Addressing an Unmet Need in Managing Noninfectious Intermediate Uveitis, Posterior Uveitis, and Panuveitis

With Thomas Albini, MD; Sunir J. Garg, MD; Vinit B. Mahajan, MD, PhD; Christopher D. Riemann, MD; and Steven Yeh, MD

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**INTRODUCTION**

Uveitis is an umbrella term for a group of diseases in which inflammation in the eye leads to loss of visual acuity. Anterior uveitis involves inflammation of the iris and anterior chamber of the eye and comprises the majority of uveitis cases. Noninfectious uveitis of the posterior segment (intermediate uveitis, posterior uveitis, and panuveitis), which can affect the vitreous cavity, the pars plana, the retina, and/or the choroid, have been thought to be less common, but the Northern California Epidemiology of Uveitis Study (n = 731 898), which is the largest population-based uveitis study performed in the United States, showed the incidence of uveitis to be approximately 3 times that of previous estimates. This study showed the annual incidence of noninfectious intermediate and posterior uveitis to be 52.4 per 100 000 person-years and a period prevalence of 115.3 per 100 000 persons.

**SYMPTOMS**

The symptoms of noninfectious intermediate uveitis include sudden painless vision loss or vision decrease with appearance of floaters. In noninfectious posterior uveitis, manifestations range from a decrease in visual acuity with floaters to retinal detachment and optic nerve inflammation. Untreated uveitis may result in long-term vision-threatening complications. Recurring inflammation is a common problem in patients with uveitis, often contributing to reduced vision. Optical coherence tomography studies demonstrate that recurring inflammation is more common in these patients than previously thought, even in patients with anterior nongranulomatous uveitis. Even after the uveitis is apparently in remission, retinal pigment epithelial dysfunction, vitreomacular traction, and epiretinal membrane formation and/or inflammatory cytokines themselves can limit resolution of inflammation and recovery of vision.

**TREATMENT**

The treatment options for noninfectious uveitis affecting the posterior segment include the use of local and systemic corticosteroids and the off-label use of anti-VEGF agents and systemic biologic agents. The only 2 sustained delivery devices that are US Food and Drug Administration-approved local treatments for noninfectious intermediate and posterior uveitis are the intravitreal fluocinolone acetonide 0.59-mg implant (Retisert, Bausch + Lomb) and the dexamethasone 0.7 mg intravitreal implant (Ozurdex, Allergan Inc).

Retisert is a long-term implant designed to control recurrences of inflammation for up to 3 years. In 2 randomized, double-masked, multicenter controlled clinical trials, 224 patients with chronic (a 1 year or greater history) noninfectious uveitis affecting the posterior segment of 1 or both eyes were randomized to receive a fluocinolone acetonide 0.59-mg implant. The primary efficacy endpoint in both trials was the rate of recurrence of uveitis affecting the posterior segment of the
study eye in the 34 week preimplantation period compared to the rate of recurrence in the 34 week postimplantation period. Uveitis recurrence rates at 1, 2, and 3 year postimplantation were also compared to the 34 week preimplantation period and reduced rates were maintained through 3 years of treatment. There was a significant decrease in the need for additional medications in the implanted group. The most common side effects were increased intraocular pressure (IOP) and cataract progression. At 3 years, which was the duration of the fluocinolone acetonide 0.59-mg implant trial, the implant was shown to provide long-term continuous control of inflammation (Figure 1).

The pivotal clinical trial for the dexamethasone intravitreal implant evaluated the safety and efficacy of 2 doses of the dexamethasone intravitreal implant for the treatment of noninfectious intermediate or posterior uveitis. The primary outcome measure in this trial was the proportion of patients with a vitreous haze score of 0 at week 8. Additional outcome measures were vitreous haze through week 26, best corrected visual acuity, adverse events, IOP, and biomicroscopy/ophthalmoscopy.

The results of the trial showed that a single dexamethasone intravitreal implant was significantly more effective than sham at eliminating vitreous haze. At the primary endpoint of week 8, approximately 4 times more eyes treated with the dexamethasone implant 0.7 mg had complete resolution of vitreous haze compared with sham. Treatment with the dexamethasone intravitreal implant also led to a significant improvement in BCVA by week 3 that persisted through week 26.

In regard to safety, IOP increases were relatively low in the treatment groups. There was no statistically significant difference in rate of cataract surgery between treatment groups and sham at 6 months.

Important Risk Information about RETISERT®

- Surgical placement of RETISERT® is contraindicated in active viral, bacterial, mycobacterial or fungal infections of the eye.

- Based on clinical trials with RETISERT®, during the 3-year post-implantation period, nearly all phakic eyes are expected to develop cataracts and require cataract surgery. As with any surgical procedure, there is risk involved. Potential complications accompanying intraocular surgery to place RETISERT® into the vitreous cavity may include, but are not limited to, the following: cataract formation, choroidal detachment, temporary decreased visual acuity, endophthalmitis, hypotony, increased intraocular pressure, exacerbation of intraocular inflammation, retinal detachment, vitreous hemorrhage, vitreous loss, wound complication, wound site erythema and wound dehiscence.

- Following implantation of RETISERT®, nearly all patients will experience an immediate and temporary decrease in visual acuity in the implanted eye which lasts for approximately one to four weeks postoperatively.

- Use of corticosteroids may result in elevated IOP and/or glaucoma. Based on clinical trials with RETISERT®, within 3 years post-implantation, approximately 77% of patients will require IOP lowering medications to control intraocular pressure and 37% of patients will require filtering procedures to control intraocular pressure.

- Patients should be advised to have ophthalmologic follow-up examinations of both eyes at appropriate intervals following implantation of RETISERT®. Physicians should periodically monitor the integrity of the implant by visual inspection.

- The most frequently reported ocular adverse events in clinical trials with RETISERT® occurring in 50-90% of patients included: cataract, increased intraocular pressure, procedural complications and eye pain. Thirty-five to forty percent (35-40%) of patients reported ocular/conjunctival hyperemia, reduced visual acuity and conjunctival hemorrhage. The most common non-ocular event reported was headache (>33%).
Other less well studied, but more commonly used forms of local therapy include periocular (sub-conjunctival or sub-Tenon) and intravitreal injections. Sub-Tenon triamcinolone injections are commonly used to treat uveitic cystoid macular edema. Risks include glaucoma, cataract, and rare cases of scleral perforation with or without retinal detachment. A typical regimen is to use triamcinolone acetonide 40 mg (1 mL) in the sub-Tenon space. Intravitreal injections of triamcinolone acetonide 1 mg to 4 mg can be considered if periocular injections are ineffective. The risk of glaucoma and cataract are greater with intravitreal injections. The use of preservative-free triamcinolone reduces the risk of sterile endophthalmitis.

In 2011, the results of the Multicenter Uveitis Steroid Trial were released.8 This study randomized patients with noninfectious intermediate uveitis, posterior uveitis, and panuveitis to local therapy with the fluocinolone implant or systemic therapy with corticosteroids and/or immunosuppressive drugs. In both treatment groups, vision improved over 2 years, with neither approach showing a statistically significant benefit over the other. Not surprisingly, the risk of glaucoma and cataract was greater in the implant group, and systemic side effects were greater in the systemic therapy group, although these side effects were usually mild and reversible. The implant achieved inflammatory control faster and more often than systemic therapy and the implant demonstrated better control of inflammation throughout the follow-up period. The results of the study suggested that the choice of therapy should be dictated by the individual patient’s particular circumstances and preferences.

A NEED FOR EDUCATION

Retina specialists who treat noninfectious intermediate uveitis, posterior uveitis, and panuveitis face a growing number of treatment options, requiring physicians and their staff to identify, learn about, and implement these newer treatments in a seamless manner. As the US population continues to age and the incidence of vascular and metabolic disorders associated with retinal diseases also increases, clinicians will need to recognize the importance of implementing treatment regimens that maximize efficacy, minimize patient burdens, and help patients manage their disease.

DISCUSSION

An expert panel of 5 retina and uveitis specialists gathered in Miami in April of 2013 to discuss the treatment of chronic noninfectious posterior segment uveitis and the importance for long-term, continuous control of inflammation. The panel members have the benefit of several years of experience with the different therapies that are currently available. The objective of this roundtable discussion was to share clinical experiences and perspectives on available therapies, patient types, and approaches to treating chronic or episodic disease. The discussion concentrated on the importance of lowering a patient’s risk for cumulative damage and proper diagnosis of chronic noninfectious posterior uveitis, intermediate uveitis, and panuveitis with an emphasis on thorough uveitic evaluations to exclude infectious etiologies prior to initiating therapy with local corticosteroid or immunomodulatory therapy.

This article is not intended to provide a complete overview of all available therapies used for the treatment of chronic noninfectious uveitis affecting the posterior segment of the eye. Instead, these expert perspectives are intended to outline various clinical considerations and to enhance the awareness of posterior segment uveitis—its diagnosis and management—and should not be misconstrued as comprehensive medical advice or a clinical practice guide.

DIAGNOSTIC WORKUP

Thomas Albini, MD: What is your approach to medical history, clinical evaluation, and diagnostic workup for patients who present with inflammation suspected for posterior uveitis?

Steven Yeh, MD: It is important to determine whether the patient has risk factors for infectious disease that might predispose them to an infectious uveitis syndrome. For noninfectious etiologies, I review the pulmonary symptoms, skin findings, and arthritic syndromes that may suggest a systemic autoimmune condition that would predispose the patient to uveitis. My diagnostic workup is based on my examination. If there are findings suggestive of a noninfectious posterior uveitis syndrome, I will begin with sarcoidosis and syphilis testing including an angiotensin-converting enzyme (ACE) level, calcium, lysozyme, RPR and MHA-TP, a chest x-ray and a PA lateral, and tuberculosis (TB) testing, usually with QuantiFERON TB Gold.

Aside from a clinical exam, I will also perform diagnostic imaging, including fluorescein angiography (FA), indocyanine green (ICG) angiography, and spectral domain optical coherence tomography (SD-OCT), particularly if I think that a chorioretinal inflammation may be present, to evaluate for other conditions like birdshot. If a diagnosis of birdshot, for example, can be made using these more sophisticated imaging modalities, I can be confident that chronic anti-inflammatory medication, either local or systemic, will be required.

Vinit B. Mahajan, MD, PhD: When a patient presents with vitreitis, I want to immediately rule out something that will either blind them or kill them, which is usually an infection of some sort or lymphoma, or another masquerade syndrome. If I think the patient may have posterior uveitis, my routine lab testing includes a similar workup as Dr. Yeh described.

If there is an autoimmune condition present, I will involve a rheumatologist.

Dr. Albini: I would add that among the key things to look for, particularly in eyes that are also at risk for endogenous endophthalmitis, are recent hospitalizations or HIV, both of which make infectious disease more likely and then differential of infectious entities more broad. For these patients, a diagnostic vitrectomy may be helpful. In cases of infectious uveitis, it is important to rule out a necrotizing retinitis or toxoplasmosis, for which steroid monotherapy is not the best treatment.

Sunir J. Garg, MD: Evaluating these patients for possible infectious causes and malignancy is important. Diagnosing acute infectious posterior uveitis is usually pretty straightforward although chronic infections can be tricky sometimes. I check everyone for Lyme and syphilis, and check for TB in high-risk groups. If vitreoretinal lymphoma crosses my mind, I’ll pursue this aggressively, and I have a low threshold for a diagnostic vitrectomy in this scenario. Otherwise my workup is similar to my colleagues’.

Christopher D. Riemann, MD: I agree with my colleagues and would like to emphasize that the ophthalmologist is key to assure that an appropriate and complete workup is done on these patients. We all know that uveitis can be sight threatening and may also be associated with life threatening disease. These patients often initially present with vision complaints and the ophthalmologist must initiate the workup and comanage with infectious disease, hematology oncology, or rheumatology specialists as appropriate. In the
long term, every ophthalmologist will determine his or her own involvement according to comfort level and individual skill set, but the burden of ordering the initial workup—or ensuring that someone else does so—falls to the ophthalmologist.

**CHOOSING THERAPY**

**Dr. Albini:** Dr. Mahajan, what disease entities will benefit the most from long-term immunosuppression and what are some of the more common entities you see that would benefit from short-term therapy?

**Dr. Mahajan:** We have reported on the need for long-term therapy, for example, in patients with sympathetic ophthalmia and inherited uveitis. Postsurgical patients are often short term; however, it is quite variable. I have some patients who become inflamed the moment the immunosuppression wears off and they cannot miss 1 day of therapy. Other patients, however, can remain quiet for an extended period of time, so I handle these cases on an individual basis.

**Dr. Yeh:** The conditions that I think will benefit the most from long-term immunosuppression include Behçet disease, birdshot retinochoroidopathy, and serpiginous choroidopathy.

**Dr. Garg:** Many of the patients that I see require long-term immunosuppression. In addition to systemic conditions such as Behçet disease and sarcoidosis, patients with birdshot chorioretinopathy, multifocal choroiditis, sympathethic ophthalmia, and serpiginous chorioretinopathy may benefit from immunosuppression.

**Dr. Albini:** Does local therapy do a better job of reducing recurrences of posterior segment uveitis vs systemic immunosuppression?

**Dr. Mahajan:** It can vary from patient to patient. Some do well with systemic immunotherapy, but it can take longer to select the right medications and adjust the doses to find that “magic” combination that keeps a patient stable for many years without significantly negative side effects. Local therapy can be more immediate.

There may also be some physician bias in answering this question. I am a surgeon, so I am more comfortable using the flucinolone acetonide 0.59-mg implant. A rheumatologist, on the other hand, may be more comfortable managing the side effects associated with systemic medications.

**Dr. Albini:** Dr. Riemann, what is your decision-making process for whether a patient should receive topical therapy, a steroid implant, or systemic immunosuppression?

**Dr. Riemann:** I always start with a stepped approach using aggressive topical therapy first. If that does not work, or if the eye drop burden is too great and causes compliance issues, I will use periocular steroids, moving next to intraocular steroids. I usually administer a series of 3 intravitreal injections of triamcinolone acetonide 4 mg to 8 mg (Triesence, Alcon), and if the patient responds well without significant side effects and appears to require long-term therapy, I am quick to offer the patient the flucinolone acetonide 0.59-mg implant (Retisert, Bausch + Lomb).

The patient’s response to steroid therapy dictates my threshold for involving a rheumatologist to assist with systemic medication. Methotrexate is a good systemic medication with which to start.

**Dr. Mahajan:** It is very personalized and disease specific. For cases such as juvenile idiopathic arthritic uveitis, we use infliximab and methotrexate. For a patient with acute monocular idiopathic uveitis, we control the disease with oral corticosteroids, and after tapering these medications, we focus on the eye with either a periocular or intravitreal steroid (Triesence). We have started to use the dexamethasone 0.7-mg intravitreal implant (Ozurdex, Allergan) more in lieu of triamcinolone acetonide 40 mg/mL, because the side effect profile for intraocular pressure (IOP) is thought to be better. However, there are no head-to-head studies showing this. Although the dexamethasone 0.7 mg intravitreal implant’s label states that it delivers steroid for 6 months, my clinical impression is that it may only last about as long as a steroid injection, which is about 3 to 4 months.

If a patient responds well to these steroids, but has continued recurrences, I will offer the flucinolone acetonide 0.59 mg implant. My practice is in Iowa, and many of my patients live in very rural areas and travel a great distance, so follow-up visits are not trivial. The flucinolone acetonide 0.59 mg implant buys us longer intervals between exams and in between patients’ visits to me, they can be seen by local ophthalmologists.

**Dr. Riemann:** For patients who require longer-term control with intravitreal steroids, it would be difficult to determine dosing intervals and it is important to avoid recurring inflammation. The flucinolone acetonide 0.59-mg implant offers the advantage of avoiding the
inflammation yo-yo effect by providing continuous control. In the case of systemic diseases, it is important to remember that the eyes are connected to the rest of the body and that systemic therapy may be mandated for systemic manifestations of diseases including JRA, sarcoid, or rheumatoid arthritis.

**Dr. Garg:** For most cases of active posterior uveitis, topical therapy does not provide a long-term solution. If they have an active systemic disease such as Behcet or pulmonary involvement from sarcoid, I can treat the eye and the extraocular manifestations of their disease with systemic immunosuppression. If they have only one eye involved, cannot tolerate/do not like systemic treatment, or are getting worse despite systemic therapy, intraocular steroid implants are a great choice.

**Dr. Albini:** Dr. Yeh, do you have any thoughts about the clinical differences between treating with repeated shorter-term steroids, such as a 3-month duration as with intravitreal triamcinolone 4 mg/mL or the dexamethasone 0.7-mg intravitreal implant, vs a longer-term duration of 2.5 years as with the fluocinolone acetonide 0.59-mg implant?

**Dr. Yeh:** One of the problems to which Dr. Riemann alludes, is that patients with persistent macular edema also have degeneration of the photoreceptors over time, decreasing the potential for good visual acuity. Patients who are referred for treatment can have great OCTs, but visual acuity of only 20/60 to 20/80 because of the chronic recurring macular edema. For these patients, I am more apt to consider sustained-release corticosteroids. We are fortunate to practice at a time when we have effective intravitreal therapies, both via injections and implants.

**Dr. Garg:** When I see these patients, I want to do 2 things: 1) put the fire out; and 2) keep it out. The rollercoaster of rebound inflammation takes a big toll on them, both in terms of their vision as Dr. Yeh just mentioned, as well as psychologically. Regardless of whether I am using a shorter-acting steroid such as triamcinolone, or a slightly longer-acting steroid such as the dexamethasone implant, I counsel the patient that they are likely to receive an injection every 3 to 4 months for a long time. For the most part, the fluocinolone implant allows us to control the inflammation for 2.5 to 3 years.

**CONTROLLING INFLAMMATION FLARE-UPS**

**Dr. Albini:** Dr. Mahajan, do you think that recurring inflammation may be one of the key causes of vision loss in uveitis patients, and, do these patients have better results with systemic therapy or local intraocular steroid therapy?

**Dr. Mahajan:** I believe it is. Recurrent inflammatory damage can cause permanent visual acuity loss. In particular, I am concerned about patients who depend on their fellow eye and are unaware of visual acuity decline the eye with chronic inflammation. Also, inflammation that is obvious on OCT may be missed in a clinical exam. If I detect inflammation, I treat immediately with some kind of local therapy.

**Dr. Albini:** So, if a patient with birdshot chorioretinopathy shows signs of inflammation, and the patient is already on topical steroids, would your next step be to give a sub-Tenon steroid injection?

**Dr. Mahajan:** Usually we will inject sub-Tenon triamcinolone and then we might ask the patient’s rheumatologist to help increase systemic medications, but that communication can be tricky. I also have patients who are not compliant with their systemic medications because they do not like the side effects. If I inject depo steroid I do not have to worry about compliance.

**Dr. Albini:** Do you think that patients with birdshot chorioretinopathy who require chronic immunosuppression therapy may benefit from an antimetabolite with sub-Tenon triamcinolone as adjunctive therapy?

**Dr. Mahajan:** The effect of many systemic medications is not immediate. We may have to wait for someone to see his or her primary care physician or rheumatologist, receive a change in dose, and wait for an effect and any side effects that would negate the use of the medication. These factors, along with health insurance coverage issues and compliance, all add up to time lost. If I give a patient depo steroid, there is usually a response, and I have bought time to spend on getting these other issues sorted out.

**Dr. Albini:** Which patients with birdshot chorioretinopathy and inflammation may benefit from a sustained-release steroid?
Dr. Mahajan: Patients who are intolerant of their systemic medications or who have difficulty coming to follow-up appointments would benefit from a sustained-delivery steroid such as the fluocinolone acetonide 0.59-mg intravitreal implant.

Dr. Riemann: I agree, as long as they can be seen by a local doctor who will monitor their IOP.

Dr. Yeh: This is a complex issue. I like to involve my patients with birdshot chorioretinopathy in the decision-making process as to whether we will approach the disease systemically, locally with injection therapy, or with a more long-term approach with a corticosteroid implant.

Thorne et al3 conducted a retrospective study showing that patients who received long-term immunosuppressive therapy had a lower risk of inflammation and a better visual prognosis that those who presented late after the onset of birdshot chorioretinopathy.

Patients with CME in particular benefit from locally administered steroids, so I will discuss the use of a sub-Tenon or pericocular steroid injection or the dexamethasone 0.7 mg intravitreal implant in addition to systemic immunosuppression. The alternative would be another form of combination therapy using oral prednisone with the initiation of an antimetabolite, such as mycophenolate mofetil (Cellcept, Genentech) or methotrexate, as an initial approach. My preference, however, is to use prednisone or a pericocular corticosteroid initially, allowing the patient to consider the option of systemic immunosuppression prior to initiation, rather than starting several medications at the same time. This strategy also makes it easier to evaluate the side effects.

Dr. Mahajan: In regard to recurrence and long-term control of inflammation, I have had patients with multifocal choroiditis, for example, in whom I implanted the fluocinolone acetonide 0.59-mg implant because they had lesions very close to the fovea. These patients tend to have very good central vision, but there is a creeping degeneration of the retina directly adjacent to the fovea in this scenario. A single recurrent episode of inflammation in such a scenario could be blinding. This is an important consideration that emphasizes the importance of long-term control, particularly for our patients who are monocular or who have a small visual field.

In the MUST (Multicenter Uveitis Steroid Treatment Trial) study, recurrences were less frequent in the fluocinolone acetonide 0.59-mg implant group. The data show that uveitis was more often controlled at 2 years in the implant group than the systemic therapy group (88% vs 71%; *P* = 0.001).4

Dr. Albini: How much of a role does patient compliance play in recurrence of inflammation?

Dr. Yeh: Compliance is always an issue with any medication that is taken daily.

Dr. Mahajan: Occasionally, I will see patients at a follow-up visit who complain that they dislike the oral drug and it is expensive, and I learn that they have not been taking the medication.

Dr. Albini: Some patients will have a very difficult time with nausea or other perturbations. Some of these patients will even reduce their dose without reporting it.

In my opinion, the benefits of the fluocinolone acetonide 0.59-mg implant vs systemic immunosuppression include better control of inflammation, as was shown in the MUST trial, decreased recurrences of inflammation, also from the MUST trial, and overall patient compliance, which is always achieved with the implant. The downsides include the local side effects, including cataract and the 30% risk of glaucoma surgery.

Dr. Garg: Recurrent inflammation essentially beats up the eye. In a boxing match of uveitis vs the eye, the eye can take a beating and get back up only so many times before it goes down for the count. Once I determine that inflammation is damaging the eye, I aggressively treat. I will start many patients on 60 mg of prednisone and will keep them on that for 2 weeks. If they still have moderately active disease, I ask myself if my diagnosis is wrong (maybe it is infectious) or perhaps they have some really bad disease such as Behcet’s. If they are quiet on 60 mg of prednisone, I’ll do a slow taper of prednisone seeing them at each step along the way. If I can keep them quiet on 7.5 mg of prednisone daily, I’m happy with that. If they require higher doses of prednisone to remain quiet, I’ll consider an antimetabolite such as methotrexate/azathioprine/mycophenylate mofetil, or a biologic agent.
Various factors are thought to influence the prognosis of a patient with uveitis, including:

- Delay in presentation to a subspecialist
- Poor compliance with follow-up visits
- Total duration of uveitis
- Presence of posterior segment uveitis (intermediate uveitis, posterior uveitis, or panuveitis)
- Number of recurrent episodes of inflammation
- Development of glaucoma or hypotony
- Evidence of ocular atrophy
- Incomplete control of uveitis

### Switching Therapies

**Dr. Albini:** What is a clinical scenario where you would switch a patient from systemic therapy to the fluocinolone acetonide 0.59-mg implant?

**Dr. Yeh:** When I have a patient who presents with refractory posterior uveitis, I start a course of systemic medications if the patient agrees. The exceptions are cases of unilateral disease, patients who are pseudophakic, those who do not develop a corticosteroid-associated elevation of their IOP, or who have undergone filtering surgery. Additionally, women in their childbearing years considering pregnancy are less suitable for antimetabolites or systemic drugs. In general, I have a higher proportion of patients for whom I will initiate systemic immunosuppression. If I find systemic immunosuppression ineffective or intolerable, I will consider and discuss the fluocinolone acetonide 0.59-mg implant. Some patients will choose to have a second immunosuppressive medication rather than have surgery, while others will go ahead with the implant.

I do not have a specific visual acuity threshold for feeling more comfortable using the implant, but I think that all surgical risk factors and side effects of the long-term local steroid should be discussed. I have had patients with 20/20 vision who are extremely symptomatic from vitreitis and will achieve a significant benefit from the fluocinolone acetonide 0.59-mg implant and conversely, I have had patients with 20/80 and 20/100 visual acuities who do not want to undergo surgery and would prefer to take several immunosuppressive medications. In general, however, I do not like putting patients on more than 2 systemic medications and I will recommend the fluocinolone acetonide 0.59-mg implant when a third medication is required.

**Dr. Albini:** If you use the fluocinolone acetonide 0.59-mg implant, do you taper the systemic medications, do you just discontinue them after a period of time, or do you continue using 1 immunosuppressive in conjunction with the implant? Let’s say the patient was taking mycophenolate mofetil and cyclosporine.

**Dr. Yeh:** Fortunately it is rare in my experience that patients require multiple immunosuppressive medications. If I am using oral prednisone, I do not keep patients on a dose of 10 mg or higher for more than 3 months. If I cannot lower the dose to lower than 7.5 mg, I then use a stepped combination approach. When I switch to a fluocinolone acetonide 0.59-mg implant, I will usually stop 1 of the medications and taper the other. In the scenario you present, I would stop the cyclosporine because I think it has a worse side effect profile and I would taper the mycophenolate mofetil.

**Dr. Albini:** When patients are not responding to systemic immunosuppression and I have to keep adding or changing medications, I will discuss the challenging and difficult nature of this situation and how there are among 2 possibilities: continuing with often complicated systemic drugs or trying a steroid implant.

**Dr. Garg:** If I have adjusted a patient’s systemic medications to the strongest tolerable combination and still cannot keep the eye quiet, or if the patient does not like the side effects of systemic treatment, I will encourage him or her to consider the fluocinolone implant.

### Patient Counseling

**Dr. Albini:** When I am talking to patients about the therapies that are available for posterior uveitis, I use the data from the MUST study to open a discussion on what we know about systemic vs local therapy.

In the MUST trial, 479 eyes with uveitis (n=255) were randomized to therapy with either the fluocinolone acetonide 0.59 mg implant or systemic immunosuppression, treating inflammation at baseline in the systemic group with prednisone until controlled, at which time the prednisone was tapered. At 24 months, the implant gained 6 letters of vision vs 3.2 letters in the systemic therapy group, which was not statistically significant. The vision-related quality-of-life improvements at 24 months were 11.4 units in the implant group vs 6.8 units in the systemic therapy group. Twelve percent of patients in the implant group had active uveitis at 24 months vs 29% of patients in the systemic therapy group. Those in the implant group were more likely to require cataract surgery and require treatment for increased IOP and patients in the systemic therapy group were more likely to contract infections that required prescription medication; however, these did not have a significant effect over the long term. Both groups had few systemic adverse events.
“Patients with uveitis can sometimes be paralyzed by the complexity of the choices that we present for them.”

— Christopher D. Riemann, MD

I share this information with my patients in the context that both options are effective and relatively safe, with the implant having a higher risk of ocular complications.

**Dr. Mahajan:** One thing that surprised me about the MUST trial was that the side effect profile of systemic medications was comparatively very low. I had expected a higher rate of side effects, but it tells us that systemic immunomodulation can be a safe option for patients and their doctors to consider.

**Dr. Riemann:** Did the inclusion and exclusion criteria allow patients who had a higher risk of complications from systemic therapy to be enrolled?

**Dr. Albini:** Patients with glaucoma or ocular hypertension, uncontrolled diabetes, a known allergy to study medications, history of scleritis, an ocular toxoplasmosis scar, or those who were pregnant or breastfeeding were excluded. Also, patients with a known HIV infection or other immunodeficiency disease were excluded. As far as I am aware, there were no criteria that would have affected complications.

**Dr. Riemann,** how do you counsel patients who are making a choice between systemic immunosuppression and the fluocinolone acetonide 0.59-mg implant?

**Dr. Riemann:** Patients with uveitis can sometimes be paralyzed by the complexity of the choices that we present for them. If I think it is the right thing for the patient, I will sometimes direct the conversation. For example, Dr. Yeh mentioned patients who have had filtering surgery—in these cases, it makes all the sense in the world to proceed with heavy local therapy such as with the fluocinolone acetonide 0.59-mg implant. Even though the MUST trial showed that systemic therapy is relatively safe compared to local therapy with the fluocinolone acetonide 0.59-mg implant, even though the MUST trial showed that systemic therapy is relatively safe compared to local therapy with the fluocinolone acetonide 0.59-mg implant, weaning them off all their medications, who have said that they strongly prefer the implant. These are often patients who have been failing for years on systemic medications.

**Dr. Yeh:** According to the MUST study, the quality of life for patients in the implant group was reported as better than those patients in the systemic therapy group at 6 months. The difference, however, dwindled to a smaller, less important advantage for the implant group at 24 months.

**Dr. Mahajan:** I have several patients who were on systemic medications and who we switched the fluocinolone acetonide 0.59-mg implant, weaning them off all their medications, who have said that they strongly prefer the implant. These are often patients who have been failing for years on systemic medications.

**Dr. Riemann:** Untreated uveitis is an excellent way to get a cataract, as well.

**Dr. Mahajan:** Correct. The main side effect that I worry about is the glaucoma. Before choosing the fluocinolone acetonide 0.59-mg implant, I make sure that the patient truly understands that he or she might need a second glaucoma filtering surgery.

**Dr. Riemann:** I agree that glaucoma as a side effect is very important to consider, but I think we have to remember that as with the cataract side effect, glaucoma can be managed, which, in the setting of a treatment that can control severe inflammatory disease, is reasonable.

Part of managing patients with uveitis involves communication with other medical or ophthalmic specialists who are involved such as glaucoma specialists. If we choose heavy treatment with steroids, such as with the fluocinolone acetonide 0.59-mg implant, we know that we will be creating glaucoma that will have to be managed. If a patient will have to travel long distances to see
his or her specialists, using such options may treat the uveitis but blind the patient from inducing glaucoma that cannot be managed properly. On the flip side, compliance with visits to a medical specialist to monitor for systemic side effects of systemic immunomodulators as well as access to a primary care doctor who is facile in managing routine diseases such as cellulitis or pneumonia in an immunocompromised patient is crucial for a long-term satisfactory outcome. In my case at the Cincinnati Eye Institute, we have a great glaucoma center and I am confident that cases of glaucoma will be well managed unless the patient simply does not show up.

**Dr. Yeh:** I agree that ocular hypertension is a serious concern with exuberant corticosteroid response. A local injection can allow the doctor to gauge the response and to some degree, patients who do not have that strong response may be more amenable to treatment with the long-term fluocinolone acetonide 0.59 mg implant. I am sure to talk to my patients about the potential of glaucoma in terms of percentages from the clinical trials for the fluocinolone acetonide 0.59 mg implant, and from MUST. Thirty-eight percent to 40% of patients in the clinical trials developed glaucoma in the clinical trials and 17% in MUST. Corticosteroid injections and secondary complications related to the anatomy, including peripheral anterior synechiae and closure of the trabecular meshwork, however, can also cause glaucoma, so these are considerations that should be shared with patients.

**Dr. Garg:** This is a long, confusing discussion for many patients. The most important thing is helping them understand what happens without adequate treatment. Without treatment, they will develop cataracts, glaucoma, and structural complications that can permanently damage their eye. With treatment, they will likely develop cataracts and glaucoma, but we can avoid structural complications. For patients who are developing a cataract anyway, I have no reservations pursuing the fluocinolone implant, leaving glaucoma as the outstanding issue. Although I do not want any patient to have glaucoma surgery, many patients welcome getting off systemic immunosuppression.

**Dr. Riemann:** I strongly agree. If expertly placed, a tube shunt and a fluocinolone acetonide 0.59-mg implant can be compatible with superb long-term outcomes in selected uveitis patients.

**DIFFERENCES IN STEROID FORMULATIONS**

**Dr. Albini:** What are the differences between the locally delivered steroids, such as triamcinolone acetonide, fluocinolone acetonide, and dexamethasone in terms of duration of action and potency?

**Dr. Yeh:** Triamcinolone acetonide administered via a posterior sub-Tenon route lasts anywhere between 3 and 6 months, but the response can be unpredictable. I do not routinely administer triamcinolone acetonide via intravitreal injection for posterior uveitis. The intravitreal dexamethasone implant is an excellent option for control of inflammation and macular edema and lasts between 3 and 6 months. The fluocinolone acetonide implant achieves excellent control of inflammation and macular edema, particularly in patients who need long-term, continuous therapy and lasts for 36 months or longer in some patients.

**Dr. Mahajan:** From a practical standpoint, intravitreal dexamethasone injection is the most potent but it lasts less than a week, so I typically do not use this. The dexamethasone implant extends the duration to 3 to 5 months. Intravitreal triamcinolone acetonide is less potent than dexamethasone, but will last 3 months or longer. The fluocinolone acetonide implant seems as potent and lasts 3 years. This guides my follow-up appointment scheduling, but it can vary with individual patients.

**Dr. Riemann:** I am a fan of starting local therapy with a 4-mg triamcinolone acetonide injection. This drug is cost-effective, last for 3 to 6 months, and it works. There is also very little drama involved in reimbursement from third-party insurance carriers.

In monocular patients, the dexamethasone implant avoids the transient visual loss from snow-globe effect of injecting a suspension into the eye. For known steroid responders, my clinical impression is that the dexamethasone implant may be a bit less glaucomogenic than triamcinolone, but I am unaware of any hard data to back up my assertion. It seems to last for 3 to 5 months.

The fluocinolone implant is an excellent option in that it lasts 30 to 36 months. Patients receive excellent long-term control of their inflammation with reduced need for additional ocular or systemic therapies—and fewer visits to the doctor.

**Dr. Garg:** I do not routinely perform intraocular triamcinolone injections because I have a hard time predicting their duration of effect, and the side effects are disproportionate to the short-term benefit. The dexamethasone implant is a good option for many patients because it is well tolerated and is easy to inject, but it only lasts 3 to 5 months. For a chronic disease that takes a toll on ocular health, the fluocinolone acetonide implant is a great choice, in my opinion.

**Dr. Albini:** Are there any differences in vitrectomized eye vs nonvitrectomized eyes?

**Dr. Riemann:** There was a recent study published in *Retina*® that showed that the dexamethasone 0.7-mg
intravitreal implant was safe and effective for vitrectomized eyes with uveitis.

Dr. Albini: For vitrectomized eyes, an injection of triamcinolone acetonide will work for only 2 weeks, whereas the implant releases effective amounts of dexamethasone for up to 6 months. The fluocinolone acetonide 0.59 mg implant works very well in vitrectomized eyes.

Dr. Yeh: I use the fluocinolone acetonide 0.59 mg implant in vitrectomized eyes.

SUMMARY

Dr. Yeh: It is remarkable that we have so much data with regard to different options for therapy, including the systemic and local. There are benefits and side effects with either approach, and patient counseling is important.

Dr. Mahajan: In my patients with frequent, recurrent inflammatory episodes, fovea-threatening lesions, or difficulty with compliance, the fluocinolone acetonide 0.59 mg implant has saved their sight. My laboratory is focused on personalized proteomics to identify local targets in the vitreous of uveitis patients, and I believe that localized, highly specific therapy is the future.

Dr. Riemann: Sometimes uveitis patients need a “physician” to meticulously wade through the myriad of treatment options and their associated risks, benefits, alternatives, complications and unknowns with them. But sometimes, this discussion becomes so overwhelming that it can undermine the patient-physician relationship itself. Some patients need a “doctor” to take a stand after assessing the patient’s uveitic challenges, and putting these into the appropriate perspective given the actual fact pattern that is at play including geographic, transportation, and follow-up limitations. The precise skill sets of the patient’s local medical community must also play a role in decision making.

Dr. Garg: Our ability to diagnose and treat patients with uveitis has advanced tremendously the past few years. The more aggressively patients are treated earlier in their disease process, the better the results. Early consultation with a uveitis specialist of is of benefit to both patients and their primary eye care provider.

Dr. Albini: Taking an optimistic view, as suggested by Dr. Yeh earlier, the MUST study showed we have many great options for treating noninfectious posterior uveitis. However, not any single approach is the correct choice for all patients. The decision of how to tailor treatment for individual patients is not simple, but manageable. As good as our options are, it remains essential for the treating physician to understand the strengths and weaknesses of all approaches.

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Retisert.
(flucinolone acetonide intravitreal implant) 0.59 mg
STERILE

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use RETISERT safely and effectively. See full prescribing information for RETISERT.

RETISERT (flucinolone acetonide intravitreal implant) 0.59 mg for intravitreal use Initial U.S. Approval: 1963

--------------------------INDICATIONS AND USAGE--------------------------
RETISERT is a corticosteroid indicated for the treatment of chronic noninfectious uveitis affecting the posterior segment of the eye.(1)

--------------------------DOSE AND ADMINISTRATION--------------------------
• RETISERT is surgically implanted into the posterior segment of the affected eye through a pars plana incision. (2.1)
• RETISERT is designed to release flucinolone acetonide at a nominal initial rate of 0.6 μg/day, decreasing over the first month to a steady state between 0.3-0.4 μg/day over approximately 30 months. (2.1)
• Aseptic technique should be maintained at all times prior to and during the surgical implantation procedure. (2.2)

--------------------------DOSEAGE FORMS AND STRENGTHS--------------------------
• 0.59 mg flucinolone acetonide intravitreal implant. (3)

--------------------------CONTRAINDICATIONS--------------------------
• Surgical placement of RETISERT is contraindicated in active viral, bacterial, mycobacterial and fungal infections of ocular structures. (4.1)

--------------------------WARNINGS AND PRECAUTIONS--------------------------
• Cataract formation: Nearly all phakic patients are expected to develop cataracts and require cataract surgery. (5.1)
• Endophthalmitis: Late onset endophthalmitis has been observed. (5.2)
• Increase in intraocular pressure: Use of corticosteroids may result in elevated IOP and/or glaucoma. (5.3) IOP lowering medications were required in > 75% of patients; filtering surgeries were required in > 35% of patients. (6.1)
• Separation of implant components: Physicians should periodically monitor the integrity of the implant by visual inspection. (5.4)

--------------------------ADVERSE REACTIONS--------------------------
• Ocular adverse events included procedural complications, and eye pain (> 50%). Thirty-five to forty percent of patients reported ocular/viral, bacterial, mycobacterial and fungal infections of ocular structures. (4.1)

To report SUSPECTED ADVERSE REACTIONS, contact Bausch & Lomb at 1-800-323-0000 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

See 17 for PATIENT COUNSELING INFORMATION

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  2.2 Handling of Implant
3 DOSEAGE FORMS AND STRENGTHS
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5 WARNINGS AND PRECAUTIONS
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*Sections or subsections omitted from the full prescribing information are not listed

Revised 05/2012
FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE
RETISERT is indicated for the treatment of chronic non-infectious uveitis affecting the posterior segment of the eye.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information
RETISERT (fluocinolone acetonide intravitreal implant) 0.59 mg is implanted into the posterior segment of the affected eye through a pars plana incision.

The implant contains one tablet of 0.59 mg of fluocinolone acetonide. RETISERT is designed to release fluocinolone acetonide at a nominal initial rate of 0.6 μg/day, decreasing over the first month to a steady state between 0.3-0.4 μg/day over approximately 30 months. Following depletion of fluocinolone acetonide as evidenced by recurrence of uveitis, RETISERT may be replaced.

2.2 Handling of Implant
Caution should be exercised in handling RETISERT in order to avoid damage to the implant, which may result in an increased rate of drug release from the implant. Thus, RETISERT should be handled only by the suture tab. Care should be taken during implantation and explantation to avoid sheer forces on the implant that could disengage the silicone cup reservoir (which contains a fluocinolone acetonide tablet) from the suture tab. Aseptic technique should be maintained at all times prior to and during the surgical implantation procedure.

RETISERT should not be resterilized by any method.

3 DOSAGE FORMS AND STRENGTHS
0.59 mg fluocinolone acetonide intravitreal implant.

4 CONTRAINDICATIONS

4.1 Viral, Bacterial, Mycobacterial and Fungal Infections of Ocular Structures
Surgical placement of RETISERT is contraindicated in active viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in active bacterial, mycobacterial or fungal infections of the eye.

5 WARNINGS AND PRECAUTIONS

5.1 Cataract Formation
Use of corticosteroids may result in posterior subcapsular cataract formation. Based on clinical trials with RETISERT, during the 3-year post implantation period, nearly all phakic eyes are expected to develop cataracts and require cataract surgery.

5.2 Endophthalmitis and Surgical Complications
Late onset endophthalmitis has been observed. These events are often related to the integrity of the surgical wound site. Careful attention to assure tight closure of the scleral wound and the integrity of the overlying conjunctiva at the wound site is important.

Potential complications accompanying intraocular surgery to place RETISERT into the vitreous cavity may include, but are not limited to, the following: cataract formation, choroidal detachment, endophthalmitis, hypopyon, increased intraocular pressure, exacerbation of intraocular inflammation, retinal detachment, vitreous hemorrhage, vitreous loss, and wound dehiscence.

Following implantation of RETISERT, nearly all patients will experience an immediate and temporary decrease in visual acuity in the implanted eye which lasts for approximately one to four weeks post-operatively.

5.3 Increase in Intraocular Pressure
Prolonged use of corticosteroids may result in elevated IOP and/or glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. Steroids should be used with caution in the presence of glaucoma. Patients must be monitored for elevated IOP.

Based on clinical trials with RETISERT, within 3-years post implantation, approximately 77% of patients will require IOP lowering medications to control intraocular pressure and 37% of patients will require filtering procedures to control intraocular pressure. (see 6.1 Clinical Trials Experience - Ocular Events section).

5.4 Separation of Implant Components
In vitro stability studies show that the strength of the adhesive bond between the silicone cup reservoir and the suture tab is reduced with prolonged hydration, indicating a potential for the separation of these components. The suture tab composition is a silicone elastomer reinforced with a polyester mesh. Physicians should periodically monitor the integrity of the implant by visual inspection.

5.5 Other Corticosteroid Induced Adverse Reactions
RETISERT should be used with caution in patients with a history of herpes simplex requiring (including herpes simplex). Employment of a corticosteroid medication and may exacerbate the severity of many viral infections of the eye (including herpes simplex). The possibility of fungal invasion should be considered in any persistent corneal ulceration where steroid treatment has been used.

Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections (bacterial, fungal, and viral). In acute purulent conditions of the eye, steroids may mask infection or enhance existing infection. Fungal and viral infections of the cornea are particularly prone to develop coincidentally with long-term application of steroids. The possibility of fungal invasion should be considered in any persistent corneal ulceration where steroid treatment has been used.

Since resistance to infections is known to be reduced by corticosteroids, simultaneous bilateral implantation should not be carried out, in order to limit the potential for bilateral post-operative infection.

Ocular administration of corticosteroids has also been associated with delayed wound healing and perforation of the globe where there is thinning of the sclera.

The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience - Ocular Events
The available safety data includes exposure to RETISERT in patients with chronic non-infectious uveitis affecting the posterior segment in two multicenter controlled clinical trials. Patients were randomized to dosage regimens of 0.59 mg or 2.1 mg implants.

The most frequently reported ocular adverse events were cataract, increased intraocular pressure, procedural complication, and eye pain.
These events occurred in approximately 50 - 90% of patients. Cataract includes aggravated cataract, and posterior capsular opacification. Procedural complications include post-op complication, post-op wound complication, post-op wound site erythema, and wound dehiscence.

Based on clinical trials with RETISERT, during the 3-year post-implantation period, nearly all phakic eyes are expected to develop cataracts and require cataract surgery. IOP lowering medications to lower intraocular pressure were required in approximately 77% of patients; filtering surgeries were required to control intraocular pressure in 37% of patients. Ocular adverse events occurring in approximately 10 - 40% of patients in decreasing order of incidence were ocular/conjunctival hyperemia, reduced visual acuity, glaucoma, conjunctival hemorrhage, blurred vision, abnormal sensation in the eye, eye irritation, maculopathy, vitreous floaters, hypotony, ptosis, paresthesia, increased tearing, vitreous hemorrhage, dry eye, eyelid edema, macula edema and visual disturbance.

Ocular adverse events occurring in approximately 5 - 9% of patients in decreasing order of incidence were eye discharge, photophobia, blepharitis, corneal edema, iris adhesions, choroidal detachment, diplopia, eye swelling, retinal detachment, photopsia, retinal hemorrhage and hyphema.

6.2 Clinical Trials Experience - Non-Ocular Events
The most frequently reported non-ocular adverse event was headache (33%). Other non-ocular adverse events occurring in approximately 5-20% of patients in decreasing order of incidence were nasopharyngitis, arthralgia, sinusitis, dizziness, pyrexia, upper respiratory tract infection, influenza, vomiting, nausea, cough, back pain, limb pain, and rash.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Category C
No adequate animal reproduction studies have been conducted with fluocinolone acetonide. Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Fluocinolone acetonide when administered subcutaneously at a dose of 0.13 mg/kg/day (approximately 10,000 times the daily clinical dose of RETISERT), during days 6 to 18 of pregnancy in the rabbit, induced abortion at the end of the third and at the beginning of the fourth gestational week. When administered subcutaneously to rats and rabbits during gestation at a maternal toxic dose of 50 μg/kg/day (approximately 4,000 times the clinical dose of RETISERT), fluocinolone acetonide caused abortions and malformations in a few surviving fetuses.

There are no adequate and well-controlled studies in pregnant women. RETISERT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 Nursing Mothers
It is not known whether ocular administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Systemic steroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Caution should be exercised when RETISERT is implanted in a nursing woman.

8.4 Pediatric Use
Safety and effectiveness in pediatric patients below the age of 12 years have not been established.

8.5 Geriatric Use
No overall differences in safety and effectiveness have been observed between elderly and younger patients.

11 DESCRIPTION
RETISERT® (fluocinolone acetonide intravitreal implant) 0.59 mg is a sterile implant designed to release fluocinolone acetonide locally to the posterior segment of the eye at a nominal initial rate of 0.6 μg/day, decreasing over the first month to a steady state between 0.3-0.4 μg/day over approximately 30 months. The drug substance is the synthetic corticosteroid fluocinolone acetonide, represented by the following structural formula:

C_{20}H_{24}F_{20}O_8, Mol. Wt. 452.50

Chemical Name: Pregna-1,4-diene-3,20-dione,6,9-difluoro-11,21-dihydroxy- 16,17-[(1-methyl-ethylidene)bis(oxy)],(6α,11β,16α)-.

Fluocinolone acetonide is a white crystalline powder, insoluble in water, and soluble in methanol. It has a melting point of 265-266°C.

Each RETISERT consists of a tablet containing 0.59 mg of the active ingredient, Fluocinolone Acetonide, USP, and the following inactives: microcrystalline cellulose, polyvinyl alcohol, and magnesium stearate.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism Of Action
Corticosteroids inhibit the inflammatory response to a variety of inciting agents and probably delay or slow healing. They inhibit the edema, fibrin deposition, capillary dilation, leukocyte migration, capillary proliferation, fibroblast proliferation, deposition of collagen, and scar formation associated with inflammation.

There is no generally accepted explanation for the mechanism of action of ocular corticosteroids. However, corticosteroids are thought to act by the induction of phospholipase A, inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A, Corticosteroids are capable of producing a rise in intraocular pressure.

12.2 Pharmacokinetics
In a subset of patients who received the intravitreal implant, and had blood samples taken at various times (weeks 1, 4 and 34) after implantation, plasma levels of fluocinolone acetonide were below the limit of detection (0.2 ng/mL) at all times. Aqueous and vitreous humor samples were assayed for fluocinolone acetonide in a further subset of patients. While detectable concentrations of fluocinolone acetonide were seen throughout the observation interval (up to 34 months), the concentrations were highly variable, ranging from below the limit of detection (0.2 ng/mL) to 589 ng/mL.
13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment Of Fertility
Long-term animal studies have not been performed on RETISERT to evaluate the carcinogenic potential or the effect on fertility of fluocinolone acetonide.

Fluocinolone acetonide was not genotoxic in vitro in the Ames test, the mouse lymphoma TK assay, or in vivo in the mouse bone marrow micronucleus assay.

14 CLINICAL STUDIES
In two randomized, double-masked, multicenter controlled clinical trials, 224 patients with chronic (a one year or greater history) non-infectious uveitis affecting the posterior segment of one or both eyes were randomized to receive a 0.59 mg RETISERT. The primary efficacy endpoint in both trials was the rate of recurrence of uveitis affecting the posterior segment of the study eye in the 34 week pre-implantation period compared to the rate of recurrence in the 34 week post-implantation period. Uveitis recurrence rates at 1, 2, and 3 year post-implantation were also compared to the 34 week preimplantation period.

Detailed results are shown in table 1 below:

<table>
<thead>
<tr>
<th>TIME POINT</th>
<th>STUDY 1</th>
<th>STUDY 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=108</td>
<td>N=116</td>
</tr>
<tr>
<td>Uveitis Recurrence Rates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>34 Weeks Pre-implantation</td>
<td>58 (53.7)</td>
<td>46 (39.7)</td>
</tr>
<tr>
<td>34 Weeks Post-implantation</td>
<td>2 (1.8)</td>
<td>15 (12.9)</td>
</tr>
<tr>
<td>1 Year Post-implantation</td>
<td>4 (3.7)</td>
<td>15 (12.9)</td>
</tr>
<tr>
<td>2 Years Post-implantation</td>
<td>11 (10.2)</td>
<td>16 (13.8)</td>
</tr>
<tr>
<td>3 Years Post-implantation</td>
<td>22 (20.4)</td>
<td>20 (17.2)</td>
</tr>
<tr>
<td>3 Years Post-implantation</td>
<td>33 (30.6)</td>
<td>28 (24.1)</td>
</tr>
</tbody>
</table>

1 Recurrence of uveitis for all post-implantation time points was compared to the 34 weeks pre-implantation time point.
2 p-value <0.01 from McNemar’s χ² test.
3 Results presented include imputed recurrences. Recurrences were imputed when a subject was not seen within 10 weeks of their final scheduled visit.

16 HOW SUPPLIED/STORAGE AND HANDLING
The implant consists of a tablet encased in a silicone elastomer cup containing a release orifice and a polyvinyl alcohol membrane positioned between the tablet and the orifice. The silicone elastomer cup assembly is attached to a silicone elastomer suture tab with silicone adhesive. Each RETISERT is approximately 3 mm x 2 mm x 5 mm.

Each implant is stored in a clear polycarbonate case within a foil pouch within a Tyvek peelable overwrap. Each packaged implant is provided in a carton which includes the package insert.

NDC 24208-416-01

Storage:
Store in the original container at 15°C - 25°C (59°F - 77°F). Protect from freezing.

17 PATIENT COUNSELING INFORMATION
Patients should be advised to have ophthalmologic follow-up examinations of both eyes at appropriate intervals following implantation of RETISERT.

As with any surgical procedure, there is risk involved. Potential complications accompanying intraocular surgery to place RETISERT into the vitreous cavity may include, but are not limited to, the following: cataract formation, choroidal detachment, temporary decreased visual acuity, endophthalmitis, hypotony, increased intraocular pressure, exacerbation of intraocular inflammation, retinal detachment, vitreous hemorrhage, vitreous loss, and wound dehiscence.

Following implantation of RETISERT, nearly all patients will experience an immediate and temporary decrease in visual acuity in the implanted eye which lasts for approximately one to four weeks post-operatively.

Based on clinical trials with RETISERT, within 3 years post-implantation, approximately 77% of patients will require IOP lowering medications to control intraocular pressure and 37% of patients will require filtering procedures to control intraocular pressure. (see 6.1 Clinical Trials Experience - Ocular Events section).

Based on clinical trials with RETISERT, during the 3-year post-implantation period, nearly all phakic eyes are expected to develop cataracts and require cataract surgery.

MANUFACTURER INFORMATION
Revised May 2012
Marketed by:
Bausch & Lomb Incorporated
Rochester, NY 14609
Manufactured by:
Bausch & Lomb Incorporated
Waterford, Ireland
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