TARGETING INFLAMMATION IN DRY EYE DISEASE

A review of some current and potential treatment options.

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The field of dry eye diagnosis and treatment has grown substantially during the past 2 decades. Twenty years ago, patients with dry eye disease (DED) often went unnoticed and treated themselves with artificial tears. In 2003, the first antiinflammatory eye drop, cyclosporine (CsA) ophthalmic emulsion 0.05% (Restasis, Allergan/AbbVie), was introduced, providing relief to many patients. It quickly became evident, however, that the treatment approach would not be sufficient for all patients.

In the past decade, various diagnostic tools and treatment options aimed at more effectively targeting ocular surface inflammation have been the introduced. Today, the prevalence of DED and the role of inflammation in the disease process are more widely recognized.

CURRENT DED TREATMENT LANDSCAPE

The growth of premium IOL surgery increased recognition of the impact of ocular surface health on postoperative visual quality and patient satisfaction. This has prompted greater interest and investment in the area by health care providers and industry.

Pharmacologic. The introduction of lifitegrast ophthalmic solution 5% (Xiidra, Novartis) in 2016, newer CsA options such as Cequa (CsA ophthalmic solution 0.09%, Sun Ophthalmics) in 2018, and generic CsA 0.05% in 2022 has fueled growth in the market. In addition to these antiinflammatory medications, a low-dose steroid, loteprednol etabonate ophthalmic suspension 0.25% (Eysuvis, Kala Pharmaceuticals), was approved for the treatment of dry eye signs and symptoms in 2020.

In 2021, the FDA approved varenicline nasal spray 0.03 mg (Tyrvaya, Oyster Point Pharma). As a highly selective nicotinic acetylcholine receptor agonist, varenicline binds to cholinergic receptors in the nasal mucosa to activate the trigeminal parasympathetic pathway, thereby increasing production of the basal tear film. Many patients appreciate the alternative delivery method offered by the nasal spray compared to traditional eye drop administration.

Lid margin. Alongside the various pharmacologic treatments for DED, a variety of procedural interventions for the treatment of DED have been developed that are directed primarily toward the lid margin. These include thermal pulsation treatments with devices such as iLux (Alcon) and the LipiFlow Thermal Pulsation System (Johnson & Johnson Vision), microblepharoexfoliation with devices such as BlephEx (BlephEx) and MiBoFlo (MiBo Medical Group), and intense pulsed light therapy with devices such as the Optima IPL (Lumenis).

Recognizing and treating underlying autoimmune or inflammatory systemic diseases often helps to control DED.

CHALLENGES IN DED TREATMENT

The chronic nature of DED frustrates many patients, sometimes leading to poor adherence to long-term treatment and management of the condition. Hormonal changes, moreover, and other systemic and ocular factors that may worsen with age can lead to DED progression over time. These challenges

AT A GLANCE

- Inflammation plays a significant role in dry eye disease (DED), and treatment options have expanded over the past decade.
- Challenges in DED treatment include the chronic nature of the disease, patient frustration, and lack of adherence to long-term treatment, highlighting the need for advances in the field.
- Several promising products are in the DED treatment pipeline, including AZR-MD-001 (Azura Ophthalmics) for evaporative DED; CycIASol (0.1% cyclosporine A, Bausch + Lomb), a water-free formulation of cyclosporine; NOV03 (perfluorohexyloctane, Bausch + Lomb) for meibomian gland dysfunction; Reproxalap 0.25% (Aldyra Therapeutics), a reactive aldehyde species inhibitor; and TP-03 (Tarsus Pharmaceuticals) for *Demodex* blepharitis.

CHALLENGES IN DRY EYE TREATMENT

Chronic Nature

- Patients may become frustrated by the ongoing need for management
- Long-term treatment adherence can be difficult

Hormonal Changes

- Hormonal imbalances can worsen dry eye symptoms
- Age-related factors can contribute to disease progression

Systemic and Ocular Factors

- Coexisting medical conditions may exacerbate dry eye disease
- Ocular surface issues, such as inflammation, can complicate treatment

highlight the need for further advances in treatment.

FIVE PRODUCTS TO WATCH

Product development in the field of DED has been slow relative to other diseases. The following are five exciting products in the pipeline, in alphabetical order.

AZR-MD-001 (Azura Ophthalmics). Currently in a phase 2 trial,[1] this twice-weekly ointment is derived from selenium sulfide. The product is designed to prevent buildup within the meibomian gland ducts to reduce keratinization and relieve symptoms associated with evaporative DED by improving meibum quality. It is also hypothesized to stimulate lipogenesis to increase the quantity of lipid produced by the meibomian glands.

Several small preliminary studies have indicated that the product is safe and well tolerated. A prospective, multicenter, placebo-controlled trial of 23 patients demonstrated potential efficacy. Study outcomes suggest that AZR-MD-001 0.5% can significantly restore gland function in patients with meibomian gland dysfunction (MGD) and improve symptoms (as measured by the Visual Analog Scale score). The benefits of AZR-MD-001 were consistently observed across all patients at month 3 but reached statistical significance only in a small subset of patients with mild to moderate MGD.

Larger studies are warranted, but AZR-MD-001 shows promise as the first drug to deliver improvements in both the signs and symptoms of MGD through the reduction of keratinization.

CyclASol (0.1% CsA, Bausch + Lomb/Novaliq). CyclASol is an ocular surface protectant with CsA. Currently in phase 3 trials, this topical antiinflammatory and immunomodulating ophthalmic solution has a unique tolerability profile, as demonstrated in two pivotal studies.[2] Owing to its water-free formulation, CyclASol offers high bioavailability with an onset of action within 2 weeks. It will be available as a multidose, preservative-free formulation.

The ESSENCE 1 and 2 trials evaluated CyclASol's efficacy over a 52-week treatment period. A total of 328 patients were enrolled in this prospective, 12-week, multicenter, randomized, double-masked, vehicle-controlled study. The primary efficacy endpoints were total corneal fluorescein staining (tCFS) and the change from baseline in the Ocular Surface Disease Index score at 4 weeks. Secondary endpoints and safety assessments included conjunctival lissamine green staining, visual analog scales for dry eye symptoms, and adverse events.

In the study, treatment with CyclASol 0.1% was superior to the vehicle in the primary endpoint tCFS at week 4 (Δ 20.8; 95% CI: 21.3–20.4; $P = .0002$, analysis of covariance). This difference had already reached statistical significance after 2 weeks and was maintained throughout the study. CyclASol 0.1% treatment also showed a statistically significant improvement compared with the vehicle in the eye dryness score at week 4 (Δ 4.78; 95% CI: -9.13 to -0.44; $P = .0311$). Overall, CyclASol 0.1% was effective in treating the signs and symptoms of DED. It significantly reduced corneal and conjunctival staining and improved ocular dryness compared with the vehicle while demonstrating excellent tolerability.

NOV03 (perfluorohexyloctane, Bausch + Lomb). Already approved in Australia, Europe, and New Zealand, the product has a dual mechanism of action. It acts directly on the meibomian glands to dissolve thick, abnormal meibum and interacts with the lipophilic component of the tear film to stabilize tears and prevent evaporation.[3] NOV03 works in as little as 2 weeks (a key secondary endpoint in the pivotal phase 3 GOBI trial).

In the trial, the product met both coprimary endpoints and all secondary endpoints, with statistical significance achieved as early as day 15.[3] The GOBI trial was a multicenter, randomized, hypotonic saline-controlled, double-masked trial with 597 adult patients who were randomly assigned to receive NOV03 or hypotonic saline solution four times daily.

At week 8, clinical signs had improved, as indicated by an improvement in tCFS in the NOV03 arm compared to the control saline group (least-squares mean treatment difference: -0.97; 95% CI: -1.40 vs -0.55; $P < .001$). Clinical symptoms also showed progress at week 8 as evidenced by a significant improvement in the eye dryness Visual Analog Scale score in the NOV03 group relative to the control group (least-squares mean treatment difference: -7.6; 95% CI: -11.8 vs -3.4; $P < .001$). NOV03 was well tolerated, with few patients experiencing ocular adverse events (9.6% in the NOV03 group and 7.5% in the control group).

Reproxalap 0.25% (Aldyra Therapeutics). This reactive aldehyde species (RASP) inhibitor represents a novel antiinflammatory approach to DED

treatment.[4] RASP are elevated in a variety of inflammatory diseases. Currently undergoing phase 3 clinical trials, reproxalap 0.25% has shown promise, with some patients experiencing symptom relief within hours of treatment.

In a randomized, double-masked, parallel-group, phase 2a trial of three topical ocular reproxalap formulations (0.1% ophthalmic solution, 0.5% ophthalmic solution, and 0.5% lipid ophthalmic solution), 51 patients with DED were randomly assigned 1:1:1 at a single site in the United States. Bilateral treatment was administered four times daily for 28 days. Standard dry eye signs and symptoms were assessed at baseline and after 7 and 28 days of dosing. Tear RASP levels were assessed at baseline and day 28.

The effect of treatment on the signs and symptoms of DED was similar across the treatment arms. Pooled data from the 28-day treatment period demonstrated a significant improvement from baseline in Symptom Assessment in Dry Eye Disease score ($P = .003$), Ocular Discomfort Scale score ($P < .0001$), Ocular Discomfort Score and 4-Symptom Questionnaire overall score ($P = .0004$), Schirmer test ($P = .008$), tear osmolarity ($P = .003$), and lissamine green total staining score ($P = .002$). Improvements in DED symptoms were evident within 1 week of therapy. The drop was well tolerated, and no significant safety issues were observed.

The study authors concluded the RASP inhibitor may be able to mitigate the signs and symptoms of DED and may represent a new, rapid, and broadly active approach to DED treatment.

TP-03 (Tarsus Pharmaceuticals). TP-03 is a topical ophthalmic formulation of lotilaner for the treatment of *Demodex* blepharitis.[5,6] It could become the first product to target the eradication of *Demodex* directly, potentially helping more than 25 million patients. The product is dosed twice daily over the course of 6 weeks. *Demodex* is thought to be a common cause or exacerbator of MGD and blepharitis.

The SATURN trials evaluated the safety and efficacy of TP-03, which met all primary and secondary endpoints. The primary endpoint, complete collarette cure—defined as 0 to 2 collarettes per lid at day 43—was achieved by 56% of patients treated with TP-03 compared to 13% who received the vehicle. Clinically meaningful collarette cure—defined as collarette grade 0 to 1—at day 43 was experienced by 89% of treated patients compared to 33% who received the vehicle. A decrease in lid erythema was seen in 31% of the TP-03 patients compared to 9% of patients who received the vehicle.

The drop was well tolerated; 91% of patients rated it as neutral to comfortable ($P < .001$). There were no serious adverse events. Currently, the treatment of *Demodex* blepharitis can frustrate both patients and providers because it requires long-term, daily lid washing that is highly dependent on patient compliance. TP-03 represents a potential solution. ■

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