologic therapy does Adamantiades-Behçet disease respond?
  - Interleukin-6
  - Interferon
  - Lymphocytes
  - Tumor necrosis factor

