Noninfectious posterior uveitis is a potentially blinding condition that requires vigilant treatment.1,2 This disease affects adults of all ages, with an estimated prevalence of 10 per 100,000 persons.2 Relentless placoid chorioretinitis (RPC), formerly known as ampiginous chorioretinitis, is a chronic posterior uveitis that was originally described by Jones et al. in 2000.3-5 RPC resembles acute posterior multifocal placoid pigment epitheliopathy (APMPPE) or serpiginous chorioiditis initially in the disease course.4,5 However, a relentless course beyond 6 months differentiates it from APMPPE.5 Additionally, retinal lesions in RPC have a distinctive retinal distribution in the mid and far periphery, unlike APMPPE or serpiginous chorioiditis.4 The disease entity affects men and women equally and tends to appear between the 2nd and 6th decades of life.5 Visual symptoms often include blurred vision, metamorphopsia, paracentral scotomas, and/or floaters.5 The following case study describes a patient with RPC whose disease was slowly progressing in one eye despite systemic immunosuppression. The patient elected to receive RETISERT (fluocinolone acetonide intravitreal implant) 0.59 mg therapy, which allowed the patient’s eye to maintain quiescence without the need for systemic therapy.

Case Report: Relentless Placoid Chorioretinitis

BACKGROUND: A 30-year-old female patient was referred to my clinic with a diagnosis of posterior uveitis. Her symptoms included flashing lights, blurred vision, and scotomas in both eyes for the previous 5 to 6 months. She had prescription eyeglasses to correct for myopia and was generally healthy with no other systemic conditions or need for medications.

DIAGNOSIS: The patient underwent a number of laboratory tests including quantiferon gold, rapid plasma reagin, and fluorescent treponemal antibody absorption, which were all negative and minimized the possibility of infectious uveitis due to tuberculosis or syphilis.6 Additionally, chest x-rays were normal, minimizing the possibility of sarcoidosis.7 A baseline eye examination indicated that her vision was 20/20 in the right eye with an IOP of 16 mm Hg. The vision in her left eye was 20/40 with an IOP of 15 mm Hg. Examination of the anterior segment was unremarkable, with a clear lens, and no detectable anterior chamber cells. However, there were trace cells visible in the vitreous.

Indication
RETISERT® (fluocinolone acetonide intravitreal implant) 0.59 mg is a corticosteroid indicated for the treatment of chronic noninfectious uveitis affecting the posterior segment of the eye.

Important Safety Information
- Surgical placement of RETISERT® (fluocinolone acetonide intravitreal implant) 0.59 mg is contraindicated in active viral, bacterial, mycobacterial or fungal infections of the eye.

Please see additional Important Safety Information throughout and full Prescribing Information for RETISERT® on pages 5-7.
**DIAGNOSIS (CONT’D):** Evaluation of the fundus revealed changes in the retinal pigment epithelium (RPE) and chorioretinal scarring in the macula in both eyes (Figure 1). OCT examination revealed RPE and outer retinal disruption in both eyes, with subfoveal involvement in the left eye (Figure 2), consistent with foveal lesions present in RPC. All clinical signs were suggestive of noninfectious posterior uveitis, and the patient was ultimately diagnosed with RPC.

**TREATMENT:** The patient began treatment with oral prednisone (60 mg daily) with a slow taper. During the taper, the patient experienced uveitis flare in both eyes. As a result, she was placed on a steroid-sparing immunomodulatory therapy (IMT) in addition to oral prednisone. The dose of steroid-sparing IMT was increased due to insufficient inflammatory control at the lower dose. After 1 year of therapy, the steroid-sparing IMT was discontinued due to elevation of liver enzymes and the need for intravitreal corticosteroid injections every 3 to 4 months. The patient then began another steroid-sparing IMT in place of the previous one. She continued to experience persistent disease activity, and there was a slow enlargement of the chorioretinal lesions. As a result, adalimumab therapy at 40 mg SQ every 2 weeks was added to her treatment regimen. She remained on this treatment regimen for 3 years and required approximately 1 to 2 intravitreal corticosteroid injections per year to maintain disease quiescence. Additionally, she developed cataracts in both eyes from the multiple intravitreal corticosteroid injections and required surgery for cataract removal.

After 4 years of her initial presentation and systemic therapy, the patient’s vision was maintained. Her VA was 20/20 in the right eye and 20/30 in the left eye. However, ultrawide-field imaging revealed new chorioretinal lesions in the right eye and enlargement of the chorioretinal lesion in the left eye (Figures 3A-B). Autofluorescence photos confirmed disease progression in both eyes as areas of hypoautofluorescence with areas of speckled hyperautofluorescence were visible (Figure 3C-D). In the left eye, it was apparent that atrophy was progressing and threatening the fovea (Figure 3D). OCT imaging demonstrated stable RPE and outer retinal disruption in right eye (Figure 4A). In the left eye there was a progression of outer retinal and RPE atrophy extending close to the fovea (Figure 4B).

**Figure 1. Chorioretinal scarring in the macula.** Baseline fundus photos of the right (A) and left (B) eyes demonstrated RPE changes and chorioretinal scarring in the macula (arrows).

**Figure 2. RPE and outer retinal disruption at baseline.** OCT horizontal line scans of the right (A) and left (B) eyes demonstrated RPE and outer retinal disruption in both eyes (arrows). Subfoveal involvement was observed in the left eye.

**Figure 3. Disease progression 4 years after presentation.** Ultrawide-field Optomap images demonstrated new chorioretinal lesions in the right eye (A, arrow) and enlargement of the chorioretinal lesion in the left eye (B, arrow). Autofluorescence images revealed areas of hypoautofluorescence with areas of speckled hyperautofluorescence in the right (C) and left (D) eyes (arrows). Autofluorescence of the left eye (D) indicated progression of atrophy that was threatening the fovea.
why RETISERT? The slow progression of chorioretinitis despite immunosuppression was threatening the fovea in the left eye and required long-term control. Over the years, the patient’s disease had been responsive to intravitreal corticosteroids, thus making her an appropriate candidate for a RETISERT implant, which delivers corticosteroid therapy over 2.5 years. The patient was concerned about side effects associated with systemic exposure while receiving systemic therapy. Thus, she was motivated to get off all systemic immunosuppression as she desired an alternate therapy that would deliver long-term control with minimal systemic exposure.

RETISERT is a corticosteroid implant indicated for the treatment of chronic noninfectious uveitis affecting the posterior segment of the eye. RETISERT is designed to release fluocinolone acetonide locally to the posterior segment of the eye with minimal systemic exposure. RETISERT is a viable alternative for patients with chronic conditions such as RPC who cannot tolerate or who do not desire to be on systemic corticosteroid therapy. The patient was counseled on the benefits and risks of RETISERT, including cataract development and IOP elevation, and elected to receive a RETISERT implant in her left eye. Since the patient was bilaterally pseudophakic at the time of RETISERT implantation, she was not at risk for RETISERT-induced cataract formation.

PATIENT FOLLOW-UP: After surgical implantation of RETISERT in the left eye, the patient’s vision was temporarily reduced from 20/30 to 20/40 on the first day after surgery and remained at 20/40 until 1 week after implantation. At 1 month following surgical implantation, her vision had returned to baseline (20/30). She was tapered off all systemic immunosuppression by 3 months following RETISERT implantation, and she didn’t receive topical corticosteroids in either eye. Chorioretinal atrophy was stable in her left eye at 3 months post-implantation (Figure 5). Her right eye experienced a flare 1 month after ending systemic immunosuppression therapy, and was treated with a local corticosteroid injection (Figure 6). Her right eye continues to be managed with intravitreal corticosteroid injections every 2 to 3 months.

After 9 months of RETISERT therapy, the patient’s left eye was quiescent. IOP in the left eye had increased to 26 mm Hg approximately 4 months following implantation and was managed with dorzolamide hydrochloride/timolol maleate (2%/0.5%) ophthalmic solution BID. IOP in her left eye was 19 mm Hg at 9 months following RETISERT implantation.

Important Safety Information (cont’d)
• 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. Please see additional Important Safety Information throughout and full Prescribing Information for RETISERT® on pages 5-7.
Conclusions
This case study describes a patient who was diagnosed with RPC, a chronic bilateral noninfectious posterior uveitis that is characterized with lesions that are often found in the mid and far periphery with subsequent involvement of the posterior pole and/or macula. In the years following her diagnosis, the patient was treated with systemic immunosuppression, which did not provide adequate or consistent control of inflammation. Although she was able to maintain her vision, the chorioretinal lesions enlarged, and it was apparent that the disease was progressing. With a RETISERT implant in her left eye, the lesions had stabilized, and her eye was quiescent. The patient was able to achieve inflammatory control in both eyes with local corticosteroid therapy without the need for systemic immunosuppression.

Important Safety Information (cont’d)

- 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, 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.

- 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.

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

- 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. The most common non-ocular event reported was headache (33%).

Please see additional Important Safety Information throughout and full Prescribing Information for RETISERT® on pages 5-7.

• Ocular administration of corticosteroids has been associated with delayed wound healing and perforation of the globe where there
• Patients should be advised to have ophthalmologic follow-up examinations of both eyes at appropriate intervals following implantation
• Use of corticosteroids may result in elevated IOP and/or glaucoma. Based on clinical trials with RETISERT®, within 3 years

References:
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, deficits 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 Adverse Reactions (6.1)].

### 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 a viral, bacterial, mycobacterial or fungal infection of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia and varicella. Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex). Employment of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution.

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 uveits affecting the posterior segment in two multicenter controlled clinical trials. Patients were randomized to dosage regimens of 0.59 mcg or 2.1 mcg 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 includes 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, hypopyon, pruritus, ptosis, increased tearing, vitreous hemorrhage, dry eye, eyelid edema, macular 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

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 mcg/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 mcg/day, decreasing over the first month to a steady state between 0.3-0.4 mcg/day over approximately 30 months. The drug substance is the synthetic corticosteroid fluocinolone acetonide, represented by the following structural formula:

![Chemical Structure](image)

**C₂₄H₃₀F₂O₆** 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,17β)-

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: magnesium stearate, microcrystalline cellulose, and polyvinyl alcohol.

### 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 A₂ 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 A₂. 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 pre-implantation period.

Detailed results are shown in Table 1 below:

Table 1: Uveitis Recurrence Rates

<table>
<thead>
<tr>
<th>TIME POINT</th>
<th>STUDY 1</th>
<th>STUDY 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</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 0.59 mg 1 count

Storage: Store in the original container at 15°-25°C (59°-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, hyptony, increased intracocular 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 Adverse Reactions (6.1)].

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.
Missed an edition of RETISERT READY?

VISIT
www.eyetube.net/collections/retisert
TO SEE PREVIOUS CASE STUDIES