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Treatment of Posterior Segment Disease: Exploring the Suprachoroidal Space

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Content Source

This continuing medical education (CME) activity captures content from a live satellite symposium.

Activity Description

This supplement highlights a panel discussion on the suprachoroidal space as a novel route of drug delivery for the treatment of retinal diseases such as uveitic macular edema, diabetic retinopathy/diabetic macular edema, and neovascular age-related macular degeneration. Through a series of case discussions, the faculty review data from key trials examining the suprachoroidal space injections and proper administration techniques, plus an engaging discussion on how these advanced therapies may alter the treatment landscape.

Target Audience

This certified CME activity is designed for retina specialists.

Learning Objectives

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

- **Interpret** results of key trials examining the suprachoroidal space injections for the treatment of retinal diseases and how new data may eventually influence practice.
- **Describe** proper administration techniques of suprachoroidal injections, solutions to common challenges, and best practices in patient education and informed consent.
- **Differentiate** future applications of suprachoroidal injections and how advanced therapies may alter the treatment landscape.

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Please complete prior to accessing the material and submit with Posttest/Activity Evaluation/Satisfaction Measures for credit.

1. Please rate your confidence in your ability to interpret results of key trials examining the suprachoroidal space injections for the treatment of retinal diseases (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. What percentage of patients with intermediate, posterior, or panuveitis develop macular edema (ME)?

a. 5 to 10%
b. 10 to 20%
c. 20 to 40%
d. 40 to 60%

3. A 35-year-old man presents complaining of blurry vision and floaters. His VA is 20/50. He has several tattoos, but reports no itching or swelling at his tattoo sites. He is extremely photosensitive and reports intermittent hyperemia and feelings of exhaustion. Upon examination, you note bilateral granulomatous panuveitis with chorioretinitis and vitreous haze. What are you most suspicious for as a differential diagnosis?

a. Tubulointerstitial nephritis and uveitis
b. Neurosyphilis
c. Sarcoidosis
d. Intermediate uveitis

4. What was the key clinical takeaway of the POINT trial?

a. Intravitreal steroids may be the preferred initial therapy for uveitic ME
b. Periocular steroids may be the preferred initial therapy for uveitic ME
c. Periocular steroids result in too high of an increase in intraocular pressure and should no longer be used for uveitic ME
d. Intravitreal steroids are noninferior to suprachoroidal space injections for the treatment of uveitic ME

5. What are the clinical advantages of suprachoroidal space injections? Select all that apply.

a. Suprachoroidal space injections are more comfortable for patients than traditional intravitreal injections
b. Steroid delivering through the suprachoroidal space injections do not increase intraocular pressure
c. Suprachoroidal space injections allow for preferential targeting of posterior segment tissue
d. Suprachoroidal space injections have improved drug durability when compared to intravitreal injections

6. According to clinical trial data, what percentage of patients may need to be switched to the 1,100 µm needle from the 900 µm needle when using the SCS micro injector?

a. 70%
b. 29%
c. 39%
d. 10%

7. Based on PEACHTREE data, how quickly can patients experience anatomic improvement after treatment with CLS-TA?

a. 2 weeks
b. 3 weeks
c. 4 weeks
d. 6 weeks

8. Identify the key aspects of a suprachoroidal space injection. Select all that apply.

a. The injection site should be 5 mm from the limbus
b. The injection should be given slowly and consistently
c. Every patient should start with the 900 µm needle
d. The injection should be approached at a horizontal angle

Treatment of Posterior Segment Disease: Exploring the Suprachoroidal Space

The suprachoroidal space (SCS), the potential anatomical space between the sclera and choroid, has long been studied as a prospective pathway for novel drug delivery systems to treat posterior segment eye diseases, including uveitic macular edema (ME).[1,2] *ME is the most common complication of noninfectious uveitis, occurring in 8.3% of patients.*[3] *SCS injections may offer several clinical benefits in controlling uveitic ME over standard-of-care treatments, including preferential targeting of posterior segment tissue; reduction in drug exposure to the anterior chamber and vitreous, which may confer safety advantages; and improved pharmacokinetics and drug durability. The US FDA recently approved triamcinolone acetonide injectable suspension (CLS-TA) for the suprachoroidal use for the treatment uveitic ME. This is a noteworthy development, as CLS-TA is the first therapy approved in the United States that harnesses the SCS for the treatment uveitic ME. The following summary of a panel discussion features insights from thought leaders in retina on the diagnosis of uveitis, the management of challenging cases, and how to incorporate CLS-TA into the clinic.*

— Sunil K. Srivastava, MD, Program Chair

THE PREVALENCE AND CLASSIFICATION OF UVEITIS

Dr. Srivastava: Uveitis, defined as inflammation in the uveal tract, is a global problem that is responsible for 10% of legal blindness in the United States.[4] Uveitis is the fifth leading cause of vision loss in developing countries, and ME is the leading cause of vision loss in uveitis.[4] Although it's not that common, it has a devastating effect on the eye, leading to significant damage. It typical affects younger patients, age 25 to 44 years—the working-age population.[4] Blindness is bad at any age, but the inability to work has significant socioeconomic impact on these patients.[5]

There are multiple classifications of uveitis, including systemic versus ocular and anatomic location (anterior, intermediate, posterior, and panuveitis).[6] Unfortunately, ME is common and occurs in 40 to 60% of patients with intermediate, posterior, and panuveitis; approximately 20% of patients with anterior uveitis also develop ME.[3]

Q | Depending on where you are, the type of uveitis may be localized. Dr. Yeh, you recently moved from Atlanta to Nebraska. Is the uveitis you're seeing different?

Steven Yeh, MD: When you think about patient demographic, there are some regional differences. Omaha, where I'm currently working, has a different demographic than Atlanta, which raises the question of varying clinical phenotypes in different racial groups. There are nuances in disease presentation. Sarcoidosis, for example, can look different in patients of European and Caucasian heritage versus African American patients. In addition, the Midwest region has a uveitis population with an increased prevalence of conditions such as presumed ocular histoplasmosis syndrome.[7] Given these regional differences within the United States and globally, it's important to understand the demographic and what disease entities to include in your differential diagnostic considerations.

Dilraj S. Grewal, MD: The regional differences impact your considerations with infectious uveitis as well. My father works in India and sees a lot of infectious uveitis from tuberculosis; infectious uveitis in endemic regions such as India is usually considered to be associated with tuberculosis unless proven otherwise.[8] I saw a fair amount of this in larger cities such as Chicago and London during training because there is a large, diverse immigrant population. It's a very different demographic in North Carolina where I practice now; for example, we see a lot more toxoplasmosis due to dietary issues,[6,9] but it's very rare to see other nematode-based infections or tuberculosis.

CASE 1: SARCOIDOSIS IN A DIABETIC PATIENT WITH SUDDEN-ONSET BLURRY VISION

Dr. Srivastava: Our first case is of a 37-year-old African American woman who woke up with blurry vision in her left eye 2 days prior. Her VA is 20/30 in her left eye and is 20/20 in her right eye. She has diabetes but has nothing else of significance in her history. Her social and family history are benign. Figure 1 shows the fundus autofluorescence in her right and left eyes. Her right eye has some subretinal fluid (SRF) superiorly and tortuous vessels in the periphery, and her left eye has SRF, retinal pigment epithelial mottling, and choroidal folds. Dr. Yeh, what do you see here that's interesting to you?

Dr. Yeh: With autofluorescence, we have to think about how we classify these diseases. I see areas of hyper-autofluorescence in both eyes. We also want to look at the shape of the autofluorescence areas of abnormality. In that left eye, it's not quite circular, but the pattern is ovoid. There's a similar pattern on the right eye. It's interesting that her VA is 20/20 in this eye. The fovea is not involved, so we need to start to think about what structures are involved.

Dr. Srivastava: Let's say you're in a practice that doesn't have fundus autofluorescence, so you get an optical coherence tomography (OCT) and fluorescein angiography (FA), as shown in Figure 2. Dr. Grewal, what do you see here that we should all be aware of?

Dr. Grewal: If you look at the vitreous, you'll see that there's some hyper-reflective foci, which often are a sign of inflammation. The

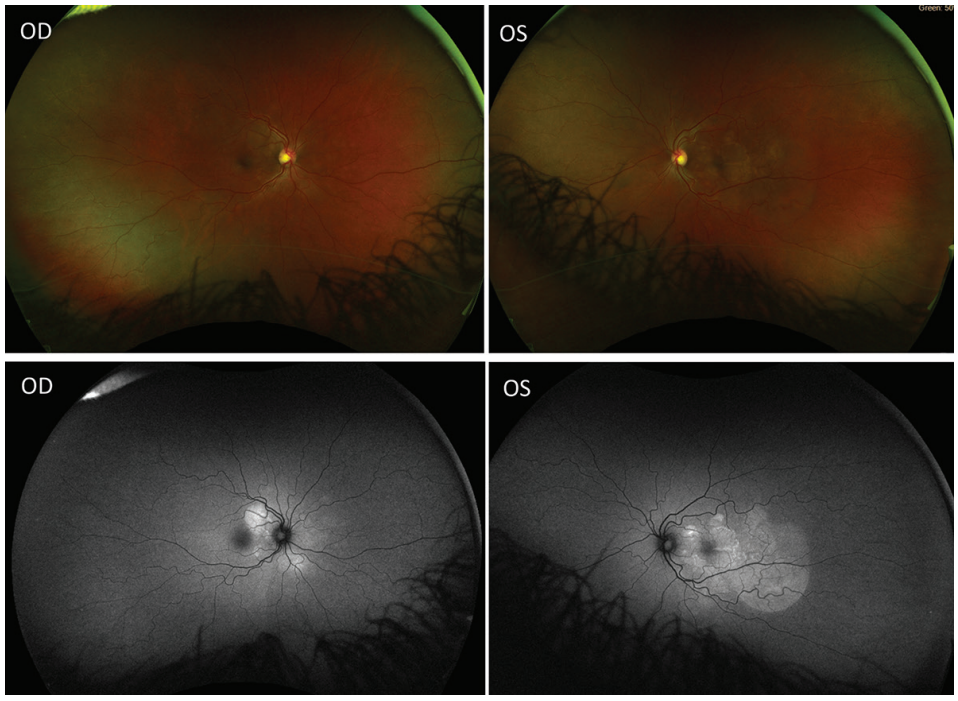


Figure 1. Case 1: Color photos and fundus autofluorescence images at presentation. Color fundus photos reveal SRF in the macula of both eyes. Fundus autofluorescence displays hyper-autofluorescence mirroring the areas of SRF accumulation.

inner retina is healthy. There is a bleb of SRF superiorly in the right eye, but the left eye is really where the SRF stands out; there is also a bacillary layer detachment. There's some fibrinous subretinal hyperreflective material underneath the retina. It's hard to appreciate the thickness of the choroid, but I imagine that if you had an enhanced depth imaging OCT, the choroid might be thickened as well.

Dr. Srivastava: What goes through your mind when you see a bacillary layer detachment?

Dr. Grewal: Bacillary layer detachment can be present in many noninflammatory pathologies including age-related macular degeneration, inflammatory conditions such as Vogt-Koyanagi-Harada (VKH) disease, and acute placoid multifocal posterior pigment epitheliopathy, among others.[10-12] These inflammatory conditions are high on my differential list for this patient. You also always want to rule out infectious causes like syphilis and tuberculosis.[6,13] You also want to consider sarcoidosis, which is a great masquerader that can present as anything.

Q | **Dr. Srivastava:** Dr. Yeh, what about vitreous cell. Do you think of central serous chorioretinopathy (CSR) in a case like this?

Dr. Yeh: Multifocal CSR is also a diagnostic consideration because treating CSR with corticosteroids can lead to some serious damage.[14]

Dr. Srivastava: The resident treating this patient asked her some follow-up questions. She reports no headache, tinnitus, or skin changes; no cough or breathing issues; and no recent foreign travel. She has multiple tattoos, but denies tattoo inflammation. She previously used nasal inhaled steroids for allergies, but discontinued those 6 months prior; she has no other history of steroid use. Her ACE is a little high, but otherwise her labs are normal; she's negative for tuberculous, syphilis, and toxoplasmosis. Given this, would you be comfortable starting her on systemic corticosteroids?

Dr. Grewal: I would be comfortable starting her on systemic corticosteroids with the caveat that her sugars need to be monitored, considering she has diabetes.

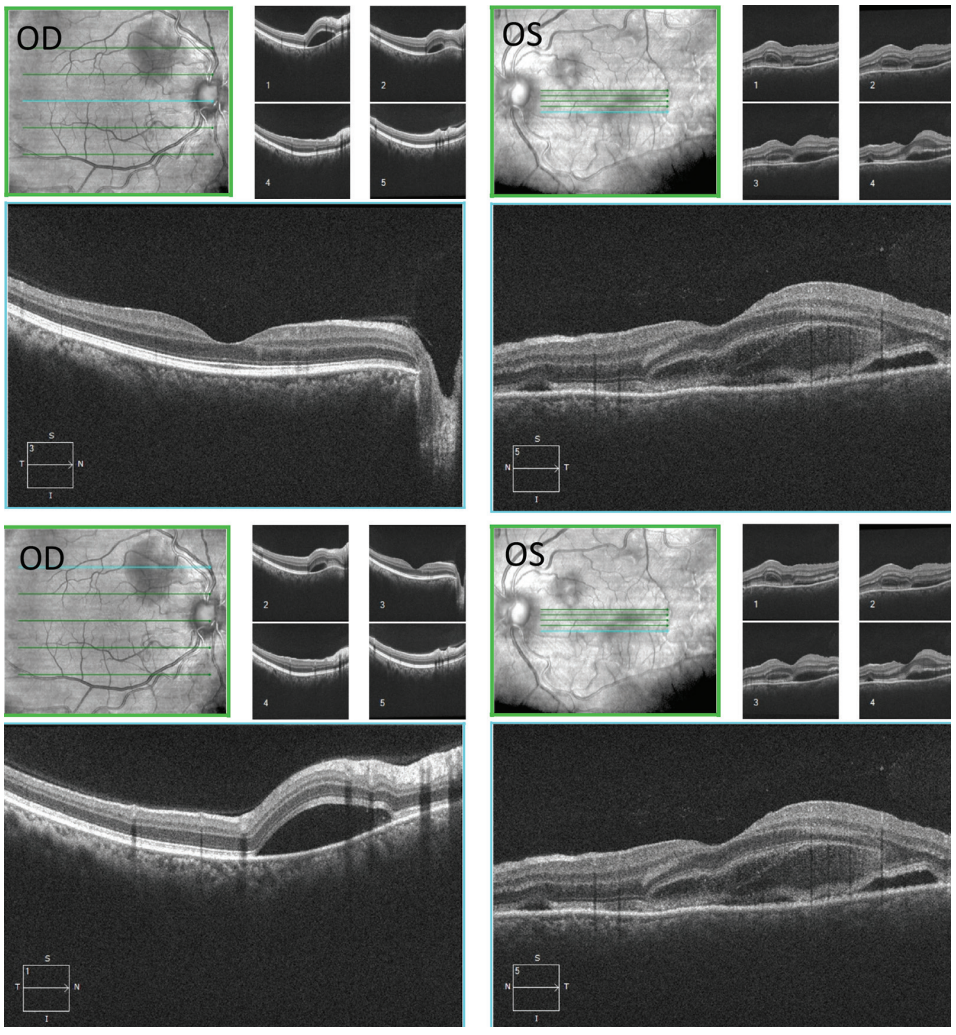
Dr. Srivastava: That's a good point. We started her on 60 mg of prednisone, and there's response on the OCT within a couple of weeks. Her VA has returned to 20/20 OU. We taper her off prednisone with no other workup. The working diagnosis is VKH versus sarcoidosis. Two months later, she comes off the prednisone and develops headaches, neck pain, tinnitus, body aches, and itching tattoos within 10 days. Dr. Grewal, what's the next step for you at this point?

Dr. Grewal: We need additional imaging. Now that she's off the steroid, it's a good time to acquire neuroimaging and a high-resolution CT chest scan to evaluate for sarcoidosis. Tattoos being elevated or raised is a very specific symptom of sarcoidosis.[7] We don't typically see that with VKH.[15]

Dr. Srivastava: Her MRI is negative. Her chest CT shows calcified mediastinal lymph nodes that are consistent with sarcoidosis, which is confirmed through biopsy. We start her on methotrexate. Over the next 18 months, she has repeated bouts of ME that causes her vision to decline. She has a systemic disease. She's tolerating the immune suppression fine, but her ME is persistent despite the adequate control of inflammation. Dr. Yeh, what are the options for this patient at this stage?

Dr. Yeh: Sometimes if they have breakdown of the blood-ocular barrier, they can have some persistent ME. I'd start to think about local corticosteroids, which we know have a very low risk of elevating blood sugar.

Dr. Srivastava: ME is obviously a huge cause of vision loss in patients with uveitis. We all know about diabetic macular edema (DME) playing a large role, but I think we neglect sometimes that uveitic ME is a much more devastating disease than DME. Dr. Grewal, what are your thoughts?



Images courtesy of Steven Yeh, MD

Figure 2. Case 1: Optical coherence tomography and fluorescein angiography at presentation.

Dr. Grewal: Undertreatment of uveitis is one of the leading causes of permanent visual impairment and loss of quality of vision, which significantly impacts quality of life. Chronic persistent uveitic ME results in retinal neurodegeneration, which is irreversible. In terms of achieving adequate control, the options include supplemental local therapy or escalating the immunosuppression.

Dr. Yeh: We've already tried systemic immunosuppression, so the various options left include topical, intravitreal, or periocular steroids. We know that intravitreal steroids are very effective, but they confer an increased risk of elevated intraocular pressure (IOP).[16] The choice depends on the severity of the ME. If it's severe, I'd try intravitreal steroids. If it's mild to moderate, I might consider a periocular steroid, especially if they have a history of an IOP response. I would say that in a situation like this, since they have recurrent disease, sometimes there's some retinal vascular leakage that we're not getting a good handle on. I find that ultra-widefield FA allows us to get a good perspective of the inflammation that may be occurring that we don't image by OCT.[17]

Dr. Grewal: I would also add indocyanine green angiography to the list of imaging tests.[18] The choroid can be frequently involved in sarcoidosis, which is something that we don't pick up on FA.

Dr. Srivastava: The POINT study is the only study that has addressed this question of periocular versus intravitreal steroids for uveitic ME.[19] POINT randomized patients with uveitic ME 1:1:1 to treatment with periocular triamcinolone acetonide, intravitreal triamcinolone acetonide, and intravitreal dexamethasone implant. The primary outcome was the proportion of baseline central subfield thickness (CST) at 8 weeks. Secondary outcomes included at least 20% improvement and resolution of ME, best-corrected visual acuity (BCVA), and IOP events over 24 weeks. All treatment arms had improvements in ME throughout the follow-up period. However, at 8 weeks the intravitreal groups had demonstrated greater improvements in CST baseline than the periocular group. The authors concluded that intravitreal therapy may be the preferred initial therapy for uveitic ME.[19]

Q | Dr. Yeh, what did you take away from the POINT trial, given the results showed intravitreal therapy is superior to periocular? Did this change your use of periocular steroids?

Dr. Yeh: We know that intravitreal dexamethasone and triamcinolone shows superiority generally in terms of ME control.[20,21] We also know that at least from the standpoint of IOP elevation, there was an increased risk of IOP with the intravitreal steroids.[22] This has helped me from a counseling perspective and thinking through when I'd consider an intravitreal versus periocular steroid.

Dr. Srivastava: IOP is pretty controllable, but it sometimes falls by the wayside. How many injections does it take before you see an IOP response?

Dr. Grewal: In robust steroid responders, it'll typically be after the first. But you can also see a moderate level of IOP increase as you get sequential injections.

Dr. Srivastava: The most challenging thing for me is that patients do well. They're happy. But then they call back 2 weeks later reporting that their vision dropped, and it's because their IOP is extremely high. Dr. Yeh, what are the limitations for you in using intravitreal therapy in your clinic?

Dr. Yeh: I'm hesitant in younger patients and in phakic patients, and I also think about steroid responders. If an individual has a robust steroid response, even with a topical corticosteroid, there's a good chance they're going to be calling you for an elevated IOP, which can lead to an urgent visit and potentially be unnerving.

SUPRACHOROIDAL SPACE INJECTIONS FOR UVEITIC MACULAR EDEMA

Dr. Srivastava: We're going to move on the discuss SCS injections. In October 2021, the FDA approved suprachoroidal CLS-TA for the treatment of uveitic ME based on PEACHTREE and MAGNOLIA data.[23,24] The SCS may offer several clinical advantages to traditional pathways. First, there's potentially preferential targeting of posterior segment tissue. Second, there's a reduction in drug exposure to the anterior chamber and vitreous, which may confer safety advantages, and third, there's improved pharmacokinetics and drug durability.[1,25] CLS-TA is administered into the SCS using a proprietary SCS microinjector syringe. CLS-TA actually comes with two needles of different sizes (900 and 1,100 µm) to accommodate variation in patient anatomy.

Q | Dr. Yeh and Dr. Grewal, you were both in several CLS-TA trials. How often did you use one needle over the other?

Dr. Yeh: We've looked at these data from the standpoint of how often the switch is needed. Just over 70% of individuals who were in the trial would receive the SCS injection with a 900 µm needle. The other patients, 29%, switched over to 1,100 µm.

Dr. Yeh: Dr. Grewal, what is the patient experience like?

Dr. Grewal: The vast majority of patients do really well. As long as you're slow and deliberate with the injection, the expansion with SCS is controlled. It is rare nowadays for patients to experience severe pain. They may experience mild discomfort, but the vast majority do well.

Dr. Srivastava: I've found that subconjunctival achieves better anesthesia from a comfort perspective. When the medication goes into the SCS, the SCS expands. That pressure sensation feels different for patients who have had intravitreal injections. I like them to be as comfortable as possible. Slow and deliberate injection is important. As we've gained more experience with SCS injections, the technique has improved. What is the learning curve like for retinal specialists?

Dr. Yeh: It is a nuanced technique in terms of just feeling the loss of resistance as the medication goes into the SCS. Being slow and deliberate with the injection is key, but I think it can be performed as long as the needle is very perpendicular, which allows you to take the full advantage of that 900 µm depth.

Safety and efficacy data for CLS-TA

Dr. Srivastava: Looking at the data we have from the clinical trials, the safety profile has been good in comparison to intravitreal steroids. Dr. Grewal, talk us through the data we have from PEACHTREE and MAGNOLIA.[23,24,26]

Dr. Grewal: PEACHTREE was a phase 3 randomized, controlled, double-masked, multicenter trial over 24 weeks.[23] Unique to this trial was that all anatomical types of uveitis with cystoid macular edema were included. The primary endpoint was the proportion of patients who gained 3 or more lines or at least 15 ETDRS letters at week 24. Patients were randomized 3:2 to CLS-TA or sham. Importantly, there was a rescue therapy allowed according to the prespecified criteria.

Patients in this trial had noninfectious uveitis, ME, and CST of 300 µm or more. Their inflammation could be active or controlled. VA was between 20/40 to 20/800; patients with IOP of at least 22 mm Hg were excluded. Interestingly, we had categorization of the anatomic subtypes of uveitis, and there was a pretty good balance between the suprachoroidal and control groups in terms of the anterior, intermediate, posterior, and panuveitis. This is valuable because we don't have a lot of clinical trial data on the efficacy of local therapy toward different anatomic subtypes.

The trial met its primary endpoint, and almost half the patients in the CLS-TA group gained 3 lines or more vision at 24 weeks compared to only 15% in the sham group. If you look at the change in visual acuity data, you really start to see a divergence starting at 4 weeks onwards that persists all the way out to 6 months. That tells you that the suprachoroidal approach results in a quick anatomic improvement with resulting visual acuity improvement.

Q | **Dr. Srivastava**: Were you impressed with the speed of improvement?

Dr. Grewal: Yes. I'm impressed by that because one of the key differentiators between a periocular and intravitreal approach is the intravitreal approach gives us that immediate inflammation reduction we need for quick control. One of the concerns we had initially with the suprachoroidal approach was that similar to periocular injections; it may take longer to see an effect. To see a robust response at 4 weeks was quite impressive.

There was also a dramatic reduction in CST at 4 weeks. Improvement in vision can often lag improvement in anatomy by 6 to 8 weeks. Therefore, seeing such a robust improvement in CST in 4 weeks is very encouraging. There were also improvements in anterior chamber cell, anterior chamber haze, and vitreous haze with CLS-TA versus sham. Finally, only 13% of patients in the CLS-TA arm required rescue therapy versus 72% in the control arm. Rescue criteria included the loss of 2 lines of vision, increase in CST of at least 100 µm or 20% from baseline, or at the discretion of the investigator if there were intraocular signs of inflammation.

Dr. Srivastava: Tell us about the MAGNOLIA extension study.

Dr. Grewal: In MAGNOLIA, we were interested in the durability of the medication.[24] This was the 24-week extension trial of patients who completed PEACHTREE and who had not received

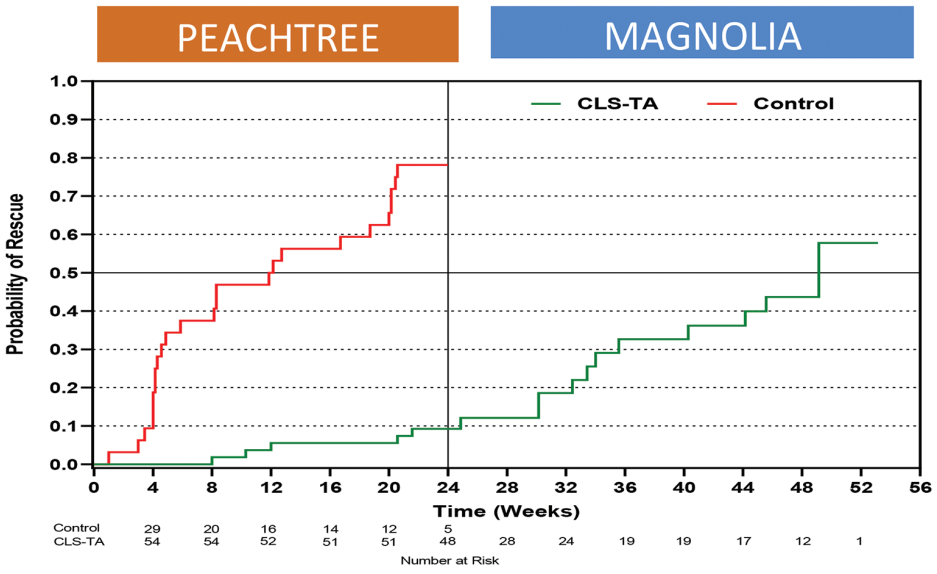


Figure 3. MAGNOLIA Kaplan-Meier time to first rescue.[23,24]

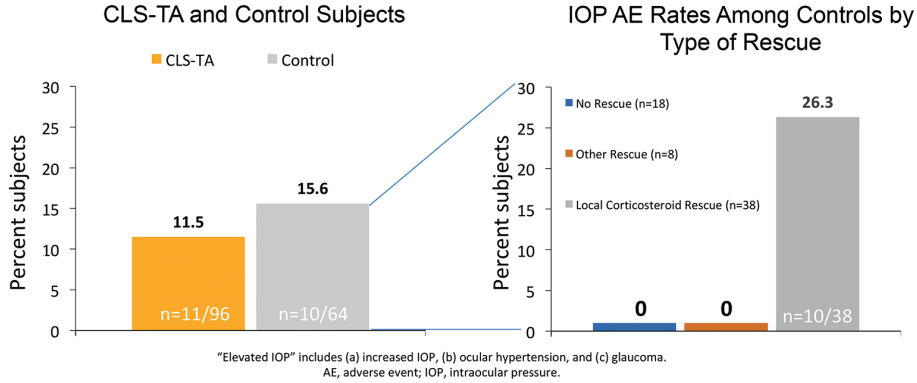


Figure 4. MAGNOLIA: Elevated IOP adverse events.[24]

rescue. The primary endpoint was a time to rescue relative to day 0 of PEACHTREE. Half of the patients in the CLS-TA group did not receive any additional medication through week 48, that is 9 months from their last suprachoroidal dose, which is very impressive. The divergence of the graph, illustrated in Figure 3, hones the point that the duration of effect can be sustained. We also know that there is data from the MUST trial, for example, with the fluocinolone implant that is designed to last 3 years, but the therapeutic effect can be sustained for up to 7 years.[27]

CLS-TA was also safe, with the most common ocular adverse events being elevated IOP, eye pain, and cataract. Digging into the IOP data a bit more, patients in the CLS-TA arm had an 11% rise in pressure compared to a 16% increase in the control group (Figure 4). When we take a closer look at control patients who developed IOP elevation, these were all patients who required rescue therapy with local steroids. It is notable that in the patients rescued with topical steroid or steroid injections, 26% developed IOP elevation. We know from the POINT data that intravitreal steroids are the ones that can cause the most robust IOP rise. In terms of cataract formation, the rate of new or worsening cataract was low (6 to 7%, both groups).

To summarize, the primary endpoint was met with 47% of patients gaining at least 15 ETDRS letters. Suprachoroidally injected CLS-TA significantly improved vision and ME in all anatomical subtypes of uveitis. Anterior segment and vitreous inflammation resolved in the majority of CLS-TA patients with low rates of elevated IOP and cataract formation.[28] The type of rescue used was at the discretion of the investigator. Figure 5 shows the rate of rescue medications by type for both the CLS-TA and control groups, categorized by the most targeted and type of rescue used. Rescued patients often received more than one types of rescue treatment during the study. Overall, control patients were rescued earlier in the study and, therefore, had more time to progress in the hierarchy of treatment.

Dr. Srivastava: That is an interesting point. Just so I understand: if the patient received rescue therapy, they received intravitreal therapy and never caught up to the suprachoroidal group within the 24 weeks of the trial. That's clearly a lag, right?

Dr. Grewal: I think it comes back to the point that early, aggressive treatment with sustained therapy is advantageous for both anatomy and vision. Once you gain control of the ME and you keep it under control, you are much further ahead of somebody who's playing catch up with intravitreal steroids.

CASE 2: EFFICACY OF CLS-TA TREATMENT IN A PATIENT WITH SARCOIDOSIS AND INTERMEDIATE UVEITIS

Dr. Srivastava: Our next case is a 45-year-old patient with a history of biopsy-proven sarcoidosis and intermediate uveitis with a significant amount of ME (Figure 6A). Their VA is 20/80. They were previously treated with dexamethasone intravitreal implant 6 months ago. They've had two rounds of periocular steroids, and they deferred systemic immunomodulatory therapy. They expressed interest in new therapy options. The patient enrolled in the phase 2 CLS-TA trial (DOGWOOD).[29] Figure 6B shows the angiogram 2 months after CLS-TA injection and it looks a lot better; the optic nerve is no longer leaking, the peripapillary angiographic cystoid macular edema is gone, and there's a resolution of the SRF. If you look at the outer retina, the ellipsoid zone and the external limiting membrane are back in place, which correlates with the improvement in VA to 20/30. This is

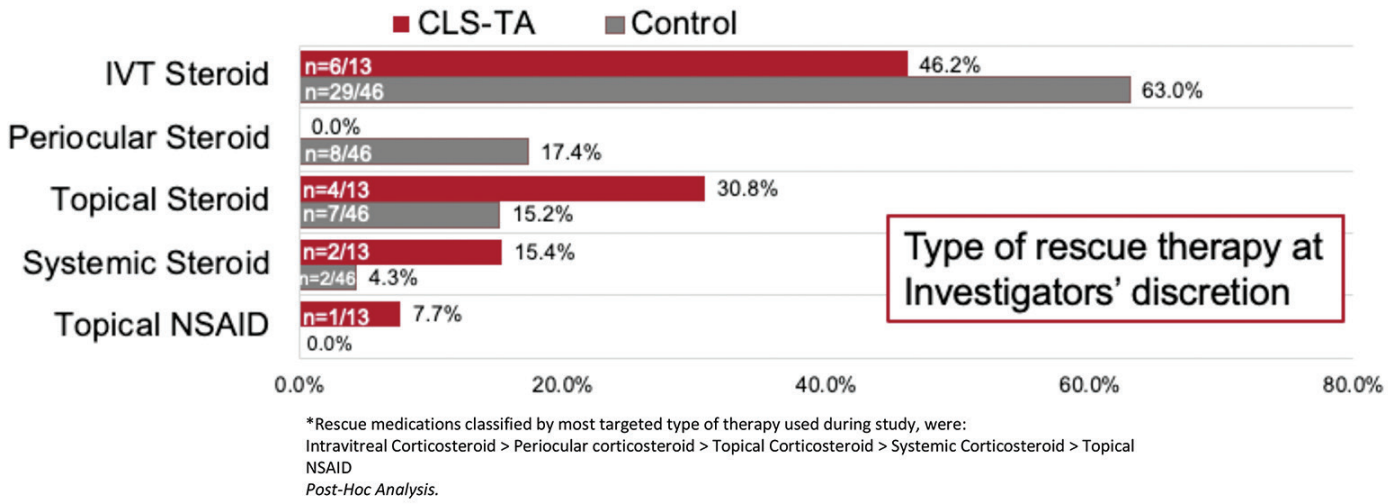


Figure 5. Rescue therapy rates: CLS-TA (13.5%) versus control (71.8%).[28]

2 months after the CLS-TA injection and speaks to what we saw in the data that the onset starts as early as 4 weeks.

Dr. Srivastava: I'm looking forward to seeing what the 6- and 9-month fluorescein data shows, because that is going to tell us how durable this is. Dr. Yeh, talk a little bit about your injection technique.

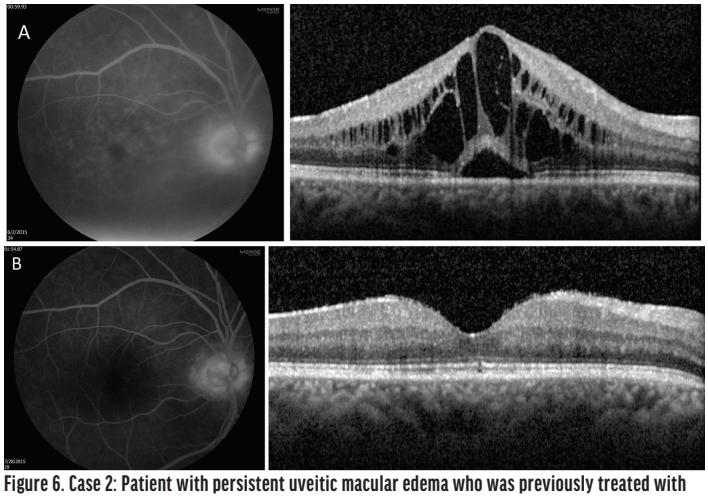
Dr. Yeh: When you first give a CLS-TA injection, there is a certain faith and skill element in terms of whether it's been administered in the correct location because you can't visualize the medication in the same manner as an intravitreal injection. You should be 4 mm from the limbus. You need to be perpendicular so that you can see the tip that creates a circular dimpling effect. Then it's a matter of getting a sense for what that loss of resistance feels like as medication is correctly administered in the suprachoroidal space.

Dr. Grewal: A SCS injection is more nuanced than an intravitreal injection because you have to be careful that you are correctly entering the suprachoroidal space. I would start every patient with the 900 µm needle. If that doesn't go through, which you'll feel immediately, will switch to the 1,100 µm needle.

Dr. Srivastava: What is it like for the patient when you have to switch needles?

Dr. Grewal: Early on, it was a little awkward because you've attempted a few times with the 900 µm needle. But the switch is faster as you get a better understanding of the injection. The moment you realize the 900 µm needle is too short, you immediately switch over, and it's more comfortable for the patient.

Dr. Yeh: I appreciate when I don't have to switch, but if I do, it's a matter of preparing the patient in advance and letting them know we may have to switch needles because of the thickness of their sclera.



Images courtesy of Steven Yeh, MD

Figure 6. Case 2: Patient with persistent uveitic macular edema who was previously treated with dexamethasone intravitreal implant. The images show the patient before (A) and after treatment with CLS-TA (B). The fluorescein angiogram and OCT show reduction in leakage and intraretinal fluid, respectively, after treatment with CLS-TA.

PIPELINE THERAPIES THAT HARNESS THE SUPRACHOROIDAL SPACE

Dr. Srivastava: There are several therapies in the pipeline that harness the SCS. RGX-314 is in phase 2 trials for both wet AMD (AAVIATE) and diabetic retinopathy (DR; ALTITUDE).[30,31] AAVIATE will evaluate the mean change in BCVA for RGX-314 compared with ranibizumab monthly injection at week 40 in up to 40 patients with wet AMD. Secondary endpoints include the safety and tolerability of RGX-314, change in CRT, and need for anti-VEGF rescue injections. Based on data so far, RGX-314 appears well-tolerated in cohorts 1 through 3, with no drug-related serious AEs. In cohort 1 (n = 15), patients treated with RGX-314 experienced mild ocular AEs, including conjunctival hemorrhage (33%); intraocular inflammation (27%), which resolved with topical steroid treatment; worsening wet AMD (20%); conjunctival hyperemia (13%); and dry eye (13%). There

were no reports of chorioretinal vasculitis, chorioretinal occlusion, or hypotony. Patients in cohort 1 treated with RGX-314 also had stable vision and CRT through month 6 with a 75.9% reduction in injection burden.[32]

The ALTITUDE trial will evaluate the proportion of patients with a 2 or more step improvement in severity on the Diabetic Retinopathy Severity Scale at 48 weeks in up to 40 patients with DR. Secondary endpoints will include the safety and tolerability of RGX-314, the development of DR-related ocular complications, and the need for standard of care interventions. Based on the data so far, RGX-314 appears to be well-tolerated and effective among the 15 patients in cohort 1 dosed with RGX-314. No intraocular inflammation has been observed, and one patient had mild episcleritis, which resolved with topical steroids. Five patients treated with RGX-314 (33%) demonstrated 2 or more ETDRS improvement at 3 months versus zero patients in the control group. One patient who received RGX-314 had a 4-step improvement.[33]

Q | These are just two of the therapies that are coming in the SCS; there are more studies being conducted. If we can get the delivery working, do you think SCS injections will replace intravitreal injections?

Dr. Grewal: It depends on the therapy. Because it's such a vascular space, if you inject pure anti-VEGF into the SCS, it will wash out quickly. Sustained release formulations gives us a lot of potential options. As we advance further with potential antifibrotic treatments being developed as well, I think it's a very exciting space.

CASE 3: THE IMPORTANCE OF TESTING FOR TUBULOINTERSTITIAL NEPHRITIS AND UVEITIS

Dr. Srivastava: Our next case is an 18-year-old woman who presents with a several month history of vision loss in both eyes. She has known disc edema and now has a working diagnosis of idiopathic intracranial hypertension. Her VA is 20/40 and 20/30 and she has ME. She was sent to me for an evaluation and she has 1+ vitreous cell. Figure 7A shows her OCT. Dr. Grewal, what do you see here that is concerning?

Dr. Grewal: There is ME in her right eye. There's thickening of the optic nerve and swelling of the nerve fiber layer. We need to take a step back and further work up this patient to see what's going on.

Dr. Srivastava: I agree. Figure 7B shows her FA. Dr. Yeh, when you see a pattern like this in such a young person, what comes to your mind?

Dr. Yeh: We previously alluded to the importance of taking a step back big picture and thinking about infectious versus noninfectious conditions. I'd want to make sure there is a good infectious disease workup with that amount of optic disc edema. Could it be neuroretinitis? I would keep that on the differential diagnosis list.

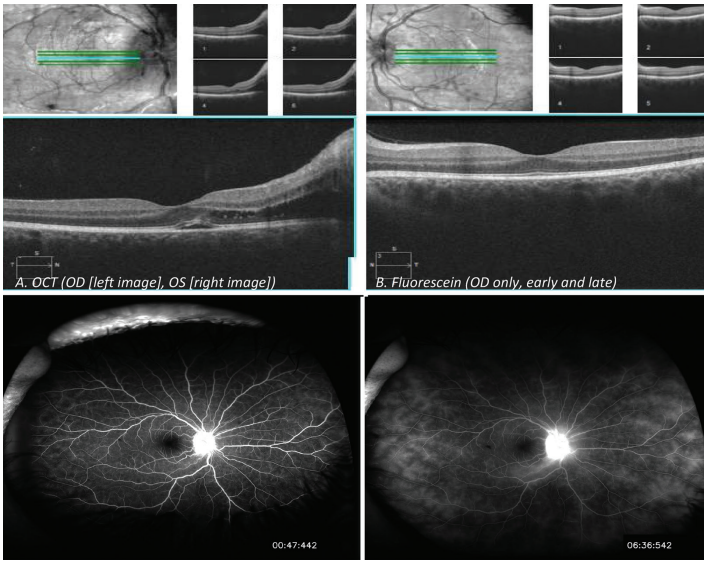


Figure 7. Case 3: Optical coherence tomography and fluorescein imaging in a teenager with bilateral vision loss. OCT images reveal intraretinal fluid and subretinal fluid in the right eye with fluid emanating from the temporal portion of the nerve (A). Fluorescein angiogram reveals leakage at the nerve and in the retina along the vessels and into the periphery (B).

Dr. Srivastava: My differential diagnosis included tubulointerstitial nephritis and uveitis (TINU) syndrome; sarcoidosis, multiple sclerosis-associated intermediate uveitis, inflammatory bowel disease (IBD), syphilis, tuberculosis, and pars plana, which really is an idiopathic disease. Her urine beta-2 macroglobulin and creatinine were elevated. We performed a renal biopsy and she was positive for the changes that we see in TINU.[34] Do we test for TINU enough or is this something that people aren't aware of?

Dr. Grewal: Urine beta-2 macroglobulin is a first-line test for me during a uveitis workup. The manifestations of TINU are not just anterior or intermediate, chorioretinal lesions can be seen as well, consistent with posterior or panuveitis.

Dr. Yeh: I probably don't think about TINU enough. I know your group at Cole Eye Institute has published work about posterior segment manifestations. Are there clinical pearls you could offer on this topic?

Dr. Srivastava: I'll credit my partners, Drs. Sumit Sharma and Careen Y. Lowder who have written a couple of papers on the posterior manifestations.[35,36] TINU is No. 1 on my list, especially in cases like this. She improved after 1 year of immune suppression.

CASE 4: PATIENT WITH CROHN DISEASE AND UVEITIS NOT RESPONDING TO INFLIXIMAB

Dr. Srivastava: Our next case is a 33-year-old man with 4- to 6-week history of blurred vision. He has a history of Crohn disease and has been diagnosed with anterior uveitis. He's been treated with topical and is already on infliximab every 4 weeks. His VA is 20/20 and 20/70. He's 2+ cell in the right eye and 3+ cell in the left eye.

I want to highlight the amount of vitritis in the left eye on Figure 8. I can't say for certain if it's retinitis, but there is an area that looks like sheathing on the vessel. I see a fair amount of leakage within the retina itself that extends from the 6 o'clock to the 3 o'clock hour.

Q | Is this intermediate uveitis that is common in patients with irritable bowel syndrome? What should we do now? Should I supplement with local therapy because this patient is not responding to infliximab?

Dr. Grewal: This is a concerning situation. We're either undertreating the uveitis or we are treating him for the wrong diagnosis. This level of inflammation is atypical for Crohn-associated uveitis. I'd take a step back, look at the workup again, and make sure that we are not missing an infection. I'd start by checking his antibodies for infliximab. Sometimes the biosimilars are not as effective as the reference drug.

Dr. Srivastava: I decided to work up this patient again and suggested starting him on oral prednisone. I'm a little worried that I'm undertreating the disease. I talked to his referring physician because usually IBD and uveitis associated with IBD don't necessarily go together. It turns out the patient is already on 20 mg of prednisone for his Crohn disease. He didn't mention it because he thought I only wanted to know about the medications for his eyes. Dr. Yeh, are you more worried now or less worried knowing he's on both prednisone and infliximab?

Dr. Yeh: I'm more concerned at this point. Your differential diagnosis is broad. You never want to miss an infection. This might be fungal or viral, like acute retinal necrosis or herpetic retinitis. I would consider doing an anterior chamber tap. Syphilis and tuberculosis are other important diagnostic considerations as well.

Dr. Srivastava: I agree. I reworked this patient, and the toxoplasmosis IgG and IgM were negative. However, syphilis IgG and rapid plasma reagin were both positive. He has no idea how he got syphilis. I put him on penicillin for 2 weeks and treated this as neurosyphilis.[37] To answer everyone's question, it was retinitis in the imaging. You can see retinitis and retinal pigment epithelial loss in these patients as well.

Q | How often do you treat these patients who are syphilitic and who still have a little bit of inflammation? Before you put an intravitreal steroid in somebody's eyes, do you put them on oral steroids first and wait for a response?

Dr. Grewal: I would always want to assess response to oral prednisone to make sure that the inflammation is steroid sensitive. You have to rule out an infection. Nobody's going to go blind from ME persisting for a few more weeks while you're waiting for your workup and your response to be assessed before proceeding with intravitreal steroids.

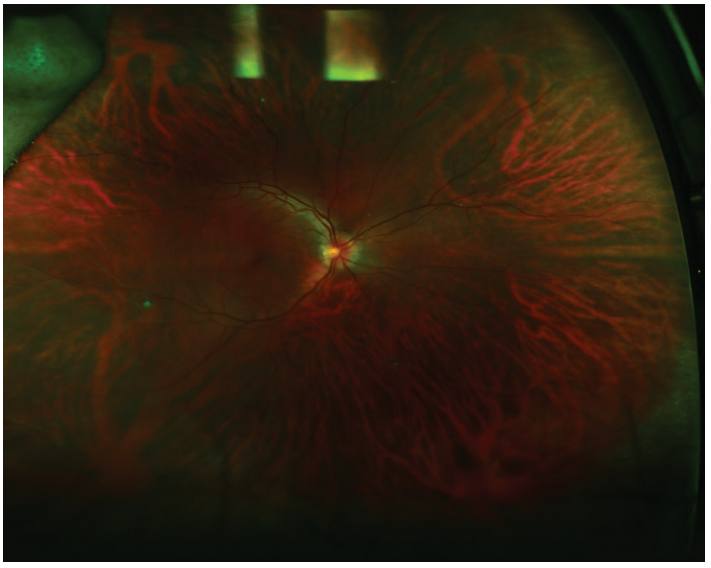


Figure 8. Case 4: Patient with anterior uveitis not responding to infliximab (OD).

Dr. Yeh: We don't see it very often, but syphilis testing should be included in general for uveitis as well as other workups to rule out infection.

CASE 5: RITUXIMAB FOR REFRACTORY SCLERITIS AND UVEITIS

Dr. Yeh: Our final case is a 64-year-old woman who had previous cataract surgery. She has rheumatoid arthritis and chronic inflammatory demyelinating polyneuropathy. Unfortunately, it was a very severe disease process—bilateral diffuse anterior and posterior scleritis with panuveitis. Oftentimes we're trained to believe that with scleritis we don't see much intraocular inflammation, but I think we do.[38] I definitely see it in my practice.

She's had multiple medications. She was on methotrexate at a time, cyclophosphamide, adalimumab, and oral prednisone. Figure 9A shows multiple large granulomatous lesions in the subretinal space and deep in the retina. She has severe persistent inflammation, 20/400 VA, and a large exudative detachment. It was very bad.

It reminded me of granulomatous polyangiitis, formerly known as Wegener granulomatosis. There is clinical trial data looking at rituximab and its ability to be as efficacious as cyclophosphamide for systemic granulomatous polyangiitis.[39] We gave her rituximab and IV methylprednisolone. Unfortunately, she had a fair amount of fibrosis, but there was some improvement in her visual acuity (Figure 9B).

Q | This was a very challenging case. How often do you see cases like this? Do you treat these types of cases more aggressively when you have necrotizing disease or intraocular involvement?

Dr. Grewal: Yes, absolutely. Like you said, there are not many options for such recalcitrant cases. I will say we had some success with IL-6 agents, particularly in patients with whom we were unable

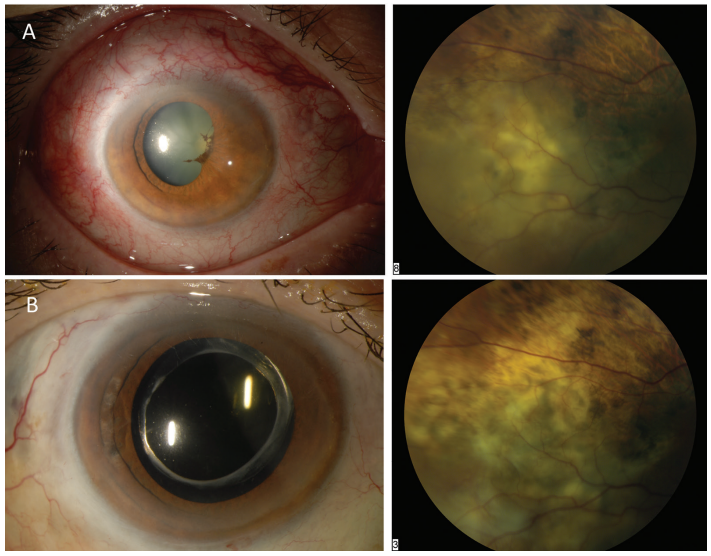


Figure 9. Case 5: Rituximab for refractory scleritis and uveitis. The top images before rituximab and IV methylprednisolone (A) and the bottom images show the patient's eye after rituximab and IV methylprednisolone (B).

to weaken their immune systems to the extent we can with rituximab.[40,41] We often give a concurrent infusion of methylprednisolone 125 or 250 mg, along with the IL-6, which can help.[42]

Dr. Srivastava: I agree with everything you did here. Rituximab or cyclophosphamide are the only things that control this. Now that we're living in a world with COVID-19, there's a risk factor in patients on rituximab for becoming very ill with COVID-19.[43,44] We have to make sure these patients are vaccinated or at least strongly recommend vaccination in order to make sure they are protecting themselves. The systemic immune suppression that we use now has implications for their survival for some of these bad COVID-19 infections.

Dr. Yeh: It also has implications for their response to the vaccine.[45]

Dr. Srivastava: Does anyone have final thoughts on SCS injections?

Dr. Grewal: I'm very optimistic. I think it's going to be a fantastic adjunct to our treatments, and am looking forward to it using it.

Dr. Yeh: I'm excited about the clinical trial data. The CLS-TA SCS injection is unique and an example of the intersect between engineering design and medicine.

Dr. Srivastava: Thank you all for participating in this panel discussion and your valuable comments on harnessing the SCS for the treatment of uveitis. ■

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TREATMENT OF POSTERIOR SEGMENT DISEASE: EXPLORING THE SUPRACHOROIDAL SPACE

Release Date: January 2022
Expiration Date: February 2023

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Profession
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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
___ Northeast
___ Northwest
___ Midwest
___ Southeast
___ Southwest

LEARNING OBJECTIVES

Did the program meet the following educational objectives?	**Agree**	**Neutral**	**Disagree**
Interpret results of key trials examining the suprachoroidal space injections for the treatment of retinal diseases and how new data may eventually influence practice.	_____	_____	_____
Describe proper administration techniques of suprachoroidal injections, solutions to common challenges, and best practices in patient education and informed consent.	_____	_____	_____
Differentiate future applications of suprachoroidal injections and how advanced therapies may alter the treatment landscape.	_____	_____	_____

POSTTEST QUESTIONS

Please complete at the conclusion of the program.

1. Based on this activity, please rate your confidence in your ability to interpret results of key trials examining the suprachoroidal space injections for the treatment of retinal diseases (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. What percentage of patients with intermediate, posterior, or panuveitis develop macular edema (ME)?

a. 5 to 10%
b. 10 to 20%
c. 20 to 40%
d. 40 to 60%

3. A 35-year-old man presents complaining of blurry vision and floaters. His VA is 20/50. He has several tattoos, but reports no itching or swelling at his tattoo sites. He is extremely photosensitive and reports intermittent hyperemia and feelings of exhaustion. Upon examination, you note bilateral granulomatous panuveitis with chorioretinitis and vitreous haze. What are you most suspicious for as a differential diagnosis?

a. Tubulointerstitial nephritis and uveitis
b. Neurosyphilis
c. Sarcoidosis
d. Intermediate uveitis

4. What was the key clinical takeaway of the POINT trial?

a. Intravitreal steroids may be the preferred initial therapy for uveitic ME
b. Periocular steroids may be the preferred initial therapy for uveitic ME
c. Periocular steroids result in too high of an increase in intraocular pressure and should no longer be used for uveitic ME
d. Intravitreal steroids are noninferior to suprachoroidal space injections for the treatment of uveitic ME

5. What are the clinical advantages of suprachoroidal space injections? Select all that apply.

a. Suprachoroidal space injections are more comfortable for patients than traditional intravitreal injections
b. Steroid delivering through the suprachoroidal space injections do not increase intraocular pressure
c. Suprachoroidal space injections allow for preferential targeting of posterior segment tissue
d. Suprachoroidal space injections have improved drug durability when compared to intravitreal injections

6. According to clinical trial data, what percentage of patients may need to be switched to the 1,100 µm needle from the 900 µm needle when using the SCS micro injector?

a. 70%
b. 29%
c. 39%
d. 10%

7. Based on PEACHTREE data, how quickly can patients experience anatomic improvement after treatment with CLS-TA?

a. 2 weeks
b. 3 weeks
c. 4 weeks
d. 6 weeks

8. Identify the key aspects of a suprachoroidal space injection. Select all that apply.

a. The injection site should be 5 mm from the limbus
b. The injection should be given slowly and consistently
c. Every patient should start with the 900 µm needle
d. The injection should be approached at a horizontal angle

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

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

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

Additional comments:

_____

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

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

_____

_____