Exploring the Rationale for Steroid Use in Noninfectious Posterior Uveitis
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During the Vit-Buckle 2.0 Meeting in March 2014, 6 renowned clinicians came together to provide a glimpse into how corticosteroids are used in the management of noninfectious posterior uveitis, with a focus on quality-of-life considerations, adverse events, and nonresponders to steroids at appropriate doses.

MODERATOR

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CURRENT THERAPEUTIC CONSIDERATIONS

Thomas A. Albini, MD: Steroids are a popular choice for the treatment of uveitis and are available in various formulations, including oral, topical, periocular, intravitreal, and/or sustained-release delivery. Please describe your practice and how you use steroids for noninfectious uveitis.

Steven Yeh, MD: I am a vitreoretinal surgeon and uveitis specialist, and about 60% to 70% of my practice is dedicated to uveitis. My treatment algorithm for uveitis is defined by the patient’s condition, the disease’s severity, the potential for visual morbidity, and laterality. For patients with severe bilateral disease, I will typically consider a systemic corticosteroid followed by systemic steroid sparing immunosuppression. For pseudophakic patients with unilateral disease or asymmetric, bilateral disease, I will consider a local and/or with periocular corticosteroids or intravitreal dexamethasone or triamcinolone. Patients who require long-term corticosteroid therapy may warrant a fluocinolone acetonide implant 0.59 mg (Retisert, Bausch & Lomb) (Figure 1). Patients with bilateral disease may require local therapy, and there are situations when patients with unilateral disease will also need systemic therapy. In all patients on corticosteroids, however, side effects warrant careful consideration.

Nisha Acharya, MD: I only see patients with uveitis. In my practice, we start with periocular injections of triamcinolone. We sometimes use intraocular injections of preserved triamcinolone acetonide (Kenalog-40, Bristol-Myers Squibb) in the absence of other options. Otherwise, for intravitreal injections, I mostly use preservative-free triamcinolone acetonide (Triesence, Alcon). Also, my use of the intravitreal dexamethasone implant (Ozurdex, Allergan) has increased during the past 1 or 2 years, although I refer these individuals to retina specialists when our patients need implants.

Sunir Garg, MD: My practice is 70% retina and 30% uveitis. I most commonly use Kenalog via sub-Tenon injection, followed by the dexamethasone implant, and then the 0.59-mg fluorocinolone acetonide intravitreal implant. I use intraocular injections of Triesence the least.

James Rosenbaum, MD: I am a rheumatologist working in an ophthalmological setting where I started a uveitis clinic 28 years ago. I do not perform intravitreal or periocular injections. In my clinic, the uveitis or retina fellow performs the injections. We always try the periocular route before we enter the eye. We still use Kenalog because of cost, and we also consider Triesence and the dexamethasone implant. One of our retina colleagues performs Retisert implants.

Harry W. Flynn Jr, MD: I am a vitreoretinal surgeon and I have a special interest in endophthalmitis, but my practice is greater than 95% retina. I most commonly use dexamethasone in conjunction with intravitreal antibiotics for endophthalmitis. I also use intravitreal triamcinolone for selected patients with diabetic macular edema (DME) and cystoid macular edema (CME).

TREATMENT CRITERIA

Dr. Albini: What criteria determine your use of topical, sub-Tenon injections, or systemic corticosteroids in patients with posterior segment uveitis?

Dr. Rosenbaum: In my opinion, oral steroids are the best and worst drugs. They are inexpensive, have rapid results, and some patients feel better when they are on them. Conversely, being on steroids is a miserable experience for some patients.

Dr. Acharya: I use regional and systemic steroids. An important consideration is whether the patient will need long-term therapy. Certain conditions such as multifocal choroiditis or birdshot chorioretinopathy will require long-term treatment. If long-term treatment is required, I use local or systemic steroids to gain control quickly while introducing slower-acting systemic immunosuppressive agents.

Dr. Albini: In some cases of chronic low-grade uveitis,
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oral steroids may not be necessary. In birdshot chorioretinopathy, for instance, patients can present with only a few cells and no CME or vasculitis, so steroids are not necessary. In these rare cases, the patient needs long-term immunosuppression, and we start with an anti-metabolite, knowing that it will take 2 months to kick in. There are also patients who have had previous bad experiences while on steroids and refuse to take them again. In this subset, an intravitreal steroid injection may be a good idea.

I have used oral cyclosporine for patients who need a quick-acting steroid-sparing immunosuppressive agent. Although anti-tumor necrosis factor (anti-TNF) drugs like infliximab (Remicade, Janssen Biotech) or adalimumab (Humira, AbbVie) may be quicker acting than traditional steroid-sparing agents, I have not had experience using anti-TNFs as a quick-acting substitute for steroids.

Dr. Rosenbaum: We do not typically use biologics or anti-TNFs as primary therapy, because they are expensive, and third-party payers may refuse to reimburse unless something else is tried first. On the rare occasion when I do use a biologic, I usually try it for a minimum of 3 months before giving up on it. Biologics can have a rapid onset of action in some patients, but not in others.

Dr. Yeh: Patients with bilateral disease, such as sympathetic ophthalmia or Behçet disease, respond well to systemic corticosteroids. Behçet disease can be easily confused with acute retinal necrosis. For patients who have the latter, a local or periocular corticosteroid can result in blindness. In the case of Behçet disease, oral prednisone is preferred, because there is adequate time to change course if the patient’s condition worsens. Ruling out an infectious etiology is critical, but in cases where I am not sure if there could be an infection, I would consider oral prednisone.

Dr. Garg: Because of its pharmacokinetics, oral prednisone can be initiated and stopped as needed, whereas a periocular steroid injection lasts for 3 to 4 months.

Dr. Albini: When using topical steroids, which topical preparations do you typically use, and have you had any difficulties with them?

Dr. Flynn: In my experience, patients being treated with difluprednate (Durezol, Alcon) 4 times a day may complain of stinging, and if they use it more frequently, they may not tolerate it. An alternative choice may be topical methylprednisolone 1%, which is available through compounding pharmacies. I often use methylprednisolone 1% for patients with endophthalmitis in the postrecovery, postantibiotic timeframe, because it has no preservative and is generally well tolerated. I use methylprednisolone 1% when the treatment will last for 2 or more months, but this nonpreserved medication requires a replacement bottle after 2 weeks.

Dr. Albini: I use compounded preservative-free methylprednisolone in patients who have had corneal issues or are sensitive to preservatives.

Dr. Albini: Has anyone else encountered stinging associated with difluprednate? In my experience, patients do not complain as much about stinging with difluprednate as with topical nonsteroidal anti-inflammatory drugs (NSAIDs).

Dr. Rosenbaum: The maximum dose schedule in the label is 4 times a day, and that is what we commonly use.

Dr. Garg: Because of its pharmacokinetics, oral prednisone can be initiated and stopped as needed, whereas a periocular steroid injection lasts for 3 to 4 months.

Dr. Albini: In patients with severe inflammation, should difluprednate be used more than 4 times a day?

Dr. Rosenbaum: The maximum dose schedule in the label is 4 times a day, and that is what we commonly use.

CONSIDERATIONS FOR SUB-TENON INJECTIONS

Dr. Albini: What is the typical scenario for sub-Tenon injections in your practice? Describe your technique.
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Dr. Garg: Patients with inflammation after cataract surgery and those with idiopathic intermediate uveitis do well with sub-Tenon steroid injections. It is also useful for patients whose uveitis is otherwise under control but who have residual macular edema. Finally, if I have a patient who has really good but not perfect control with a systemic medication, sometimes a periodic sub-Tenon injection will keep an eye quiet for 6 months.

In my clinic, I mostly use a superotemporal approach, especially in the presence of significant macular edema. Additionally, the more posteriorly you inject, the less the chance there is of an IOP rise. Occasionally, I inject inferiorly. One of the complications of repeat pericocular steroid injections is conjunctival scarring. Patients will tolerate 3 or 4 superior or inferior injections, but after that, conjunctival scarring makes additional injections difficult.

I use topical proparacaine or tetracaine followed by 1 drop of 5% povidone-iodine, because I want to limit the risk of infection in case the needle inadvertently goes intraocular. I use a 25-gauge short needle with a 3-cc syringe. Patients tolerate the procedure very well; it is probably the least uncomfortable procedure that I perform.

Dr. Flynn: Following universal precautions is always a good idea. Povidone iodine is easy to use and only takes 30 seconds to be effective. It is inexpensive and reduces the colony count on the ocular surface. Some of our patients are immunosuppressed or have other systemic factors that may increase the risk of an infection.

Dr. Garg: If you are giving someone an intracocular steroid injection, do you also keep them on a topical nonsteroidal?

Dr. Flynn: I have used topical steroids after a triamcinolone injection to get the maximum benefit of each, but it is probably is not necessary when using intravitreal steroids.

Dr. Albini: Where do intravitreal triamcinolone injections fit into your management of patients with posterior segment uveitis?

Dr. Yeh: Whether it is CME or vitreous haze, I prefer to use a retroseptal (sub-Tenons) corticosteroid injection as a first option. However, patients with severe uveitic...
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CME do not respond well to a periocular corticosteroid injection, so in those cases I consider an intravitreal corticosteroid injection.

**Dr. Albini:** In what other clinical scenarios do you use intravitreal steroid injections?

**Dr. Acharya:** Patients who are on systemic immunosuppressive therapy can have a flare-up of uveitis. Sometimes, I use an intravitreal steroid injection to gain quick control of an acute flare-up, and then I reassess their long-term treatment plan. I may need to increase their systemic immunosuppression, but it may take some time to achieve the increased immunosuppression. For example, in a patient who is reasonably well controlled but has active vascular leakage, a steroid can get a quick response in the eye, and that gives us time to increase the systemic immunosuppressant. Generally, I prefer to avoid serial intravitreal steroid injections in these patients, but as an occasional adjunctive therapy, it is helpful.

**Dr. Yeh:** An intravitreal steroid injection can also avoid multiple oral prednisone tapers, and it presents another rationale for using intravitreal rather than oral steroids. If a patient has already gone through 1 corticosteroid taper recently, an intravitreal corticosteroid injection is a good option to avoid the side effects of an increased dose of oral prednisone over a prolonged period of time, particularly if the patient is not ready for systemic immunosuppression or other local immunosuppressive options.

**Dr. Garg:** In the case of a patient who is on a systemic immunosuppressant and does not have active inflammation but still has persistent edema, an intraocular or periocular injection helps to eliminate the edema (Figure 3). Usually, only 1 treatment is needed.

**Dr. Albini:** When do you think the dexamethasone implant is the best option for a patient who needs intravitreal steroids?

**Dr. Acharya:** I am relatively new to using the dexamethasone implant, but my use is increasing, mostly in patients with uveitic macular edema when I want a longer effect. In our experience, the dexamethasone implant works well for macular edema, and lasts 4 to 6 months. Although this is anecdotal, our experience has been that we see a little less IOP rise with the implant. I have had patients who experienced IOP increases with Triesence, but less so with the implant. I should mention, however, that I have had a few patients who required glaucoma surgery after receiving the dexamethasone implant.

**Dr. Rosenbaum:** In my clinical experience, I see a peak effect in the first 3 months after using the dexamethasone implant, so I like using it in conjunction with systemic treatments. If I have a patient with vitritis who is on an antimetabolite and develops vascular leakage, the dexamethasone implant is useful and may last for 6 months or longer.

It is also worthwhile to note that the pharmacodynamics of the dexamethasone implant allow for it to be used in vitrectomized eyes. Although there is occasional anterior migration of the implant in eyes in which the posterior capsule is compromised, there is no issue of anterior migration in eyes with an intact posterior capsule.

**Dr. Flynn:** In your experience, do injectable drug delivery devices solve the problem of topical steroid noncompliance?

**Dr. Garg:** Yes, they do, but there is a tradeoff. We have had patients who received an implantable steroid, and their uveitis quieted down and they felt better. But because they felt better, they did not come back for follow-up care for several months. Meanwhile, they were going blind from glaucoma, because they had a significant increase in their IOP.

Figure 3. Despite having systemic immunosuppression with no active inflammation, this patient experienced an epiretinal membrane and cystoid macular edema due to uveitis. Supplemental topical, periocular, or intraocular steroids can help resolve the edema. However, some patients with epiretinal membrane will still need vitrectomy and a membrane peel to achieve long-term resolution of the macular edema.
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Dr. Albini: The same problem is seen with the Retisert implant, where a treated patient may not return for follow-up care. Paradoxically, this means that noncompliance is not a good indication for switching to the fluocinolone acetonide implant, even though it seems like it should be.

THE MULTICENTER UVEITIS STEROID TREATMENT TRIAL

Dr. Albini: The Multicenter Uveitis Steroid Treatment (MUST) Trial tested the noninferiority of the 0.59-mg fluocinolone implant relative to standard systemic therapy. In some of the secondary outcomes, such as control of inflammation, the implant actually performed better than systemic treatment at all time points. When do you start therapy with the 0.59-mg fluocinolone implant instead of following the systemic route?

Dr. Garg: If the disease is bilateral, I try oral corticosteroids first and then add a steroid-sparing agent. I use the 0.59 mg fluocinolone implant, if 1 eye is inflamed; I am having trouble controlling the inflammation; the patient cannot tolerate the systemic effects of steroids; or the biologics are not covered by insurance.

Dr. Albini: Some physicians with whom I have spoken are using the fluocinolone implant 0.59 mg in patients who need to be chronically immunosuppressed, but not as a first-line treatment. Examples of this strategy include patients with sympathetic ophthalmia, birdshot, or Vogt-Koyanagi-Harada disease.

Dr. Yeh: Some patients will come in specifically for a fluocinolone implant. Examples include those who have unilateral disease or pseudophakia, or those who have had a tube shunt or trabeculectomy. I try to avoid surgical implants in patients who are phakic or of working age, especially if they have bilateral disease.

SYSTEMIC CORTICOSTEROIDS

Dr. Albini: If you were to start systemic prednisone for noninfectious posterior uveitis, what dose would you use?

Dr. Yeh: When using systemic prednisone for treatment of noninfectious posterior uveitis, I typically start with between 0.5 mg/kg and 1.0 mg/kg. It depends how much inflammation I see clinically and the patient’s tolerance to previous systemic therapy with steroids.

Dr. Rosenbaum: Some data suggest that a daily dose of 2.0 to 5.0 mg of oral prednisone shortens life expectancy. Other reports say that if the dose is less than 8.0 mg a day, there is no effect on life expectancy. The adverse event profile of a patient on oral steroids depends on the individual patient. People vary in terms of weight gain, mood change, appetite, tolerance, blood glucose elevation, and osteoporosis. Therefore, we adjust treatment to individuals, but we generally keep a patient’s daily prednisone dosage to less than 8.0 mg a day, and in some cases we avoid it.

Dr. Albini: What is your protocol for tapering patients off of a 60-mg per day dosage?

Dr. Rosenbaum: It depends on how the drug affects the patient’s mood and what he or she thinks of the drug. Another thing to consider is that some individuals are intolerant to prednisone at one point, and then can tolerate it a few years later.

Dr. Acharya: For most patients with moderate-to-severe inflammation, I start at 1.0 mg per kg and maintain that dose for 2 to 4 weeks until I see a significant reduction in inflammation before I taper. For patients who have severe disease, such as Vogt-Koyanagi-Harada with a detached retina, I generally taper to about 10 mg per day over a few months. If the patient is intolerant, I taper more quickly. When I get down to below 5.0 mg per day, I taper slowly, because of the risk of adrenal insufficiency. At that point, I reduce the dose by 1.0 mg every 2 to 4 weeks until the steroids can be stopped.

Dr. Albini: What is the maximum dose of oral steroids that can be stopped with no tapering?

Dr. Rosenbaum: When tapering oral steroids, one must consider both dose and duration. Someone could take 60 mg per day for 5 days and stop abruptly, but if they have been taking 60 mg per day for a month, they administered 3 times a day has greater efficacy than 60 mg applied in the morning. If it is taken in the evening, its potency is increased. There is an occasional patient for whom we will use 1.0 g of methylprednisolone intravenously, such as a child with Vogt-Koyanagi-Harada disease.
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should taper. Another strategy for patients on a high dose of daily oral steroids is to switch to an alternate day dosing schedule. The disease state also influences how I taper. For example, patients with the “corticosteroid deficiency disease” Vogt-Koyanagi-Harada probably need 6 to 12 months of steroids, whereas patients with birdshot may require only 3 months of steroid treatment because the primary therapy is another modality.

**Dr. Albini:** In what percentage of immunosuppressed patients using mycophenolate mofetil (CellCept, Genetech) can you taper and stop steroids completely?

**Dr. Yeh:** Approximately 70% to 80% of these patients can be taken off steroids; about 20% to 30% will require a low dose of oral steroids.

**Dr. Albini:** In the Systemic Immunosuppressive Therapy for Eye Diseases (SITE) study, the most stringent outcome measure was complete control, which meant no cells and no steroids. Approximately 40% to 60% of patients achieved complete control, depending on the steroid-sparing drug selected.

**VASCULAR LEAKAGE**

**Dr. Albini:** Does the presence of vascular leakage change your decision making?

**Dr. Rosenbaum:** Now that we get widefield fluorescein angiograms on our uveitis patients, we see a lot of vascular leakage. Although a leaky vessel indicates some activity, seeing leakage on an angiogram does not necessarily make me treat more aggressively. I note the leakage, but if the patient is not symptomatic from it, I may or may not step up my therapy. If the leakage is peripheral, I would just watch it.

**Dr. Yeh:** If the disease is associated with vasculitis that will potentially lead to vaso-occlusion (such as systemic lupus with intermediate uveitis), and I detect leakage with widefield fluorescein angiography (Figure 4), I leave them on their current therapy rather than escalate if: their visual acuity is unchanged, the patient is asymptomatic, and there is no CME—all provided that there is no evidence of new areas of nonperfusion.

Similarly, if we have a patient with uveitis associated with multiple sclerosis, he or she can simply be watched if they are asymptomatic, have 20/20 vision, and a little leakage. My preference is to not use additional medications, particularly if they may already be on an immunomodulatory agent for the multiple sclerosis.

**ADVERSE EVENTS AND QUALITY OF LIFE**

**Dr. Albini:** What are the implications for treating with systemic steroids in terms of adverse events and quality of life?

**Dr. Rosenbaum:** Steroids work quickly and efficiently, but they are not a long-term solution. The list of adverse events is lengthy and includes: mood change (depression), lack of sleep, elevated blood glucose levels, osteoporosis, avascular necrosis, hair loss, gum disease, cataract, glaucoma, central serous retinopathy, increased appetite, fluid retention, weight gain, fat redistribution, acne, Cushing Syndrome, and more. Patients being treated with systemic steroids are at greater risk for activating tuberculosis (TB) and fungal infections compared with any antimetabolite that we use.

**Dr. Garg:** Do you check patients for TB prior to starting them on oral prednisone, or only if they are at high risk? For example, with a biologic such as an anti-TNF, you should always check for TB. Is that also true with prednisone?

**Dr. Rosenbaum:** It is recommended that if you are going to use methotrexate or another immunosuppressant, you should screen for TB. We screen everyone with a chest X-ray, but not everyone with TB has pulmonary TB.

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**Figure 4.** An ultra-widefield fluorescein angiogram highlights the extent of nonperfusion in a patient with panuveitis and occlusive retinal vasculitis. This venous-phase ultra-widefield angiogram shows hyperfluorescence and leakage of the disc and retinal vessels.

(Courtesy of Steven Yeh, MD)
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Dr. Albini: For locally delivered corticosteroids, there is a risk of glaucoma and cataracts. What is the frequency of glaucoma and cataract associated with topical and sub-Tenon injection, and the intravitreal dexamethasone and 0.59-mg fluocinolone acetonide implants? Starting with topical administration, if you are treating a child for uveitis with prednisolone acetate ophthalmic suspension, do you worry about cataract formation, and what doses do you think are reasonable for long-term management?

Dr. Yeh: Our goal is to get children off of prednisolone acetate ophthalmic suspension. Data from Jennifer E. Thorne, MD, PhD, show the risk of cataract increases when topical corticosteroids are used more frequently than 3 times a day. With adults, I adopt a similar practice. If a patient is phakic and using topical corticosteroids more than 3 times a day, he or she is at high risk for developing cataracts. In a clinical study with the dexamethasone implant, the rate of cataract development after 6 months of treatment was about 15%, compared with about 7% in the placebo group, although this difference was not statistically significant. Other studies have shown there was an increased risk of cataract with repeated use of the implant. Similarly, with retroseptal steroid injections, Dr. Thorne’s data showed that at 3 months the percentage of phakic patients developing cataracts was not high, but with repeated injections, it approached 50%. With intravitreal corticosteroids, the rate of cataract development was higher.

Dr. Flynn: After treatment with intravitreal steroids, roughly two-thirds of patients will develop a substantial cataract by 2 years. This means that 6-month data is just not long enough. You need at least 1 year of follow-up on patients to get a realistic number.

Dr. Acharya: Studies have shown that 5 intravitreal injections lead to a cataract that requires surgery.

Dr. Yeh: The MUST study showed that the incidence of cataract was 91% at 2 years when Retisert is used.

Dr. Albini: The incidence of cataract and glaucoma appears to be lower with the intravitreal dexamethasone implant than with Retisert or even depot triamcinolone. In the 3-year MEAD study, the rate of cataract progression was almost 70%, but the rate of incisional glaucoma surgery was less than 1%.

Dr. Flynn: In the DRCR.net protocol B study, about 33% of patients treated with triamcinolone 4 mg had an IOP elevation from baseline of 10 mm Hg or more at 1 year, but only about 1% of patients required glaucoma surgery. The incidence of pressure elevation was substantially higher in the 4.0-mg group compared with the 1.0-mg group (33% vs 16% respectively).

Dr. Albini: In addition to cataract and glaucoma, ptosis is also a complication of sub-Tenon injections. The incidence of ptosis is in the range of 1% to 2%, and while it is usually transient, it sometimes requires surgery. Although permanent ptosis is uncommon, it is important when it does occur.

Dr. Flynn: Ptosis must be included in the informed consent. Some patients will not continue in a clinical trial if ptosis develops after an injection.

ENDOPHTHALMITIS AND OTHER COMPLICATIONS

Dr. Albini: Are you at all concerned about endophthalmitis and pseudoendophthalmitis?

Dr. Flynn: With older brands of triamcinolones, there was a problem with crystals migrating around the zones of Zinn into the anterior chamber during the immediate postinjection period. It looked like endophthalmitis, but it was actually pseudoendophthalmitis caused by crystal migration. We have since learned that patients with pseudoendophthalmitis have no fibrin in the anterior chamber and the eye is externally quiet. There may be a snowstorm of steroids in the vitreous cavity causing reduced visual acuity in these postinjection patients. It is the reduced acuity that brings them back to the clinic for an examination. At this time, however, most clinicians can distinguish the noninfectious from infectious processes.

Dr. Albini: I think migration of the implant is another thing worth talking about here. A series of patients...
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treated with the intravitreal dexamethasone implant experienced migration of the implant into the anterior chamber. These patients had a compromised posterior capsule or were aphakic, and all had been previous vitrectomized. There was also a high rate of corneal toxicity and the implant needed to be removed. The data in this series showed that quick removal of the implant was better than delayed removal.

Dr. Flynn: Corneal endothelial damage is caused by the implant coming into the anterior chamber and causing direct trauma to the endothelium. Removing the implant is not as easy as it looks, because the implant can be difficult to manipulate and it tends to fragment.

Dr. Albini: Aside from a steroid trial, is there any way we can identify steroid responders so that we can select the ideal candidate for steroids versus the one who is going to develop severe glaucoma?

Dr. Acharya: I know that researchers have looked at different genetic markers, but to my knowledge, there are not yet any genetic markers that identify steroid responders.

Dr. Albini: If you compare the free-floating fluocinolone implant to the anchored fluocinolone implant, there seems to be a much lower rate of incisional glaucoma surgery required in the cohort of patients with the free-floating implant. This may mean that the location of the actual drug delivery does matter, and the closer the implant is positioned to the trabecular meshwork, the higher the rate of glaucoma.

Dr. Yeh: In 1 of the earlier studies with the dexamethasone implant using magnetic resonance imaging to determine the direction of drug migration, it appeared that when the drug was delivered more posteriorly, it was associated with a decreased incidence of elevated IOP.

Dr. Albini: In terms of complications, has anyone encountered hypotony following use of the Retisert implant?

Dr. Garg: I have not personally encountered that, but it has been reported that in some patients, when you finally get them inflammation free, their ciliary body ceases to function and they develop hypotony.

Dr. Acharya: My impression has been that patients who have hypotony after the Retisert implant are those who have a lot of inflammation going into the surgery. That is a risk with any uveitic patient. We found that treating them in the perioperative period with oral steroids, or with a quick-acting steroid injection, can sometimes help the ciliary body maintain function and result in less hypotony.

Dr. Albini: Many patients with chronic and severe uveitis have a ciliary body that produces very little aqueous, which is accompanied by minimal outflow, so their IOP is fine. After the inflammation is reduced pharmacologically, the outflow increases and the IOP decreases, resulting in hypotony. Another scenario is that there has been 1 intervention too many to the eye and the ciliary body shuts down. A third scenario could be related to insufficient wound closure.

Dr. Flynn: I agree. Sometimes the wound just does not heal, but more often, it is lack of aqueous production.

Dr. Yeh: The incidence of hypotony was about 11% in one of the clinical trials. From my point of view, chronic inflammation plays a role and so do multiple surgeries.

Another thing to consider is that some uveitis patients develop elevated IOP. These patients often need a tube shunt or a trabeculectomy. After the Retisert implant becomes nonfunctioning, at around the 30-month time point, the patient still has a tube or a functioning trabeculectomy, but their IOP is no longer elevated in response to the steroid.

Dr. Flynn: Which diseases are more likely to have that scenario?

Dr. Yeh: I have seen it frequently in patients with Vogt-Koyanagi-Harada disease and in patients with chronic granulomatous diseases, such as sarcoidosis, but not in patients with birdshot chorioretinopathy.

Dr. Acharya: Another complication associated with Retisert that I have seen recently is that the implant separates from the strut and floats around. The strut remains sutured to the pars plana, but the medicine reservoir disassociates.

Dr. Albini: Dr. Yeh and I wrote an article about removing the Retisert because the device can spontaneously fall apart. The impetus for the article was a surgery that
should have taken 30 minutes and ended up taking 90 minutes because it involved a vitrectomy and foreign body removal, because the implant fell apart. We put together a case series and the result was that Bausch & Lomb redesigned the implant with a new adhesive in an attempt to alleviate the problem. Physicians need to be aware of this issue, however, because it still sometimes happens. We have a video on Eyetube.net that demonstrates some surgical strategies that can be employed to avoid having these implants spontaneously self-destruct during removal.

**Dr. Yeh:** With the new implant redesign, I think the likelihood of dissociation will decrease, but we do not have long-term data.

### SYSTEMIC STEROIDS

**Dr. Albini:** Are there any special considerations for treating adverse events associated with systemic steroids?

**Dr. Rosenbaum:** Although we can sometimes use an alternative, some uveitis patients need systemic steroids. For example, there is not a good alternative to systemic steroids in patients with Vogt-Koyanagi-Harada disease or giant cell arteritis. The following can and do become issues with systemic steroids: elevated blood glucose, weight gain, mood changes, and central serous retinopathy. Avascular necrosis is a horrible complication, which is one of the reasons I try to avoid doses greater than 60 mg. Osteoporosis is another complication we watch carefully. Lastly, infections can dictate our treatment plan, and if a patient needs other surgeries, wound healing and adrenal suppression become issues.

**Dr. Albini:** I instruct adult uveitis patients with diabetes or hypertension to make an appointment with a general practitioner. I then send a letter to the general practitioner to make him or her aware, and I tell my patient to do whatever the physician thinks is reasonable. For all pediatric patients, I immediately call the pediatrician and do not start steroids until I know the pediatrician is on board and ready to comanage the complications of systemic steroids, because I do not feel that I can manage these cases alone.

**Dr. Rosenbaum:** I had a patient on oral steroids and the ophthalmologist was convinced that the steroids were not doing their job because the patient’s vision was not improving. However, the problem was that variations in blood glucose were causing lens edema. The inflammation was well controlled, but visual acuity was terrible because of the lens edema.

**Dr. Albini:** There is another complication that we have not mentioned, and that is the possibility of unmasking an infectious uveitis that was not apparent, such as cytomegaloviral retinitis (CMV) or syphilis.

**Dr. Acharya:** There is consensus on the need to check every uveitis patient for syphilis because there is no way to predict who has it. We should think about potentially unmasking infection before initiating steroids or poor outcomes could result.

**Dr. Rosenbaum:** We see the occasional patient with toxoplasmosis and there is no view of the fundus. If that patient has an intravitreal or periocular injection it could be a disaster.

**Dr. Flynn:** There was a case reported at the Vit-Buckle 2.0 Meeting by Dr. Acharya in which a patient was vaccinated with varicella vaccine (Varivax, Merck). The patient was immunosuppressed because of a gastrointestinal disorder and developed acute retinal necrosis and severe visual loss. The facts of this case led me to believe that patients should be asked a basic set series of questions before receiving a live-virus vaccine. It should be in the forefront of our thinking to ask these questions, especially in patients who are immunosuppressed.

**Dr. Garg:** What was the dose of prednisone in this case?

**Dr. Acharya:** He was on prednisone 20 mg, but he was also on remicade for the gastrointestinal disease.

**Dr. Rosenbaum:** The Centers for Disease Control and Prevention suggest avoiding the use of a live vaccine in someone who is on an immunosuppressive agent. The American College of Rheumatology warns against using a live vaccine in someone who is on a biologic, but it says if the immunosuppressed patient is on an antimetabolite like...
methotrexate, vaccination with zoster vaccine (Zostavax, Merck) can be considered.

**Dr. Acharya:** What about prednisone?

**Dr. Rosenbaum:** I am uncomfortable recommending a live vaccine while a patient is receiving a 20-mg dose, but I would feel fairly comfortable at 10 mg or below.

**Dr. Albini:** What percentage of patients is nonresponsive to typical oral systemic corticosteroids in contrast to intravenous corticosteroids?

**Dr. Yeh:** As a first-line agent, about 90% to 95% are responsive to oral systemic corticosteroids; so about 5% to 10% do not respond.

**Dr. Albini:** I agree. I have had 1 or 2 patients with Vogt-Koyanagi-Harada disease who did not respond to 80 mg of oral steroids, but did respond to intravenous Solu-Medrol (methylprednisolone sodium succinate, Pharmacia and Upjohn).

**Dr. Rosenbaum:** Some patients with inflammatory bowel disease have absorption issues so they do not get the full benefit of taking the medication. It makes me very anxious when someone is not responding to corticosteroids.

**CONSIDERATIONS FOR ADDING THERAPY**

**Dr. Albini:** For those patients who do not respond, would you consider alkylating agents or more aggressive immunosuppression?

**Dr. Yeh:** I would consider more aggressive immunosuppression, as long as there is no underlying infection.

**Dr. Rosenbaum:** Initially, we must reassess whether or not we have completely excluded infection and malignancy. The second thing to consider is whether the steroids are helping. Patients can also develop central serous retinopathy on steroids. Patients with Vogt-Koyanagi-Harada disease who do not appear to be responding may have central serous retinopathy. Another example might be a patient with an elevated blood glucose of 450 mg/dL who may have lenticular swelling. It is in these types of patients in whom we administer antimetabolites or sometimes, though rarely, an alkylator or biologic agent.

**Dr. Albini:** What about combination therapies such as immunomodulators and biologics?

**Dr. Acharya:** When I move beyond steroids and need systemic immuno-suppression, I generally start with the antimetabolites and typically use methotrexate.

**Dr. Albini:** For the treatment of posterior uveitis, is there greater efficacy with oral methotrexate or with oral mycophenolate (CellCept, Genentech)?

**Dr. Acharya:** Personally, I am undecided. Some of the retrospective studies from the SITE study\(^5\) show that mycophenolate may work better for posterior uveitis. I used to differentiate anterior from posterior uveitis, and I preferred mycophenolate for posterior uveitis.

I conducted a pilot trial in collaboration with Aravind Eye Hospital in India comparing methotrexate and mycophenolate in 80 patients with intermediate, posterior, or panuveitis. Patients in the methotrexate arm (25 mg weekly) had a 20% higher rate of steroid-sparing control of inflammation at 6 months, but the \(P\) value was not significant.\(^{15}\) Because of this experience, I am now more open to using methotrexate or mycophenolate for uveitis affecting the posterior segment of the eye, and I think we need a larger study to definitively answer this question.

**Dr. Albini:** In my opinion, a lot of factors make methotrexate a more attractive option than mycophenolate, such as the cost and the ease of taking a once-weekly dose compared with twice-weekly dosing. It is likely that methotrexate is noninferior to mycophenolate, but we need a prospective randomized comparative trial to know.

**Dr. Albini:** Does anyone use calcineurin inhibitors?

**Dr. Rosenbaum:** If the patient is not responding to methotrexate as much as we would like, I add a calcineurin antagonist.

**Dr. Yeh:** I like to begin with an antimetabolite as a first-line agent as long as there is no contraindication. If the patient is not completely responsive, I have moved away from adding a calcineurin inhibitor, because of my concern about renal insufficiency and hypertension. Now, I prefer to use a biologic in consultation with a rheumatologist.

**Dr. Albini:** What about cyclosporine compared with tacrolimus?

**Dr. Rosenbaum:** I am more comfortable with cyclosporine and it is less expensive, so I use it more. However,
I think tacrolimus is a better drug. There are some diseases, such as multifocal choroidopathy and serpiginous choroidopathy, when an antimetabolite alone is probably not going to be adequate. I treat patients with these diseases with combination therapy.

**Dr. Yeh:** I have found that patients do not tolerate combination treatments very well. In patients with serpiginous choroidopathy, there is a concern about TB.

**Dr. Albini:** What diseases have you found respond to treatment with biologics?

**Dr. Yeh:** Behçet disease responds well to TNF-alpha blockers. HLA–B27-associated spondyloarthropathies may respond well to either adalimumab or infliximab.

**Dr. Rosenbaum:** I agree with that. We used infliximab in an open-label trial for all patients with uveitis. About 10% of patients developed drug-induced lupus. Several patients had solid tumors, and some had thrombotic events. When treating a local disease and you give infliximab, you get really high peaks; it is a dangerous drug. Personally, I do not use infliximab unless there is an underlying systemic disease. For idiopathic uveitis, I do not like infliximab.

**Dr. Yeh:** I prefer adalimumab as my TNF-alpha blocker, partly for convenience for the patient. I also think that adalimumab works well for patients with Vogt-Koyanagi-Harada disease or sympathetic ophthalmia. We had a pediatric patient with Vogt-Koyanagi-Harada and the pediatric rheumatologist prescribed methotrexate followed by a TNF-alpha blocker. It worked very well.

**Dr. Albini:** Pediatric rheumatologists seem to be comfortable with methotrexate plus an anti-TNF for treatment of many conditions.

**Dr. Rosenbaum:** All inflammation is not alike. Methotrexate works well for rheumatoid arthritis, while mycophenolate is not very effective for that condition. Mycophenolate seems to be a great drug for lupus, while methotrexate is okay, but you would not use it for renal disease in lupus.

**Dr. Albini:** Is anyone using interferon-alpha?

**Dr. Acharya:** It is not used often in the United States.

**Dr. Acharya:** Our European colleagues have experienced excellent outcomes with interferon-alpha.

**Dr. Rosenbaum:** In treating patients with Behçet disease, the clear choice is infliximab. We have had about 6 patients with chronic macular edema who did not respond to local steroids, but did respond well to interferon-alpha. Also, there are new data that type-1 interferon is an effective drug for treating intermediate uveitis. It has not caught on as much here in the United States, however, because patients do not like it, and it is not easy to get it approved by insurance carriers. It requires an injection, and it has some downsides such as depression and influenza-like symptoms. It is not as expensive as an anti-TNF, but it is probably about $1000 or more a month.

**Dr. Garg:** That ends up being an issue because all these systemic drugs are being used off-label, and getting insurance companies to cover these expensive drugs can be very hard.

**Dr. Albini:** In the SITE Study, no single agent worked 100% of the time. If you titrate upward toward the maximum dose, how long do you wait before you switch to another agent?

**Dr. Acharya:** In the SITE study, success rates increased from 6 to 12 months, so waiting up to 12 months will increase success. Personally, I do not do that. Uveitis is a bad disease and I am uncomfortable waiting that long and so are my patients. Realistically, we wait at least 3 to 4 months, because some of the slower agents take that long to work. I am not comfortable waiting more than 6 months. If the disease is severe and the response is poor, sometimes we move quickly and switch after 2 to 3 months.

**Dr. Garg:** Although gradual improvements are expected, most of these patients have active disease. If they are not demonstrating meaningful improvement...
over 2 to 3 months, I will consider modifying my treatment strategy.

**Dr. Acharya:** If a patient is on a tapering dose of steroids and the inflammation increases, I will increase the dose, wait for a response, and then taper even more slowly.

**Dr. Rosenbaum:** If 70% of patients respond to methotrexate and 70% respond to azathioprine (Imuran, Prometheus Laboratories), I still cannot predict the response of an individual patient. It is empiric, and sometimes you do not know what will work until you try it. I believe 3 months is an adequate trial. One issue with a drug like methotrexate is that the optimal route is injection, because it is poorly absorbed at more than 15 mg/week. However, very few of my patients are willing to start with an injection. So I initiate treatment using the oral route and treat them with 20 mg for 3 months, hoping their liver enzymes are normal. If they have a hint of a response, it is tempting to convince them to switch to an injection.

**THE PIPELINE**

**Dr. Albini:** With respect to possibilities in the pipeline, I am excited about being able to use the fluocinolone acetonide implant 0.19 mg from Alimera Sciences (Iluvien) for uveitis. It was recently approved for DME. It will likely be used for uveitis, and it may be a safer form of treatment than Retisert, although it is a third of the dose. It will be interesting to see the relative efficacy.

**Dr. Yeh:** Many monoclonal antibodies that are being introduced in clinical practice for retinal disease, including biologic agents that are injected intravitreally. There are also kinase inhibitors in development, and some inhibit the inflammatory pathways and could be used for uveitis.

**Dr. Albini:** Anything that can be delivered intravitreally that is not a steroid will be a welcome addition.

**Dr. Yeh:** It is important to consider what has recently been found in prospective clinical trials. Although there is a lot of excitement about intravitreal TNF-alpha blockers, data from Pan American trials revealed many inflammatory reactions. A moratorium has since been suggested for the use of these drugs in retinal treatment. I think it is important that these agents be evaluated in a controlled fashion.

**Dr. Albini:** Dr. Flynn, what do you think the future holds regarding uveitis treatment?

**Dr. Flynn:** I am eager to use the fluocinolone acetonide implant 0.19 mg injectable fluocinolone implant, Iluvien, that was recently approved by the US Food and Drug Administration (FDA), because we all have cases of chronic CME that have been only partially responsive to traditional intravitreal injection steroid therapy. This implant may provide an alternative treatment or may be used in combination with other agents.

**Dr. Acharya:** For decades, uveitis research has not advanced through clinical trials. I am encouraged that local options such as mammalian target of rapamycin (mTOR) inhibition and systemic options like interleukin 1 blockers are being studied. For uveitis, there is not going to be one medicine that works for everyone, so it is great to have different options approved and added to our armamentarium.

**Dr. Garg:** For a long time we only had oral prednisone, and then we borrowed some medications from rheumatology; now we have some great options. As much as I love the systemic treatment options, my concern is that most ophthalmologists remain comfortable only with oral prednisone. When it comes to methotrexate, a drug that has been around for 50 years with a great safety record, most ophthalmologists will not prescribe it, nor do they feel comfortable recommending it. They prefer that the treatment is initiated by an internist. Even if we have new systemic therapy, I am concerned that its utilization will be confined to the uveitis community. As for local therapy, whether it is an mTOR inhibitor such as sirolimus or an intraocular steroid, I think retina specialists would be comfortable administering them, which will allow more patients to be treated outside of a tertiary treatment center.

**Dr. Rosenbaum:** Intravitreal slow-release steroids and intravitreal rapamycin are probably the farthest along. Voclosporin, a novel calcineurin inhibitor, is also in development, although the early results are not promising. XOMA and Abbvie are also conducting trials, but they are having a difficult time enrolling patients because of eligibility criteria. My view is that the endpoints of these clinical trials are poorly crafted, and that there is considerable heterogeneity in the underlying disease state. My concern is that although there is a huge need, the companies conducting the studies may become discouraged by their clinical results because of the study design.

**Dr. Acharya:** I think we have a major issue with trial design and the selected endpoints. Furthermore, the
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endpoints and the inclusion criteria required by the FDA are not fully in line with the population of patients that we treat with immunosuppressant agents.

**Dr. Albini:** We could consider targeting uveitic CME. Uveitic CME can be objectively measured, and those measurements do correlate with inflammation. Optical coherence tomography (OCT) measurements could be used as endpoints. However, I am not sure the FDA would agree with this approach.

**Dr. Rosenbaum:** A problem with this targeted approach is that only a subset of patients with uveitis has macular edema. A second problem, according to my colleagues, is that the FDA reportedly does not accept that OCT is a validated methodology to study uveitis.

**Dr. Albini:** We now have data from the MUST study that show what degree of OCT change is visually significant in uveitis patients.²

**Dr. Acharya:** It is a 20% reduction in thickness.

**Dr. Yeh:** If you look at the central retinal vein occlusion (CRVO) trials, we treat macular edema associated with CRVO by decreasing VEGF levels and not reversing the CRVO. We measure effectiveness in part by using OCT.

**Dr. Albini:** Considering the difficulties that we are having with the vitreous haze model, perhaps uveitic CME should be considered.

**CONCLUSION**

**Dr. Albini:** As Dr. Rosenbaum remarked early in the discussion, steroids are both uniquely effective in controlling uveitis and at the same time prone to complications. Systemic steroids are still a mainstay in the treatment of acute uveitis, but often result in hypertension, blood sugar elevation, insomnia, acne, fluid retention and increased appetite. In the long term, steroids can lead to aseptic necrosis of the bone, osteoporosis, and cushingoid body habitus. For these reasons, it is unacceptable in most cases to have patients take more than 10 mg of oral prednisone a day. Local steroids may cause glaucoma and cataract but avoid the systemic complications of oral steroids. The fluocinolone implant has been demonstrated to be as effective as conventional oral therapy for uveitis in a prospective multicenter trial, the MUST trial; however, this implant 0.59 mg was associated with significant risk of glaucoma.² Newer sustained-release steroid implants seem to offer a reduced risk of incisional surgery for glaucoma; however, their relative efficacy has not been demonstrated. Local treatment with agents other than steroids may in the future provide the least systemic and local complications, and would be a highly welcomed addition to the armamentarium currently available for the treatment of posterior segment inflammatory eye disease.
