CME MONOGRAPH

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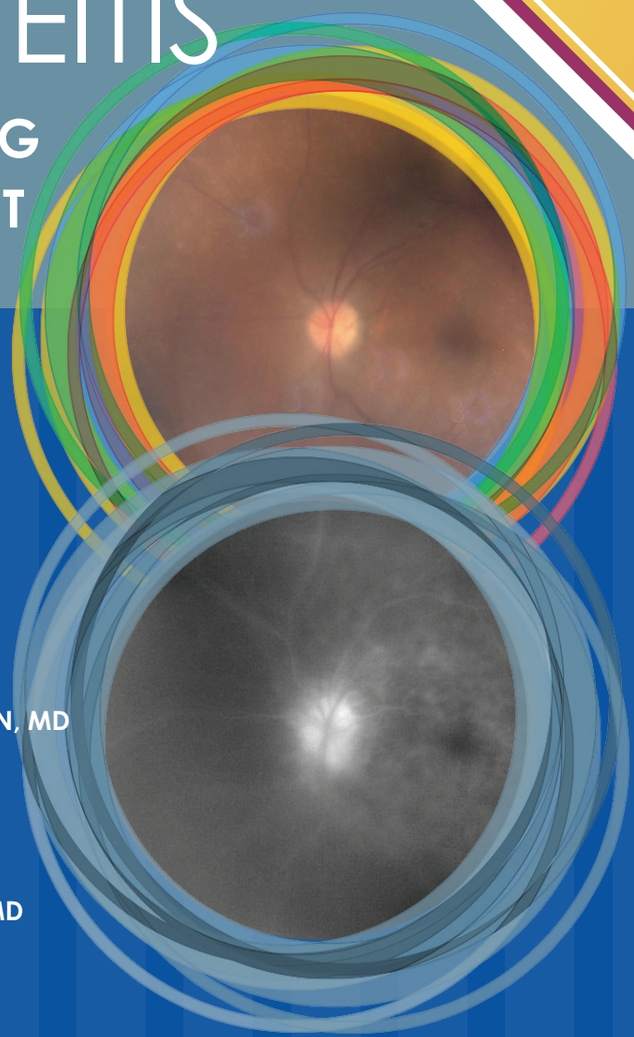
NONINFECTIOUS POSTERIOR UVEITIS

BRINGING NEW AND EMERGING TREATMENTS TO THE FOREFRONT



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ACTIVITY DESCRIPTION

Noninfectious uveitis involving the posterior segment is an important cause of vision loss. Oral corticosteroid therapy is the mainstay for initial treatment, but depending on its underlying cause, uveitis often cannot be controlled after tapering of the steroid to a dose that is safe for chronic treatment. In addition to steroid-sparing immunosuppressive therapy, local corticosteroid injections have a role for providing long-term suppression of inflammation while mitigating the risks of systemic steroids. The desired results of this activity are to educate clinicians on current options for the treatment of uveitis that can improve outcomes in patients.

TARGET AUDIENCE

This educational activity is intended for retina specialists and other ophthalmologists.

LEARNING OBJECTIVES

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

- Use appropriate assessments to accurately diagnose noninfectious uveitis of the posterior segment
- Describe which patients with noninfectious uveitis of the posterior segment would be referred to a uveitis specialist
- Discuss the efficacy of local treatments to manage patients with noninfectious uveitis of the posterior segment
- Explain the safety of local treatments to manage patients with noninfectious uveitis of the posterior segment
- Apply information on the efficacy and safety data for local therapies to manage patients with noninfectious uveitis of the posterior segment

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Cover images courtesy of Pauline T. Merrill, MD.

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NONINFECTIOUS POSTERIOR UVEITIS

BRINGING NEW AND EMERGING TREATMENTS TO THE FOREFRONT

INTRODUCTION

Noninfectious uveitis involving the posterior segment is an important cause of vision loss. Oral corticosteroid therapy is the mainstay for initial treatment, but depending on its underlying cause, uveitis often cannot be controlled after tapering of the steroid to a dose that is safe for chronic treatment. Steroid-sparing immunosuppressive therapy and local corticosteroid injections can have a role for providing long-term suppression of inflammation while mitigating the risks of systemic steroids.

The first long-acting steroid implant for treating noninfectious uveitis involving the posterior segment, fluocinolone acetonide (FA) 0.59-mg intravitreal implant, became commercially available in 2005.[1] In 2018, the FA 0.18-mg intravitreal implant was approved by the US Food and Drug Administration (FDA) for treating noninfectious uveitis involving the posterior segment.[2]

This activity presents insights from uveitis experts on the diagnosis and management of noninfectious uveitis involving the posterior segment, with a focus on the safety and efficacy of newer local steroid treatments. Case-based discussions and commentary from a glaucoma specialist on intraocular pressure (IOP) management provide information on patient selection for the newer long-acting implant and follow-up care.

–Quan Dong Nguyen, MD, MSc

REVIEW OF CURRENT STANDARD OF CARE IN UVEITIS

Thomas Albini, MD

Diagnosis

Uveitis encompasses a large group of inflammatory diseases that can be classified as anterior, intermediate, posterior, or panuveitis according to the primary site of inflammation, and by etiology as infectious or noninfectious conditions. Infectious causes of uveitis require treatment with a pathogen-specific antimicrobial agent and should be excluded before starting immunosuppressive therapy.

The prevalence of different infectious causes of uveitis varies geographically. In the United States, the most common and damaging etiologies of infectious uveitis are syphilis, toxoplasmosis, and herpes family viruses.[3] Other infectious causes of uveitis include tuberculosis, endogenous endophthalmitis, Lyme disease, and *Bartonella*.[3,4]

Diagnosis of uveitis begins with a detailed history, thorough ophthalmic examination, and review of systems that can provide clues to the underlying etiology. Multimodality imaging has revolutionized the diagnosis of uveitis by allowing more comprehensive assessment of areas of involvement. Imaging techniques that are used include optical coherence tomography—

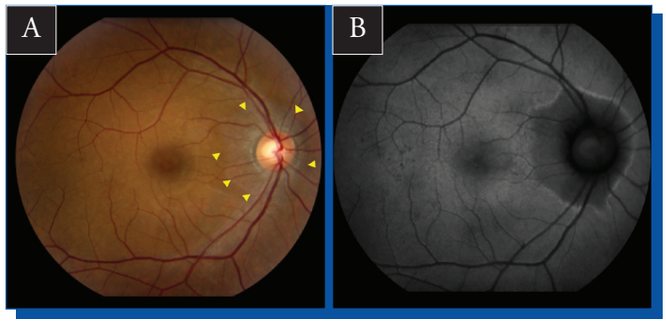

Figure 1. Images from a 35-year-old female with photopsias and electroretinography changes associated with acute zonal occult outer retinopathy. The fundus photograph (A) shows an enlarged blind spot, but the outer retina/retinal pigment epithelium changes are not obvious. The fundus autofluorescence image (B) is striking, showing hypoautofluorescence in the peripapillary region surrounded by a hyperautofluorescent halo. The autofluoresence highlights the pathologic features in a way that clinical examination or other currently available imaging technologies may not do as well.

which is invaluable for following changes in cystoid macular edema (CME)—fundus autofluorescence **(Figure 1)**, fluorescein angiography, indocyanine green angiography, ultrasound B-scan, and ultrasound biomicroscopy.

If infection seems unlikely on the basis of an appropriate evaluation—including history, clinical examination, blood studies, and multimodal imaging—and if corticosteroid treatment is initiated to control inflammation, it is necessary to monitor the patient closely, keeping in mind that uveitis not responding to corticosteroid therapy may have an infectious cause. If a physician is managing a case that is not responding to treatment appropriately, early referral for second opinion, hopefully to a uveitis specialist, can only be helpful, especially if done before severe vision loss. Referral to a uveitis practitioner is also very helpful if long-term immunosuppression is required and if the treating physician is uncomfortable with prescribing systemic steroid-sparing agents or intravitreal sustained-release steroids. Referral to a rheumatologist may be helpful for systemic evaluation, especially if a patient has joint or other extraocular symptoms.

Discussion

Dr Nguyen: Dr Albini, what initial testing would you recommend to rule out an infectious cause for uveitis involving the posterior segment?

Dr Albini: The initial workup for posterior uveitis should include serology for syphilis in all adolescents and adults and a test for tuberculosis, either the Mantoux tuberculin skin test or blood interferon-gamma release assay. Tuberculosis is not a common cause of uveitis in the United States,[5] but testing is important to identify latent disease that could be activated by steroid or other immunosuppressive therapy. In my clinic, the most worrisome common causes of infectious uveitis are toxoplasmosis, viral retinitis, syphilis, and endogenous endophthalmitis; tuberculosis is an uncommon cause, but is always somewhere at the back end of the differential diagnosis. Consequently, the key things to elicit in a history are prior inflammatory events in either eye (because toxoplasmosis tends to be a recurrent infection), prior herpes or varicella infections, a history of encephalitis at birth (often associated with herpes simplex virus [HSV] type 2 retinitis), or high-risk sexual behavior, which may put the patient at risk for syphilis. Recent surgeries or hospitalizations and venous access or recreational drug use may suggest the possibility of endogenous endophthalmitis. Known exposure to tuberculosis or origin in an endemic area may increase the risk of ocular tuberculosis.

Further testing should be guided by suspicion for certain infectious etiologies, considering the patient's history and findings from clinical examination. For example, focal necrotizing retinitis adjacent to a scar is a characteristic feature of toxoplasmosis.[3] Viral etiology should be suspected if there is acute retinal necrosis. Because vitritis can limit posterior visualization, an anterior chamber tap to obtain a specimen for polymerase chain reaction (PCR) assay and initiation of antiviral treatment can be considered until viral uveitis is ruled out.

To test for syphilis, obtaining both a treponemal test, such as fluorescent treponemal antibody absorption test, and a nontreponemal test, such as the rapid plasma reagin, is optimal. If both test results are positive, then you have confirmed your diagnosis of syphilis. If the treponemal test result is positive and the nontreponemal test result is negative, you could obtain a second nontreponemal test, like the Venereal Disease Research Laboratory test, to evaluate further. If the reverse is true, the nontreponemal test result is likely a false-positive. It is important to note that a treponemal test is more sensitive for latent and tertiary syphilis than is a nontreponemal test.[6] This makes a treponemal test a better screening test than a nontreponemal test if only 1 can be obtained.

To evaluate for toxoplasmosis, serum immunoglobulin G (IgG) and immunoglobulin M (IgM) tests can be helpful. A positive IgM test result is rare, but very likely represents a new infection. A negative IgG test result means the patient is very unlikely to have toxoplasmosis. Serology for HSV and varicella zoster virus is helpful only if negative because so many people have been exposed to these viruses. PCR of anterior chamber tap fluid for HSV-1, HSV-2, and varicella zoster virus is highly sensitive and specific for viral retinitis.[7] PCR for toxoplasmosis is highly specific but less sensitive.[8] In atypical cases of toxoplasmosis, PCR may be essential.

Dr Merrill: I would like to emphasize the importance of testing for syphilis. Ophthalmologists may refer patients with uveitis for a diagnostic workup to an internist or rheumatologist, who might not routinely test for syphilis. We recently published a paper describing 3 patients with undiagnosed syphilitic uveitis who were treated with a tumor necrosis factor alpha (TNF-α) inhibitor.[9] Once appropriate antibiotic treatment was started, it still took a long time to get the inflammation under control.

Dr Nguyen: If the diagnosis of noninfectious uveitis is uncertain, it is safer to start steroid treatment with systemic therapy. Under what conditions should a clinician feel comfortable using local steroid therapy for uveitis involving the posterior segment?

Dr Callanan: I believe it would be acceptable to start local therapy if syphilis is ruled out and if there are no focal retinal lesions or retinitis because then the likelihood of an infectious cause for the uveitis is very low. Any recent intraocular surgery would be a contraindication for local steroids because of the risk of bacterial infection. If there is focal retinitis, it is important to consider an anterior chamber tap, and not just order serology for viruses.

Treatment Goals and Options

The goal for the treatment of uveitis is to suppress inflammation that can lead to tissue damage and subsequent permanent loss of vision.[10,11] Corticosteroids are the standard treatment for initial control of active inflammation in uveitis, and uveitis involving the posterior segment necessitates administration orally or by local injection.[12-14] Compared with other immunosuppressive options, steroids act more rapidly to control inflammation, but side effects limit their long-term use. Therefore, guidelines recommend adding a steroid-sparing immunosuppressive agent if, after 2 to 3 months, inflammation cannot be controlled with < 7.5 to 10 mg/d of prednisone (or equivalent).[12-14]

Nonsteroidal Immunosuppressive Agents

Several classes of immunosuppressive agents can be considered steroid-sparing agents, including antimetabolites (azathioprine, methotrexate, mycophenolate mofetil), T-cell/calcineurin inhibitors (cyclosporine, tacrolimus), alkylating agents (chlorambucil, cyclophosphamide), and biologics (adalimumab, infliximab).[13,15] There are no randomized controlled trials evaluating the efficacy and safety of many of these agents as treatment for uveitis. The multicenter, retrospective SITE (Systemic Immunosuppressive Therapy for Eye Diseases) cohort study analyzed outcomes of patients treated for ocular inflammatory disease with mycophenolate, cyclosporine, cyclophosphamide, methotrexate, or azathioprine, and reported 1-year success rates for these agents, ranging from 52% to 76% **(Table)**.[16-20]

Table. Patient Outcomes in the Systemic Immunosuppressive Therapy for Eye Diseases Cohort Study

Drug	Percentage of Patients		
	Success at 1 Year	≤ 10 mg of Prednisone	Discontinuation Within 1 Year
Mycophenolate (N = 236)[16]	73	55	34
Cyclosporine (N = 373)[17]	52	36	11
Cyclophosphamide (N = 215)[18]	76	61	33.5
Methotrexate (N = 384)[19]	66	58	42
Azathioprine (N = 145)[20]	62	47	68

It can be concluded from the SITE study data that the various immunosuppressive agents can each be effective some of the time, but that none guarantees success.[16-20] There are no clear algorithms to guide selection of a particular immunosuppressive agent for treating noninfectious posterior uveitis in different clinical situations. In general, methotrexate is often used in children because it has an established safety record in the pediatric population for treating juvenile idiopathic arthritis. The randomized FAST (First-Line Antimetabolites as Steroid-Sparing Treatment) study was undertaken to explore the belief that mycophenolate may be more effective and better tolerated than methotrexate for controlling inflammation in adults with noninfectious uveitis involving the posterior segment, but it did not find a difference between the 2 antimetabolites.[21]

The fully human monoclonal TNF-α antibody adalimumab is approved by the FDA for the management of noninfectious intermediate uveitis, posterior uveitis, and panuveitis.[22] It was approved for the treatment of adults according to results from the VISUAL I and VISUAL II studies,[23,24] and the indication was expanded to include pediatric patients aged ≥ 2 years on the basis of the SYCAMORE study that included patients with active juvenile idiopathic arthritis-associated uveitis on a stable dose of methotrexate.[22,25] Adalimumab was generally well tolerated,[23-25] but the antimetabolites might be preferred as first-line steroid-sparing therapy for noninfectious uveitis involving the posterior segment, considering the availability of more long-term safety data and their lower cost. The ongoing ADVISE (Adalimumab vs Conventional Immunosuppression for Uveitis) trial is investigating the comparative effectiveness of adalimumab vs conventional immunosuppressive agents for the treatment of noninfectious, intermediate, posterior, and panuveitides.[26]

The chimeric TNF-α monoclonal antibody infliximab has demonstrated efficacy for treatment of uveitis in several studies, including a retrospective study that found its effectiveness was similar to that of adalimumab for the treatment of refractory uveitis.[13,27] On the basis of a systematic review, an expert panel of the American Uveitis Society recommended infliximab or adalimumab as a first-line therapy for Behçet disease and as a second-line therapy for juvenile idiopathic arthritis–related uveitis.[28]

Repository corticotropin has an FDA-approved indication for the treatment of severe and chronic inflammatory processes involving the eye, such as iritis, iridocyclitis, diffuse posterior uveitis and choroiditis, chorioretinitis, and anterior segment inflammation, among others.[29] Granted in 1952, its approval was on the basis of safety alone. Ongoing studies are investigating the efficacy and safety of repository corticotropin for treating uveitis because there is a lack of good evidence relating to its use for this indication.[30]

Steroid Therapy

Oral high-dose prednisone should be considered for initial control of inflammation in most cases of noninfectious uveitis involving the posterior segment.[12,13] Because of the potential for steroid-related systemic side effects, local therapy with periocular or intravitreal administration may be more appropriate for treating uveitis that is unilateral or not associated with a systemic disease. In addition, local steroid therapy has a role as adjunctive therapy for managing uveitis or its complications that have not responded sufficiently to systemic therapy and in patients who require ≥ 2 systemic treatments for uveitis control. In particular, local steroid therapy can be very effective for controlling vascular leakage and therefore for improving CME or retinal vasculitis.[31]

Local steroid therapy may also be considered for patients who are not candidates for systemic treatment because of refusal, intolerance, or contraindications, including pregnancy. Taking into account the risks of local steroid therapy, patients who are pseudophakic or status post–glaucoma surgery might be considered particularly good candidates. Existing glaucoma, a clear lens in a pediatric patient, and anticipation that a patient will be unreliable to return for follow-up visits are relative contraindications for using local steroid therapy. Because it is difficult to halt the effects of steroids given as a periocular injection or into the vitreous, local therapy should never be used as initial treatment for uveitis if an infectious etiology has not been ruled out.

Because locally injected steroid suspensions or solutions have a relatively short duration of action, they may need to be repeated to maintain uveitis control.[13] There is a lack of evidence, however, to show the efficacy of serial steroid injections. In fact, a management approach relying on intermittent use of short-acting steroids to treat exacerbations may enable cumulative structural damage over time that can lead to saw-tooth visual decline.[13,32]

Intravitreal steroid implants that provide sustained release of an effective anti-inflammatory dose can address the latter limitation. Three intravitreal steroid implants are now commercially available, with an FDA-approved indication for the treatment of noninfectious uveitis affecting the posterior segment.[33-35] Fluocinolone acetonide intravitreal implant, 0.59 mg, is a nonbiodegradable device that is sutured in the pars plana in a surgical procedure, and releases the drug over a period of 2.5 to 3 years.[36,37] Dexamethasone intravitreal implant, 0.7 mg, is introduced into the vitreous in an in-office procedure using a 22-gauge injector. It has a biodegradable delivery system that releases dexamethasone in a biphasic pattern over approximately 6 months, with the highest rate of release during the first 2 months.[38]

The safety and efficacy of long-acting local therapy with the FA 0.59-mg implant and systemic immunosuppression were compared in the randomized MUST (Multicenter Uveitis Steroid Treatment Trial) that enrolled 255 patients.[39-41] The implant primary end point analyzing best-corrected visual acuity (BCVA) at 2 years found no difference between treatment groups,[39] but the implant was associated with faster and better control of inflammation at 2 years and through a follow-up of 4.5 years.[39,40] Data from 215 patients observed thereafter showed that at 7 years, the visual outcome was better in the systemic therapy group, and the only significant difference in systemic adverse outcomes between groups was a higher rate of antibiotic-treated infections among patients receiving systemic therapy.[41] In the systemic therapy group at 7 years, 34% of patients were taking oral corticosteroids (median dose, 6.25 mg), 43% were receiving ≥ 1 immunosuppressant or biologic agents, and 18% had received a steroid implant. At 7 years, 45% of eyes in the implant group had undergone glaucoma surgery vs 12% of eyes in the systemic therapy group. Among phakic eyes, the rate of cataract surgery at 7 years was 90% in the implant group and 50% in the systemic therapy group.

The efficacy of the dexamethasone 0.7-mg implant for improving intraocular inflammation and visual acuity in patients with noninfectious intermediate or posterior uveitis was demonstrated in the randomized, sham-controlled HURON (Chronic Uveitis Evaluation of the Intravitreal Dexamethasone Implant) trial that followed 229 patients for 26 weeks.[42] An increase in IOP of ≥ 25 mm Hg occurred in 7.1% of the 77 eyes receiving the dexamethasone 0.7-mg implant and in 4.2% of the 76 control eyes; among phakic eyes, cataract developed in 15% of the 62 eyes receiving the dexamethasone 0.7-mg implant and in 7% of the 55 control eyes. In a retrospective analysis of postmarketing experience with the dexamethasone implant for the treatment of noninfectious uveitis, 82 eyes received a total of 142 injections over a period of up to 35 months.[43] An increase in IOP of ≥ 21 mm Hg occurred in 33 eyes (40.2%), of which 32 required medical treatment and 2 underwent glaucoma surgery. Cataract surgery was performed in 4 (10%) of 40 phakic eyes.

A chart review of 27 eyes treated for uveitis with the FA 0.59-mg implant or the dexamethasone 0.7-mg implant concluded the 2 treatments had similar efficacy for preventing recurrence of noninfectious uveitis and improving inflammation and BCVA.[44] The FA implant was associated with higher rates of cataract progression and need for IOP-lowering intervention.

An FA intravitreal implant containing 0.19 mg of the active ingredient is available in the United States, with an indication for the treatment of diabetic macular edema in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in IOP.[45] The new FA 0.18-mg intravitreal implant uses the same nonbiodegradable sustained-release drug delivery system as the FA 0.19-mg and 0.59-mg implants, and releases FA for up to 3 years.[34,46] Compared with the FA 0.59-mg implant, the FA 0.18-mg implant is smaller and is delivered in an in-office procedure using a 25-gauge needle.[33,46]

Discussion

Dr Nguyen: I think there are 2 key messages about steroid treatment for uveitis. First, accurate diagnosis of noninfectious uveitis is critical before starting a steroid. Second, very few chronic uveitic entities can be successfully managed long term using a safe dose of prednisone alone.[12,13] Often, the employment of immunomodulatory therapy, with various steroid-sparing agents, is necessary to achieve disease remission and/or quiescence.

Dr Albini: Certainly, MUST reinforces that uveitis can be a chronic disease that requires chronic immunosuppression.[41] Perhaps one reason outcomes were better at 7 years in the systemic therapy arm is that there were a low number of reimplantation procedures in the FA 0.59-mg implant group, suggesting that patients were undertreated. The procedure for implanting the FA 0.59-mg implant is straightforward, but retreatment will be easier using the injectable FA 0.18-mg implant.

NEW THERAPEUTIC ADVANCES

David Callanan, MD

Fluocinolone Acetonide 0.18-mg Implant

The FA 0.18-mg intravitreal implant received FDA approval for the treatment of chronic noninfectious uveitis affecting the posterior segment of the eye on the basis of the results of 2 multicenter, randomized, double-masked phase 3 clinical trials (PSV-FAI-001 and PSV-FAI-005).[34,47,48] Patients were eligible for enrollment in these studies if they had a > 1-year history of recurrent noninfectious posterior uveitis requiring ≥ 3 months of systemic therapy or ≥ 2 steroid injections, relatively well-controlled disease (< 10 anterior chamber cells/high power field and ≤ 2+ vitreous haze), BCVA ≥ 15 Early Treatment Diabetic Retinopathy Study letters, and IOP of 6 to 21 mm Hg on no medications. Patients with glaucoma or ocular hypertension were eligible if they had a history of incisional glaucoma surgery and IOP of 10 to 21 mm Hg. Patients who had received the FA 0.59-mg implant within the past 36 months, the dexamethasone implant within the past 6 months, or an ocular steroid injection within the past 3 months were excluded. Existing systemic medications were tapered over a period of no more than 3 months once patients were enrolled.[49]

Study PSV-FAI-001, which was conducted at centers in the United States, Europe, and Asia, included 87 patients in the FA group and 42 patients in the sham group; their mean duration of uveitis was 7.8 and 5.6 years,

respectively.[49] Recurrence of uveitis, defined as ≥ 2+ increase in vitreous haze or ≥ 15-letter loss of BCVA, was analyzed as the primary end point, and it was imputed for any missing data or rescue treatment for ocular inflammation that could be given at the investigator's discretion. In a Kaplan-Meier analysis, the median time to first recurrence was 1051 days in the FA group and 95 days in the sham group. Considering the observed and imputed cases, the 36-month recurrence rate was 56.3% in the FA group and 92.9% in the sham group; counting only observed cases, the rates were 8.0% and 21.4%, respectively.

Analyses of secondary end points showed less need for adjunctive treatment in the FA group than in the control group, considering both local steroid injections (19.5% vs 69%, respectively) and systemic treatment with a steroid or another immunosuppressive agent (34.5% vs 50%, respectively).[49] In a subgroup of eyes with CME at baseline, the CME resolution rate at 36 months was higher in the FA group than in the sham group (85% vs 70%, respectively), despite the much higher rate of rescue treatment with local steroid injections in the sham group. The incidence of CME through 36 months was lower in the FA group than in the control group (13.8% vs 28.6%, respectively). The study was not statistically powered to detect a statistically significant difference between the 2 groups in change from baseline BCVA, but the data showed a trend for a greater mean gain in the FA group compared with the sham group (+9.1 vs +2.5 letters, respectively).

A steroid-induced IOP response was generally not seen for at least 1 to 2 months in the FA group posttreatment; after 18 months, the risk seemed to decrease.[49,50] Thirty-seven patients (42.5%) in the FA group and 14 patients (33.3%) in the control group received medical therapy for elevated IOP. IOP-lowering surgery was performed in 5 patients (5.7%) in the FA group and in 5 patients (11.9%) in the control group. Cataract surgery was performed in 31 (73.8%) of the 42 phakic eyes in the FA group and in 5 (23.8%) of the 21 phakic eyes in the sham group.[49,51]

Reduced BCVA occurred in 16 eyes (18.4%) in the FA group and in 5 eyes (11.9%) in the sham group; the higher rate in the FA group may be related to cataract formation.[49] Other adverse events reported in ≥ 5% of patients in the FA and sham groups were eye pain (14.9% and 21.4%, respectively), conjunctival hemorrhage (14.9% and 11.9%, respectively), and hypotony (6.9% and 4.8%, respectively).

Discussion

Dr Albini: It is interesting to compare the data on IOP increase and glaucoma from the FA 0.18-mg trial with those reported in clinical trials for the FA 0.59-mg implant.[33,49,50] After 3 years, approximately 77% of patients who received the FA 0.59-mg implant developed ocular hypertension and 37% had undergone glaucoma filtering surgery.[33]

Dr Callanan: The FA 0.59-mg implant is placed right next to the crystalline lens and ciliary body, whereas the FA 0.18-mg implant may reside more posteriorly. This difference in location and in steroid dose may explain the difference in IOP-related events. The data from the sham group in the FA 0.18-mg implant study are a reminder, however, that IOP elevation can occur in patients with uveitis, even without local sustained steroid delivery.[49,50]

Dr Goldberg: The predictive value of a steroid challenge to identify an IOP responder is not perfect, but it adds some level of confidence. Have you been doing a local steroid challenge first when you are planning to use an FA implant?

Dr Callanan: I have been giving patients a dexamethasone implant before treating them with the FA 0.18-mg implant, and I plan to continue doing that going forward.

Dr Albini: I think that is a reasonable approach. I do not think an oral steroid or topical prednisolone acetate would provide a potent enough challenge. As a caveat, however, I think a challenge is not necessary in situations in which the FA implant is being used as the last resort for preserving vision. Risk of glaucoma does not matter in a situation in which the patient is likely to go blind without the treatment.

Dr Merrill: I know that some clinicians will use topical difluprednate to test for a steroid response. I prefer to use a shorter-acting intravitreal steroid injection, either the dexamethasone implant or preservative-free triamcinolone acetonide.

CASE DISCUSSIONS

Case 1
From the Files of Pauline T. Merrill, MD

A 77-year-old African American female presented in November 2017 reporting gradually decreasing vision in her left eye over the past 6 months. Her right eye was impaled by glass at age 2 and is phthisical. She had cataract surgery in the left eye in 1999, followed by Nd:YAG (neodymium-doped yttrium aluminum garnet) capsulotomy. Medical history is notable for lung cancer, but she had been doing well after starting treatment in 2016 with the checkpoint inhibitor nivolumab. Findings on examination of the left eye were BCVA of 20/80, IOP of 16 mm Hg, 1+ cells in the anterior chamber, slightly subluxed intraocular lens (IOL), open posterior capsule, and 1+ vitreous haze ***(Figure 2A)****. CME was confirmed on fluorescein angiography and optical coherence tomography images* ***(Figures 2B and 2C)****. Results from serologic tests for syphilis and tuberculosis were negative.*

Because checkpoint inhibitors have been associated with uveitis and because the patient had begun to lose vision shortly after starting nivolumab, nivolumab was assumed to be the cause of the patient's uveitis.[52] However, the patient and her oncologist wanted to continue nivolumab.

Treatment was initiated with oral prednisone 60 mg/d for 2 weeks, then tapered slowly. When seen in March 2018, the patient was taking prednisone 20 mg/d, BCVA was 20/30, IOP was 19 mm Hg, and central foveal thickness was 295 µm. The next month, on 10 mg/d of prednisone, the patient's BCVA was 20/70, and the CME had also worsened ***(Figure 3A)****. She was treated with a sub-Tenon injection of triamcinolone. When seen 1 month later, her BCVA was 20/50 and IOP was 16 mm Hg, but she still had significant CME* ***(Figure 3B)****. Treatment options were discussed, and the patient was treated with the dexamethasone 0.7-mg intravitreal implant. Two months later, BCVA was 20/25, the CME was almost resolved* ***(Figure 3C)****, and IOP was 13 mm Hg.*

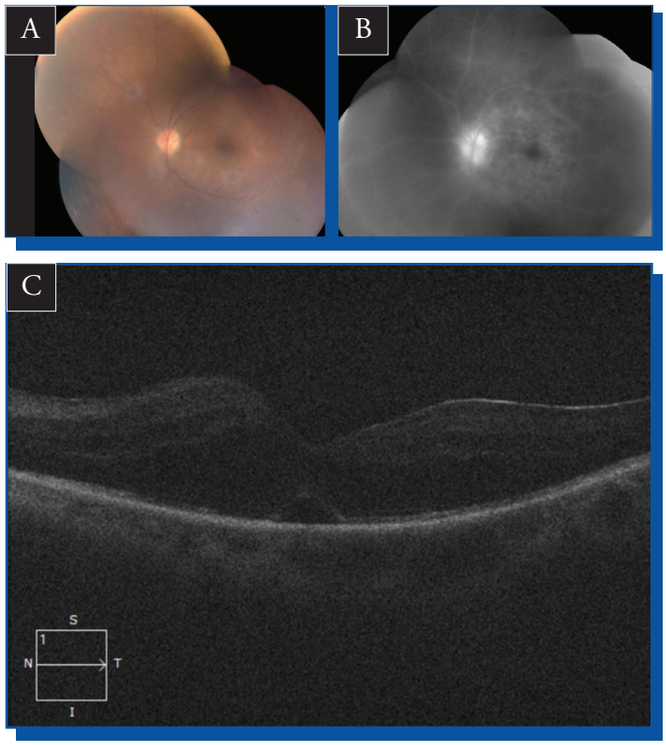

Figure 2. Images of the patient in Case 1 obtained at presentation. (A) The fundus photograph shows vitreous haze. (B) Fluorescein angiography image shows staining of the optic nerve, retinal vasculitis, and cystoid macular edema. (C) Optical coherence tomography images show cystoid macular edema, with intraretinal and subretinal fluid; central foveal thickness was 441 µm.

At 3 months postimplantation of the dexamethasone implant, the patient's BCVA was 20/50, CME was recurring, and IOP was 10 mm Hg. She was given another dexamethasone implant and benefited, with BCVA and central foveal thickness improvement, but again, her visual outcomes worsened at 3 months postimplantation. She continued receiving injections of the dexamethasone implant every 3 months.

When the patient presented in July 2019 for her next treatment, she had received 6 dexamethasone injections, and during the course of the treatment, her maximum IOP was 20 mm Hg. The FA 0.18-mg implant had now become available. After a discussion of the pros and cons of the long-acting implant, the patient consented to treatment and has done well during the available follow-up.

Dr Merrill: This patient seemed to be a good candidate for the FA implant because her CME responded well to intravitreal steroid treatment and she did not have an IOP response. In addition, she was pseudophakic. As an aside, when there is significant inflammation, I think it is often better to start treatment with the dexamethasone implant rather than with the FA 0.18-mg implant because the dexamethasone implant releases a higher dose of steroid initially and therefore may control inflammation more rapidly.

When I first saw the patient, I contacted her oncologist, who told me that other types of inflammatory side effects of checkpoint inhibitors can be controlled with an oral steroid and often do not recur. Therefore, I was hopeful that she would do well with a short course of prednisone. If a patient has persistent unilateral inflammation, however, I would rather use a steroid implant than an oral steroid.

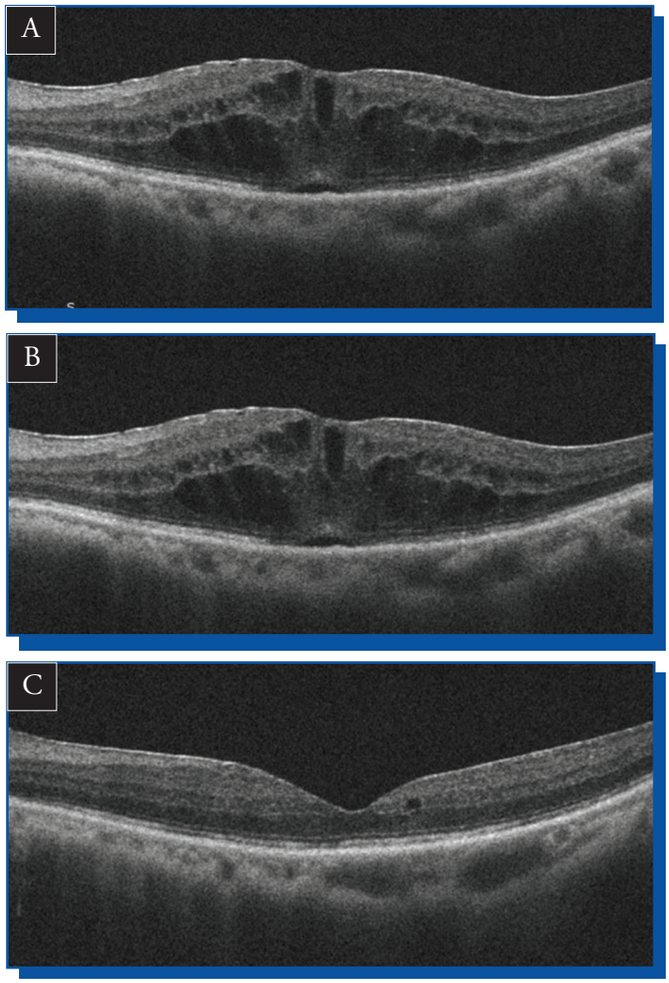

Figure 3. Serial optical coherence tomography images from visits before (A) and 1 month after (B) sub-Tenon triamcinolone injection and 2 months after (C) injection of the dexamethasone 0.7-mg intravitreal implant

Issues that might be considered reasons for not to use the FA implant in this case include the patient's monocular status and her open posterior capsule with temporally subluxed posterior chamber IOL that might enable implant migration into the anterior chamber. Would you hesitate to use the implant in a monocular patient?

Dr Nguyen: We often want to avoid ocular procedures in patients who are monocular for fear of causing sight-threatening complications. However, the patient in this case had a good response to intraocular steroid treatment, and we might consider the possibility that systemic immunosuppressive treatment could interfere with her oncologic control. For these reasons, local therapy seems appropriate.

Dr Merrill: Anecdotally, I am aware of cases in which the FA 0.19-mg implant migrated into the anterior chamber without adverse sequelae. Are you concerned that the FA implant might migrate into the anterior chamber in this patient with an open posterior capsule and subluxed IOL?

Dr Callanan: I think the worst-case scenario is that the implant can be removed if it is causing corneal edema. Having said that, I am not aware of any case reports in which migration of an FA implant into the anterior chamber resulted in corneal edema.

Case 2
From the Files of David Callanan, MD

A 29-year-old Asian male presented to a retina specialist with new onset of floaters and blurred vision in the right eye. BCVA was 20/30 OD and 20/20 OS, and he was diagnosed with focal retinitis ***(Figure 4A)****. The physician ordered some laboratory tests and started the patient on a topical corticosteroid. When the patient came back several days later, the retinitis had worsened* ***(Figure 4B)****. The physician treated the patient with an intravitreal injection of triamcinolone acetonide suspension.*

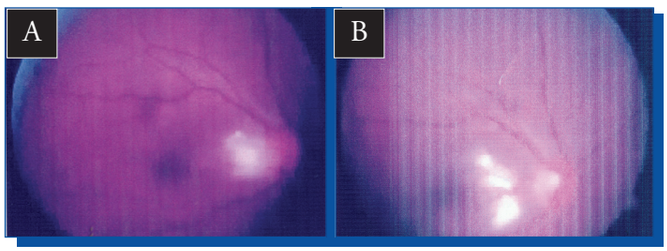

Figure 4. Images of the patient in Case 2 obtained at presentation (A) and 1 week later (B)

Two months later, the patient presented for a second opinion. BCVA was hand motion. The fundus examination showed widespread necrosis of the retina ***(Figure 5)****. Serologic testing was positive for toxoplasmosis (IgG titer 1:512). Because of the progressive permanent structural damage, the patient's vision loss was beyond rescue treatment.*

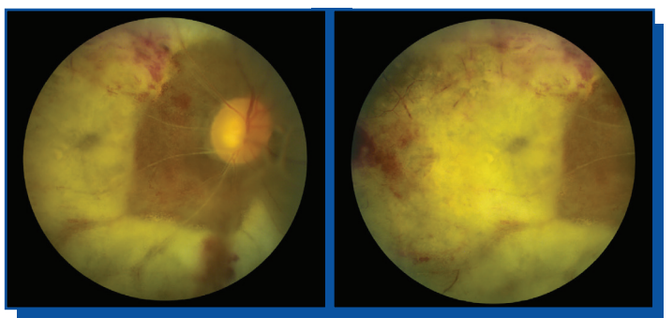

Figure 5. Images of right eye with widespread necrosis

Dr Nguyen: This case provides an excellent illustration of the importance of ruling out infection before using local steroid therapy to treat posterior uveitis.

Dr Callanan: The prescribing information for triamcinolone acetonide suspension warns that latent disease may be activated or that there may be an exacerbation of intercurrent infections due to pathogens, including *Toxoplasma*.[53] I strongly discourage the use of intraocular steroids when an active retinitis is present until all infectious causes have been ruled out. When in doubt, an anterior or posterior chamber sample can be obtained for pathologic examination. PCR testing can now be performed for most common pathogens.[54]

CONSIDERATIONS FOR INTRAOCULAR PRESSURE MANAGEMENT WITH LONG-ACTING STEROID IMPLANTS

Intraocular pressure (IOP) elevation and the development of glaucoma due to the use of long-acting steroid treatment is concerning to many retina specialists and might be a barrier to providing optimal care to our patients with noninfectious posterior uveitis. The following commentary from Jeffrey L. Goldberg, MD, PhD, a clinician, basic scientist, and glaucoma specialist, offers meaningful perspectives on this concern and provides guidance on how IOP can be easily assessed before treatment and during routine follow-up—and successfully managed.

–Quan Dong Nguyen, MD, MSc

A Glaucoma Specialist's Perspective
Jeffrey L. Goldberg, MD, PhD

Before using a long-acting steroid implant to treat a patient with uveitis, clinicians should get a baseline IOP measurement by taking multiple readings on the same day or across multiple preimplantation visits to obtain reliable data. If not done already through the course of prior topical or injected steroids, they might also consider a steroid challenge to assess for a clinically significant IOP response.

An IOP response can occur at any time posttreatment, even within a few days. Such early cases are seen most often in patients who are status postsurgery, so it is not clear if the elevated IOP is related to the surgery or to the steroid. Patients with preexisting ocular hypertension or glaucoma are at a higher risk of an IOP steroid response than patients with normal IOP.[1]

Follow-up for measurement of IOP should be scheduled at least every 3 months and perhaps more frequently (eg, monthly) in patients with known ocular hypertension or glaucoma, including prior steroid-response glaucoma, because these patients are at an increased risk for an IOP response and are more susceptible to experience glaucomatous progression from having sustained IOP elevation. IOP measurement performed reliably in the retina or uveitis clinic, if it is not changing from baseline, is adequate for managing this vigilance. A general rule of thumb used by glaucoma specialists is that patients with good reserve can probably tolerate an IOP of between 30 and 40 mm Hg for a few weeks without developing detectable damage, but detectable damage can occur within days to weeks if IOP is ≥ 40 mm Hg. This points to an important message for treating physicians to be very attentive to obtaining IOP measurements and to have a low threshold for referral to a glaucoma specialist.

If a patient does not need to be seen for follow-up of uveitis at 3-month intervals, IOP monitoring can be done by an optometrist, general ophthalmologist, or other referring provider. Patients need to be educated about the importance of returning for these evaluations because unlike cataract, ocular hypertension and early glaucoma are asymptomatic.

Ophthalmologists treating patients with a steroid implant should have a low threshold for comanagement with a glaucoma colleague.

Any patient who develops ocular hypertension should be referred to a glaucoma specialist who can examine anterior segment anatomy and follow the patient with evaluations of structure and function to detect progression to glaucoma. Starting treatment with a topical IOP-lowering medication and following the patient for IOP control without such indicated testing is not sufficient care.

There is no need to refer all patients starting on systemic or implantable steroid therapy to a glaucoma specialist for a baseline evaluation because an appreciable proportion will not develop ocular hypertension. Furthermore, data from the steroid implant clinical trials in patients with uveitis and in those with diabetic macular edema show there is not a strong risk for glaucomatous progression if ocular hypertension develops.[2-5] The benefit of treatment with the steroid for controlling inflammation and preserving vision in these trials to date seems to far outweigh the risk of glaucomatous progression, which can be comanaged appropriately upon detection.

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TAKE-HOME POINTS

Diagnosis

- Exclude infectious causes for uveitis before starting steroid treatment
- Use multimodal imaging for case characterization in initial diagnosis and for monitoring
- Carefully monitor for response to treatment to enable timely reassessment of diagnosis

Management

- Long-term immunosuppression is required in many cases of noninfectious uveitis involving the posterior segment and is better for preserving vision than repeat treatment of acute exacerbations
- The FA 0.18-mg implant administered as an intravitreal injection in an in-office procedure is a safe and effective treatment for noninfectious uveitis
- The FA 0.18-mg implant may have a lower risk of causing ocular hypertension than the FA 0.59-mg implant, but IOP elevation and glaucoma can still occur, so baseline IOP measurement and regular follow-up (at least every 3 months) are necessary

Referral

- Refer patients with uveitis involving the posterior segment to a uveitis specialist if the diagnosis is uncertain, if the condition is not responding to the chosen therapy, if the uveitis is associated with a systemic disease, or if systemic immunosuppressive therapy is indicated and the ophthalmologist lacks familiarity with its use
- Refer patients who develop ocular hypertension after starting steroid therapy for uveitis to a glaucoma specialist who can evaluate and follow the patient with structural and functional tests for glaucomatous progression

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1. Which of the following laboratory tests is recommended to be done routinely in the initial workup of adult patients with uveitis involving the posterior segment?
   A. Human leukocyte antigen B27 typing
   B. Serology for syphilis
   C. Serology for HSV
   D. Serology for varicella zoster virus

2. Which imaging technique should be included in multimodal imaging for a comprehensive diagnostic assessment of pathology in eyes with posterior uveitis?
   A. Indocyanine green angiography
   B. Fluorescein angiography
   C. Fundus autofluorescence
   D. All the above

3. Oral prednisone is initiated to treat a patient with noninfectious posterior uveitis and achieves disease control. Systemic immunosuppressive therapy should be considered if the prednisone dose required to maintain chronic suppression:
   A. Cannot be tapered to discontinuation
   B. Exceeds 1 mg/d
   C. Exceeds 5 mg/d
   D. Exceeds 7.5 mg/d to 10 mg/d

4. Treatment of uveitis using a periocular corticosteroid injection:
   A. Is appropriate for anterior or intermediate uveitis, but not for posterior uveitis or panuveitis
   B. Is the preferred route for initiating corticosteroid treatment until an infectious etiology is excluded
   C. Is more likely than oral prednisone to cause IOP elevation
   D. Is appropriate because it provides cumulative benefits with repeat injections

5. Which of the following is a true statement about the FA 0.59-mg implant that is approved for treatment of chronic noninfectious uveitis involving the posterior segment?
   A. It delivers corticosteroid for approximately 6 months
   B. It was associated with better visual outcomes than systemic immunosuppression after 7 years of follow-up in MUST
   C. It necessitates suturing to the sclera
   D. It was associated with a low rate of IOP elevation in clinical trials

6. Local steroid therapy should be avoided in all the following patients, EXCEPT:
   A. Patient with pseudophakia
   B. Child without cataract
   C. Patient with uveitis well controlled on single-agent immunosuppression
   D. Patient with possible infectious etiology

7. In the PSV-FAI-001 study, which outcome was NOT seen with the FA 0.18-mg implant vs sham treatment at 36 months?
   A. Increased likelihood of achieving and maintaining inflammation control
   B. Reduced likelihood of need for systemic or local rescue therapy
   C. Similar rate of cataract extraction
   D. Similar rate of treatment for elevated IOP

8. Which of the following is a true statement about the FA 0.18-mg implant delivery system?
   A. It is biodegradable
   B. It is intended for suprachoroidal placement
   C. It is administered through an in-office procedure
   D. It releases FA in a biphasic pattern

9. A patient is determined to be a candidate for long-term suppression of uveitis using a long-acting FA implant. Intraocular pressure was normal preimplantation and remained controlled during 3 months of follow-up after implantation of the dexamethasone 0.7-mg implant. The patient receives the FA 0.18-mg implant. How often should the patient return for IOP monitoring?
   A. At least every 3 months
   B. At least every 6 months
   C. At least every 9 months
   D. At least every 12 months

10. A male patient with Behçet disease presents with uveitis involving the posterior segment and is started on high-dose prednisone to control the ocular inflammation. At his 2-week visit, the uveitis appears to be worsening. What is your next step?
    A. Treat with intravenous methylprednisolone and raise the prednisone dose
    B. Inject the dexamethasone implant
    C. Refer the patient to a uveitis specialist
    D. Wait 2 more weeks to see if there is improvement