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Following the Signs:

Practical Pearls for Diagnosing and Managing Uveitis

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Following the Signs: Practical Pearls for Diagnosing and Managing Uveitis

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Content Source

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

Activity Description

This supplement summarizes keys to diagnosing and classifying uveitis and presents data on sustained-release treatments on the market and in the pipeline.

Target Audience

This certified CME activity is designed for retina specialists and general ophthalmologists.

Learning Objectives

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

- **Summarize** the clinical features of common uveitic presentations including postoperative and localized disease
- **Differentiate** between acute, recurrent, and chronic uveitis
- **Describe** the pharmacokinetics, safety, and efficacy of sustained-release uveitis treatments on market and in the pipeline
- **Interpret** clinical trial data to create personalized treatment plans for patients with chronic uveitis

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1. **Please rate your confidence in your ability to interpret clinical trial data to create personalized treatment plans for patients with chronic uveitis (based on a scale of 1 to 5, with 1 being not at all confident and 5 being extremely confident).**
   a. 1
   b. 2
   c. 3
   d. 4
   e. 5

2. **A 48-year-old man presents to your clinic with photophobia and blurry vision. On slit lamp exam you note 10 cells/high powered field. According to the Standardization of Uveitis Nomenclature Working Group Grading Scheme, what grade of anterior chamber cell does he have?**
   a. Grade 0
   b. Grade 0.5+
   c. Grade 1+
   d. Grade 2+

3. **Severe vision loss occurs in ____% of uveitis cases?**
   a. ~10%
   b. ~25%
   c. ~50%
   d. ~75%

4. **Which of the following statements about uveitis treatment is TRUE?**
   a. Topical corticosteroids are effective for posterior segment disease
   b. High-dose corticosteroids do not work in the treatment of uveitis
   c. Repeated bouts of inflammation increase risk of vision loss
   d. Treatment can only be administered intravitreally

5. **A 53-year-old woman presents to your office for evaluation. She has a history of recurrent anterior uveitis that you have treated with topical prednisolone drops. During the past 12 months, however, she has had five flare-ups. What is the most appropriate next step in management of this patient?**
   a. Prescribe topical prednisolone
   b. Prescribe oral steroids
   c. Consider chronic therapy based on her flare-ups
   d. Consider intravitreal ranibizumab

Following the Signs:
Practical Pearls for Diagnosing and Managing Uveitis

Uveitis are a group of inflammatory diseases of the eye and ocular surface affecting about 300,000 patients within the United States, 20,000 of whom are children.[1,2] Uveitis is thought to cause up to 10% of blindness in the United States, with 30,000 new cases of incident blindness worldwide each year.[3] Inflammatory diseases of the eye and the ocular surface are often lumped together because of necessity, but uveitis is not a single disease. Therefore, there's no one-size-fits-all treatment, diagnostic laboratory workup, or treatment paradigm. A differential diagnosis is critical because subtypes require different management strategies. Prompt therapy to rapidly control inflammation is critical to minimize vision loss in patients with uveitis. Corticosteroids, administered either systemically or locally, are the gold standard of uveitis treatment, as they can effectively control inflammation. However, local corticosteroid therapy has a high risk of local complications and systemic corticosteroid therapy has higher rates of systemic side effects. Newly approved treatment options, such has sustained-release implants, may have better efficacy with fewer side effects. The following supplement discusses keys to diagnosing and classifying uveitis as well as the new treatment options in our armamentarium.

– Sumit Sharma, MD

INFECTIOUS OR NONINFECTIOUS UVEITIS? KNOW BEFORE YOU TREAT

Steven Yeh, MD: The anatomic classification of uveitis is important when we think about the pharmacokinetics of medication and how we effectively treat these sight-threatening diseases. There are multiple uveitis syndromes that have vision-threatening implications if not recognized promptly and treated assertively and sometimes require more aggressive treatment. There are uveitides with systemic and public health significance as well. Syphilitic uveitis, for example, is on the rise. Acute retinal necrosis, which we see in both retina and uveitis clinics, can be rapidly progressive. Birdshot retinochoroidopathy, while indolent, can also present with protean manifestations. Primary vitreoretinal lymphoma or intraocular lymphoma also can have certainly systemic consequences as well. We often need imaging to diagnose these conditions.

How do we avoid the perils associated with uveitis? You first need to determine if the uveitis is infectious or noninfectious because treating infectious uveitis patients with corticosteroid can lead to sight-threatening sequelae and progression.

Q | **Dr. Sharma:** I agree; you have to be really careful to rule out infectious disease. What is your approach to determining if a new patient has infectious uveitis?

Dr. Yeh: I think about the history, tempo, and chronicity of disease. If a patient has an acute onset, if they have ocular disease that involves the posterior segment with retinal whitening, or any sort of retinal whitening, then I'll start to think about infectious uveitis.

I also think about the review of systems and if there's any history of zoster, shingles, or other immunocompromise. I think about all these risk factors in concert that could predispose an individual to an infectious pathology. I also think about what the patient has been treated with previously. For example, sometimes infections can improve initially with corticosteroids, making the disease presentation quite confusing at times.

Dr. Sharma: I agree, previous treatment is a big factor. I also want to emphasize that if you see anything white in the retina, you should think about infection. There are some autoimmune diseases, such as sarcoidosis and Behçet disease,[4,5] that can show areas of retinal whitening. However, if it's white and in the retina, you need to be 100% sure that it's not infectious before you put a corticosteroid in the eye. Often for me, that means covering for infection and then cautiously starting oral or systemic corticosteroids to see how the patient responds. Sometimes infections can improve with corticosteroids, but that will not last in the long term.

You also want to test for syphilis and tuberculosis because they are treatable and curable. The incidence of tuberculosis in the United States is pretty low,[6] but if they have risk factors for it, put it high on your suspicion list. The reality is both syphilis and tuberculosis can look like any type of uveitis, so you should test for them.

Dr. Yeh: If a patient has chronic inflammation lasting longer than 3 months, or if they have acute or recurrent disease or disease that's not improving, dilate the eye and take another look. Herpetic uveitis may not present initially with retinal whitening; the whitening can develop later. If we're not looking for it, we have the potential for missing it and inappropriately treating the patient with corticosteroids alone without an antiviral.

Dr. Sharma: You should also have a low threshold to refer. If someone is not responding the way you think they should be or

they're not improving, don't prescribe a corticosteroid if you're not comfortable with it. Refer them out.

Dr. Yeh: Classification systems for uveitis are available and widely used. Uveitis can be acute, chronic, or recurrent (Table 1).[7]

TABLE 1. UVEITIS CLASSIFICATION BASED ON DURATION[7]

Acute uveitis	Sudden onset; resolves in 3 months
Chronic uveitis	Persistent; relapse less than 3 months after treatment discontinuation
Recurrent uveitis	Repeat episodes after inactive periods without treatment

Patients with anterior uveitis tend to present with a red, painful eye and have anterior chamber cell and flare. I find that oftentimes the cell will clear before the flare, and then the visual acuity improvement actually will occur even after you've effectively treated the patient.

Patients with intermediate uveitis may complain of worsening floaters and decreased vision. Clinical signs include vitreous cell and haze. Vitreous haze scores are measured by fundus photography based on how much of the optic nerve and vessels are visualized. We grade these from an objective perspective. I find that we're increasingly using ophthalmic imaging to observe these patients very objectively, but this can be difficult because of posterior synechiae and media opacity, which can sometimes confound our vitreous haze grades.

Symptoms and clinical signs of posterior uveitis include worsening vision, visual field changes, chorioretinal lesions, and retinitis, among others. Patients with panuveitis may have significant declines in visual acuity, floaters, and a red, painful eye. Table 2 lists the classification, symptoms, clinical signs, and epidemiology of uveitis.

There was some recent work led by Doug Jabs et al, looking at the use of machine learning in classification criteria for the uveitic syndromes.[7] There was quite a bit of work done by many uveitis experts around the United States and really worldwide to classify the 25 most common uveitis syndromes.[8-32] Cases were collected in a database that was designed for informatics analysis.[7] There were more than 4,000 cases, including Vogt-Koyanagi-Harada syndrome, intermediate uveitis, Behçet disease, and others.

Ultimately, these cases were assessed by trained providers and split into a training and a validation set. Using a number of machine learning algorithms, they found that there was about a 94% to 99% accuracy for a number of uveitis syndromes, including anterior, intermediate, posterior, and panuveitis. The reason I mention this is because oftentimes we'll see patients who may or may not fit certain diagnostic criteria. Sometimes you'll have partial or incomplete phenotypes that can help direct you in terms of disease classification. We're increasingly finding that there are disease-specific entities and disease-specific therapies.

As we think about an approach to diagnosis, we classify the anatomic location of the uveitis using multimodality diagnostic imaging and assess the structural damage. One of the most important things is to rule out infection and to perform a diagnostic workup, including varicella-zoster virus (VZV), herpes simplex virus (HSV), and cytomegalovirus (CMV) testing.[7] I find that I'm using molecular testing more frequently now. You also need to think about systemic disease associations and laboratory investigations with our consultants. Dr. Sharma, how do you approach molecular testing for some of these diagnostics?

Dr. Sharma: I have a low threshold for getting VZV, HSV, and CMV testing, especially because there's a very high yield from an anterior chamber sample. You don't have to put the patient at the risk of a vitreous tap in order to get a diagnosis. I haven't personally used metagenomic deep sequencing as much.

TABLE 2. CLASSIFICATION, SYMPTOMS, CLINICAL SIGNS, AND EPIDEMIOLOGY OF UVEITIS[7]

Type	Symptoms	Clinical Signs	Percent of Cases	Includes
Anterior uveitis	• Red, painful eye	• Anterior chamber cell and flare • Iris nodules • Posterior synechiae • Keratic precipitates	25.0%-92.2%	• Iritis • Iridocyclitis • Anterior cyclitis
Intermediate uveitis	• Worsening floaters • Decreased vision	• Vitreous cell and haze • Snowballs • Pars plana snowbank • Cystoid macular edema	1.3%-26.0%	• Pars planitis • Posterior cyclitis • Hyalitis
Posterior uveitis	• Worsening vision • Visual field changes	• Chorioretinal lesions • Retinitis • Retinal vascular sheathing • Papillitis	4.7%-38.4%	• Choroiditis (focal, multifocal diffuse) • Chorioretinitis • Retinochoroiditis • Retinitis • Neuroretinitis
Panuveitis	• Red, painful eye • Severely depressed visual acuity • Floaters	• All the above	0.8%-38.0%	

Dr. Yeh: Metagenomic deep sequencing is more commonly used for research, but I'll do molecular testing to evaluate undifferentiated pathogens, panbacterial, and panfungal polymerase chain reaction (PCR). I do testing through the University of Washington, so if something doesn't look viral in nature from a phenotype standpoint, then I'll think about the other panpathogen detection techniques. It's a send-out, and it's infrequent. Sometimes we get false positives, which can confound our results.

Dr. Sharma: My big issue with panpathogen molecular testing is the cost. It's a last resort for me because it's a large out-of-pocket cost for the patient. Most insurances will not cover it. I tend to use it if I've tested for everything else and still don't know what's going on. But you have to discuss it with the patient since it's a significant expenditure.

Dr. Yeh: Great points. We must think about the practical considerations so patients aren't stuck with a big bill without information that will impact their next steps.

DEVELOPING A DIFFERENTIAL DIAGNOSIS

Dr. Yeh: When you approach the patient, you first have to determine if it's uveitis instead of a masquerading syndrome. You'll need to develop a differential diagnosis based on the classification of the uveitis, ruling out infection and ultimately controlling inflammation to preserve vision and ocular anatomy. I'm using imaging more frequently in clinical practice to ensure that we're preserving ocular anatomy for visual acuity outcomes.

One question I get asked frequently is what is included in a standard uveitis workup. The reality is there's no definite "standard" workup; it's really tailored to the pretest probability of disease. For instance, if someone has kidney disease and retinal vasculitis in a young or middle-aged female patient, then I'll think about the potential for systemic lupus erythematosus. But if it's an isolated anterior uveitis, the antinuclear antibody test is not necessarily useful. On the other hand, we talked about PCR testing. If the patient has findings of retinal whitening and a history of zoster shingles, then certainly PCR and molecular testing are indicated. I think about each workup in the context of the clinical presentation and their history, as well as what's going to help drive the therapy after we establish a diagnosis and formulate our treatment plan. Avoid the shotgun workup. The predictive value really depends on the pretest likelihood of disease.

Dr. Sharma: I often seen Lyme testing ordered, yet I don't think I've ever ordered a Lyme test on a patient with uveitis. I also see a lot of human leukocyte antigen (HLA) testing. Other than B27 and A29, I don't think there's much utility for HLA testing.

Dr. Yeh: We know A29 is associated with birdshot retinochoroidopathy and HLA-B27. We know it can impact how we think about the patient's disease, thinking about ankylosing spondylitis and spondyloarthropathy. There are certain therapies, including antimetabolites and TNF-alpha inhibitors, that work very well with the B27-associated conditions. I agree with you that there are lots of minor HLA associations, but B27 and A29 are the key ones we think of that correlate with the disease phenotypes we most commonly treat.

Dr. Sharma: I'm only using A29 in a patient with creamy, yellowish lesions that resemble characteristic birdshot retinochoroidopathy with a retinal vasculitis on fluorescein. I'm not using it in a shotgun approach on every patient with retinal vasculitis. You need to think about the pretest probability of disease before making workup decisions.

TREATMENT OPTIONS FOR UVEITIS

Dr. Sharma: We know that we get severe vision loss in a 25% to 33% of all uveitis cases.[33] Repeated bouts of inflammation increase the risk of severe vision loss. With the exception of difluprednate, I don't find topical corticosteroids to be very effective for posterior segment disease. High-dose oral or systemic corticosteroids work very well, but have high morbidity; there are a lot of side effects with long-term use. In cases with active inflammation despite initial oral corticosteroid therapy or recurrence on tapering therapy you need to consider local therapy. Before we discuss the local corticosteroid options I want to bring up two less frequently used noncorticosteroid options for uveitis.

Q | **Dr. Sharma:** There are two noncorticosteroid local injection therapies for noninfectious uveitis: anti-VEGF (ranibizumab) and intravitreal methotrexate.[34,35] Anti-VEGF is used because patients with uveitis can develop choroidal neovascularization (CNV). Even in the absence of CNV, sometimes macular edema does respond to anti-VEGF in these patients. Dr. Yeh, do you use either of these agents often?

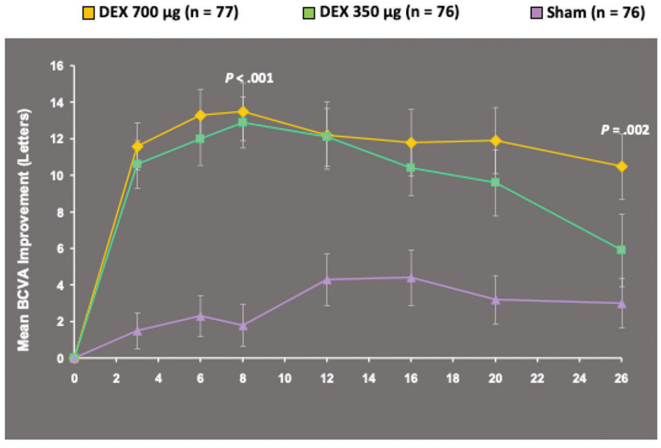
Dr. Yeh: It's pretty unusual for me to use this as primary treatment. I'll consider anti-VEGF in more refractory cases and in patients who can't tolerate corticosteroids. I'll also consider anti-VEGF patients with punctate inner choroidopathy, where there's a little bit of uncertainty between CNV and cystoid macular edema in the context of inflammation. It's unusual for me to use methotrexate, but I will in refractory cases. I use it mainly for primary vitreoretinal lymphoma. There are some studies on methotrexate underway, such as Co-THEIA (NCT04798755), which is looking at the efficacy, safety, and costs of methotrexate, adalimumab, or their combination in noninfectious, nonanterior uveitis.[36]

Dr. Sharma: We have a couple of local corticosteroid options, including perseverative-free intravitreal triamcinolone and the dexamethasone 0.7 mg intravitreal injection.[37,38] Many of us are very familiar with these treatments, but studies that compared them were limited until recently[39,40] A few years back the POINT study compared intravitreal triamcinolone versus periocular triamcinolone versus intravitreal dexamethasone implant to treat uveitic macular edema.[38] First, let's talk about each of these agents then we will circle back to the POINT study.

The dexamethasone 0.7 mg implant is a biodegradable, bioerodible injection given with a proprietary 22-gauge needle. It has been

approved for the treatment of noninfectious posterior uveitis since 2010.[41] The initial trials indicated that it is a 6-month treatment but, in my hands, it's a 3-month treatment.[37,42] There is an increased risk for cataract with the dexamethasone, which increases with repeated injections. There's also a risk of increased IOP elevation, although the need for incisional surgery is pretty low.[41,43] You do need to worry about anterior chamber migration. If they have an ACIOL or they're aphakic, you really shouldn't be injecting this because it can come into the anterior chamber, leading corneal decompensation pretty rapidly. If you see the dexamethasone migrate into the anterior chamber, you do need to remove it quickly.

The HURON study is what led to the primary approval and indication from the FDA.[37] HURON compared two different doses: the 700 µg dose, which is what's on the market now, and the 350 µg dose, which is not on the market and not available, compared to sham injection. HURON was a 26-week trial with about 76 patients in each arm. The primary outcome measure at the time was achieving a vitreous haze score of 0 at week 8. At week 8, 47% of the patients with the 0.7 mg dose showed a vitreous haze score of 0 compared to only 12% of the sham patients. A total of 7% of patients had an IOP elevation greater than 25 mm Hg with 0.7 mg implant group versus only 4% of patients in the sham group. There were low rates of cataract because this was a single injection study. By week 24, the effect seems to be wearing off in terms of both best corrected visual acuity improvement and the vitreous haze (Figure 1).



Note: *P* values are for the dexamethasone 700 µg vs sham.
Abbreviations: BCVA, best-correct visual acuity; DEX, dexamethasone.

Figure 1. Mean BCVA improvement over 26 weeks in the HURON trial.[37] ***(Adapted from: Lowder C, et al. Arch Ophthalmol. 2011;129(5):545-553.)***

Q | **Dr. Sharma:** Dr. Yeh, are you hesitant to start a prostaglandin analogue to manage IOP in uveitic patients with a dexamethasone pressure spike?

Dr. Yeh: My first-line choice is not usually a prostaglandin analogue. However, if they have an IOP spike and we need to manage it, then I'll use it.

Dr. Sharma: I agree. My first-line choice is dorzolamide/timolol, and then I'll usually add brimonidine. If I still need another agent, then I will add a prostaglandin analogue. I don't consider it my first line for an IOP spike for corticosteroid response, but I will use it after I've used the other two.

Moving on, we also have intravitreal triamcinolone injection.[44,45] Triesence is FDA approved for intraocular use,[46] but we have had a hard time getting it recently. It's been on backorder for a while, then it was available for a little bit, and then it was on backorder again. The label for Kenalog specifically says it's prohibited for use in the eye.[47] For an intraocular intravitreal injection of Kenalog, you have to be very careful.

Triesence 4 mg/0.1 mL is preservative-free and lasts about 3 months. There is a risk of IOP elevation and cataract, and that risk is pretty similar to the dexamethasone injection.[44,45] In my hands, I find triamcinolone and dexamethasone to be pretty equivalent except if an eye is vitrectomized. In that case, triamcinolone doesn't last as long; dexamethasone will have greater duration.

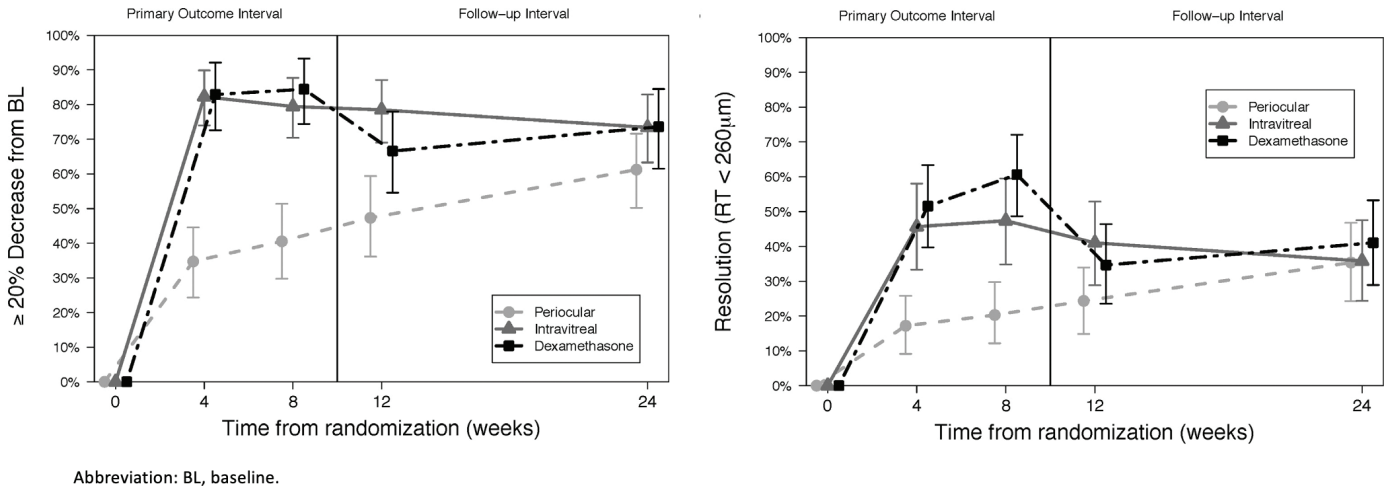
I'm often asked what volume of intravitreal triamcinolone I use. We did a study on this a few years back and compared 2 mg versus 4 mg triamcinolone acetonide.[48] We found the efficacy was very similar. I almost exclusively use 2 mg because the rate of IOP elevation and cataract formation was lower with 2 mg versus 4 mg.

Finally, we have anterior and posterior triamcinolone subtenon injection (20 mg/0.5 mL or 40 mg/1 mL, respectively).[47] I still do a fair number of these injections, although less than I used to. I almost exclusively use posterior subtenon injection. This is a preserved formulation of triamcinolone. It's approved for intramuscular and intra-articular use.

Q | **Dr. Sharma:** Anterior subtenon injections come with a greater risk of IOP elevation and cataract. With posterior subtenon injections the cataract rate is a little bit lower because the corticosteroid is presumably farther away, but you still do get cataract with repeated injections. Posterior subtenon injections have a greater risk of lid ptosis and orbital fibrosis. Other rare complications include perforating the globe, cannulating an artery, and central retinal artery occlusion. Dr. Yeh, how much are you using triamcinolone subtenon injection nowadays?

Dr. Yeh: I use it less often now. When I teach my residents and fellows how to use triamcinolone subtenon injection, I show them a supratemporal approach. I also explain that we don't need to be overly aggressive in how far back they try to get the medication. It's pretty forgiving in mild to moderate macular edema. I have had one patient several years ago who needed filtration surgery. It's pretty unusual, but it can happen and just a reminder that each of our therapies involves a balance between efficacy and safety.

Dr. Sharma: Circling back to the POINT study, this study looked at periocular subtenon triamcinolone versus intravitreal triamcinolone versus intravitreal dexamethasone.[38] Figure 2 also shows the optical coherence tomography (OCT) results, looking



Abbreviation: BL, baseline.

Figure 2. POINT trial optical coherence tomography results.[38]

at either improvement or resolution of macular edema. The two lines on the top of Figure 2 are the intravitreal triamcinolone in the triangles, and then the squares are the intravitreal dexamethasone. Time from randomization is on the bottom.

The percentage decrease of the baseline retinal thickness at week 8 was the primary outcome measure, seen on the Y axis of Figure 2. There is a rapid reduction compared to the subtenon injection. The intravitreal injections wears off around that 3-month time point. Retreatment with triamcinolone (either subtenon or intravitreal) was allowed at 8 weeks and retreatment with dexamethasone was allowed at 12 weeks provided retreatment criteria were met. What's interesting is the periocular starts to catch up, and by 6 months they're pretty equivalent.

At 8 weeks, each group had clinically meaningful reductions in central subfield thickness (CST) relative to baseline with reductions of 23%, 39%, and 46% for periocular subtenon triamcinolone, intravitreal triamcinolone, and dexamethasone, respectively. Intravitreal triamcinolone and dexamethasone had larger reductions in CST than periocular subtenon triamcinolone ($P < .0001$). Intravitreal dexamethasone was noninferior to intravitreal triamcinolone at 8 weeks, but by week 24, the periocular subtenon triamcinolone started to catch up. As a result of this trial, I don't use periocular subtenon triamcinolone as much as I used to.

LOCAL CORTICOSTEROID OPTIONS

Q | **Dr. Sharma:** Next, we will discuss three other local corticosteroid options: fluocinolone acetonide 0.59 mg, a surgical intravitreal implant; suprachoroidally injected triamcinolone acetonide 4 mg; and fluocinolone acetonide 0.18 mg, an injectable intravitreal insert. Dr. Yeh, what are your impressions of these options?

Dr. Yeh: The fluocinolone acetonide 0.59 mg is intravitreally implanted in the operating room and lasts 2.5 to 3 years. I find that with the newer implant that the duration I'm getting is probably closer to 2.5 years versus the older implant. All patients who undergo this surgical procedure will develop cataract over time, and about 33% will need glaucoma filtration surgery.[39,49]

The MUST study looked at the very important question of corticosteroid-sparing, immunosuppressive therapy versus a long-acting, sustained-release implant for the treatment of noninfectious uveitis.[39] Patients with active uveitis were randomly assigned to oral prednisone with systemic immunosuppressive agents versus surgical fluocinolone acetonide intravitreal implant 0.59 mg. When we look at the various efficacy and safety signals, we know that visual acuity is a critical metric, possibly the most important metric to our patients personally. Visual acuity improvements were actually comparable between systemic antiinflammatory therapy and the fluocinolone acetonide implant. Interestingly, residual active inflammation favored the fluocinolone acetonide implant versus systemic therapy (12% vs 29%, respectively). There were higher rates of cataract that required surgery in the patients who received the fluocinolone acetonide implant, and nearly 20% of individuals required glaucoma filtration surgery.

Patients in the systemic antiinflammatory therapy group experienced a higher rate of prescription-requiring infections. There may be some degree of bias knowing that a patient is on immunosuppressive therapy if they have respiratory symptoms or symptoms of febrile illness. But this is something we need to be aware of when we think about systemic immunosuppression, particularly in the era of COVID-19.

In the MUST extension trial, by the 7-year time point, visual acuity was actually better in the systemic group than the fluocinolone acetonide implant group.[50] This was a nonprespecified endpoint. Patients in the implant group only received one implant, meaning when the implant ran out, they may not have received another one.

Figure 3 shows eyes with uveitis activity in the MUST extension trial. The graph shows fairly comparable levels of low uveitis activity in both groups.

What's clear is that the patients who had the corticosteroid implant were a bit undertreated with some degree of activity to a

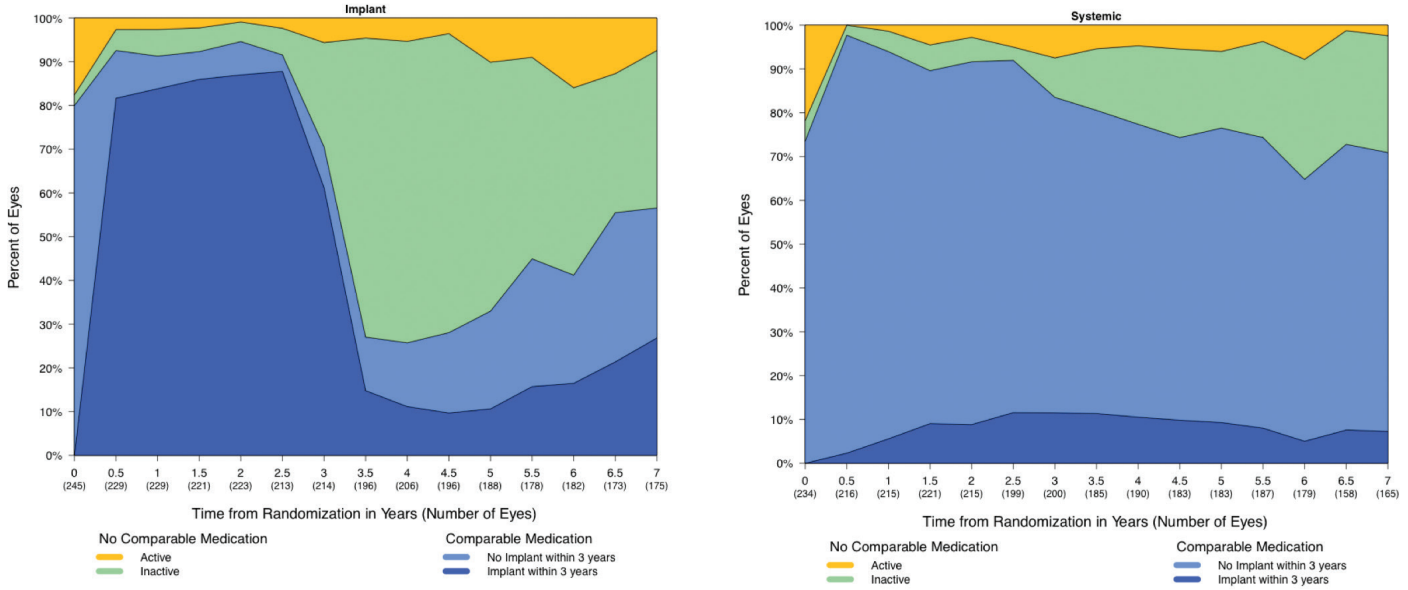


Figure 3. Uveitis activity in implant versus systemic therapy groups in MUST extension trial.[50]

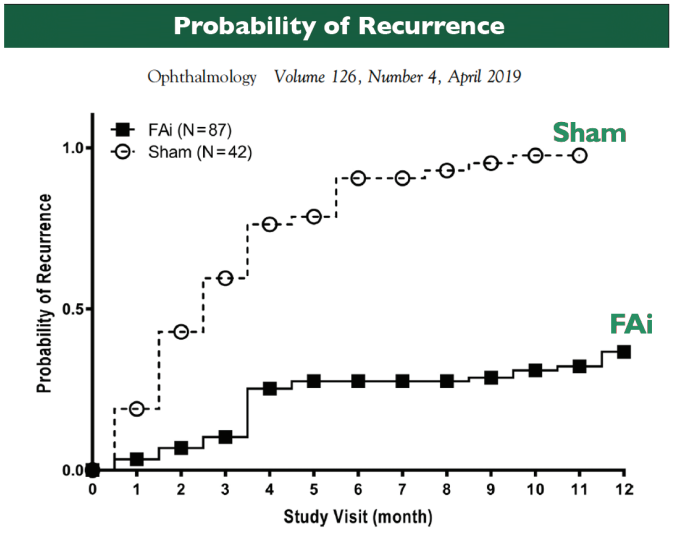
greater degree than patients who received systemic medication. I think it's important to bear in mind that even with the local therapies, it may not necessarily be a one-and-done type therapy; patients need to continue to be monitored over time. Uveitis can be a chronic condition. We need to continue to follow-up so patients don't lose vision.

Dr. Sharma: I agree that in very severe eyes, the implant lasts 2.5 to 3 years. However, the majority of patients get 3 to 4.5 years. What I take away from these data is that I start to look at inactive patients more closely around year 4 because that's when they have signs of recurrence.

The other big caveat, and I think why that 7-year paper results aren't that interesting to me, is that 10% of patients in the systemic group had a fluocinolone acetonide implant. At year 4, that was the same percentage as the implant group that had one within 3 years. I think their conclusion that the systemic group performed better long-term than the implant group, were a little disingenuous. If you're undertreating patients, of course they're going to do worse.

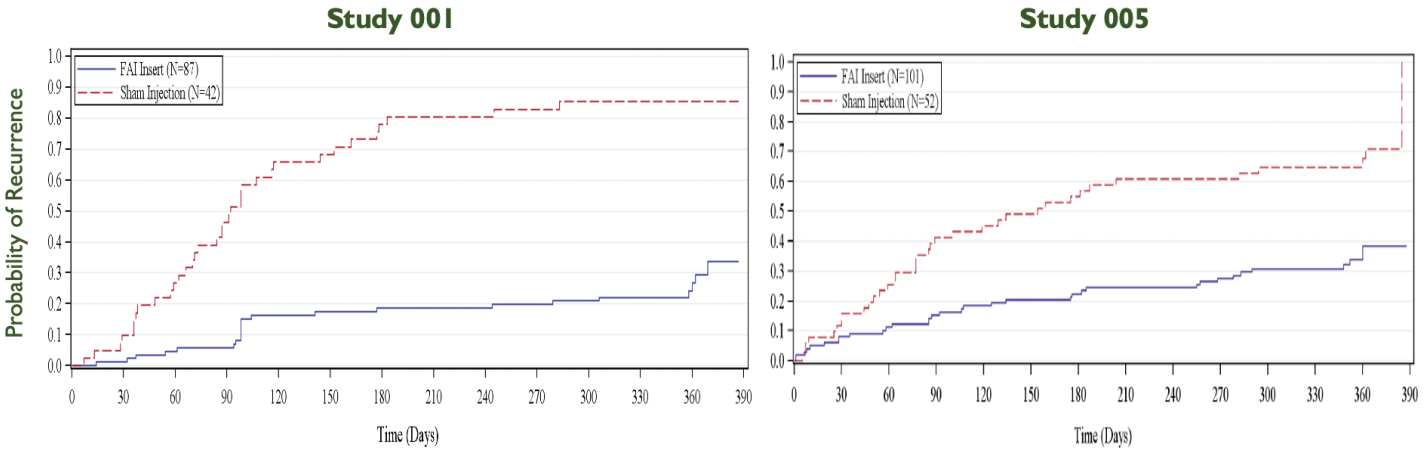
Dr. Yeh: Yes, I agree. There can also be considerable variation in disease severity. For instance, a patient with Behçet disease who recurs may lose vision quickly, whereas other patients with other more chronic, smoldering disease may have ongoing inflammation that needs to be monitored. They'll need additional therapy at some point, but not as quickly as other patients with more acute disease.

Moving on, the fluocinolone acetonide injectable intravitreal microinsert 0.18 mg is a rod-shaped, nonbioerodible device. This is an injectable medication that has been FDA approved for the treatment of noninfectious uveitis. It lasts up to 36 months. There were two pivotal trials that looked at the fluocinolone acetonide microinsert versus sham: PSV-FAi-001, a multinational trial, and PSV-FAi-005, a multisite trial from India.[51,52] The primary endpoint was the proportion of individuals who required rescue therapy after either receiving the fluocinolone acetonide implant or sham therapy within the 6-month time period. At the 6-month time point, what we found is that individuals who received a sham therapy had a much higher rate of recurrence requiring rescue therapy. A total of 28% of individuals in the fluocinolone acetonide insert group versus 91% of patients in the sham group had recurrences that required rescue therapy ($P < .001$; Figure 4). At 12 months, there's a slight increase in patients who received the corticosteroid



Abbreviation: FAi, fluocinolone acetonide insert.

Figure 4. Probability of recurrence: fluocinolone acetonide microinsert 0.18 mg for macular edema due to noninfectious uveitis.[48]



Abbreviations: FAi, fluocinolone acetonide insert; NIU, noninfectious uveitis; IOP, intraocular pressure.

Figure 5. Comparison of studies of fluocinolone acetonide microinsert 0.18 mg for macular edema due to noninfectious uveitis.[48]

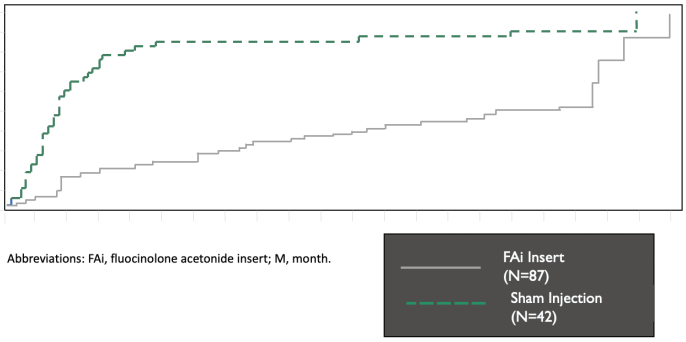
implant (38% vs 98%, *P* < .001). The vast majority of patients who were in the sham group required rescue therapy.

There was a higher rate of cataract in the patients receiving local corticosteroid and, interestingly, the IOP-lowering medications that were required in both groups were comparable during this trial. But importantly, from a visual acuity standpoint, there was a reduced rate of vision loss and a reduced need for adjunctive therapies in individuals who received corticosteroid therapy.

Figure 5 compares the 001 and the 005 trials.[51,52] There are vast differences in the probability of recurrence in individuals who received sham therapy in these two studies versus individuals who received the fluocinolone acetonide microinsert.

About 33% of patients who received the fluocinolone acetonide microinsert required cataract surgery versus 5% of patients in the sham group. IOP-lowering medications were seen in about 25% of individuals actually in both groups. Figure 6 shows the time to first recurrence through 36 months.[51]

Time to First Recurrence		
	FAi	Sham
Median	1051 days	95 days
95% CI of Median	(686.00, 1125.00)	(71.00, 117.00)

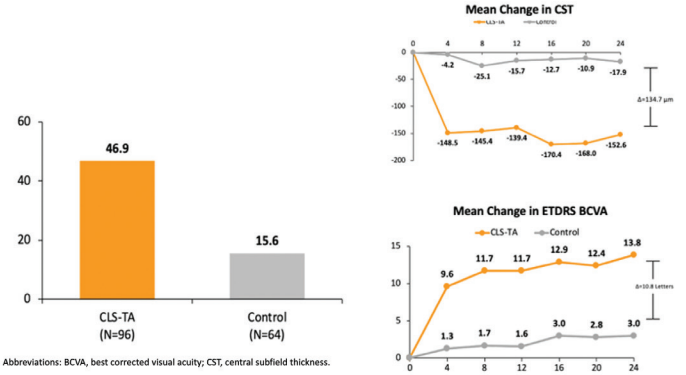


Abbreviations: FAi, fluocinolone acetonide insert; M, month.

Figure 6. Fluocinolone acetonide microinsert 0.18 mg for macular edema due to noninfectious uveitis: time to first recurrence through 36 months.[51]

The median time to the first recurrence was more than 1,000 days for patients who received the fluocinolone acetonide implant.[51] We're talking about anywhere between 2.5 to 3 years. That's a long period of time before requiring rescue therapy.

Finally, I do want to talk a little bit about suprachoroidal injections.[53-55] Triamcinolone acetonide with the suprachoroidal space microinjector was recently FDA approved for the treatment of macular edema due to noninfectious uveitis. This technology was studied in the context of the pivotal phase 3 PEACHTREE study.[56] Patients with macular edema due to noninfectious uveitis were randomly assigned to either the suprachoroidal triamcinolone acetonide versus sham. Patients were given injections at day 0 and week 12 with the readout at week 24, the primary readout being visual acuity. In individuals who received the suprachoroidal corticosteroid, about 47% showed a 3 line or greater visual acuity gain compared to 16% of sham patients. This was reflected by the OCT outcomes, which showed a reduction in CST by the week 4 time point of 150 µm. This was sustained for the duration of 24 weeks (Figure 7). There were two injections administered in the treatment group. Interestingly, when you look back at the data, you start to see improvement between week 4 and week 8, and you continue to see improvement to about 14 letters by week 24.



Abbreviations: BCVA, best corrected visual acuity; CST, central subfield thickness.

Figure 7. PEACHTREE efficacy data.[56]

Figure 8. Case 1: Classic birdshot retinochoroidopathy.

Q | **Dr. Sharma:** I've done a few suprachoroidal injections in the clinical trials, and now I've done a few in practice. Do you have any tips?

Dr. Yeh: Suprachoroidal injection is a different technique from intravitreal injection. You need to be perpendicular to the surface of the eye and make sure there's dimpling of the conjunctiva as you're injecting. Because the suprachoroidal space is a lower resistance space, you'll feel a loss of resistance as the medication enters the suprachoroidal space. You need to also let patients know that this is a different sensation from intravitreal injections; they may feel some pressure as the medication is being introduced.

Dr. Sharma: To summarize, there are a few tenets with regard to thinking about therapy. You want to treat patients with active uveitis assertively and aggressively. Hit hard and taper fast. With regard to systemic corticosteroids, I will use a 1 mg/kg dose, with the goal to get under 5 mg by 3 months. You'll want a faster taper in children because of the risks associated with systemic corticosteroid use. If inflammation cannot be controlled with less than 5 mg prednisone within 3 months, add a corticosteroid-sparing agent.[57] We have a big list of tools in our armamentarium now. How do you decide who gets what treatment?

Dr. Yeh: It's an exciting time because we have so many therapies, but it can be a bit confusing. If the patient has an aggressive disease, such as Behçet, then I'll lean toward systemic immunosuppression earlier, especially if they have some systemic autoimmune condition that warrants a consultation with rheumatology. I'll also consider systemic immunosuppression for conditions that are known to lead to continuous or a sawtooth decline in visual acuity, such as birdshot retinochoroidopathy. On the other hand, if there's macular edema that needs local therapy, then I'll start to think about local therapies, either the short- or longer-acting, depending on whether the patient is likely to develop macular edema and recurrent episodes of macular edema that can lead to visual decline.

Dr. Sharma: I agree. If a patient has multiple episodes of recurrence, I move to long-acting therapies. For me, right now, I'll use either the injectable fluocinolone acetonide insert or fluocinolone acetonide surgical implant. I tend to break it down by how severe the disease is and how likely the patient is to respond. If they have very severe disease, I'll consider the surgical implant. But for most patients, I consider the injectable fluocinolone acetonide insert for long-term control.

PIPELINE

Dr. Sharma: There are some interesting new treatments coming down the pipeline. One company is starting a phase 3, multicenter study on the safety and efficacy of a novel intravitreal anti-IL6 antibody for the treatment of uveitic macular edema secondary to noninfectious uveitis. This has the promise of being a nonsteroidal therapy, which may avoid many of the side effects we see with steroids. I am excited to see this launch of the phase 3 study. The study has not started yet.

Another company is evaluating a new dexamethasone ophthalmic insert for the management of pain and inflammation in patients with anterior uveitis compared to topical steroids in the DiverT trial (NCT04426734).[58] Both of these will be interesting. It is an exciting time in the uveitis space.

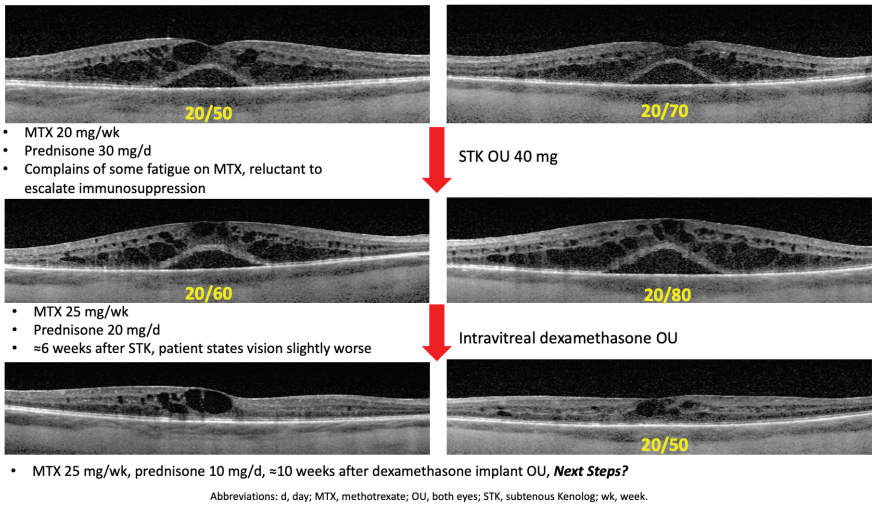


Figure 9. Case 1: Patient response after therapy for birdshot retinochoroidopathy.

CASE 1: CLASSIC BIRDSHOT RETINOCHOROIDOPATHY

Dr. Yeh: Our first case is of a 54-year-old woman with classic, HLA-A29+ birdshot lesions (Figure 8). The pretest probability was quite high for this being birdshot retinochoroidopathy. She had a history of nyctalopia and some photopsia as well. She's 20/50 in the right eye, and 20/70 in the left eye with intraretinal and subretinal fluid.

There are a number of therapies we think about with birdshot retinochoroidopathy. This is driven by systemic autoimmunity. We started her initially on an antimetabolite in conjunction with prednisone 60 mg per day. She had a pretty good response, but she still had some persistent macular edema (Figure 9). She was concerned about anything intravitreal initially so we proceeded with methotrexate

20 mg once a week. She reported some fatigue and was reluctant about switching to another immunosuppressive. Her visual acuity was about 20/60 in the right eye and 20/80 in the left eye (Figure 9). We eventually decided to give her the intravitreal dexamethasone implant. Interestingly, we escalated her antimetabolite therapy. She's on low-dose prednisone, but you can see that she still has some cystoid spaces in both the right and left eyes and a reduction in visual acuity (Figure 9). At this point, her VA is 20/50 in both eyes.

She's had an intravitreal corticosteroid, a periocular corticosteroid, and she's on immunosuppressive therapy. What do you reach for next?

Dr. Sharma: Escalating immunosuppression and putting the patient at risk for systemic side effects and infections is always a concern. We would have a long discussion about that; however, as I think it is an option. In this case, after an antimetabolite, I would typically add an anti-TNF agent if that's the direction that the patient chooses to go. But in a patient with birdshot retinochoroidopathy who doesn't completely respond to an intravitreal corticosteroid, I'm often reaching for the surgical fluocinolone acetonide implant because I find that these eyes are difficult to treat. If I can't control them with an intravitreal corticosteroid, then I'm reaching for the surgical implant.

Dr. Yeh: I agree. I find that the surgical implant is one of the most effective ways of treating this type of macular edema. Do you find that the intravitreal injected fluocinolone acetonide implant can handle this type of inflammation?

Dr. Sharma: You get differential responses. It's not unusual to find that a patient responds better to one corticosteroid than another. I've got some patients who have zero response to dexamethasone but who respond beautifully to triamcinolone intravitreal. The vice-versa situation can also happen. It's the same thing with fluocinolone; sometimes they respond to that but they don't respond to dexamethasone or triamcinolone. I don't find the injectable implant works as well as the surgical implant in very severely inflamed eyes.

CASE 2: PATIENT WITH CHRONIC PANUVEITIS/ MULTIFOCAL CHOROIDITIS

Dr. Yeh: Our next patient is a 35-year-old woman with a history of chronic panuveitis/multifocal choroiditis and inflammatory bowel disease. She was previously treated with vedolizumab, and she complained of blurred vision for a couple months. She has had multiple treatments, including the surgical fluocinolone acetonide implant, intravitreal dexamethasone, and intravitreal triamcinolone. Her VA was counting fingers at 4 feet in the right eye and 20/200 in the left eye. She was symptomatic. She had inflammatory cells in her vitreous in the right eye more so than the left eye, multiple chorioretinal scars in both eyes, and optic nerve swelling. Her laboratory work had been done several years prior, and I didn't repeat it. I thought the laboratory was very thorough, but the diagnosis from an anatomic perspective was a multifocal choroiditis with panuveitis. She also had chronic macular edema in the right and the left eyes, again with active vitreous inflammation in both eyes. Figure 10 shows her imaging.

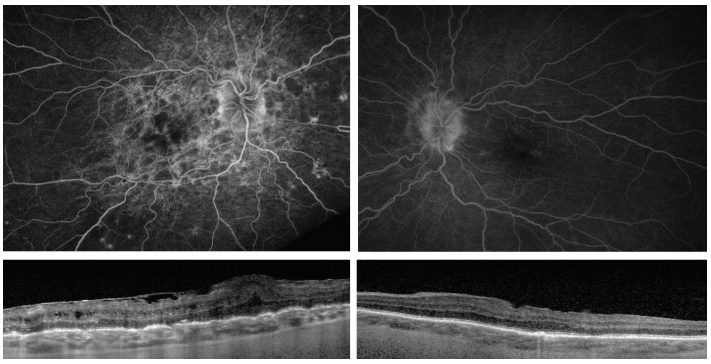


Figure 10. Case 2: Chronic panuveitis/multifocal choroiditis prior to treatment with fluocinolone acetonide 0.18 mg intravitreal insert.

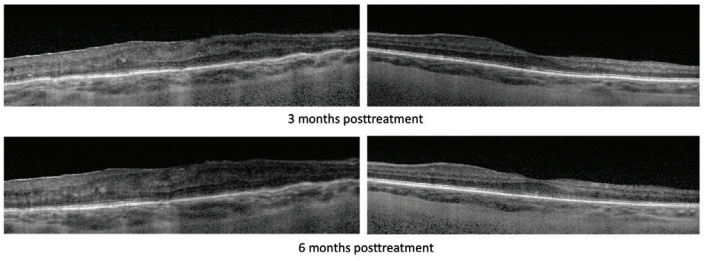


Figure 11. Case 2: Chronic panuveitis/multifocal choroiditis 3 and 6 months posttreatment with the fluocinolone acetonide 0.18 mg intravitreal insert.

Her imaging shows some evidence of this diffuse hypofluorescence, prominent epiretinal membrane, and some choroidal thickening. She certainly has a decline in visual acuity from the vitreous inflammation. How do you approach this case?

Dr. Sharma: We are seeing more cases of eyes that had the surgical implant and then experience recurrence. She's had a lot of loss in the right eye from chronic scarring, and you can see the ellipsoid zone is nearly gone. So she has outer retinal loss from chronic inflammation in that right eye. In the left eye, it looks like she has some outer retinal loss, but it's not as bad. What strikes me here, though, is the overall leakiness on fluorescein is pretty low. I would consider the injectable fluocinolone acetonide insert 0.18 mg in this patient, because I think that the severity of the inflammation is not that high. There's a good chance she'd respond well to it.

Dr. Yeh: I agree. I call these cases the chronic smoldering situations. You know that they need some level of corticosteroid. Stabilizing blood vessels helps with any low-grade inflammation. That's why we went with the fluocinolone acetonide in this situation. Interestingly, she improved better than I thought she would even before treatment. Her VA improved to 20/200 in the right eye, and 20/70 in the left eye, with very mild cell in both eyes. She did have chorioretinal folds, but had prior glaucoma filtration surgery with epiretinal membrane in the right eye.

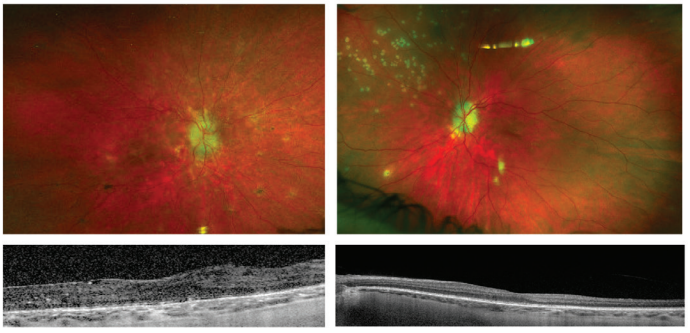


Figure 12. Case 2: Chronic panuveitis/multifocal choroiditis 24-months after fluocinolone acetonide 0.18 mg intravitreal insert.

Figure 11 shows her follow-up 3 and 6 months posttreatment. Some of these irregularities in the contour of the fovea have improved. Six months out, she has some stability the left eye and a little bit of additional thickening in the right eye, but overall, she was pleased with her outcome.

Interestingly, 24 months after her intravitreal insert, she had a drop in VA to 20/400 in the right eye and 20/100 in the left eye (Figure 12). She had some new lesions supranasal to the optic disc. While initially I thought she had a chronic smolder, it looks like she has activity. What are your next steps? Do you repeat the insert?

Dr. Sharma: I've seen the insert last between a 1.5 to 4 years. Given how well she responded initially, I would consider a second one.

Dr. Yeh: That's what we decided to do, and she did have some visual acuity improvement. She had no vitreous haze, and there was some resolution of the chorioretinal lesions. We are continuing to observe her.

Dr. Sharma: This case highlights that you can use longer-acting treatments in smoldering disease, where without treatment they would have progressive vision loss over time.

CONCLUDING STATEMENTS

Dr. Sharma: In summary, we have a number of medications, including new drug-delivery platforms and new mechanisms of action that are FDA approved and that have shown promising efficacy and safety for both noninfectious uveitis and macular edema associated with noninfectious uveitis. We must balance the systemic and local therapeutic options and weigh the evidence when trying to decide how to treat these patients. If they have disease with both systemic and ocular involvement, then adding systemic therapy in conjunction with either uveitis specialist or working with a rheumatologist that's comfortable working with ophthalmologists is a very good idea.

Both chronic local therapy and systemic therapy are excellent options for patients with chronic uveitis. However, local therapy has a high risk of local complications. Systemic therapy has higher rates of individual drug failure and systemic side effects. Newer therapies in the pipeline offer potential paths for reduction in side effects and improvements in control. ■

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Following the Signs:
Practical Pearls for Diagnosing and Managing Uveitis

Release Date: December 2022
Expiration Date: December 2023

INSTRUCTIONS FOR CREDIT

To receive credit, you must complete the attached **Pretest/Posttest/Activity Evaluation/Satisfaction Measures Form** and mail or fax to Evolve Medical Education LLC; 353 West Lancaster Avenue, Second Floor, Wayne, PA 19087; Fax: (215) 933-3950. To answer these questions online and receive real-time results, go to https://evolvemeded.com/course/2237-supp. If you experience problems with the online test, email us at info@evolvemeded.com. *NOTE: Certificates are issued electronically.*

Please type or print clearly, or we will be unable to issue your certificate.

Full Name_____ DOB (MM/DD): _____

Phone (required) _____ Email (required*) _____

Address/P.O. Box_____

City _____ State/Country _____ Zip _____

License Number:_____OE Tracker Number:_____National Provider ID:_____

*Evolve does not share email addresses with third parties.

DEMOGRAPHIC INFORMATION

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

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

Patients Seen Per Week
(with the disease targeted
in this educational activity)
___ 0
___ 1-15
___ 16-30
___ 31-50
_____ >50

Region
___ Midwest
___ Northeast
___ Northwest
___ Southeast
___ Southwest

LEARNING OBJECTIVES

Did the program meet the following educational objectives?	Agree	Neutral	Disagree
Summarize the clinical features of common uveitic presentations including postoperative and localized disease	_____	_____	_____
Differentiate between acute, recurrent, and chronic uveitis	_____	_____	_____
Describe the pharmacokinetics, safety, and efficacy of sustained-release uveitis treatments on market and in the pipeline	_____	_____	_____
Interpret clinical trial data to create personalized treatment plans for patients with chronic uveitis	_____	_____	_____

POSTTEST QUESTIONS

Please complete at the conclusion of the program.

1. Based on this activity, please rate your confidence in your ability to interpret clinical trial data to create personalized treatment plans for patients with chronic uveitis (based on a scale of 1 to 5, with 1 being not at all confident and 5 being extremely confident).
   a. 1
   b. 2
   c. 3
   d. 4
   e. 5

2. A 48-year-old man presents to your clinic with photophobia and blurry vision. On slit lamp exam you note 10 cells/high powered field. According to the Standardization of Uveitis Nomenclature Working Group Grading Scheme, what grade of anterior chamber cell does he have?
   a. Grade 0
   b. Grade 0.5+
   c. Grade 1+
   d. Grade 2+

3. Severe vision loss occurs in ____% of uveitis cases?
   a. ~10%
   b. ~25%
   c. ~50%
   d. ~75%

4. Which of the following statements about uveitis treatment is TRUE?
   a. Topical corticosteroids are effective for posterior segment disease
   b. High-dose corticosteroids do not work in the treatment of uveitis
   c. Repeated bouts of inflammation increase risk of vision loss
   d. Treatment can only be administered intravitreally

5. A 53-year-old woman presents to your office for evaluation. She has a history of recurrent anterior uveitis that you have treated with topical prednisolone drops. During the past 12 months, however, she has had five flare-ups. What is the most appropriate next step in management of this patient?
   a. Prescribe topical prednisolone
   b. Prescribe oral steroids
   c. Consider chronic therapy based on her flare-ups
   d. Consider intravitreal ranibizumab

ACTIVITY EVALUATION

Your responses to the questions below will help us evaluate this activity. They will provide us with evidence that improvements were made in patient care as a result of this activity.

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

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

This activity improved my competence in managing patients with this disease/condition/symptom. _____ Yes _____No

Probability of changing practice behavior based on this activity: _____High _____ Low _____No change needed

If you plan to change your practice behavior, what type of changes do you plan to implement? (check all that apply)

Change in pharmaceutical therapy _____
Change in nonpharmaceutical therapy _____
Change in diagnostic testing _____
Choice of treatment/management approach _____
Change in current practice for referral _____
Change in differential diagnosis _____
My practice has been reinforced _____
I do not plan to implement any new changes in practice _____

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

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

The design of the program was effective for the content conveyed	___ Yes	___ No
The content supported the identified learning objectives	___ Yes	___ No
The content was free of commercial bias	___ Yes	___ No
The content was relative to your practice	___ Yes	___ No
The faculty was effective	___ Yes	___ No
You were satisfied overall with the activity	___ Yes	___ No
You would recommend this program to your colleagues	___ Yes	___ No

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

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

Additional comments:

_____

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

This information will help evaluate this activity; may we contact you by email in 3 months to inquire if you have made changes to your practice based on this activity? If so, please provide your email address below.

_____