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Lifitegrast (Xiidra®): A Novel Treatment for Dry Eye Disease

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Dry eye disease (DED) is a complex disease that includes diagnosis via identifying separate signs and symptoms. DED is specifically defined as a "multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface".[1] DED is estimated to affect an estimated 20-25 million people in the United States.[2] Persons affected include both sexes, but more commonly presenting in females, and prevalence increases with aging. DED has a significant effect on daily life, regardless of severity. It may affect a person's visual capability, and therefore, impacts work performance, driving, reading, and other necessary daily activities. This can easily affect a person's self-confidence and cause emotional distress.[2]

Diagnosis of DED involves the combination of patient history, physical examination and diagnostic test performance. Diagnostic tests are highly subjective and therefore more than one test is performed to increase objectivity. No single test can provide an absolute diagnosis for DED. The Ocular Surface Disease Index (OSDI) is used to assess the impact on quality of life DED is having on the patient. Physicians also need to consider a potential underlying systemic condition such as thyroid eye disease or Sjögren syndrome that causes dry eye.

Lifitegrast was approved by the FDA on Monday, July 11, 2016 for the treatment of DED. It is the first medication in the new class of drugs called lymphocyte function-associated antigen (LFA-1) antagonist. The purpose of this article is to review the pharmacology, clinical trials, efficacy, dosing and administration and safety of this novel treatment in adults.

IN THIS ISSUE

Current Classification and Treatment

It is important to note the differentiation between signs and symptoms, as this can be confusing to patients since they are usually combined. Signs refers to the objective clinical manifestations, while symptoms describe to the overall feeling a patient experiences. Furthermore, one can have symptoms without the signs of dry eye. Recently about one-third of patients with moderate to severe symptoms had no surface staining.[3] The severity of symptoms is generally taken into higher account when diagnosing DED.[3]

Mild DED applies to patients who describe symptoms associated with dry eye but without clinical signs upon examination.[4] Patients should remove sources of ocular irritation and begin a trial of artificial tears for symptomatic relief. Sources of ocular irritation involve medications (diuretics, antihistamines) and environmental factors (smoke, low-humidity, air drafts).[4] Artificial tears can have a preserved or nonpreserved formulation; however, for extended use, nonpreserved is preferred. As DED increases in severity other topical agents such as gels and ointments are appropriate options.

As patients progress to moderate DED, punctal plugs and/or the immunosuppressant cyclosporine can be considered in addition to the treatments for mild dry eye. Punctal plugs are an option for those with aqueous tear deficiency in which other means of aqueous enhancement, such as those used in mild and moderate, have failed due to ineffectiveness or impracticality. Restasis® (cyclosporine ophthalmic emulsion) 0.05% is an FDA approved option, but only for increasing tear production, not improving symptoms associated with dry eyes.[5] Cyclosporine reduces inflammation by inhibiting T-cell activation, acting as a partial immunomodulatory, however, the exact mechanism in DED is unknown.[5]

Severe DED treatment includes surgical treatments and medications in combination with mild and moderate dry eye treatments. The dominant surgical procedure is permanent punctal occlusion via cauterization. This procedure assumes that a patient's natural tear production can adequately lubricate the eye. Medication treatment options include systemic cholinergic agonists (i.e., pilocarpine, cevimeline) to increase tear production and mucolytic agents (acetylcysteine) for when mucus discharge is present.[4]

Pharmacology

Mechanism of Action

Lifitegrast's major activity results in decreased T-cell-mediated inflammation which is commonly associated with DED. An immunological response occurs when the cell surface protein lymphocyte function-associated antigen-1 (LFA-1) binds to intercellular adhesion molecule-1 (ICAM-1). T-cells are subsequently activated and migrate to tissues. T-cells release inflammatory cyto-

Table 1 | Summary of phase III lifitegrast clinical trials [9,10,12]

	OPUS-1	OPUS-2	SONATA
Completed	May 2012	October 2013	March 2014
NCT	NCT01421498	NCT01743729	NCT01636206
Sample Size	588	718	331
Duration	84 days	84 days	360 days
Notable Inclusion Criteria	• ≥18 years old with DED • Corneal staining score 2 • STT ≥1 and ≤10mm • Change in ICSS ≥+1	• ≥18 years old with DED • Corneal staining score ≥2 • STT ≥1 and ≤10mm • ICSS ≥0.5 • EDS ≥40 • No artificial tears within 30 days	• ≥18 years old with DED • Corneal staining score ≥2 • STT ≥1 and ≤10mm
Notable Exclusion Criteria	• Contraindications or hypersensitivity to the study drug or its components • Active ocular inflammation (including active lid margin disease • Active ocular infection, • Any ocular surgery within the past 12 months • Need for contact lens use • Pregnancy.	• Contraindications or hypersensitivity to the study drug or its components • Active ocular infection, • Previous lifitegrast use • Any ocular surgery within the past 12 months • Need for contact lens use • Pregnancy	• Contraindications or hypersensitivity to the study drug or its components • Active ocular infection, • Previous lifitegrast us • Any ocular surgery within the past 12 months • Need for contact lens use • Pregnancy
Primary Outcomes	Efficacy measure of mean change of ICSS and VR-OSDI from baseline to day 84	Change from baseline to day 84 in ICSS and EDS (VAS)	Percentage and severity of TEAEs
Results	• ICSS: Lifitegrast superior to placebo (p<0.0001) • VR-OSDI: No between-group difference (p=0.7894)	• ICSS: No between-group difference (p=0.6186) • EDS: Lifitegrast superior to placebo (p< 0.0001)	• Most TEAE severity mild to moderate. • Experienced ≥1 ocular TEAE: Lifitegrast 53.6% vs placebo 34.2%

DED = dry eye disease; EDS = eye dryness score; ICSS = inferior corneal staining score; STT = Schirmer Tear Test; TEAEs = treatment-emergent adverse events; VAS = visual analog scale; VR-OSDI = visual-related Ocular Surface Disease Index

kines at target tissue sites. Lifitegrast actively binds to the cell surface protein LFA-1 and blocks its interaction with ICAM-1, thereby inhibiting the release of inflammatory cytokines.[6] The direct mechanism pertaining to DED is unknown. However, ICAM-1 may be overexpressed in corneal and conjunctival tissues of patients with DED.

Pharmacokinetics

Lifitegrast was designed to have a favorable pharmacokinetic profile in the eye. The characteristics noted below combine to create a strong inhibition of T-cell adhesion to ICAM-1. The formulation of lifitegrast allows for concentrations of ≤100 mg/ml (10%) to be isotonic with human tears at ~300 mOsmol/l.[7] In order to exhibit high solubility in aqueous media, lifitegrast was formulated as a sodium salt. As a salt, the drug has higher solubility and therefore greater permeability, which allows it to penetrate into targeted ocular tissues. With this increased permeability lifitegrast is rapidly absorbed into ocular tissues. Ocular tissue irritation is the source for the most troublesome symptoms for patients. Semba and colleagues conducted a phase Ib study with healthy adults and concluded that lifitegrast exhibits limited to no systemic exposure and the low levels that were detected were cleared within 1-4 hours.[8]

Clinical Trials

Phase II

Semba and colleagues performed a phase II safety and pharmacokinetic dose-escalation study in order to find the appropriate dosing for lifitegrast. The study design was a randomized, multicenter, prospective, double-masked and placebo-controlled trial. Notable baseline characteristics included and average age of 62.3 years, 77.8% female and 92.6% white. The 230 patients were randomized a 1:1:1:1 ratio into four treatment groups which included placebo group, lifitegrast at a concentration of 0.1%, 1.0% or 5.0%. Subjects administered their assigned eye drops twice daily for 84 days. The trial was conducted from August 2009 to February 2010, and during this study no supplemental artificial tears

were allowed at any point.

Eligibility criteria only needed to be met for one of the participant's eyes. In order to qualify for the study, the designated study eye has to meet the following criteria: exacerbation in corneal staining (0-4 scale) and ocular symptoms (0-4 scale) with controlled adverse environment exposure, no active lid margin disease, and Schirmer test (mm/5 min) >1 and <10.[2] If both eyes met the requirements the worst eye was chosen, however if both eyes were equal the right eye was chosen for the study. Subjects were excluded from the study if they were found to have a score of 4.0 in corneal staining score or ocular discomfort score. On average, for both the placebo and lifitegrast arms, the mean baseline ICSS of 1.71 and mean baseline EDS of 51.7.[2] The primary objective efficacy endpoint was the inferior corneal staining score at day 84 using the 0−4 point Ora scale. Secondary objective endpoints were Schirmer test, conjunctival staining score, tear film break-up time, and blink rate. Secondary subjective endpoints were the OSDI, ocular discomfort score, and visual analogue scale.

The authors found that lifitegrast was well tolerated and showed improvements in signs and symptoms of dry eye compared to placebo in as little as 14 days. The visual-related function subscale (visual-related ocular surface disease index, VR-OSDI) identified statistically significant changes from baseline to day 14 for lifitegrast 1.0% (p=0.0231) and 5.0% (p=0.0465) and baseline to day 84 lifitegrast 1.0% (p=0.0342) and 5.0% (p=0.0394).[2] Proportionally, subjects demonstrated an overall improvement in the VR-OSDI score at day 84 compared to baseline at 19.6% for placebo, and 38.6% for the 0.1% (p=0.0267), 57.1% for the 1.0% (p<0.0001), and 50.0% for the 5.0% (p<0.0001) lifitegrast dose groups.[2] Furthermore, the 5.0% lifitegrast concentration showed rapid improvement and onset (~14 days) of tear production (p=0.392) with a statistically trending dose-related response at day 84 (p=0.0905).[2] The overall dose-related response supports the use of and further exploration of the 5.0% lifitegrast concentration. Adverse events were mild to moderate and transient in nature. Occurrence and severity of adverse events were clinically and statistically insignificant with increase in lifitegrast concentration.

Phase III Trials

Three phase III clinical trials for lifitegrast have thus far been completed. These trials were all designed as randomized, double-masked, placebo-controlled, parallel arm and multicenter studies. All three trials were similar in design and compared the safety and efficacy of lifitegrast to placebo. **Table 1** provides a brief description of phase III trials.

OPUS-1

Lifitegrast 5.0% Ophthalmic Solution Reduces Ocular Surface Staining and Improves Symptoms in Patients with Dry Eye Disease (OPUS-1) trial was designed to compare the safety and efficacy of lifitegrast 5.0% solution compared to placebo applied twice daily for 84 days. The study aimed to identify the efficacy of lifitegrast in treatment of both dry eye signs and symptoms. **Table 1** includes notable inclusion and exclusion criteria. Patient baseline characteristics were similar across both groups. Characteristics included an average age of ~60 years of age, female (~75.9%) and white (~92.9%) and patients who exhibited mild-to-moderate dry eye symptomology. Primary outcome was mean change from baseline in inferior corneal staining score (ICSS) at day 84 and the mean change from baseline in the VR-OSDI. An important supportive measure was symptom scores from baseline to day 84.

Mean ICSS values at baseline was not statistically different for lifitegrast and placebo groups. Lifitegrast demonstrated superiority compared with placebo (p=0.0007) in reduction of inferior corneal staining at day 84.[9] The lifitegrast arm demonstrated ≥1.0-point reduction in ICSS in approximately 22% of its participants compared to 13.9% of placebo subjects.[9] At baseline, mean values for the VR-OSDI were not statistically different at 0.86 and 0.93 for lifitegrast and placebo. The mean change from baseline to endpoint showed no difference in reduction between the two groups (p=0.7894).[9] Symptom scores were collected using a VAS, ocular discomfort score (ODS) and OSDI. The VAS demonstrated that lifitegrast produced significant reduction in the mean eye dryness score at day 42 (p=0.0441).[9] These beneficial effects persisted until day 84 compared with placebo (p=0.0291).[9] In general, all other symptom parameters demonstrated general improvement, however all were not statistically significant. The ODS produced similar results with lifitegrast exhibiting a significant difference in mean compared to placebo at day 84 (p=0.0273).[9] However statistical significance did not appear before this measured time. The OSDI measured symptoms, environmental triggers and total score. The index showed no statistically significant difference between lifitegrast and placebo from baseline to day 84.[9] The majority of adverse effects, included dysgeusia in 13% of subjects in the lifitegrast group and in both groups overall administration site irritation (4% vs 24%) and pain (4% vs 22%).[9] The events were transient and ranged from mild to moderate in severity.[9]

OPUS-2

The purpose of OPUS-2 was to evaluate the efficacy and safety of lifitegrast 5.0% for the treatment of DED compared to a placebo applied twice daily in patients with mild, moderate and severe dry eye symptoms. Subjects administered lifitegrast 5.0% or placebo twice daily for 12 weeks. This trial only selected patients actively using artificial tears, however during this trial the use of artificial tears or other ophthalmic medications was prohibited. The recent us of artificial tears may have increased the probability of enrolling patients who were more symptomatic. Other notable inclusion and exclusion criteria are shown in **Table 1**.

The demographic patient characteristics were similar between the placebo and lifitegrast arms. Dominant characteristics for both arms included: a mean age of ~59 years of age, female (~76.6%) and white (84.7%). The primary outcomes were change in eye dryness score (VAS, both eyes) and the inferior corneal fluorescein staining score (designated study eye) from baseline to day 84.

Lifitegrast-treated subjects experienced greater improvement in eye dryness than placebo-treated subjects (p<0.0001).[10] The mean change from baseline to day 84 (represented by a negative value) for lifitegrast was -35.30 compared to -22.75 for placebo, a treatment effect of 12.61.[10] There was no between-group difference in inferior corneal staining, -071 for placebo and -0.73 for lifitegrast. (p=0.6186).[10]

The secondary endpoints of ocular discomfort (p=0.0005) and eye discomfort (p<0.0001) followed the same trend with nominally significant improvement in the lifitegrast 5.0% group compared to placebo.[10] Since other forms of ophthalmic treatment were prohibited, all improvement in symptoms can be directly attributed to lifitegrast. Most ocular treatment-emergent adverse events (TEAEs) were mild to moderate and none were unexpected or drug-related. Lifitegrast-treated subjects experienced greater ocular TEAEs frequency than placebo-treated subjects (33.7% vs 16.4%).[10]

OPUS-3

The OPUS-3 phase III trial (NCT02284516) was completed in October 2015 and the results were released just 11 days after the FDA's initial rejection of the manufacturer's new drug application (NDA). The exceptionally positive, significant results of this trial influenced the FDA to resubmit the NDA with a Priority Review designation in April 2015, accelerating the decision from twelve months to eight months.[11] The results of the study is expected to be published in late 2016, meanwhile the manufacturer has released key study information.

OPUS-3 evaluated the safety and efficacy of the application of twice daily lifitegrast compared to placebo. The dose/strength of lifitegrast used in this trial has not been released. Included patients had a history of artificial tear use within the past 30 days and an eye dryness score of ≥40. The study included more than 2,500 individuals with patient separated into lifitegrast and placebo arm, twice-daily application for 84 days.[11]

The primary outcome was met when improvement in patient-reported dry eye symptoms from baseline to 84 days in those receiving lifitegrast twice-daily was significantly greater than the placebo arm ($p=0.0007$).[11] The co-primary outcome of the trial was to show improvement in dry eye symptoms from baseline to 14 and 42 days versus placebo. The outcome was met when significant, therapeutic benefit was observed in the lifitegrast arm in as early as two weeks from initiation ($p<0.0001$ for both endpoints).[11] This outcome replicated and confirmed OPUS-2 results. The trial did not evaluate the OPUS-1 primary outcome of improvement in dry eye signs. Tolerability and safety of lifitegrast was evaluated based on adverse events (not including those present prior to treatment initiation). OPUS-3 generated a profile similar to profiles in other lifitegrast trials.[11]

SONATA

The SONATA trial (Safety Of a 5.0% coNcentrATion of lifitegrAst ophthalmic solution) was designed to evaluate the one year (long-term or 360 days) safety of lifitegrast 5.0% in patients with DED. The study design was multicenter, randomized, prospective, double-masked and placebo-controlled. The primary objective was percentage and severity of TEAEs.[12]

Patients were randomized in a 2:1 ratio, lifitegrast ophthalmic solution 5.0%:placebo. The ophthalmic drops were administered twice daily. Inclusion criteria included 18 years of age or older and dry eye disease with a Schirmer test score ≥1 and ≤10 mm plus a corneal staining score ≥2.0.[12] Baseline characteristics were similar between treatment groups. Notable characteristics include age (~60 years old), female (76.7%) and white (81.3%).

The study concluded that lifitegrast is safe and well tolerated since no serious ocular TEAEs were observed. Participants experienced ≥1 TEAE in both the placebo and lifitegrast arms (53.2% vs 72.7%).[12] The most common ocular adverse effects (34.2% vs 53.6%) identified in both arms (placebo vs lifitegrast) included instillation site irritation (4.5% vs 15.0%), instillation site reaction (1.8% vs 13.2%), reduced visual acuity (6.3% vs 11.4%); the most common nonocoular TEAE (36% vs 47.3%) was dysgeusia (1.8% vs 16.4%).[12] Rate of discontinuation because of ≥1 TEAE was 12.3% in the lifitegrast group and 9.0% in the placebo group. There was no evidence of systemic toxicity.

Precautions and Contraindications

The manufacturer engineered the preservative free formulation to decrease the likelihood and/or severity of adverse reactions. Lifitegrast is extremely well tolerated and exhibits a high degree of safety. All clinical trial evidence supports this to be true. Table 2 pools data from three phase III trials and compares the incidence of the most commonly identified adverse events.

Table 2 | Incidence of Common Lifitegrast Adverse Events Across Phase III Trials [9,10,12]

Adverse Reaction	OPUS-1 (n = 293)	OPUS-2 (n = 359)	SONATA (n = 220)
Reduced visual acuity	14%	5%	11.4%
Instillation site irritation	24%	7.8%	15%
Instillation site reaction	17%	7.0%	13.2%
Dysgeusia	13%	16.2%	16.4%

Lifitegrast does not have any contradictions at this time. It appears to be safe to use in pregnancy and breastfeeding due to limited systemic absorption. Efficacy has not been established in persons less than 18 years of age. The clinical trials did not include patients younger than 18 years of age since DED does not typically occur in this population subgroup.

Dosing and Administration

This novel drug is available as a single-dose container, ophthalmic solution containing lifitegrast 5.0% (50 mg/mL).[6] This formulation is preservative free in order to minimize potential aggravation of dry eye. The indicated administration regimen is one drop in each eye twice daily approximately 12 hours apart.[6] All trials support using a twice daily dosing regimen. Contact lenses should be removed prior to administration and can be inserted 15 minutes after use of lifitegrast.

Conclusions

Lifitegrast is a novel integrin antagonist that specifically targets blocking the adhesion between LFA-1 and ICAM-1 to prevent inflammation. Clinical trials have demonstrated lifitegrast as highly efficacious in treating symptoms of DED in as little as 14 days. It's effect can be attributed to its formulation, high solubility and permeability. Lifitegrast treatment should be considered for all DED severity classes; however, efficacy in treating dry eye signs necessitates further examination. Nonetheless, the clinical trials have shown it has good tolerability, high efficacy and long-term safety. Therefore, lifitegrast should be considered as a first-line treatment option for DED in patients aged 18 years or older.

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Editor's Corner

2016 Updated EULAR Evidenced-based Recommendations for Gout Management

The European League Against Rheumatism (EULAR) has recently published updated recommendations for the management of gout. Previously published in 2006, the original guidelines were based on systematic literature review and expert opinion. Advancements in the knowledge and treatment of the disease have prompted the task force to provide updates to the previous overarching principles and individual recommendations.

The updated overarching principles aim to provide the general foundation for the management of gout. The EULAR recommends that patients should be educated on the disease pathophysiology, available treatments, and long-term lowering of serum uric acid (SUA). Additionally, patients should be encouraged to incorporate life-style modifications, such as weight loss and avoidance of alcohol, to decrease risk of gout attacks. The EULAR also recommends routine screening for associated comorbidities and cardiovascular (CV) risk factors in every patient with gout.

For treatment of acute gout flares, the recommended first-line options remain colchicine, NSAIDs, and corticosteroids. The choice of drug is based on contraindications, patient's previous experience, time of initiation, and number of joints involved. In the setting of frequent flares and contraindications, the EULAR suggests considering the use of IL-1 blockers, canakinumab and rilonacept, as potential options.

The EULAR updated recommendations to initiate urate-lowering therapy (ULT) earlier (i.e. first presentation of gout) given the CV and renal benefits from xanthine oxidase inhibitors (XOI). The goal SUA remains unchanged and should be maintained to <6 mg/dL. Alternatively, a lower target (<5 mg/dL) is now recommended for patients with severe gout to facilitate faster dissolution of crystals. First-line ULT in patients with normal renal function is allopurinol, initiated at a low dose and titrated to achieve goal SUA. Allopurinol remains first-line due to extensive data supporting its efficacy, safety, and lower cost. If target SUA could not be reached with allopurinol mono-therapy, second-line therapy options include switching to febuxostat or combining with a uricosuric (e.g. probenecid). In patients with refractory gout, the EULAR recommends the use of pegloticase. Pegloticase should be reserved for patients with crystal-proven severe debilitating chronic tophaceous gout where target SUA cannot be reached with first– and second-line therapies.

For additional information:
Richette P, Doherty M, Pascual E, et al. 2016 updated EULAR evidence-based recommendations for the management of gout. *Ann Rheum Dis* 2017;26(1):29-42.

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