

THERAPEUTIC OPTIONS FOR UVEITIS

Thanks to a plentiful number of choices available and in the pipeline, the future looks promising for patients with this condition.

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Uveitis is an inflammatory condition associated with visual impairment, blindness, and reduced quality of life. The condition often affects patients in their most active and economically productive years.¹ Uveitis has been

demonstrated to cause between 5% and 20% of cases of legal blindness in the United States and the European Union, and up to 25% of cases of legal blindness in developing countries.²

Immunomodulatory therapy is essential in controlling chronic noninfectious inflammation, with decreased risks compared with chronic corticosteroid use. Steroid-sparing immunomodulatory therapy, such as antimetabolites (methotrexate and mycophenolate), T-cell inhibitors, alkylating agents, and, more recently, biologics, are commonly used to manage uveitis. This article is an overview of newer available treatments for uveitis and therapies under clinical investigation (see Table, next page).

LOCAL STEROIDS

Treatment guidelines discourage use of systemic corticosteroids at doses higher than 10 mg daily due to complications associated with prolonged use. However, local steroids, especially sustained-delivery options, have had increasing importance in the management of uveitis.

Fluocinolone Acetonide

Fluocinolone Acetonide Intravitreal Implant 0.59 mg

The fluocinolone acetonide intravitreal implant 0.59 mg (Retisert, Bausch + Lomb) was approved by the US Food and Drug Administration (FDA) in 2005. It is surgically implanted to treat noninfectious intermediate uveitis, posterior uveitis, or panuveitis and releases drug for approximately 3 years.³⁻⁷

Preclinical studies demonstrated that the implant is well tolerated, with no measurable systemic drug absorption. In a multicenter trial, the implant effectively controlled inflammation for 34 weeks, preserved vision

(87% stabilized or improved), reduced cystoid macular edema (CME), and decreased the need for adjunctive therapy.⁵ The implant reduced uveitis recurrence (no more than one for any patient in the study) and the need for adjunctive therapy.^{3,5}

The MUST trial demonstrated statistically significantly better control of uveitis in the implant group (88% vs. 71%).^{7,8} Associated adverse events included increased intraocular pressure (IOP), cataract, hypotony, and suture exposure.^{3,4} The implant is contraindicated in active viral, bacterial, mycobacterial, and fungal eye infection.⁷

A follow-up study of the patients in the MUST trial concluded that patients treated with systemic therapy had better visual acuity outcomes than those in the implant group. However, in the second half of the 7-year study period, less than 30% of patients in the implant arm had had an implant placed, dampening the strength of this conclusion. The implant appears to work as well as systemic therapy while it releases drug (ie, the first 3 years after implantation). Patients with chronic inflammation

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AT A GLANCE

- Uveitis is a debilitating condition causing between 5% and 20% of legal blindness in the United States and the European Union.
- Immunomodulatory therapy is essential in controlling chronic inflammation, with decreased risks compared with chronic corticosteroid use.
- Numerous agents are in the pipeline for treatment of uveitis, including long-acting steroid delivery systems, local nonsteroidal agents, systemic therapies, gene therapies, and more.

TABLE. DRUGS FOR THE TREATMENT OF UVEITIS, AVAILABLE AND IN THE PIPELINE

Therapeutic Agent (Manufacturer)	Drug Class	Delivery Mechanism	Pivotal Clinical Trial (phase)	Clinical Trial Number
Sutured fluocinolone implant (Retisert, Bausch + Lomb)	Corticosteroid	Sustained-release implant	FDA approved 2005. Re-implantation of a fluocinolone acetonide implant for non-infectious uveitis affecting the posterior segment (phase 4)	NCT00543296
Injectable fluocinolone implant (Iluvien, Alimera Sciences)	Corticosteroid	Sustained-release implant	A Controlled, Multi-center Study of the Utilization and Safety of the MK II Inserter and the Safety of the FAI Insert in Subjects With Non-infectious Uveitis Affecting the Posterior Segment of the Eye (phase 3)	NCT02748512
Dexamethasone implant (Ozurdex, Allergan)	Corticosteroid	Sustained-release implant	Study of the Effectiveness of Ozurdex for the Control of Uveitis (phase 4)	NCT02049476
Suprachoroidal space TA (CLS-TA, Clearside Biomedical)	Corticosteroid	Suprachoroidal space	Suprachoroidal Injection of CLS-TA in Subjects With Non-infectious Uveitis (AZALEA) (phase 3) Suprachoroidal Injection of CLS-TA in Subjects With Macular Edema Associated With Non-infectious Uveitis (PEACHTREE) (phase 3)	NCT03097315 NCT02595398
Sirolimus (Opsiria, Santen)	mTOR inhibitor	Intravitreal	Intravitreal Sirolimus as Therapeutic Approach to Uveitis (SAVE-2) (phase 2) Study Assessing Double-masked Uveitis Treatment (SAKURA) (phase 3) A Phase 3b, Multinational, Multicenter, Open-Label Extension Study Assessing the Long-Term Safety of PRN Intravitreal Injections of DE-109 in Subjects With Non-Infectious Uveitis of the Posterior Segment of the Eye Who Have Participated in the SAKURA Development Program (32-009)	NCT01280669 NCT01358266 NCT02251938
Adalimumab (Humira, Abbvie)	Anti-TNF-alpha	Subcutaneous	Efficacy and Safety of Adalimumab in Patients With Active Uveitis (VISUAL I) (phase 3) Intravitreal Adalimumab Versus Subcutaneous Adalimumab in Non-infectious Uveitis (IVAS) (phase 2) A Study of the Long-term Safety and Efficacy of Adalimumab in Subjects With Intermediate-, Posterior-, or Pan-uveitis (VISUAL III) (phase 3)	NCT01138657 NCT02706704 NCT01148225

TABLE (Cont'd.). DRUGS FOR THE TREATMENT OF UVEITIS, AVAILABLE AND IN THE PIPELINE

Therapeutic Agent (Manufacturer)	Drug Class	Delivery Mechanism	Pivotal Clinical Trial (phase)	Clinical Trial Number
Tocilizumab (Actemra, Genentech)	Anti-IL-6	Intravenous	Study of the Safety, Tolerability, and Bioactivity of Tocilizumab On Patients With Non-infectious UVEITIS: The STOP-Uveitis Study (STOP-Uveitis) (phase 1/2)	NCT01717170
Sarilumab (Kevzara, Sanofi Genzyme)	Anti-IL-6	Subcutaneous	SATURN study (phase 2)	NCT01900431
EYS606 (Eyevegensys)	Anti-TNF-alpha	Electrotransfection injection system	Phase 1b study	
EGP-437 (iontophoretic dexamethasone phosphate, Eyegate Pharmaceuticals)	Corticosteroid	Iontophoresis	Safety and Efficacy of Iontophoretic Dexamethasone Phosphate Ophthalmic Solution in Non-Infectious Anterior Uveitis (EGP-437-006)(phase 3)	NCT02517619
NS2 (Aldeyra Therapeutics)	Aldehyde trap	Topical	A Safety and Efficacy Study of NS2 in Patients With Anterior Uveitis (phase 2)	NCT02406209
Corticotropin (Acthar, Mallinckrodt Pharmaceuticals)	Adrenocorticotrophic hormone analogue	Subcutaneous or intramuscular	Phase 4 study	
Abbreviations: anti-IL-6, anti-interleukin-6; anti-TNF-alpha, anti-tumor necrosis factor alpha; FDA, Food and Drug Administration; mTOR, mammalian target of rapamycin; PRN, as needed; TA, triamcinolone acetate Source: clinicaltrials.gov				

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may need to have the implant replaced every 30 months for optimum results.

Other Fluocinolone Acetonide Intravitreal Implants

The fluocinolone acetonide intravitreal implant 0.19 mg (Iluvien, Alimera Sciences) was FDA-approved in 2014 to treat eyes with diabetic macular edema.^{3,6} The implant is inserted intravitreally with a 25-gauge needle.^{3,6,7} In July, Alimera secured the rights to pursue a secondary indication for posterior uveitis in the European Union, the Middle East, and Africa.⁹

Jaffe et al³ found that the visual acuity of eyes with noninfectious intermediate uveitis, posterior uveitis, or panuveitis treated with the injectable fluocinolone acetonide implant stabilized or improved after 1 year. All 11 eyes in the study remained quiet and required less adjunctive therapy during 24 months of follow-up.³ There was evidence of resolution of anterior chamber cells; reduced vitreous haze; decreased macular thickness and volume and decreased retinal nerve fiber layer thickness on optical coherence tomography (OCT); and absence of recurrences. Adverse effects included

increased IOP and cataract progression.^{3,6}

The fluocinolone acetonide intravitreal implant 0.18 mg (Durasert, pSivida) is currently under investigation for use in posterior segment noninfectious uveitis. Phase 3 pivotal trials of 3-year treatment with this implant have met their primary endpoint with a favorable safety profile, but results have not been published.^{10,11}

Dexamethasone

The dexamethasone intravitreal implant 0.7 mg (Ozurdex, Allergan) is a sustained-release, injectable, biodegradable steroid implant approved in the United States and Europe for the treatment of noninfectious uveitis affecting the posterior segment.^{6,7} Implanted with a 22-gauge injector, the device releases dexamethasone in a biphasic manner over a 6-month period. After the first 2 months, the steroid concentration declines until month 4, when it maintains a lower concentration until month 6.

The HURON study compared the safety and efficacy of two doses (0.7 mg and 0.35 mg) of the dexamethasone intravitreal implant for the treatment of noninfectious intermediate or

posterior segment uveitis over 6 months.¹² Both doses were effective in controlling vitreous inflammation and improving visual acuity with reduction in CME, but the higher dose had a longer duration of action without a significant increase in side effects. A total of 47% of patients treated with the 0.7 mg implant achieved the primary outcome measure—a vitreous haze score of zero at 8 weeks.^{7,8} Observed side effects included raised IOP and cataract progression. The implant has also been shown to be effective in reducing macular thickness and increasing visual acuity in uveitic macular edema in vitrectomized eyes and in pediatric uveitis.⁶

The dexamethasone intravitreal implant 0.7 mg is contraindicated in patients with periocular infections and advanced glaucoma and in patients whose posterior lens capsule is not intact, due to a risk of implant migration into the anterior chamber, seen especially in vitrectomized eyes.⁷

Suprachoroidal Triamcinolone Acetonide

Triamcinolone acetonide (CLS-TA, Clearside Biomedical) is in development as a single suprachoroidal 4.0 mg or 0.8 mg injection for treatment of macular edema associated with noninfectious uveitis.

In the Dogwood trial, the primary endpoint of reducing retinal thickness was successfully achieved at 8 weeks after single treatment. The secondary endpoint of improving best corrected visual acuity (BCVA) was also achieved.¹³ Although data are limited, the hope is that suprachoroidal injection will maximize triamcinolone's effect on the retina while minimizing its effect on the lens and trabecular meshwork.

LOCAL NONSTEROIDAL AGENTS

Sirolimus

Sirolimus (Opvia, Santen) is a macrolide compound derived from *Streptomyces hygroscopicus*. It has potent immunosuppressive and antineoplastic activity that depends on its binding to specific cytosolic proteins (immunophilins) to generate an immunosuppressive complex.¹⁴ Sirolimus inhibits the activity of the serine/threonine protein kinase of mammalian target of rapamycin (mTOR).

Oral administration of sirolimus demonstrated complete inhibition of autoimmune uveitis in preclinical models.^{2,15} However, this delivery route requires laboratory and clinical monitoring for systemic toxicity (anemia and hyperlipidemia). Bimonthly intravitreal sirolimus was effective at a dose of 440 µg without systemic side effects in a phase 1 study.¹⁴ At the 6-month and 12-month primary endpoints of the SAVE study, sirolimus reduced vitreous haze and the need for systemic corticosteroids in patients with uveitis.¹⁵

The phase 3 SAKURA 1 and 2 studies reported significant improvement in reducing ocular inflammation in

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patients with active noninfectious uveitis and successful tapering of corticosteroid dose (<5 mg/d). The results suggest that intravitreal injection of sirolimus can effectively resolve ocular inflammation, often without concomitant use of other local or systemic immunoregulators.^{2,14-16} The most often encountered adverse event was worsening of inflammation, with minimal ocular hypertension or cataract progression over 2 years.¹⁵

Systemic sirolimus (Rapamune, Pfizer) is approved for several indications. The ophthalmic formulation of sirolimus has been accepted for review by the FDA.

SYSTEMIC THERAPY

Adalimumab

Adalimumab (Humira, Abbvie) is a recombinant human immunoglobulin G1 (IgG1) monoclonal antibody specific for tumor necrosis factor-alpha (TNF-alpha). Adalimumab binds TNF-alpha and blocks its interaction with its two known receptors. It is FDA-approved for the treatment of noninfectious intermediate uveitis, posterior uveitis, and panuveitis. Adalimumab is administered subcutaneously at a typical dose of 40 mg every other week.^{6,17-20}

Suhler et al showed that adalimumab was safe and effective in 68% of refractory uveitis patients 10 weeks after initial dose, and the effect was maintained in 39% after 1 year.¹⁸ Jaffe et al reported that patients who received adalimumab had a significantly lower risk of treatment failure, defined as increased vitreous haze, new active inflammatory lesions, anterior chamber cell grade, or worsening of BCVA.¹⁷ After discontinuation of immunomodulatory therapy, adalimumab achieved early and sustained disease control, reducing inflammation and visual impairment.

Its use is associated with significant reduction of macular thickness relative to baseline and with resolution of macular edema.^{17,18,20} Adverse events reported include injection site infection, allergic reactions, active tuberculosis, lupus or lupus-like reaction, and demyelinating disorder.^{17,20}

Before initiation of treatment, baseline laboratory screening should be completed, consisting of complete blood count; comprehensive metabolic panel including liver function, renal function, and electrolytes; and screening for tuberculosis by tuberculin skin test and/or interferon gamma release assay.^{17,19} Contraindications include any evidence of active infection, lymphoproliferative disorder diagnosed or treated within the previous 5 years, moderate or severe heart failure, chronic hepatitis B or C, presence of any demyelinating disorders, pneumonitis, or use in the perioperative period (1 week before and 1 week after surgery).¹⁹

“ [Sarilumab] is indicated for the treatment of rheumatoid arthritis and is undergoing clinical trials for use in the management of posterior segment noninfectious uveitis.

Tocilizumab

Tocilizumab (Actemra, Genentech) is a humanized monoclonal IgG1 antibody interleukin-6 receptor (IL-6R) synthesized by recombinant DNA technology. It is approved in the United States and other countries for treatment of several autoimmune disorders and is being studied for treatment of refractory uveitis-related macular edema.^{6,14,21,22} Tocilizumab blocks IL-6–mediated signaling by binding both soluble and transmembrane IL-6 receptors. The drug consequently reduces T-cell activation, Th17 differentiation, antibody secretion, and hepatic acute phase protein production.

Mesquida et al²¹ reported a statistically significant reduction in central foveal thickness beginning the first month after initiation of therapy and continued and sustained through 24 months, associated with visual improvement.⁶ A phase 1/2 clinical trial of tocilizumab in juvenile idiopathic

arthritis (JIA)-associated uveitis has begun.⁶ The multicenter, randomized STOP-UVEITIS study assessing the safety, tolerability, and bioactivity of two doses of tocilizumab in intermediate, posterior, and panuveitis is under way in the United States.^{6,23}

Tocilizumab appears to be effective in reducing macular edema, controlling inflammation, and maintaining or improving visual acuity as long as patients are receiving infusions.^{22,24} The adverse events reported are infections (including tuberculosis), infusion reactions, increased risk of gastrointestinal perforation, laboratory abnormalities (hyperlipidemia, elevated transaminases, neutropenia), augmented risk of neurologic disorders, and malignancies.^{21,22}

Sarilumab

Sarilumab (Kevzara, Sanofi Genzyme) is a subcutaneously administered fully human monoclonal antibody directed against the alpha subunit of the IL-6 receptor complex. It is indicated for the treatment of rheumatoid arthritis and is undergoing clinical trials for use in the management of posterior segment noninfectious uveitis.²⁵⁻²⁷ In the SATURN study, in patients with noninfectious uveitis, reductions in vitreous haze and steroid dosing were seen in treated patients.²⁵ Visual acuity and central macular thickness also improved with a 200-mg dose administered subcutaneously every 2 weeks. This drug targets a specific inflammatory mediator, and it has been associated with fewer side effects than other available therapies.^{25,27} Neutropenia and elevated alanine aminotransferase levels were reported as adverse events.²⁶

Corticotropin

Repository corticotropin injection (Acthar, Mallinckrodt Pharmaceuticals) is delivered by subcutaneous or intramuscular injection and targets melanocortin receptors. It is FDA-approved for a range of severe acute and chronic allergic and inflammatory ophthalmic conditions, including diffuse posterior uveitis. Little has been published on corticotropin's clinical efficacy in the treatment of patients with uveitis,^{28,29} but the drug may be able to reduce inflammation with less systemic effects than steroids.

GENE THERAPY

EYS606

EYS606 (Eyeveusys) is a nonviral gene therapy that uses a proprietary electrotransfection injection system to deliver plasmids encoding for the production of anti-TNF-alpha into the ciliary muscle of the eye. TNF-alpha is a cytokine that has been shown to play a pivotal role in mediating intraocular inflammation in noninfectious uveitis. EYS606 is being investigated in an open-label phase 1b study in the United Kingdom that is expected to be completed toward the end of this year.³⁰

OTHER TREATMENT OPTIONS

EGP-437

EGP-437 (Eyegate Pharmaceuticals) is a dexamethasone phosphate solution that is delivered to targeted ocular tissues using transscleral iontophoresis. Iontophoresis is a noninvasive method in which low electrical current is applied to an ionizable substance to increase its mobility across a surface through electrochemical repulsion.^{1,14,31,32}

EGP-437 has been shown to have a prolonged duration of action and to be more effective compared with other delivery routes. In 2012, Cohen et al reported that EGP-437 was well tolerated and extremely effective, achieving anterior cell chamber scores of zero within 28 days after one treatment in 60% of participants with noninfectious anterior uveitis.³¹ The most commonly reported adverse effects were conjunctival hyperemia, punctate keratitis, conjunctival edema, eye pain, and erythema and edema of the eyelid.³²

NS2

NS2 (Aldeyra Therapeutics) is an aldehyde-binding small molecule that traps aldehydes, neutralizing toxic aldehyde species that can lead to inflammation via activation of the nuclear factor kappa B pathway. Once the aldehyde is trapped, the aldehyde complex is degraded and aldehyde levels are diminished, which potentially reduces toxicity and inflammation.

In a randomized, multicenter, investigator-masked, comparator-controlled, parallel-group phase 2 clinical trial, topical NS2 reduced anterior chamber cell count in patients with noninfectious uveitis.³³ Anterior chamber cell count was reduced 53% in those receiving NS2 after 8 weeks of treatment. The drug showed effectiveness equal to that of topical corticosteroids without IOP elevation or cataract production. No serious adverse events were reported.

CONCLUSION

Uveitis can be a debilitating condition, and it affects a significant percentage of the population. As the research outlined above demonstrates, much work is being done in many centers to find more and better ways to safely and effectively treat and manage uveitis. ■

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