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TARGETING THE SUPRACHOROIDAL SPACE:

Current Evidence and Best Practices for the Treatment of Posterior Segment Eye Diseases

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Content Source

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

Activity Description

This supplement summarizes a live symposium discussion on the suprachoroidal space as a prospective pathway for novel drug delivery systems to treat posterior segment eye diseases, including uveitic macular edema.

Target Audience

This certified CME activity is designed for retina specialists.

Learning Objectives

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

- **Develop** treatment plans for uveitic macular edema that incorporate new agents when appropriate based on recent clinical data and FDA approvals.
- **Describe** proper administration techniques of suprachoroidal injections, solutions to common challenges, and best practices in patient education and informed consent.
- **Assess** clinical trial results examining the suprachoroidal space as a potential pathway for future treatments in eye diseases of the posterior segment.

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PRETEST QUESTIONS

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 is the leading cause of vision impairment and vision loss in uveitis?

a. Cataract formation
b. Retinal detachment
c. Corneal edema
d. Macular edema

3. A 46-year-old patient presents to your office for evaluation of recurrent uveitis. She has persistent macular edema despite various therapeutic agents, and she is interested in learning about suprachoroidal delivery of triamcinolone. Which of the following is TRUE about suprachoroidal injections?

a. Suprachoroidal injections result in increased drug exposure to the anterior chamber and vitreous, compared to intravitreal injections
b. Suprachoroidal injections result in decreased drug exposure to the anterior chamber and vitreous, compared to intravitreal injections
c. Suprachoroidal injections result in equivalent drug exposure to the anterior chamber and vitreous, compared to intravitreal injections
d. Suprachoroidal injections potentially preferentially target anterior segment tissue

4. You decide to administer a suprachoroidal injection of triamcinolone on the above patient. She is nervous about side effects from suprachoroidal injections, as she has never had a suprachoroidal injection before. According to studies, what is the most common treatment-related adverse event in suprachoroidal injections?

a. Eye pain
b. Vitreous hemorrhage
c. Retinal tear
d. Endophthalmitis

5. According to the PEACHTREE trial, what percentage of patients in the CLS-TA arm demonstrated at least a 15-letter improvement in ETDRS visual acuity?

a. 27%
b. 47%
c. 67%
d. 87%

6. According to the PEACHTREE trial, what percentage of patients in the CLS-TA arm had resolution of anterior chamber cell and flare by week 24?

a. ~30%
b. ~50%
c. ~70%
d. ~90%

7. You are seeing a 55-year-old patient with a history of chronic uveitis with macular edema. You determine she needs additional local corticosteroid treatment for her disease. After a risk/benefit discussion of her options, she chooses to undergo a surgical intravitreal implant for increased durability. Which of the following would be a good option for this patient?

a. Dexamethasone 0.7 mg (Ozurdex)
b. Fluocinolone acetonide 0.59 mg (Retisert)
c. Triamcinolone acetonide 4 mg (Triesence)
d. Fluocinolone acetonide 0.18 mg (Yutiq)

8. You are seeing a 48-year-old woman who presents with a history of chronic uveitis, which has been managed with oral prednisone for many years. She has a history of hypotension osteoporosis and diabetes. On ophthalmic exam, you note bilateral cataracts, keratic precipitates, and significant macular edema. All of the following can be adverse effects of steroids, EXCEPT:

a. Osteoporosis
b. Diabetes
c. Hypotension
d. Cataracts

The suprachoroidal space, 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, diabetic retinopathy (DR), diabetic macular edema (DME), and neovascular age-related macular degeneration (AMD).[1,2] Posterior segment eye diseases are chronic and potentially blinding, affecting millions of patients in the United States. Suprachoroidal injections may offer several clinical benefits over standard-of-care treatments for posterior segment eye diseases. They are also a different technique from traditional intravitreal injections, and clinicians need training before administering this treatment to patients. The following supplement discusses where suprachoroidal injections may fit into the treatment paradigm, current evidence, and best practices on injection technique.

—Sunil K. Srivastava, MD (Chair)

TREATING UVEITIS WITH LOCAL STEROIDS

Dr. Srivastava: Macular edema due to noninfectious uveitis is the leading cause of vision impairment and vision loss in patients with uveitis.[3-5] It is commonly observed across anatomic subtypes of uveitis, occurring in 34 to 66% of intermediate, posterior, and panuveitis cases and in about 11% of patients with anterior uveitis. Importantly, macular edema may persist despite the adequate control of inflammation.[3-5] When you see patients who have macular edema and their disease is clinically quiet, what does that tell you?

Sumit Sharma, MD: I can't underscore how important it is to think about what's happening to the structure, but also what's happening physiologically. Even if a patient appears clinically quiet, I consider fluorescein angiography (FA) to ensure that there isn't inflammation I need to treat. There are some situations where we control the inflammation and the macular edema will persist and, again, still lead to vision loss.[3-5]

Dr. Srivastava: Have you seen a case of macular edema, secondary to uveitis, where the fluorescein doesn't leak?

Dr. Sharma: It would be very uncommon to see no fluorescein leakage in a case of uveitic macular edema. I question whether you can say that somebody who has macular edema is quiet. I think it's a sign of activity, and I think that they're undertreated.

Steven Yeh, MD: There are some situations, especially with disease chronicity, where patients can have diseased vasculature, which results in more of a vascular permeability issue. I think they're clinically quiet or inactive, but the diseased vasculature can drive the macular edema.

Dr. Srivastava: We have many local steroid treatment options for the treatment of uveitis. Dexamethasone 0.7 mg is an intravitreal injection with a 22-gauge needle that lasts 4 to 6 months. It was approved by the FDA based on HURON study data.[6] Triamcinolone acetonide 4 mg can be an intravitreal or periocular injection using 25- or 27-gauge needles, respectively, with a duration of 4 to 6 months.[7] Fluocinolone acetonide 0.59 mg is a surgical intravitreal implant with a duration of 30 months.[8,9] Then there's the fluocinolone acetonide 0.18 mg injectable intravitreal insert, which has shown a reduction in uveitis recurrences at 6 and 12 months.[10] Finally, triamcinolone acetonide injectable suspension 40 mg is given with a 30-gauge microneedle into the suprachoroidal space.[11,12]

The POINT trial showed that intravitreal therapy, both triamcinolone and dexamethasone, is superior to periocular therapy in controlling macular edema.[7] Since the release of the POINT trial data, how much are you using periocular steroids?

Dr. Sharma: I use periocular therapy less than I used to, but I still use it because POINT also showed that the safety profile was a bit better. There are lower rates of IOP rise and lower rates of cataract formation with periocular steriods.[7] I still use periocular in the certain situations, like in vitrectomized eyes and eyes that are aphakic.

Dr. Yeh: I am also using it less than I did previously. However, there are situations including mild to moderate disease, especially if the patient has a history of elevated IOP, that I'll consider periocular steroids. Intravitreal triamcinolone 2 mg can have a great efficacy benefit as well while minimizing the safety issues.

Dr. Srivastava: I agree; triamcinolone 2 mg works very well. We all know that systemic steroids have side effects, but there is a clear use for them in ophthalmology to control inflammation. Do you use oral steroids to control uveitic macular edema?

Dr. Sharma: If someone presents to me for the first time with active inflammation, I am cautious about injecting steroids. I want to make sure it's not infectious disease, and I want to make sure they respond to steroids in a way that makes sense. I use it as a diagnostic and therapeutic trial. If they respond well to it, that's when I'd consider local therapy.

Dr. Srivastava: Do you have certain criteria that must be met before you'll give a steroid injection around the eye in order to keep the patient safe?

Dr. Yeh: It's tailored to the patient and tailored to the disease process. If you have a patient with bilateral macular edema and known systemic autoimmune conditions such as sarcoidosis, a systemic steroid is a good option. On the other hand, I'll start a conversation with the patient about oral steroids. Sometimes they'll know what the side effects are, and I'll have a conversation about the local therapies. The patient's reaction will tell you which direction you're going to go.

Dr. Srivastava: Before you give a periocular, intravitreal, or suprachoroidal injection, are you ruling out infections beforehand?

Dr. Sharma: You always want to rule out syphilis and tuberculosis. If the patient has any form of retinal whitening, you need to have a very high index of suspicion for it being an infection.

Dr. Yeh: I think about anything potentially infectious that will evolve quickly with corticosteroids, such as toxoplasmosis and herpetic retinitis.

INJECTING INTO THE SUPRACHOROIDAL SPACE

Dr. Srivastava: Injecting into the suprachoroidal space is new and may have several benefits such as potentially preferential targeting of posterior segment tissue, a reduction in drug exposure to the anterior chamber and vitreous, which may confer safety advantages, and improved pharmacokinetics and drug durability.[1,13] It potentially makes a lot of sense for us. Suprachoroidal injections are different from intravitreal injections. The suprachoroidal injections take longer, and the microinjector is designed for both hands. Do you use a numbing agent for intravitreal injections?

Dr. Yeh: I use subconjunctival lidocaine for anesthesia.

Dr. Sharma: If it's a 30- or 32-gauge needle, I use topical most of the time. However, for something like the dexamethasone implant, I use subconjunctival lidocaine.

Dr. Srivastava: Do you use a numbing agent?

Dr. Yeh: I use subconjunctival lidocaine. I'll do it away from the area specifically that I'm injecting in the rare chance that there's a subconjunctival hemorrhage.

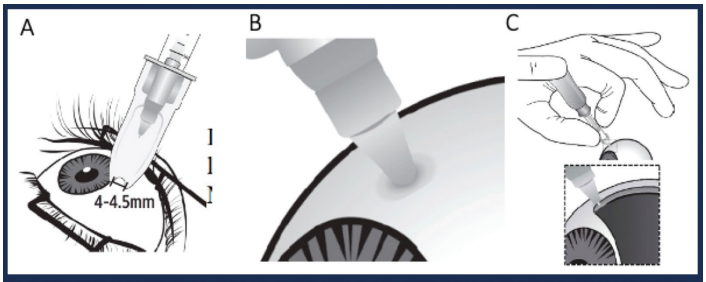
Dr. Srivastava: In a user experience survey, more than 80% of physicians stated that suprachoroidal injections presented no new challenges compared with other injection types.[14] Do you agree?

Dr. Sharma: I think that there's a bit of a learning curve for your first few injections. It's not an intravitreal injection, which we're all used to. You have to find the suprachoroidal space, and you must be 100% perpendicular to the sclera as you do the injection. You will feel a loss of resistance to pushing the plunger down on the device, and there's a learning curve in getting the hang of it. It almost feels like it's going in by itself.

Dr. Yeh: I agree. The suprachoroidal space is a lower resistance system. You should feel the loss of resistance as medication goes in.

Dr. Sharma: You also need to inject slowly. You want to count in your head at least 5 seconds and maybe even 10 seconds.

Dr. Srivastava: The injection site should be 4 mm to 4.5 mm posterior to the limbus. The needle hub must be firmly against the conjunctiva, creating a dimple. You'll know you've reached the suprachoroidal space when you feel a loss resistance. Figure 1 illustrates proper injection technique.



(A) The injection site should be 4 to 4.5 mm posterior to the limbus
(B) The needle hub must be firmly against the conjunctiva, creating a dimple
(C) Clinicians will know if the needle is in the correct location if they feel a loss of resistance

Figure 1. Proper injection technique into the suprachoroidal space.

The needle comes in two sizes, 900 µm and 1,100 µm, to accommodate variation in patient anatomy. How do you know which size to use?

Dr. Sharma: You always start with the 900 µm needle. If you look at the overall data, 80% of eyes are able to be injected with the 900 µm. It's a matter of making sure you really are perpendicular. If you're experiencing an issue, take 30 seconds to change the angle of the needle and the plunger system to make sure that the 900 µm needle will not work. There is a risk involved by switching to 1,100 µm. You want to be careful about not switching unless you absolutely need to.

Dr. Yeh: I agree; the 900 µm needle seems to work for 70 to 80% of patients. The first time a patient has this injection, I do tell them that we don't know the thickness of their sclera. Therefore, we're going to have to figure out which needle will work. I prepare them for this so that if they see me moving around in the patient room or changing and repriming the needles, then they're not worried that something's wrong. We're just finding the best fit.

Dr. Sharma: You also need to warn the patient that they will feel a lot of pressure because it's not like their regular injection. The other key is that if you're not completely perpendicular, you may see some reflux onto the scleral surface. That's okay. Finally, we're advised that the injection site should be 4 to 4.5 mm posterior to the limbus. I've been much more successful being about 4.5 mm back rather than 3.5 to 4 mm.

Dr. Srivastava: I do talk to my patients about the pain differences between suprachoroidal and intravitreal injections. The pain is real and can be minimized by injecting slowly and consistently. It will be uncomfortable, and they will feel a lot of pressure. It's tolerable, but different.

UNDERSTANDING PEACHTREE AND MAGNOLIA DATA

Dr. Yeh: PEACHTREE was the pivotal phase 3 randomized, controlled, double-masked, multicenter trial that looked specifically at suprachoroidal triamcinolone acetonide (CLS-TA).[12] Patients with macular edema due to noninfectious uveitis were randomly assigned 3:2 to either the suprachoroidal injection

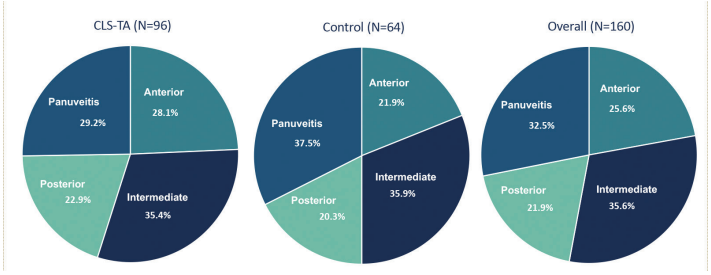


Figure 2. Anatomic subtypes enrolled in PEACHTREE.[12]

given at day zero and week 12 or to the control arm. The primary endpoint was the proportion of patients gaining at least 15 ETDRS letters in BCVA at week 24, which was really quite novel. When you think about trials for uveitis, many of our benchmarks are based on vitreous haze. However, visual acuity is the most meaningful and, oftentimes, the important metric to our patients.

During the 6-month period after the patients were randomly assigned, they were allowed to have rescue therapy according to prespecified criteria, including reduced visual acuity and increasing macular edema if there were any concerns from the investigators. Inclusion criteria included patients with macular edema with central subfield thickness (CST) of at least 300 µm, noninfectious uveitis of any associated diagnosis/etiology in any anatomic location, active or controlled inflammation, and a VA of 20/800 to 20/40 (≥ 5 to ≤ 70 ETDRS letters). Patients were excluded if they had advanced glaucoma or if they were on two IOP-lowering medications.

There was a slight preponderance of females, which we see in uveitis practice. At baseline, there's a slight increase in CST in the control arm, although this was not statistically significant. But you can see all these patients did have macular edema. Figure 2 breaks down all anatomic subtypes enrolled, which is reflective of what we see in our clinical practice.

PEACHTREE met its primary efficacy endpoint, with 47% of patients in CLS-TA group demonstrating at least a 15-letter improvement ETDRS visual acuity compared to 15% in the control group at month 6. This was statistically significant (*P*<.001). Figure 3 shows the mean change in BCVA over time and, interestingly, you start to see improvement around week 4.

Dr. Srivastava: The second shot is given at week 12, but most of the visual improvement occurs in the first 12 weeks. Is the second shot adding durability or efficacy?

Dr. Sharma: There's probably some signs of activity at that point, because between week 8 and week 12, you don't see any change. Then after that second injection, you start to see a little bit of a gain again. Therefore, there's probably some efficacy benefit.

Dr. Srivastava: Say the patient is at week 12 and comes back. The patient had 600 µm of macular edema but now has a beautiful macula. Are you re-injecting them?

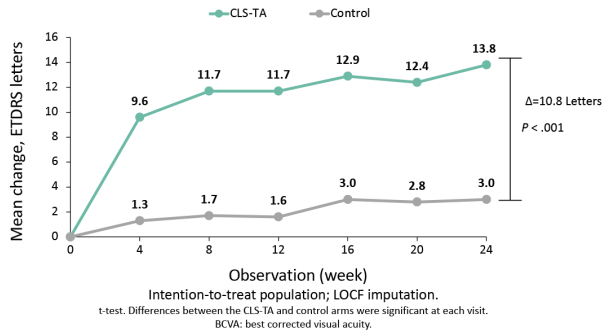


Figure 3. PEACHTREE: Mean change in BCVA through 24 weeks.[12]

Dr. Yeh: The MAGNOLIA study showed that some patients don't need an additional injection. If the macula looks good and their visual acuity has improved to baseline, I am inclined to observe.[15]

Dr. Sharma: It's tough because we don't want a rebound effect. We don't want to wait until the edema is really bad before we retreat them, but I don't think this study informs us to that regard. There are unanswered questions. What is the right interval to treat? What is the real durability of the treatment?

Dr. Yeh: When we think about visual acuity by anatomic location, at least from the standpoint of performance with suprachoroidal drug delivery, Figure 4 shows that this benefit extended across the various anatomic subtypes including anterior, intermediate, posterior, and panuveitis.

CST improved to about 150 µm at week 4, with a little plateau around week 12. But with another injection, there's some potential added benefit here as well (Figure 5).

Dr. Sharma: Patients are getting worse at week 12 compared to week 4. There's probably still some disease activity, and it's looking like it's starting to wear off at week 24, too.

Dr. Yeh: Moving ahead by anatomic location, to give you a high-level view of what's happening across the various anatomic locations, you see a greater benefit in the intermediate, posterior, and the panuveitis groups than in the anterior uveitis group (Figure 6).

We're seeing fairly consistent data in terms of the timing of the improvement and also the sustained effect at week 24. When we

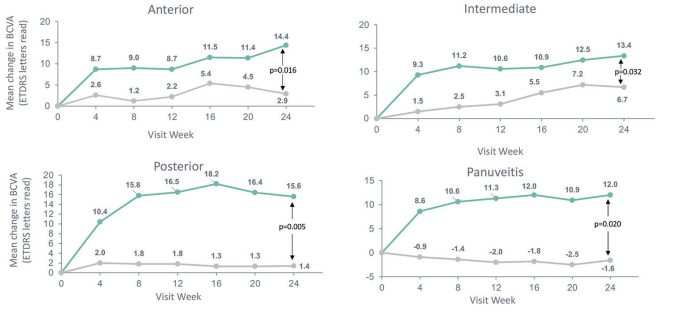


Figure 4. PEACHTREE: BCVA mean change from baseline by anatomic location.[12]

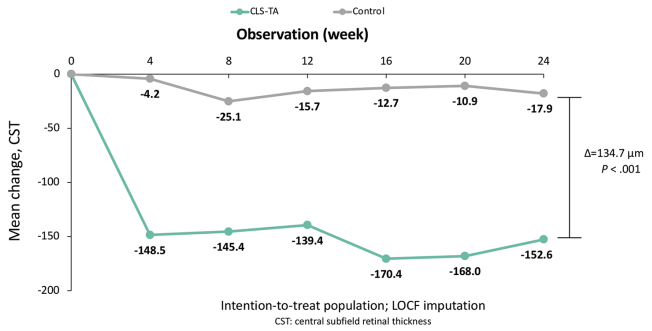


Figure 5. PEACHTREE: Mean change in CST.[12]

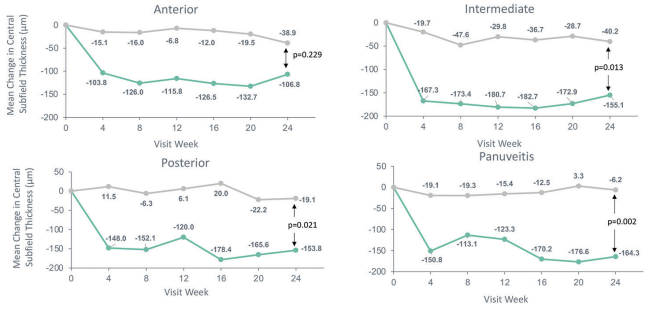


Figure 6. PEACHTREE: Mean change from baseline in CST by anatomic location.[12]

look at aggregate data, we see fluctuations of 8 to 10 µm across populations. Perhaps as a population, there were some patients who got a little bit worse. I think it's going to be interesting as we see this medication therapeutic used in practice. Who are the patients who need additional injections at week 12 versus others who need it perhaps a little bit later on?

We also looked at anterior chamber inflammation, anterior chamber cell, and anterior chamber flare. More than 70% of individuals in the suprachoroidal arm showed an improvement or resolved their anterior chamber inflammation, and 68% showed an improvement in vitreous haze.

Dr. Srivastava: Does the drug get into the front of the eye or does the anterior chamber inflammation start farther back?

Dr. Yeh: I think that ultimately, we think about the ciliary body and that location of inflammation where the cells are coming forward into the anterior chamber just because of circulation. We think about the inner and the outer blood retinal barrier. I think both locations are important in terms of disease control.

Individuals who received the suprachoroidal injection were far less likely to need a rescue therapy compared to controls (13 vs 72%). However, about 1 in 8 individuals in the suprachoroidal arm did require rescue therapy.

Regarding adverse events, there are some important things to consider. Anytime we're deploying a new drug-delivery platform and medication into clinical practice, we want to think about serious adverse events. There were no deaths and no cases of suprachoroidal hemorrhage or endophthalmitis. Ocular adverse events occurring in more than 5% of patients in the treatment arm included elevated IOP (12%), eye pain, and cataract. Interestingly, 16% of patients in the control arm also experienced elevated IOP. Why would patients in the control arm experience elevated IOP? Well, patients were allowed to receive rescue therapies. If you look specifically at the rescue therapies that were given, there are nearly 40 individuals who had rescue therapies. Of these patients who received local corticosteroid injection, about 26% of these individuals who had local corticosteroid rescue developed elevations in IOP. IOP-related adverse events were quite favorable from the standpoint of suprachoroidal injection.

MAGNOLIA was a prospective, noninterventional, masked, observational, 24-week extension trial.[15] To be eligible for MAGNOLIA, patients must have completed PEACHTREE without rescue medication. The primary endpoint was time to rescue therapy relative to day zero of PEACHTREE. Half of the patients who were in the suprachoroidal arm did not receive any rescue therapy through the week-48 time point of MAGNOLIA (Figure 7). This was about 9 months from the last suprachoroidal corticosteroid dose.

What happens with the patients who need rescue therapy? There are a number of rescue therapies that were administered at investigator discretion. Figure 8 shows the rate of rescue medications by type for both the CLS-TA and control groups, categorized by the most targeted, or localized, type of rescue used, as rescued patients often received more than one types of rescue treatments during the study. Overall, control patients were rescued earlier in the study and therefore had more time to progress in the hierarchy of treatment.

A greater mean reduction in CST was observed in unrescued CLS-TA patients when compared to control (Figure 9).

In summary, the phase 3 PEACHTREE study is the first study to use macular edema due to uveitis as the primary endpoint, a major concern of physicians and patients. A total of 96 patients were treated with CLS-TA broadly including uveitis involving all anatomic locations, reflective of clinical practice. Efficacy signals were promising, with nearly 50% of 3-line gainers, reduction of macular edema, and a vast majority of treatment patients averting the need for

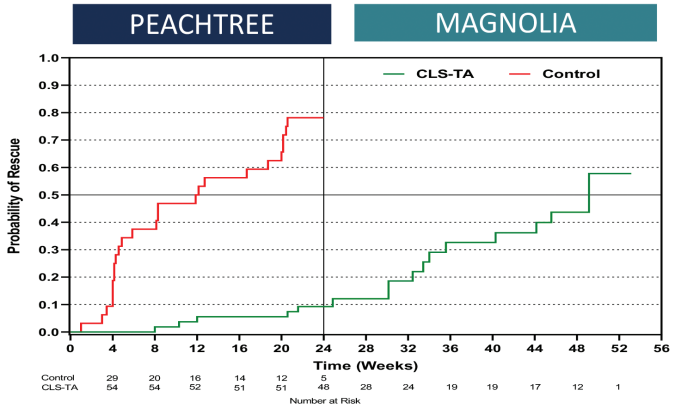


Figure 7. MAGNOLIA: Kaplan-Meier time to first rescue.[15]

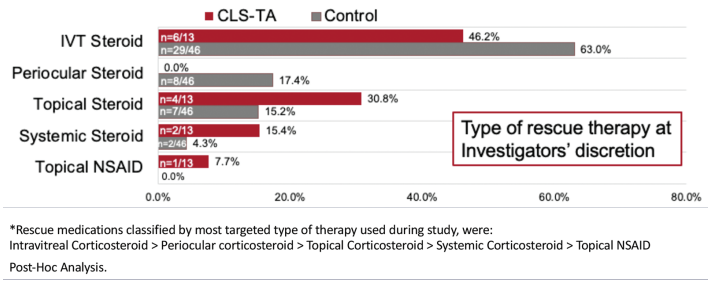


Figure 8. Rescue therapy rates: CLS-TA versus control.[16]

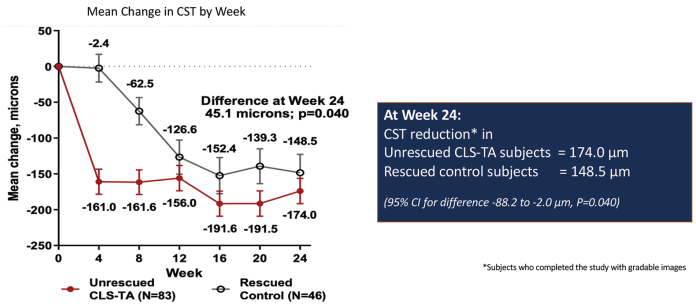


Figure 9. Mean reduction in CST for unrescued CLS-TA patients versus control.[16]

rescue therapy. Besides these promising efficacy signals, the safety profile was favorable overall with a low rate of cataract and IOP elevation. Taken together, these efficacy and safety signals suggest benefit for patients with macular edema due to uveitis, a complex, and often challenging disease condition.

Dr. Srivastava: Where does CLS-TA fit in the treatment paradigm?

Dr. Sharma: Anytime we have a new drug, we're going to use it in our most challenging cases. I am using it in my aphakic patients, in previously vitrectomized eyes, and in eyes that have had a secondary intraocular lens in which I can't use dexamethasone.

Dr. Yeh: Many of our patients have chronic disease with a tendency to recur. I think of this medication as an alternative. I talk to the patient about the new therapy and potential risks and benefits.

Dr. Srivastava: It's not very common, but I have had patients who will respond to one steroid and not another. I'd considering using CLS-TA for those patients as well.

OASIS AND TYBEE: INVESTIGATIONS INTO SUPRACHOROIDAL AXITINIB

Dr. Sharma: Let's discuss some newer studies that have been used with suprachoroidal steroids. OASIS (NCT04626128) is a phase 1/2A open-label study with the primary endpoint of safety and tolerability of escalating single-dose suprachoroidal injections of axitinib (CLS-AX), a tyrosine kinase inhibitor, following intravitreal aflibercept in patients with neovascular AMD.[17] There are four cohorts at different doses: Cohort 1, 0.03 mg; Cohort 2, 0.10 mg; and Cohort 3, 0.50 mg. The dosing for Cohort 4 is to be determined. We are also looking at secondary endpoints of visual function, ocular anatomy, and the need for additional treatment.

In this trial, patients receive 2 mg aflibercept at screening. Thirty days later they get an injection of CLS-AX, which is axitinib injected into the suprachoroidal space. Axitinib is a tyrosine kinase inhibitor, which functions as a pan-VEGF inhibitor that blocks all forms of VEGF. Patients are then assessed at weeks 4, 8, and 12 for the need of additional treatment. The criteria for additional treatment are loss of at least 10 letters in BCVA with signs of exudation, an increase in CST greater than 75 µm, or a vision-threatening macular hemorrhage. If we look at the prior treatment history of the six patients who were treated in Cohort 1, four of six were requiring monthly aflibercept or ranibizumab injections. Two of the patients had three and two injections, respectively, in the last 6 months. No patients in Cohort 1 required additional treatment at 1 month after CLS-AX injection. Two of the six patients did not require additional treatment for 3 months after CLS-AX injection (Figure 10).[18]

Dr. Srivastava: Why use the suprachoroidal space instead of intravitreal injection in these patients?

Dr. Sharma: The thought is that the safety profile and the durability would be a little bit better if it's given in the suprachoroidal space rather than intravitreal. This is a very early study, and we'll hopefully see more as that program moves along.

The phase 2 TYBEE trial evaluated the potential safety, efficacy, and durability advantages with CLS-TA in conjunction with intravitreal aflibercept compared with aflibercept monotherapy for the treatment of DME.[19] Patients are randomly assigned 1:1 to either the combination of CLS-TA plus aflibercept, which is the active control, or aflibercept monotherapy, which is the control group, and assessed over 24 weeks. Patients are all treatment-naive with BCVA between 20 and 70 letters and a CST of greater than 300 µm.

The main outcome measure is mean change in BCVA from baseline. Treatment differences were assessed with a two-sided significance level of 0.10 looking at the mean change in BCVA from baseline. Figure 11 shows the mean change in BCVA in the intention-to-treat population (A) and per protocol population (B).

Figure 11 shows there is no statistically significant difference in vision at 6 months between the active and control groups. Although this is not depicted in the figure, the combination therapy group required about half as many injections, 2.6 versus 4.6,

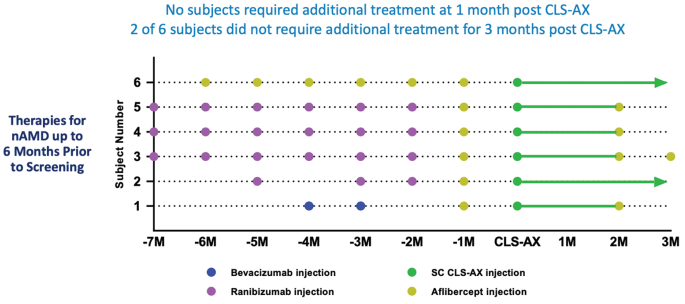


Figure 10. OASIS: Cohort 1 data.[18]

on average over that 6-month period. The combination therapy group also had greater reductions in CST compared to the individual aflibercept therapy.

What this tells me is that DME has an inflammatory component and adding that additional steroid can help reduce both treatment burden and improve CST. However, it doesn't make much of a difference on vision.

Dr. Srivastava: Anti-VEGF plus steroids make a lot of sense. The challenge for me has always been the safety profile of steroids in younger patients who have DR; there's a risk of cataract and the IOP elevation. Injection burden is also important, and if this therapy reduces the number of injections patients need, then there's a potential avenue for it. How often will we need to repeat treatment? What is the treatment burden over 2 years? We'll have to wait and see.

ONGOING INVESTIGATIONS INTO GENE THERAPY

Dr. Sharma: There's a lot of interest in delivering gene therapy in the suprachoroidal space. Gene therapy is also being investigated through intravitreal and subretinal delivery. Subretinal delivery requires taking the patient to the OR. Have either of you worked on subretinal gene therapy?

Dr. Srivastava: I haven't done subretinal gene therapy. The surgery has inherent risk.

Dr. Yeh: As we think about the morbidity associated with surgical treatment and the various complications that can occasionally come up, we have to be cautious about the risk/benefit profile.

Dr. Sharma: RGX-314 is a recombinant adeno-associated virus (AAV)-based gene therapy. Suprachoroidal injection of RGX-314 was studied in the phase 2, open label, active control, dose escalation AAVIATE trial for wet AMD.[20] Twenty patients in Cohort 1 were randomly assigned to receive RGX-314 at 2.5x1011 GC/eye versus monthly 0.5 mg ranibizumab intravitreal injection at a 3:1 ratio. Twenty patients in Cohort 2 were randomly assigned to receive RGX-314 at an increased dose level of 5x1011. Figure 12 shows AAVIATE interim data.[21] The left side of Figure 12 shows the prior injection treatments for patients in Cohorts 1 and 2. The right side of Figure 12 shows their injections after, which was per protocol. Researchers assessed the number of injections patients needed after therapy in the first 6 months compared with the prior year before therapy.

There was a reduction in the number of injections that were needed of about 75.9% and 71.8% in Cohorts 1 and 2, respectively. In terms of safety, there were four serious adverse events that weren't considered drug related. There were no cases of retinal vasculitis, retinal occlusion, or hypotony, but they did see a higher rate of intraocular inflammation, which was considered mild and only observed at the slit lamp. In Cohort 1, three patients had anterior chamber cell of various degrees of 0.5+ or 2+. One patient developed vitreous cell. In Cohort 2, three patients presented with anterior cell, which resolved

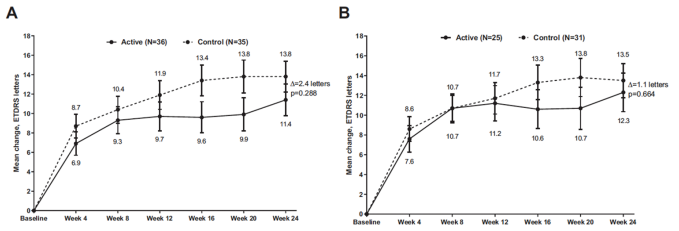


Figure 2. Graphs showing mean±standard error of the mean change in best-corrected visual acuity in the (A) intention-to-treat population and (B) per protocol population. ETDRS = Early Treatment Diabetic Retinopathy Study.

Figure 11. TYBEE trial results.[19]

with topical steroids.[21] How concerned are you about the inflammation and other treatment-related adverse events?

Dr. Srivastava: Every gene therapy will have inflammation. It's about tolerability and severity. If the inflammation is truly treatable with topical-based therapy, we can consider gene therapy. The numbers are small, so it's hard to know. Right now, it looks like 20% of patients experience inflammation. I think the concern is when you get to 1,000 patients and the inflammation rate is 20%. Is it all anterior or will some patients have severe inflammation?

This study is in the early stages, but I suspect if we try to control inflammation pretreatment, there is a pathway here. If it's truly mild, I think we'll accept it. We've been very lucky with the safety profile of anti-VEGF treatments, so any drug that causes inflammation will be a concern.

Dr. Sharma: I agree. The other concern is the episcleritis in the double-injection group. There were no instances of episcleritis in the single-injection group, but 1 out of 5 patients in the double-injection group had episcleritis at the injection site.

Dr. Srivastava: I think if it's tolerable and can be treated with topical therapies, then there's potential here. We'll have to wait and see. From a vision standpoint, I don't think we've seen any vision change in these patients, and there have been no reported cases of vasculitis. Those are all good signs, but it will come down to the severity of the complications.

Dr. Yeh: Timing is also important. When does it happen, and how long do we need to treat them?

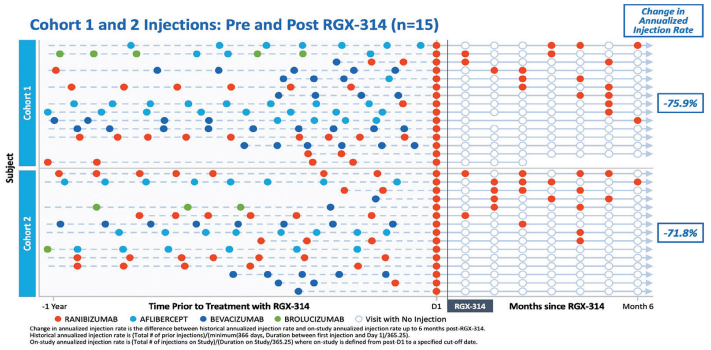


Figure 12. AAVIATE: Interim data.[21]

Dr. Sharma: ALTITUDE (NCT04567550) is a phase 2, open-label, randomized, controlled, dose-escalation study evaluating the efficacy, safety, and tolerability of suprachoroidal delivery of RGX-314 in patients with moderately severe or severe nonproliferative DR (NPDR) or mild proliferative DR (PDR). Patients have DR severity scale score (DRSS) scores between 47 and 61 without any active, center-involving DME. The primary outcome is the proportion of eyes with two-step improvement in DRSS at 48 weeks; the secondary outcomes include safety and the development and intervention of DR-related complications. Patients in Cohort 1 received a single injection of RGX-314 2.5x1011 GC/eye, and patients in Cohort 2 will be dosed with two injections of RGX-314 5.0x1011 GC/eye. Cohort 3 will be a slightly different treatment. Cohort 1 is fully enrolled, and 47% of patients had a two-step improvement in DRSS compared with observational control. Enrollment for Cohorts 2 and 3 is ongoing.

Anti-VEGF therapy is on-label for the treatment of moderately severe or severe NPDR. Are either of you doing it?

Dr. Srivastava: I do bring up anti-VEGF injections with patients. It makes sense logically for us to treat DR with anti-VEGF and prevent it. However, I don't think we've reached the point of anti-VEGF treatments for DR being routine because the time to vision change is sometimes long. But in this scenario, if you really are reversing or limiting DR with one injection, that's impressive. I think patients would be much more amenable to therapy.

Dr. Sharma: I agree. I don't often use anti-VEGF for DR because of the frequency that is required. However, if we could see improvement after one injection, then it makes a lot of sense. I do worry about the safety.

Dr. Srivastava: It's going to be an interesting time for DR. If a drug like this is approved, patients could receive one injection with extended durability.

Dr. Sharma: The 47% with a two-step improvement is comparable to 8-, 12-, or 16-week anti-VEGF injections. This could potentially be when you start to see treatment of NPDR.

CASE 1: 40-YEAR-OLD PATIENT WITH CHRONIC INTRARETINAL FLUID FOR YEARS

Dr. Srivastava: A 40-year-old man presents for evaluation of chronic intraretinal fluid that began almost 4 years ago with conjunctivitis. It was noted that he had intraretinal fluid on his optical coherence tomography (OCT) almost 4 years prior to presentation. He had a waxing and waning course, and was treated with topical NSAIDs, topical steroids, or combination. Figure 13 shows the clinical photo and the OCT. What do you notice?

Dr. Sharma: There's an unusual oval appearing area in the right eye in the foveal region. What's striking to me is that the patient is 40 years old and has cystoid macular edema (CME). That's unusual, and I'd want to see an FA. I'd also ask about other medical issues.

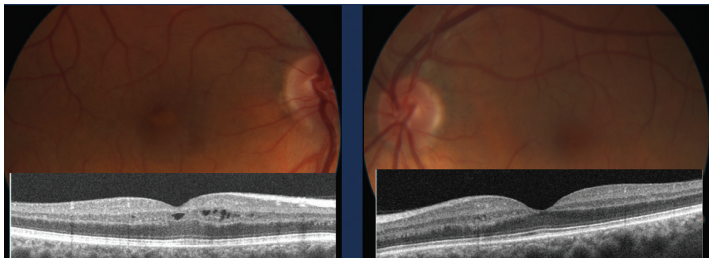


Figure 13. Case 1: Imaging 4 years prior to current presentation.

Dr. Srivastava: Figure 14 shows the FA. The unusual oval on the right eye looks like a cyst or area of petaloid leakage. There's also some petaloid leakage on the left eye. Tell me if I'm wrong, but I don't see any vascular sheathing.

The nerves don't look leaky. Remember, these images are from 4 years prior to his current presentation. Figure 15 shows his OCT at original presentation, 1 year after being treated topically, and now 3 years and 8 months later.

He began to develop CME again. There are some cells on the OCT that are certainly present at 3 years and 8 months, but they may have been there at year 1 as well. They could have been there at initial presentation, too; it's hard to tell. Now, he presents with worsening vision since his last visit and there's definite inflammation on clinical exam. His VA is 20/100 OD. He is 2+ cell OD with posterior synechiae. He comes back 2 months later, so 3 years and 10 months since his initial presentation, with worsening CME in his right eye. Figure 16 shows his OCT in both eyes over time and the FA.

Dr. Yeh: This is bilateral disease, even though structurally on the OCT, we see the disease in the right eye. In the left eye, initially on the FA, we saw some disease. When you look in the periphery of the left eye, you can see there's a diffuse retinal pigment epithelium

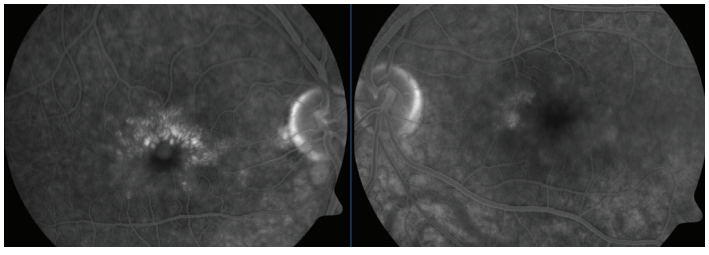


Figure 14. Case 1: FA 4 years prior to current presentation.

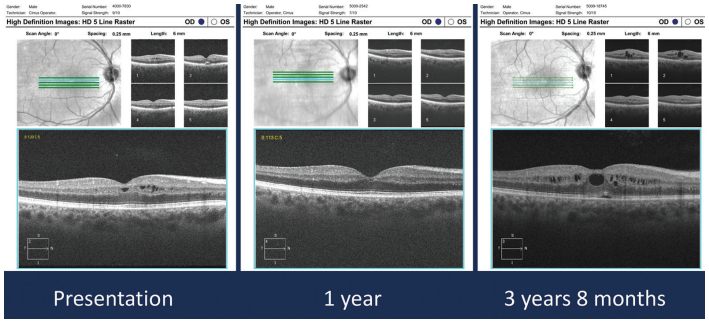


Figure 15. Case 1: OCT imaging over time.

(RPE) change, hyperfluorescence, and window defects as well as some disease. This indicates a degree of chronicity for whatever process is ongoing.

Dr. Srivastava: Is this new disease or the same disease?

Dr. Yeh: This is potentially the same disease all along. You'd mentioned it had a waxing and waning course with the initial red eye. I would take a step back and think about a laboratory workup to again rule out infectious disease. We also have to think about what's going on from a health perspective with the patient.

Dr. Srivastava: Figure 17 shows his initial differential versus his current differential. Dr. Sharma, this is your patient. Did you expect him to be syphilis IgG positive? His rapid plasma reagin (RPR) is 1:256. Do you put him on penicillin at this point?

Dr. Sharma: If I had seen this patient all along, I would have performed wide-field imaging and I would have had a high index of suspicion on someone who is 40 years old and otherwise healthy. I don't know if I would've thought it was syphilis. But the day he came in with anterior segment inflammation, synechia, and a lot of lens changes was the first time I saw him. At that point, given that granularity in the left eye, syphilis was on the list.

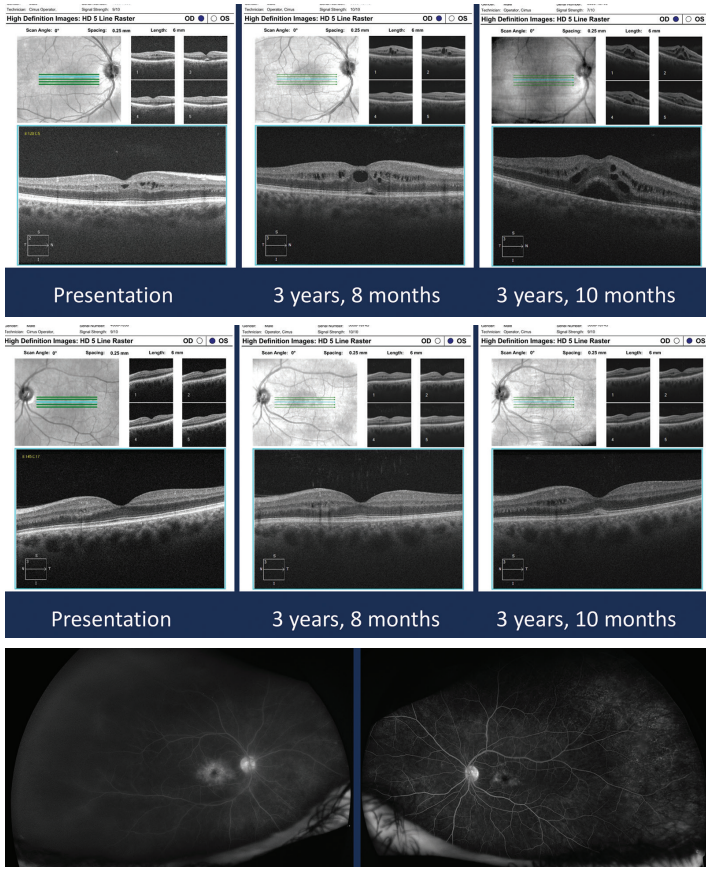


Figure 16. Case 1: OCT OU, FA.

Dr. Srivastava: The patient received penicillin and his RPR started to come down. If we look back at his OCT and FA from the beginning, there are clues that he had syphilis from the beginning. Syphilis rates continue to rise everywhere. The take-home message here is to always rule out infection, even in someone who comes in with a history of chronic intraretinal fluid.

CASE 2: SARCOIDOSIS WITH OCULAR AND PULMONARY INVOLVEMENT

Dr. Yeh: Our next case is a 45-year-old patient who had biopsy-proven sarcoidosis with ocular and pulmonary involvement. He had been previously treated with prednisone and methotrexate, but as with some of our patients, he developed elevated liver enzymes. He was treated with intravitreal dexamethasone implant about 2 months prior and has a history of ocular hypertension, for which he takes twice-daily timolol. His VA was 20/25 at baseline with an IOP of 18 mm Hg. His VA declined to 20/80. His OCT and FA show a diffuse cystoid spaces and subretinal fluid with leakage. We treated him with suprachoroidal CLS-TA. Two months later, he had a nice resolution of the cystoid spaces on OCT, and his VA improved to the 20/30 range. When you think about sarcoidosis, is it typically responsive to a medication like CLS-TA? Does the suprachoroidal delivery help with efficacy?

Dr. Sharma: In my hands, sarcoidosis responds well to even low-dose steroids. This is the perfect situation for CLS-TA. The choroid is often the primary site of involvement so it makes a lot of sense.

CASE 3: HLA-A29+ BIRDSHOT RETINOCHOROIDOPATHY

Dr. Yeh: Our next case is a 54-year-old patient with HLA-A29+ birdshot retinochoroidopathy. Her VA is 20/50 in the right eye and 20/70 in the left eye, with extensive CME in both eyes. She was initially very reluctant to have local corticosteroids. She was on methotrexate and prednisone. She had some fatigue on methotrexate and was not interested in going to another immunosuppressive medication. We tried periocular subtenon triamcinolone injection, and it didn't have a substantial benefit. Her visual acuity declined some, and her CME did not improve substantially. We gave her intravitreal dexamethasone and Ozurdex in both eyes, and she had some improvement, shown on Figure 18.

You can see that she's had some improvement. We've gradually come down in her prednisone. Her VA improved to 20/30 and 20/50. I'm interested in your opinion. How would you approach this? What would you do next?

Dr. Sharma: Did you take any images at 6 or 8 weeks after? I find that dexamethasone is often wearing off at 10 weeks and this could be rebound of the CME.

Dr. Yeh: This was several weeks after. There was initial improvement but it never went away completely.

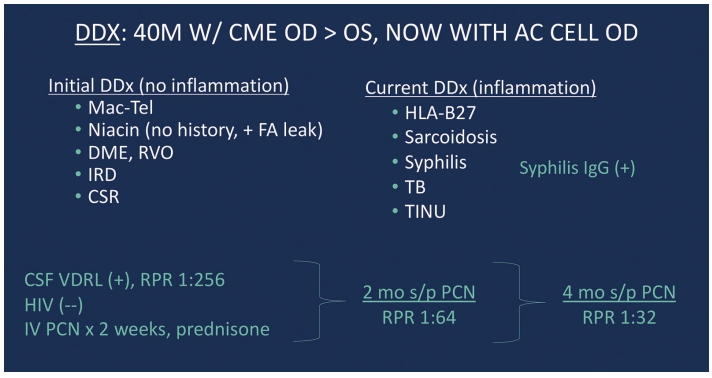


Figure 17. Case 1: Initial versus current differential diagnosis.

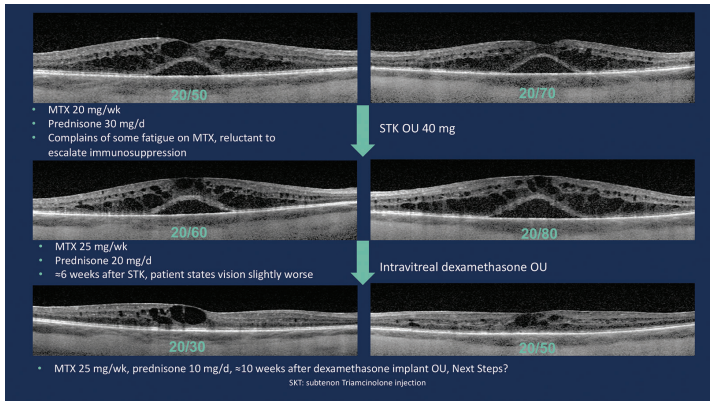


Figure 18. Case 3: OCT imaging posttreatments.

Dr. Srivastava: This is a very sick retina. It's not just the cyst, it's the size of the cyst, especially in the right eye, the diffuse nature of it, and the subretinal fluid. You almost feel the outer retina stretching. I don't know if we're properly treating the choroidal disease with 25 mg of methotrexate for 2 to 3 months. I don't think it's kicked in yet, and needs a little more time. Does it make sense to give something in the suprachoroidal space? There are some patients who need long-term steroids in the eye. This is where I start thinking about the surgical fluocinolone implant. I do want to see what happens with the suprachoroidal space because this makes sense to me. Her choroidal thickness hasn't changed and the choroid is inflamed. Dexamethasone hasn't changed that, which tells me there's extensive choroidal disease here. We're going to have to do another program to see how this turned out. ■

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TARGETING THE SUPRACHOROIDAL SPACE: CURRENT EVIDENCE AND BEST PRACTICES FOR THE TREATMENT OF POSTERIOR SEGMENT EYE DISEASES

Release Date: December 2022
Expiration Date: December 2023

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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**
Develop treatment plans for uveitic macular edema that incorporate new agents when appropriate based on recent clinical data and FDA approvals.	_____	_____	_____
Describe proper administration techniques of suprachoroidal injections, solutions to common challenges, and best practices in patient education and informed consent.	_____	_____	_____
Assess clinical trial results examining the suprachoroidal space as a potential pathway for future treatments in eye diseases of the posterior segment.	_____	_____	_____

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 is the leading cause of vision impairment and vision loss in uveitis?

a. Cataract formation
b. Retinal detachment
c. Corneal edema
d. Macular edema

3. A 46-year-old patient presents to your office for evaluation of recurrent uveitis. She has persistent macular edema despite various therapeutic agents, and she is interested in learning about suprachoroidal delivery of triamcinolone. Which of the following is TRUE about suprachoroidal injections?

a. Suprachoroidal injections result in increased drug exposure to the anterior chamber and vitreous, compared to intravitreal injections
b. Suprachoroidal injections result in decreased drug exposure to the anterior chamber and vitreous, compared to intravitreal injections
c. Suprachoroidal injections result in equivalent drug exposure to the anterior chamber and vitreous, compared to intravitreal injections
d. Suprachoroidal injections potentially preferentially target anterior segment tissue

4. You decide to administer a suprachoroidal injection of triamcinolone on the above patient. She is nervous about side effects from suprachoroidal injections, as she has never had a suprachoroidal injection before. According to studies, what is the most common treatment-related adverse event in suprachoroidal injections?

a. Eye pain
b. Vitreous hemorrhage
c. Retinal tear
d. Endophthalmitis

5. According to the PEACHTREE trial, what percentage of patients in the CLS-TA arm demonstrated at least a 15-letter improvement in ETDRS visual acuity?

a. 27%
b. 47%
c. 67%
d. 87%

6. According to the PEACHTREE trial, what percentage of patients in the CLS-TA arm had resolution of anterior chamber cell and flare by week 24?

a. ~30%
b. ~50%
c. ~70%
d. ~90%

7. You are seeing a 55-year-old patient with a history of chronic uveitis with macular edema. You determine she needs additional local corticosteroid treatment for her disease. After a risk/benefit discussion of her options, she chooses to undergo a surgical intravitreal implant for increased durability. Which of the following would be a good option for this patient?

a. Dexamethasone 0.7 mg (Ozurdex)
b. Fluocinolone acetonide 0.59 mg (Retisert)
c. Triamcinolone acetonide 4 mg (Triesence)
d. Fluocinolone acetonide 0.18 mg (Yutiq)

8. You are seeing a 48-year-old woman who presents with a history of chronic uveitis, which has been managed with oral prednisone for many years. She has a history of hypotension osteoporosis and diabetes. On ophthalmic exam, you note bilateral cataracts, keratic precipitates, and significant macular edema. All of the following can be adverse effects of steroids, EXCEPT:

a. Osteoporosis
b. Diabetes
c. Hypotension
d. Cataracts

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:

_____

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

_____

_____