

I requested that **Tina H. Chen, MD**, and **Veena Raiji, MD, MPH**, analyze and dissect recent clinical trials investigating the use of steroid-based local treatments for the management of noninfectious uveitis. There has been tremendous development in this landscape, and an update was warranted.

Interestingly, the two treatments that just completed phase 3 U.S. Food and Drug Administration (FDA) registration trials have either a unique method of delivery (suprachoroidal microneedle delivery) or utilize a drug-delivery device. In either case, both agents are quite different as one is being developed for treatment of macular edema associated with noninfectious uveitis, whereas the other is being



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developed to decrease the rate of relapse in uveitis patients. Furthermore, these trials taught us that utilizing these new technologies to deliver steroid to the eye can favorably alter the risk-benefit ratio by keeping steroid in the suprachoroidal space and keeping it away from the anterior segment structures where adverse events like cataract and IOP elevation occur.

Drs. Chen and Raiji's insights and review of this complex topic will be highly valued by our community, as these agents will likely be reviewed by the FDA for approval in several months.

Update on Emerging Steroid-Based Local Treatments for Noninfectious Uveitis

by Tina H. Chen, MD; and Veena Raiji, MD, MPH



Tina H. Chen



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Intraocular inflammation was first described by the ancient Greeks and Chinese. Initially, intraocular inflammation was thought to be infectious, largely due to syphilis and tuberculosis. Only since the 1900s have we begun to understand underlying mechanisms of inflammatory disease through the concept of autoimmunity.¹ In 1903, Uhlenhuth discovered that lens antigen is organ specific and capable of producing autoimmune responses after immunization.² In 1910, Elschnig made similar observations regarding uveal tissue, which became the basis of the concept of sympathetic ophthalmia.³

In 1929, Hench, a rheumatologist at the Mayo clinic, observed that cortisone administered to a patient with rheumatoid arthritis mysteriously improved upon an acute affliction with jaundice.⁴ Six years later, cortisone was isolated and identified as an

anti-inflammatory factor by biochemists Kendall and Reichstein. In 1948, the first exogenous injection of cortisone was used for the treatment of rheumatoid arthritis.⁴ Since then, systemic corticosteroids have played a large role in treating intraocular inflammation. However, significant systemic adverse effects limit their use.⁵

During the 1950s, experimental models of autoimmune uveitis (EAU) emerged in which bilateral uveitis develops 10 to 14 days after antigen is injected into an animal model remotely from the eye. EAU mimics autoimmune human uveitis and revealed immunotherapeutic paradigms that can be exploited to control noninfectious intraocular inflammation, making research on steroid-sparing immunomodulatory therapy possible.¹

When systemic immunomodulatory therapy is indicated, most agents are used in an off-label fashion,⁶ with the exception of adalimumab (Humira; AbbVie, North Chicago, IL), which was approved by the U.S. Food and Drug Administration (FDA) in 2016 for the treatment of non-infectious intermediate, posterior, and panuveitis in adults.⁷ On October 17, 2018, the FDA expand-

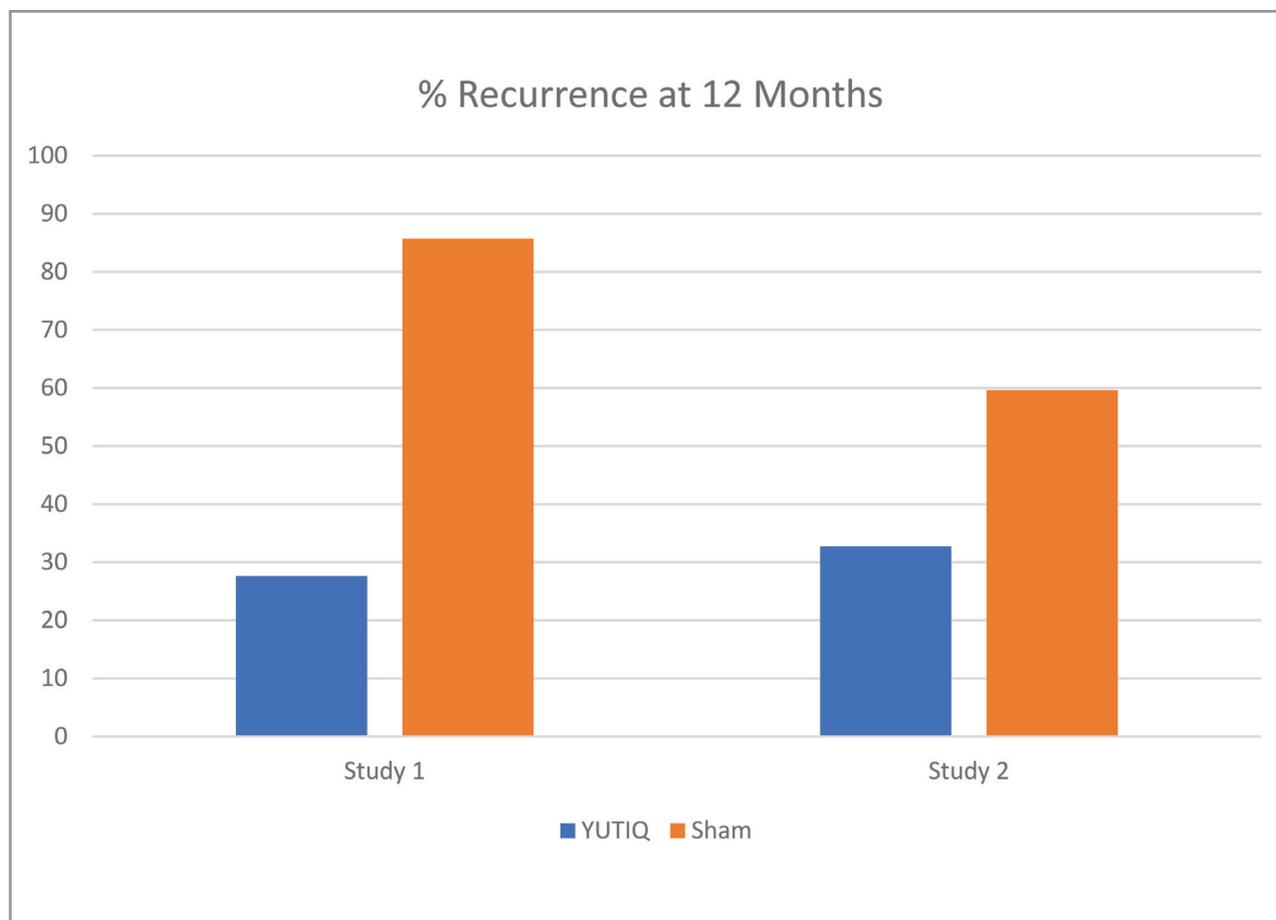


Figure 1. Twelve-month recurrence rate after YUTIQ versus sham for two parallel phase 3 studies by EyePoint Pharmaceuticals.⁹

ed its approval of the use of adalimumab to include children 2 years of age and older.

Two local steroids that are FDA-approved for the treatment of noninfectious uveitis include Retisert, a 0.59 mg fluocinolone acetonide intravitreal surgical implant (Bausch + Lomb, Rochester, NY) FDA-approved in 2005, and Ozurdex, a 0.7 mg dexamethasone injectable intravitreal implant (Allergan, Dublin, Ireland), FDA-approved in 2010. Ongoing research is further expanding treatment options for noninfectious uveitis. In this article, we highlight the latest study results on two additional emerging local treatments that have completed phase 3 studies.

NEWEST ON THE HORIZON

YUTIQ

YUTIQ (EyePoint Pharmaceuticals, Watertown, MA) is a sustained-release 0.18 mg fluocinolone intravitreal implant measuring 3.5 mm in length and 0.37 mm in diameter that utilizes EyePoint's proprietary

Durasert technology. The implant can be injected in the office using a 25-gauge needle and is designed to last up to 3 years.

EyePoint Pharmaceuticals has completed two parallel phase 3 studies of YUTIQ for the treatment of chronic noninfectious intermediate, posterior, or panuveitis. Both studies were double-masked, randomized, prospective studies involving patients with recurrent noninfectious posterior segment uveitis. Patients were randomized to YUTIQ versus sham injections. The primary endpoint was recurrence rate at 6 months. To date, 12-month results have been published, and the studies expect to gather data out to 3 years. Both studies have met its primary efficacy endpoint at both 6 and 12 months with statistical significance.

In the first parallel phase 3 study, at 12 months, 27.6% of patients in the YUTIQ group had a recurrence compared to 85.7% in the sham group ($P < .01$) (Figure 1). Patients in the YUTIQ group had an average of 1.3 mm Hg intraocular pressure (IOP) rise compared to 0.2 mm Hg in the sham group. There was a mean

Subjects Gaining ≥ 15 ETDRS Letters at Week 24 from Baseline		
	CLS-TA (N=96)	Control (Sham) (N=64)
Proportion (n) of Subjects Gaining ≥ 15 ETDRS Letters at Week 24 from Baseline	46.9% (45)	15.6% (10)
p-value	<0.001	

Figure 2. PEACHTREE XIPERE primary endpoint results at week 24 from baseline.¹²

IOP elevation of 1.3 mm Hg in the YUTIQ group compared to 0.2 mm Hg in the sham group. Cataract surgery was required in 33.3% of phakic patients in the YUTIQ group, compared to 4.8% in the sham group.⁸

Results from the second parallel phase 3 study were comparable.⁹ At 12 months, 32.7% of patients in the YUTIQ group had a recurrence of inflammation, compared to 59.6% of patients in the sham group ($P < .01$) (Figure 1). IOP increased a mean of 2.0 mm Hg for the YUTIQ group compared to 0.0 mg Hg in the sham group. Ocular hypertensive treatment was required in 50.5% of YUTIQ-treated patients by 12 months compared to 51.9% in the sham group. One patient receiving YUTIQ required glaucoma surgery during the first 12 months. Cataract surgery was required in 18.0% of YUTIQ-treated phakic patients by 12 months, compared to 8.6% in the sham group.

On October 12, 2018, EyePoint Pharmaceuticals announced that the FDA had approved YUTIQ for the treatment of chronic noninfectious uveitis affecting the posterior segment of the eye.¹⁰

XIPERE

XIPERE is a sterile, preservative-free suspension of triamcinolone acetonide (TA) from Clearside Biomedical (Alpharetta, GA). The drug is provided with a prepackaged syringe containing a needle measuring approximately 1,000 μm in length (the “microinjector”). It is injected 4 mm posterior to the limbus into the suprachoroidal space. Within seconds, the drug flows posteriorly from the injection site with absorption of drug into posterior segment tissues and with no depot at the injection site following administration. To date, no other drug delivery system shares the same unique ocular distribution profile as suprachoroidally injected XIPERE. The suprachoroidal route allows drug concentrations to be high at target sites posteriorly while minimizing drug concentra-

tions anteriorly, providing the potential for efficacy while mitigating side effects such as cataract and ocular hypertension / glaucoma. Furthermore, the suprachoroidal space delivery requires one-tenth the amount of TA compared to an intravitreal injection while maintaining similar efficacy.¹¹

Preclinical data showed that 90 days after suprachoroidal space injection, concentration of TA in the sclera, choroid, and RPE is 12 times higher compared to steroid in these same tissues following the same amount of TA injected intravitreally. Retinal concentration at 90 days was equal following suprachoroidal space and intravitreal injections. In the vitreous, lens and ciliary body, there were substantially lower concentrations of triamcinolone following suprachoroidal injection as compared to intravitreal injection. Through the 90 days after suprachoroidal injection, TA was below limits of quantification in the aqueous humor.¹¹

On March 5, 2018, Clearside Biomedical announced the results of the PEACHTREE phase 3 study of suprachoroidal XIPERE in patients with macular edema arising from any noninfectious uveitis and having any anatomic location of uveitis.¹² The randomized, controlled, masked clinical trial enrolled 160 patients, with 96 patients randomized to receive two doses of 4.0 mg suprachoroidal XIPERE 12 weeks apart. Sixty-four subjects were randomized to receive sham doses 12 weeks apart. The primary endpoint was a statistically significant difference in subjects gaining 15 or more letters from baseline after treatment with XIPERE compared to sham after 24 weeks. This phase 3 trial met its primary endpoint with a significantly greater proportion of patients in the XIPERE (47%) arm compared to those in the sham control (16%) arm gaining 15 or more ETDRS letters in BCVA ($P < .001$) (Figure 2).¹²

The study also met a secondary endpoint, which was a statistically significant reduction of central subfield thickness from baseline to week 24. At 24 weeks, the XIPERE arm saw a reduction in CST of 157 μm , compared to 19 μm in the sham group ($P < .001$). In addition, the mean gain in ETDRS letters was greater in the XIPERE arm compared to sham. Treated subjects gained 9.6 letters at 4 weeks, and 13.8 letters at 24 weeks, compared to 1.2 letters and 2.9 letters for the sham group, respectively.¹²

There were no treatment-related serious adverse events in this trial. At 24 weeks, 11.5% of patients receiving XIPERE had an adverse event related to elevated IOP, compared to no patients in the sham group.¹²

Clearside expects to file a New Drug Application for XIPERE through the FDA later this year.

CONCLUSIONS

Compared to our predecessors just decades prior, we are fortunate to have several currently FDA-approved medications available for the treatment of noninfectious uveitis, including systemic and local options. As research in immunology continues, our treatment options will continue to expand. Most recently, YUTIQ has been added to our armamentarium. In addition, we anticipate the addition of XIPERE in the near future with its recently completed successful phase 3 FDA registration trials.

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