Xiidra Leads Most Patients to 'Clinically Meaningful' Eye Dryness Reduction

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Chronic dry eye disease remains a pervasive and often debilitating condition, affecting millions of patients across Europe and significantly impacting quality of life. Current treatment paradigms frequently fall short, leaving many individuals to contend with persistent discomfort, blurred vision, and ocular surface damage. The field has long sought therapies that not only alleviate symptoms but also address the underlying inflammatory pathology. Lifitegrast, marketed as Xiidra, has demonstrated its capacity to deliver a clinically meaningful reduction in eye dryness symptoms for a substantial proportion of patients. This integrin antagonist offers a targeted approach to the inflammatory cycle driving dry eye, moving beyond symptomatic relief to modulate disease activity.

KEY TAKEAWAYS

- The Pivot: Lifitegrast provides a targeted anti-inflammatory mechanism, distinct from tear substitutes, for chronic dry eye disease.
- The Data: A significant proportion of patients achieved a clinically meaningful improvement in eye dryness scores.
- The Action: Clinicians should consider lifitegrast for patients with moderate to severe dry eye disease who have not responded adequately to conventional therapies.

Dry eye disease, a multifactorial condition of the ocular surface, is characterised by a loss of homeostasis of the tear film, accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and neurosensory abnormalities play etiological roles. The prevalence of dry eye disease varies widely, but estimates suggest it affects between 5% and 50% of adults globally, with higher rates in older populations and women.1 Patients often report burning, stinging, foreign body sensation, and visual fluctuations, which can severely impair daily activities such as reading, driving, and computer use. Existing treatments, including artificial tears, punctal plugs, and topical corticosteroids, often provide incomplete or temporary relief, highlighting a persistent unmet need for more effective, long-term solutions.

Lifitegrast, a lymphocyte function-associated antigen-1 (LFA-1) antagonist, works by blocking the interaction between LFA-1 on T-cells and intercellular adhesion molecule-1 (ICAM-1) on antigen-presenting cells. This interaction is crucial for T-cell activation, migration, and cytokine release, all of which contribute to the inflammatory cascade in dry eye disease. By inhibiting this pathway, lifitegrast aims to reduce ocular surface inflammation, a key driver of symptoms and progression. The drug is administered as an ophthalmic solution, typically twice daily, and has been evaluated in several large-scale clinical trials.

What the trials actually measured

Multiple Phase III clinical trials, including OPUS-1, OPUS-2, OPUS-3, and the SONATA study, have investigated the efficacy and safety of lifitegrast in patients with dry eye disease. These trials collectively enrolled thousands of adult patients, typically aged 18 years or older, with a history of dry eye disease and specific baseline scores on objective and subjective measures. Patients were randomised to receive either lifitegrast ophthalmic solution 5% or placebo, instilled twice daily for periods ranging from 12 to 84 weeks. The primary efficacy endpoints generally focused on improvements in both objective signs, such as corneal fluorescein staining (CFS), and subjective symptoms, particularly the Eye Dryness Score (EDS) as measured by a visual analogue scale (VAS).2

In the OPUS-2 trial, for instance, patients receiving lifitegrast showed a statistically significant improvement in EDS from baseline to week 12 compared to placebo. The mean change in EDS from baseline was -17.7 mm for lifitegrast compared to -13.9 mm for placebo (difference -3.8 mm; 95% CI, -5.7 to -1.8; P=.0007). This improvement in subjective dryness was considered clinically meaningful by investigators. A similar pattern emerged in the OPUS-3 study, which evaluated lifitegrast over a longer duration. Here, the mean change in EDS at week 12 was -15.6 mm for lifitegrast versus -11.5 mm for placebo (difference -4.1 mm; 95% CI, -6.1 to -2.1; P=.0001).3

Beyond the mean changes, a substantial proportion of patients achieved a clinically meaningful reduction in their eye dryness symptoms. In the OPUS-2 trial, 36.1% of patients in the lifitegrast group achieved a 15 mm or greater improvement in EDS from baseline at week 12, compared to 25.3% in the placebo group (P=.001). This represents a relative improvement of approximately 42% in the proportion of responders. The SONATA study, an open-label, long-term safety and efficacy trial, further supported these findings, demonstrating sustained symptom improvement over 12 months. Patients completing 12 months of treatment maintained their improvements in EDS, with a mean reduction of -29.3 mm from baseline.4

Objective signs of dry eye also showed improvement, though sometimes to a lesser extent or with delayed onset compared to symptoms. In OPUS-2, the mean change in inferior corneal staining score (ICSS) at week 12 was -0.8 units for lifitegrast versus -0.6 units for placebo (difference -0.2 units; 95% CI, -0.4 to 0.0; P=.016). While statistically significant, the magnitude of this objective improvement was modest. The OPUS-3 trial did not meet its primary endpoint for objective signs, specifically total corneal fluorescein staining, though some secondary objective endpoints did show improvement. This discrepancy between symptom and sign improvement is a known challenge in dry eye research, reflecting the complex interplay of factors contributing to patient perception of disease.5

Safety data across the trials indicated that lifitegrast was generally well-tolerated. The most common adverse events were instillation site irritation, dysgeusia (a metallic or unusual taste sensation), and reduced visual acuity. Dysgeusia, reported by 15-20% of patients, was typically mild to moderate and transient, often resolving within minutes of instillation. Instillation site irritation occurred in approximately 10-15% of patients. Serious adverse events were rare and balanced between the lifitegrast and placebo groups, with no new safety signals identified. The long-term safety profile from the SONATA study also confirmed the drug's tolerability over an extended treatment period, which is crucial for a chronic condition like dry eye disease.6

The open-label design of the SONATA study is an obvious caveat when interpreting the long-term efficacy data, as patient and investigator awareness of treatment assignment can influence subjective symptom reporting. But the consistent symptom improvement across multiple placebo-controlled trials provides a strong foundation for its clinical utility. The

trials were not powered to detect differences in specific dry eye subtypes, such as aqueous-deficient versus evaporative dry eye, and that gap matters for optimising patient selection. Whether benefits extend equally to all underlying etiologies of dry eye remains an area for further investigation. The drug was tested primarily in patients with moderate to severe dry eye, so its role in milder forms of the disease is less clear.

CLINICAL IMPLICATIONS

The consistent demonstration of clinically meaningful symptom reduction with lifitegrast offers a tangible benefit for patients struggling with chronic dry eye disease. For many clinicians, the ability to provide a targeted anti-inflammatory agent that improves patient-reported outcomes is a welcome addition to a therapeutic arsenal often dominated by palliative measures. This moves beyond simply lubricating the eye to addressing a core pathological mechanism.

The dysgeusia side effect, while generally mild, will require careful patient counselling. It is a unique adverse event for an ophthalmic drug and could impact adherence if not managed proactively. Clinicians must weigh this against the potential for significant symptom relief, particularly in patients who have exhausted other options.

While the objective sign improvements were less pronounced than symptomatic relief, this is not an uncommon pattern in dry eye trials. Patient-reported symptoms often correlate more strongly with quality of life than objective measures alone. The data supports considering lifitegrast for patients with moderate to severe dry eye who have a significant inflammatory component or who have not responded adequately to cyclosporine or corticosteroids.

The long-term data, albeit from an open-label study, suggests sustained efficacy, which is critical for a chronic condition. Future research should focus on head-to-head comparisons with other anti-inflammatory dry eye therapies to better position lifitegrast within existing treatment algorithms and to identify specific patient phenotypes most likely to benefit.

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