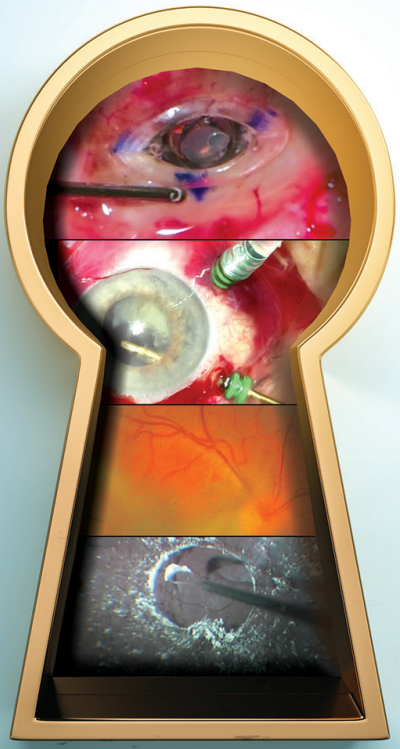
Steroid Therapy for The Long Haul



Many sustained-release options are available to help quell inflammation. Here's what you need to know.

BY KAPIL MISHRA, MD, AND THEODORE LENG, MD, MS

Sustained-release corticosteroids have become a mainstay in the retina specialist's armamentarium for an array of retinal diseases. Due to their effects on several pathways, steroids have antiinflammatory, antiangiogenic, and antipermeability properties that are advantageous for treating many retinal diseases, including diabetic macular edema (DME), retinal vein occlusion (RVO), noninfectious posterior uveitis, and cystoid macular edema (CME). Because long-term use of systemic corticosteroid therapy carries with it significant side effects, local ocular therapy has proven valuable because of its high efficacy and safe systemic profile. The push for longer-acting therapeutics has garnered us several long-duration corticosteroid therapies to choose from (Figure). This article summaries your options (Table).

TRIAMCINOLONE ACETONIDE

Triamcinolone acetonide (TA), a potent glucocorticoid, is a white crystalline powder that is insoluble in water. The two most common preparations are kenalog-40 (40 mg/ml), which is off-label for intraocular use but is often used as a sub-Tenon's injection or intravitreal injection for an array of retinal diseases, and preservative-free Triesence (40 mg/ml, Alcon), which is FDA-cleared for intraocular use.

A recent addition to the ocular steroid therapy space is suprachoroidal Xipere (triamcinolone acetonide injectable suspension, Bausch + Lomb) which gained FDA approval in October 2021 for the treatment of macular edema associated with uveitis. Approval came following results of the PEACHTREE study that included 160 patients.[1] Patients were enrolled if they had noninfectious uveitis, no other ocular disease, and central subfield thickness greater than 300 µm. Both medication and sham groups were treated at day 0 and week 12, and results showed that the suprachoroidal arm gained 15 letters or more from baseline in 46.9% of eyes compared with 15.6% in the sham group at week 24 ($P < .001$). Central subfield thickness was reduced by 153 µm in the suprachoroidal group compared with 18 µm in the sham group ($P < .001$). IOP elevation was seen in only 11.5% of eyes after two suprachoroidal injections.

DEXAMETHASONE IMPLANT

Ozurdex (Allergan), a biodegradable 0.70 mg dexamethasone implant given as an intravitreal injection via a 22-gauge needle, is FDA-cleared for DME, macular edema secondary to branch or central RVO, and noninfectious posterior uveitis. After implantation, dexamethasone is detectable in the vitreous 6 months following injection; however, peak concentration is around 2 months.

AT A GLANCE

- Local ocular therapy, as opposed to systemic steroid therapy, has proven valuable because of its high efficacy and safe systemic profile.
- A recent addition to the ocular steroid therapy space is suprachoroidal Xipere (triamcinolone acetonide injectable suspension, Bausch + Lomb).
- Retina specialists have been aware of fluocinolone implants for some time, given that the first insert gained FDA approval in 2005 for the treatment of noninfectious posterior uveitis.

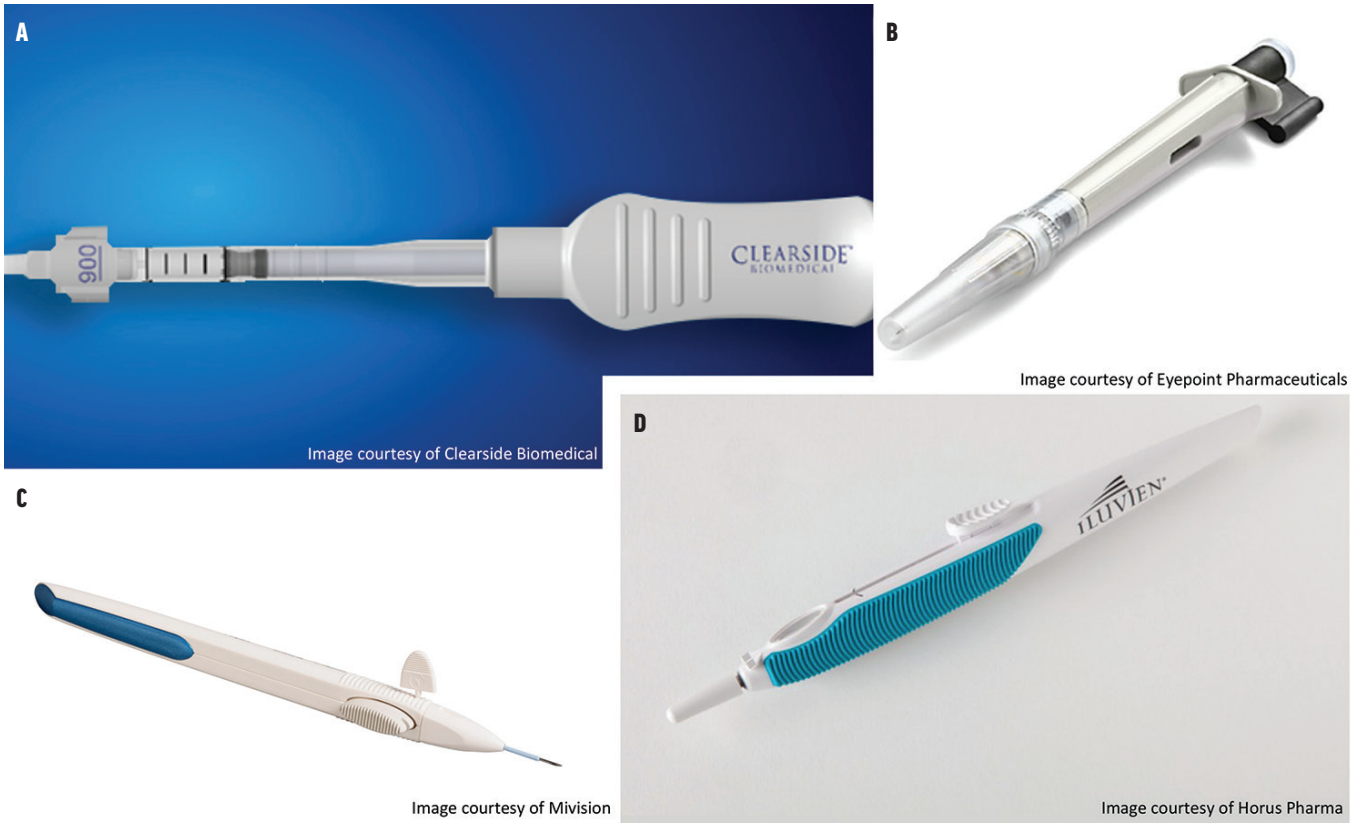


Figure. The nonsurgical long-duration steroid options each have a specialized injector to ensure safe drug delivery. Xipere uses the SCS microinjector (Clearside Biomedical) that comes with both a 900 µm and 1,100 µm length needle (A). The tip of Yutiq's single-use preloaded applicator should be oriented above the horizontal plane during the procedure to prevent the implant from falling out of the applicator (B). Ozurdex's applicator uses an accordion-style mechanism (C). Iluvien's preloaded applicator uses a spring-free mechanism to expel the implant (D).

The MEAD study assessed the 0.35 mg and 0.70 mg dexamethasone implants compared with sham in patients with DME and found a 15-letter improvement or more compared with baseline for 22.2% in the 0.70 mg group, 18.4% in the 0.35 mg group, and 12.0% in the sham group ($P < .018$).[2] Mean reduction in central subfield thickness was significantly higher in the dexamethasone groups compared with sham, and only three patients in the implant groups required glaucoma surgery.

The GENEVA trial was a pivotal study comparing the 0.70 mg dexamethasone implant with sham for macular edema due to RVO and found that the dexamethasone groups produced significantly greater improvements in visual acuity and achieved a faster 15-letter improvement compared with sham.[3] The largest differences between groups took place on days 30, 60, and 90, although visual acuity gains were diminished by day 180, suggesting low levels of dexamethasone 6 months following injection. Of patients in the dexamethasone group, 22.9% were on IOP-lowering medications at study end with a majority taking only one medication. Similar to MEAD, only three patients required incisional glaucoma surgery.

Finally, the HURON study assessed 0.35 mg and 0.70 mg dexamethasone implants for noninfectious intermediate or posterior uveitis and found a vitreous haze score of 0 at week 8 in 47% of eyes in the 0.70 mg group, 36% in the 0.35 mg group, and 12% in the sham group ($P < .001$), as well as a significantly higher proportion of eyes with a 15-letter or more gain in the treatment groups.[4]

FLUOCINOLONE ACETONIDE IMPLANTS

Fluocinolone acetonide is a synthetic corticosteroid with similar potency to dexamethasone and is used in several long-acting steroid implants.[5-7] Retina specialists have been aware of fluocinolone implants for some time, given that the first insert, Retisert (0.59 mg fluocinolone acetonide, Bausch + Lomb) gained FDA approval in 2005 for the treatment of noninfectious posterior uveitis. This surgically-implanted device can release higher concentrations of steroid than the intravitreal implants that have come after it, particularly early in the treatment course. Recent clinical data suggest that the Retisert implant is still a reasonable option for the treatment of uveitis.[8]

The MUST follow-up study was a 7-year observational study of an initial cohort that was randomized to receive either systemic antiinflammatory treatment or the Retisert implant.[8] The 2-year results demonstrated that patients with the Retisert implant fared better in terms of visual acuity and uveitis activity; however, the 7-year follow-up data appears to favor systemic therapy. It is worth noting that after the

TABLE. LONG-ACTING STEROID OPTIONS

	Indication	Delivery	Duration/Efficacy
Triamcinolone Acetonide			
Sub-Tenon's Injection (40 mg/ml)	Macular edema associated with uveitis, cystoid macular edema from various etiologies, intermediate/posterior uveitis	Sub-Tenon's space; most common medication used is kenalog-40 delivered in 0.5 mL volumes	2 to 3 months; duration may vary due to variability of kenalog crystal sizes
Preservative-Free Triesence (40 mg/ml, Alcon)	Macular edema associated with uveitis, diabetic macular edema, macular edema secondary to retinal vein occlusion	Intravitreal	4 to 6 weeks (less for vitrectomized eyes); better BCVA and OCT thickness in macular edema compared with sub-Tenon's
Xipere (Bausch + Lomb)	Macular edema associated with uveitis	Suprachoroidal, 0.1 mL administered using a 30-gauge needle	Treatment response noted up to 9 months in 50% of patients[2]
Dexamethasone			
Ozurdex (0.7 mg, Allergan)	Diabetic macular edema, retinal vein occlusion-associated macular edema, noninfectious posterior uveitis	Intravitreal, bioerodable	3 to 4 months
Fluocinolone Acetonide			
Iluvien (0.19 mg, Alimera Sciences)	Diabetic macular edema	Intravitreal, nonbioerodable	Up to 36 months
Yutiq (0.18 mg, EyePoint Pharmaceuticals)	Noninfectious posterior uveitis	Intravitreal, nonbioerodable	Up to 36 months
Retisert (0.59 mg, Bausch + Lomb)	Chronic noninfectious posterior uveitis, patients who cannot tolerate systemic therapy	Surgically implanted and sutured at pars plana	Approximately 2.5 years; uveitis recurrence rate decreased by more than 50% at 34 weeks

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2-year study, specific treatment patterns were not mandated, and patients could cross over between arms. Also, most Retisert patients only received one implant over the 7 years, while the majority of patients in the systemic group were on active therapy at the end of 7 years, suggesting that patients in the Retisert group were undertreated later in the study.

Two newer intravitreal implants are FDA-approved for retinal conditions: Iluvien (0.19 mg, Alimera Sciences) and Yutiq (0.18 mg, EyePoint Pharmaceuticals).

Iluvien is a nonbioerodable implant that releases a low dose (0.20 ug/day) of steroid into the vitreous for 36 months. This implant gained FDA approval in 2014 for the treatment of DME following efficacy results in the FAME study.[5] Patients with persistent DME despite laser treatment were randomized to a low-dose (0.20 ug/day) insert, high-dose (0.50 ug/day) insert, or sham. The primary endpoint was the percentage of patients with improvement in 15 or more letters at 2 years. The treatment groups demonstrated this outcome in 28% of patients compared with 16% in the sham group (P = .002). The implants also showed a rapid and sustained reduction in the central subfield thickness compared with sham. As with other steroid implants, cataracts and elevated IOP were the most common adverse events. Of patients who received the low-dose insert (the one that is currently available) in the FAME study, 3.7% required incisional glaucoma surgery.

A retrospective, real-world study of Iluvien noted that following the implant, 63% of eyes did not require additional DME treatments up to month 24. Rates of incisional glaucoma surgery were lower than what was reported in the FAME study, and patients who lacked a significant IOP elevation with prior steroid use were unlikely to demonstrate an IOP spike following the implant.

The other nonbioerodable intravitreal fluocinolone acetonide implant, Yutiq, is FDA-approved for the treatment of noninfectious posterior uveitis and is also designed to slowly release the drug over 36 months. Two multicenter, randomized controlled trials assessing response over 36 months

	Contraindications	Complications	Adverse Events
	Active ocular infection, advanced glaucoma	Subconjunctival hemorrhage, central retinal artery occlusion, globe perforation, ptosis, strabismus	Elevated IOP (although less likely than intravitreal options);[1] cataract formation
	Active ocular infection, advanced glaucoma	Postinjection endophthalmitis, sterile endophthalmitis (if kenalog was used)	Immediate IOP spike following injection; 26% with uveitic macular edema had at least a 10-point increase in IOP from baseline;[1] cataract formation
	Active ocular infection, known hypersensitivity to triamcinolone acetonide	Resistance during injection due to not being in the correct anatomical space; injection site pain	IOP elevation > 10 mm Hg from baseline in 14.3%;[2] lower rates of cataract compared with intravitreal options
	Active ocular infection, advanced glaucoma, or when posterior lens capsule is not intact (risk of anterior chamber migration)	Postinjection endophthalmitis, hypotony (from wound leak)	High incidence of cataract development compared with sham; IOP rise typically 4 to 6 weeks following injection
	Active ocular infection, avoid in aphakia	Postinjection endophthalmitis	18.4% had IOP > 30 mm Hg after 3 years,[3] 80% develop cataract after 3 years
	Active ocular infection, avoid in aphakia	Postinjection endophthalmitis	56% of patients developed a cataract within 1 year; 43% were on at least one IOP-lowering medication; 2% required glaucoma surgery[4]
	Active ocular infection; consider systemic therapy if patients also have systemic disease and bilateral ocular disease	Surgical complications of hypotony, vitreous hemorrhage; Postoperative complications of wound site erythema, dehiscense, hypotony (9.4% of eyes), scleral thinning over implant[5]	Within 3 years, 77% of patients require IOP drops, and 37% require filtering procedures;[5] within 3 years nearly all phakic eyes require cataract surgery

demonstrated significantly lower uveitis recurrence rates compared with sham (65.5% vs 97.6%; $P < .001$).[7] More eyes in the treatment group had a greater than 15-letter increase and improved macular edema compared with sham, and IOP was similar for both study groups at month 36.

CONCLUSION

All long-acting steroid implants require careful patient selection to mitigate the risk of elevated IOP or cataracts. With the right patient selection and careful monitoring, the implants remain valuable tools in treating various retinal diseases due to their high efficacy and durability. ■

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THEODORE LENG, MD, MS
- Director, Clinical and Translational Research, Byers Eye Institute, Stanford University School of Medicine, Palo Alto, California
- Editorial Advisory Board Member, *Retina Today*
- vision.md@gmail.com
- Financial disclosure: None

KAPIL MISHRA, MD
- Vitreoretinal Surgery Fellow, Byers Eye Institute, Stanford University School of Medicine, Palo Alto, California
- Financial disclosure: None