Lifitegrast: A novel drug for treatment of dry eye disease

Afroz Abidi, Pooja Shukla, Ali Ahmad

Department of Pharmacology, Era's Lucknow Medical College, Lucknow, Uttar Pradesh, India

Received: 19-08-2016 **Revised:** 01-10-2016 **Accepted:** 14-10-2016

ABSTRACT

Dry eye disease (DED) is an inflammatory disorder of ocular surfaces leading to severe disability, especially in the elderly age group. The mainstay of therapy includes artificial tears, punctual plugs, topical anti-inflammatory agents, and corticosteroids. In the past few years, only cyclosporine-A emulsions have been added to the existing therapy, but it is discontinued by most patients as it causes burning sensation in the eye. Hence, progress in new research for a better therapeutic option led to the discovery of lymphocyte function-associated antigen intercellular adhesion molecule 1 antagonist, lifitegrast. It hinders the T-cell activation, release of inflammatory mediators, and consequently inhibits the inflammatory pathways in DED. It was approved by the US Food and Drug Administration in July 2016 for the treatment of DED. This review highlights the development process and approval of lifitegrast.

Key words: Dry eye disease, integrin antagonist, lifitegrast, T-cell inhibitor

INTRODUCTION

Dry eye disease (DED) or syndrome, also known as keratoconjunctivitis sicca, is a complex disorder of ocular surface characterized by symptoms of visual disturbances, eye discomforts, and dryness due to tear film instability. The presumed pathogenesis includes increased osmolarity of the tear film and inflammation of ocular surfaces and lacrimal glands.[1] It is clinically classified into two subtypes: aqueous-deficient DED with decreased tear secretion and hyperevaporative DED with increased tear evaporation. The aqueous-deficient disorder accounts for 10% of patients and hyperevaporative and mixed hyperevaporative/aqueous forms account for more than 80% of cases.[2] Although the disease is multifactorial, chronic inflammation plays an important role in its pathogenesis. Evidence has suggested the role of T-cell-mediated inflammation. Specifically, CD4+ T-helper (TH1 and TH17) cells have been recognized as mediators of ocular inflammation in DED.[3] Lymphocytic infiltration into the ocular surface leads to release of pro-inflammatory cytokines, chemokines which damage the ocular tissues. Increased levels of inflammatory cytokines expressed by T-lymphocytes have been detected in the tear film of patients of DED.[4,5] Formation of immunological synapse

Access this article online	
Quick Response Code:	Website: www.jpharmacol.com
	DOI: 10.4103/0976-500X.195920

Address for correspondence:
Afroz Abidi, Flat No FF-2, Doctor's Residence, Era's Lucknow Medical College, Sarfarazganj, Hardoi Road, Lucknow - 226 003, Uttar Pradesh, India.
E-mail: afrozabidi@gmail.com

How to cite this article: Abidi A, Shukla P, Ahmad A. Lifitegrast: A novel drug for treatment of dry eye disease. J Pharmacol Pharmacother 2016;7:194-8.

by lymphocyte function-associated antigen/intercellular adhesion molecule-1 (LFA-1/ICAM-1) binding facilitates T-cell proliferation/activation, cytokine release, and recruitment of more T-cells at the inflammatory sites.[6] Hence, T-cell targeting therapies will be efficacious for treatment of DED.

Treatment options of DED include artificial tear preparations made from polyvinyl alcohol, povidone, hydroxypropyl guar, cellulose derivatives, and hyaluronic acid. They increase tear film stability and reduce ocular surface stress. The over-the-counter artificial tears may contain vasoconstrictive agents to reduce conjunctival hyperemia in DED which may be injurious to the ocular surface. Anti-inflammatory agents, corticosteroid eyedrops when used for 2–4 weeks improved the signs and symptoms of moderate to severe DED. However, the long-term use of corticosteroid eyedrops led to complications such as increased intraocular pressure and cataract, hence it is recommended only for short-term use. Immunosuppressants – 0.05% cyclosporine-A eyedrops/emulsions and tacrolimus 0.03% eyedrops and ointments reduced cytokines and inflammatory cells on ocular surfaces. Cyclosporine-A has a long onset of action and hence failed to show the desired dose response and also led to the severe burning sensation which was the major limiting factor for its use in patients of DED. Antibiotics such as tetracycline and azithromycin have been used successfully due to their additional anti-inflammatory effects but may have adverse reactions at high doses, hence recommended to be used in low doses. Omega-3 fatty acids are also currently being used as they block pro-inflammatory cytokines and inflammatory process in the eyes. Eyelid hygiene with hot compresses, warming masks/goggles, infrared heaters, and massages are also helpful. Occlusion of tear ducts by punctual plugs is effective in patients with aqueous-deficient DED.[7]

There are no specific guidelines for the treatment of DED, and the treatment has to be tailored according to patient's individual needs depending on the severity of the disease. Even with the available treatment options in hand, ophthalmologists look for newer agents which can quickly resolve the signs and symptoms of disease with a rapid onset of action and minimum adverse effects.[8] Moreover, DED is a chronic condition and requires long-term treatment; hence, we require such therapies which target the main pathoetiological condition without much adverse effects. Thus, search of novel targeting drug therapies led to the development of T-cell inhibitor lifitegrast.

HISTORY OF LIFITEGRAST

Lifitegrast was discovered in a rational design process by identifying amino acids side chains vital for LFA-1 and ICAM-1 binding.[9] Using various structural techniques, a set of lead compounds was prepared which had LFA-1 binding property. Further, their analogs were created by combinatorial series followed by secondary testing of their T-cell inhibition potency. This extensive process led to the identification of a new chemical entity SAR-1118 (lifitegrast) which could effectively block LFA-1/ICAM-1 interaction.

In vitro assays proved that lifitegrast inhibits release of cytokines, interferon δ, tumor necrosis factor alpha (TNF-α), and other interleukins (ILs).[10] *In vivo* study of lifitegrast as radiolabeled drops in rats demonstrated that it was rapidly distributed in ocular and periocular tissues, cleared by normal tear drainage, and was devoid of systemic side effects.[11] A similar dose tolerability study of lifitegrast in dogs suffering from keratoconjunctivitis sicca proved its efficacy and safety.[10]

STRUCTURE OF LIFITEGRAST

Lifitegrast is a tetrahydroisoquinoline derivative. The IUPAC name of lifitegrast is (2S)-2-[[2-(1-benzofuran-6-carbonyl)-5,7-dichloro-3,4-dihydro-1H-isoquinoline-6-carbonyl] amino]-3-(3-methylsulfonylphenyl)propanoic acid. Its molecular formula is $C_{29}H_{24}C_{l2}N_2O_7S$ and molecular weight is 615.48106 g/mol [Figure 1].[12]

MECHANISM OF ACTION OF LIFITEGRAST IN DRY EYE DISEASE

T–cell-mediated inflammatory pathway plays an important role in DED. Integrins are heterodimeric receptors present on T-cells which help them in activation, adhesion to extracellular matrix, migration, proliferation, and differentiation, following an inflammatory signal. The integrin termed as LFA-1, αLβ2, or CD11a/CD18 by binding its ligand ICAM-1 helps in the initial process of migration of T-cells to the inflammatory site.[13] The expression of LFA-1 is limited to leukocytes. ICAM-1, an adhesion protein expressed on endothelial cells/antigen presenting cells and LFA-1 are ligands for each other.[14] At the inflammatory sites, LFA-1 and ICAM-1 interaction leads to T-cell adhesion to endothelial cells, migration to inflamed tissue, antigen presentation, and recognition facilitating the formation of an immunological synapse.[15] [Figure 2] These immunological synapses facilitate the propagation of

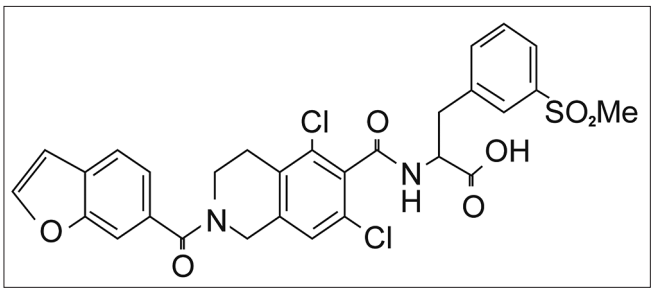

Figure 1: Structure of lifitegrast

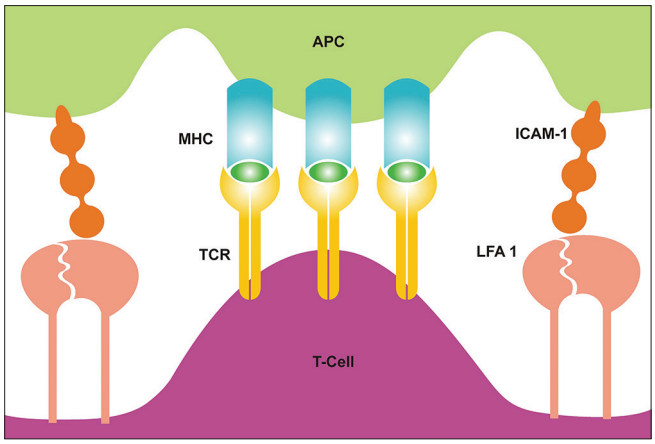

Figure 2: Formation of immunologic synapse

downstream signals which lead to release of inflammatory mediators, cytokines, chemokines, TNF-α, IL-1, which further intensify and perpetuate inflammation in ocular tissues. Hence, targeting LFA-1 and ICAM-1 interaction seemed to be a feasible approach to the development of a novel drug for DED by obstructing ocular inflammation.

Lifitegrast is a direct competitive antagonist of binding of LFA-1 to ICAM-1, thus inhibiting T-cell activation, cytokine release, formation of immunological synapse, and subsequently decreasing the ocular inflammatory cycle.[16]

CLINICAL DISCOVERY AND DEVELOPMENT

Gadek *et al*. in 2002 demonstrated that a compound coded as compound 4 had a high-binding affinity to LFA-1 and thus prevented LFA-1/ICAM 1 interaction, thus could act as a lead compound.[9] Zhong *et al*. in a series of experiments between 2010 and 2012 showed the development of a tetrahydroisoquinoline class of LFA-1/ICAM-1 antagonists, from which lifitegrast was recognized as a promising drug candidate.[17-19] The first *in vivo* study was conducted as a dose-escalation tolerability study in dogs suffering from keratoconjunctivitis sicca. The clinical efficacy was demonstrated in 10 dogs treated with SAR-1118 as 1% topical ophthalmic solution three times daily for 12 weeks. At the end of the study, the clinical signs of dry eye showed improvement as mean Schirmer's tear test values demonstrated significant increase, indicating increased tear production. No significant adverse events were reported, except for an unpredictable short period of blinking and squinting after instillation which declined after 1–2 days.[10] The first in human study was conducted by Semba *et al*. in 2011 in 28 normal healthy adults. It was a single-center, randomized, double-masked, placebo-controlled, pharmacokinetic, and dose-escalation, safety study of 0.1%, 0.3%, 1.0%, and 5.0% lifitegrast ophthalmic solution for 27 days. The results demonstrated that lifitegrast was safe up to a dose of 5% ophthalmic solution TID for 27 days. The tear drug levels were >1μM, i.e. more than therapeutic levels at 1% and 5% concentrations. There was a rapid clearance of drug from local as well as systemic sites, and there were no significant ocular adverse events.[20] The first Phase II study was a multicentric, prospective, double-masked, placebo-controlled trial on 230 dry eye patients. SAR-1118 was used in concentrations of 0.1%, 1.0%, and 5.0% eyedrops versus placebo twice daily for 84 days. There were significant improvements ($P < 0.05$) in corneal staining score, total ocular surface disease index (OSDI), and visual-related OSDI score (VR-OSDI) for SAR 1118 as compared to placebo. There was also an improvement in tear production and relief of symptoms as early as day 14. Adverse events were mild and transient only at the instillation site with 5% ophthalmic solution, but no serious ocular adverse events were reported.[21]

The favorable findings for lifitegrast in Phase II enforced the researchers to proceed further with Phase III trials. The first Phase III trial (OPUS 1) was conducted by Sheppard *et al*. in 2014 on 588 adult DED patients. It was a prospective, multicenter, randomized, double-masked, placebo-controlled trial of 5% lifitegrast solution twice daily for 84 days. The study demonstrated efficacy of lifitegrast solution as compared with placebo by significantly changing the inferior corneal staining score (ICSS) at day 84. There was also a significant reduction in corneal fluorescein staining and conjunctival lissamine staining at day 84 versus placebo. Significant improvement was also seen in ocular discomfort and eye dryness though there was no significant reduction in VR-OSDI. The most common ocular adverse event reported was transient symptoms at instillation sites such as irritation, pain, pruritus, and discomfort immediately after instillation and decreased subsequently. These ocular adverse events were mild to moderate in severity and no serious ocular adverse events were reported. The most common nonocular adverse event was dysgeusia (altered taste sensation) which was reported in 13% of patients in lifitegrast group.[22] The OPUS 2 Phase III clinical trial was again a randomized, multicenter, double-masked, placebo-controlled clinical trial of 5% lifitegrast ophthalmic solution for 84 days in 718 patients of DED. Lifitegrast patients showed better improvement in eye dryness score than placebo group. There was no significant difference in ICSS, total corneal staining, and nasal lissamine staining at day 84. The common ocular treatment-emergent adverse events (TEAEs) in lifitegrast group were transient instillation site irritation, eye irritation, decreased visual acuity, blepharitis, and blurred vision, all of which were nonserious. The nonocular adverse event reported was only dysgeusia which was again short-lived and mild to moderate in severity.[23]

Another Phase III study OPUS 3 was a multicenter, randomized, double-masked, placebo-controlled trial of 5% lifitegrast ophthalmic solution versus placebo in 700 patients of DED. The results of this study clearly demonstrated that

lifitegrast significantly reduced the eye dryness score and symptoms of DED. There were no significant TEAEs, except for instillation site irritation/reaction and dysgeusia.[24] The safety of a 5.0% concentration of lifitegrast ophthalmic solution (SONATA) study was a 1-year safety study of lifitegrast in 331 patients of DED. No serious ocular TEAEs were reported in this study. Only 53.6% of patients receiving lifitegrast experienced ≥1 ocular TEAEs whereas 34.2% placebo group patients experienced TEAEs though most of them were mild to moderate in severity. The most common TEAEs were instillation site irritation, instillation site reaction, and decreased visual acuity in 15%, 13.2%, and 11.4%, respectively. Similar to previous studies, dysgeusia was the most common nonocular TEAE reported in 16.4% patients as compared to 1.8% in placebo. This event is usually self-limiting and seen with some topical ophthalmic preparations as normal tear drainage route is through nasolacrimal duct into the nose and oropharynx. In addition, there were no signs of systemic toxicity or secondary local infective complications due to immunosuppression. Hence, this study also proved the ocular safety of lifitegrast in consistence with previous studies.[25]

Lifitegrast formulation as an ophthalmic agent for treatment of dry eye disease

Lifitegrast was tested to have a favorable pharmacokinetic profile for topical administration into the eye. The sodium salt of lifitegrast had a high solubility in aqueous media and was isotonic with human tears.[26] The drug also showed rapid absorption into ocular tissues. Animal studies on rats and dogs have confirmed that therapeutic levels of drug were detected in all ocular tissues, especially in the conjunctiva, cornea, aqueous and vitreous humor, and sclera.[10,11] In addition, peak plasma concentration of 5% lifitegrast ophthalmic solution was spotted within 5 min of topical instillation in Phase I clinical trial, thus proving its quick absorption in ocular tissues.[20] Lifitegrast also had a short half-life, high clearance rate, and low systemic exposure.[17] It was well tolerated when administered in single or multiple doses.[20] Hence, lifitegrast by virtue of its high efficacy, good pharmacokinetic profile, and little local and systemic toxicity is an optimal drug for ocular use in DED patients.

APPROVAL STATUS

In February 2015, a new drug application (NDA) was submitted which was granted priority review in April 2015 but was returned in October 2015, and a complete response letter along with product quality information was demanded by the US Food and Drug Administration (FDA). The NDA was resubmitted in January 2016 with positive data from OPUS-3, a Phase III efficacy and safety trial along with the product quality data. Thus, the NDA included data from five clinical trials, including one Phase II study, three Phase III safety and efficacy studies (OPUS-1, OPUS-2, and OPUS-3), and one long-term 1-year Phase III safety study (SONATA). The FDA confirmed that the resubmission was satisfactory and complete and assigned a 6-month review period with a goal date of July 22, 2016. On July 11, 2016, the US FDA-approved lifitegrast (Xiidra) 5% ophthalmic solution BD for the treatment of signs and symptoms of DED in adult patients.[27]

CONCLUSION

DED causes considerable impairment in functional vision, hence deteriorating the quality of life. In the last few years, many researches and trials have failed to develop better treatment options in DED. The recent studies demonstrated that inflammatory pathways are mainly involved in the pathophysiology of DED; therefore, targeting these pathways seems to be a new and promising approach for the development of drugs in DED. Lifitegrast is a novel integrin antagonist which prevents LFA-1/ICAM-1 interaction preventing T-cell activation/recruitment and release of inflammatory mediators, thereby decreasing the inflammatory responses in DED. Lifitegrast was found to be a highly potent drug in various clinical trials as it alleviates both the signs and symptoms of DED, which showed rapid onset of action and good therapeutic efficacy as ophthalmic drops. It protected the corneal surfaces and was well tolerated locally as well as systemically; hence, it was approved by FDA for use in DED as 5% eyedrops to be used twice a day.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. The definition and classification of dry eye disease: Report of the definition and classification subcommittee of the international dry eye workshop (2007). Ocul Surf 2007;5:75-92.
2. Lemp MA, Crews LA, Bron AJ, Foulks GN, Sullivan BD. Distribution of aqueous-deficient and evaporative dry eye in a clinic-based patient cohort: A retrospective study. Cornea 2012;31:472-8.
3. Stern ME, Schaumburg CS, Pflugfelder SC. Dry eye as a mucosal autoimmune disease. Int Rev Immunol 2013;32:19-41.
4. Lam H, Bleiden L, de Paiva CS, Farley W, Stern ME, Pflugfelder SC. Tear cytokine profiles in dysfunctional tear syndrome. Am J Ophthalmol 2009;147:198-205.
5. Enríquez-de-Salamanca A, Castellanos E, Stern ME, Fernández I, Carreño E, García-Vázquez C, *et al.* Tear cytokine and chemokine analysis and clinical correlations in evaporative-type dry eye disease. Mol Vis 2010;16:862-73.
6. Semba CP, Gadek TR. Development of lifitegrast: A novel T-cell inhibitor for the treatment of dry eye disease. Clin Ophthalmol 2016;10:1083-94.
7. Messmer EM. The pathophysiology, diagnosis, and treatment of dry eye disease. Dtsch Arztebl Int 2015;112:71-81.
8. Asbell PA, Spiegel S. Ophthalmologist perceptions regarding treatment of moderate to severe dry eye: Results of a physician survey. Trans Am Ophthalmol Soc 2009;107:205-10.

9. Gadek TR, Burdick DJ, McDowell RS, Stanley MS, Marsters JC Jr., Paris KJ, *et al.* Generation of an LFA-1 antagonist by the transfer of the ICAM-1 immunoregulatory epitope to a small molecule. Science 2002;295:1086-9.
10. Murphy CJ, Bentley E, Miller PE, McIntyre K, Leatherberry G, Dubielzig R, *et al.* The pharmacologic assessment of a novel lymphocyte function-associated antigen-1 antagonist (SAR 1118) for the treatment of keratoconjunctivitis sicca in dogs. Invest Ophthalmol Vis Sci 2011;52:3174-80.
11. Rao VR, Prescott E, Shelke NB, Trivedi R, Thomas P, Struble C, *et al.* Delivery of SAR 1118 to the retina via ophthalmic drops and its effectiveness in a rat streptozotocin (STZ) model of diabetic retinopathy (DR). Invest Ophthalmol Vis Sci 2010;51:5198-204.
12. Lifitegrast. National Center for Biotechnology Information. PubChem Compound Database; CID=11965427. Available from: https://www.pubchem.ncbi.nlm.nih.gov/compound/11965427. [Last accessed on 2016 Aug 15].
13. Hogg N, Laschinger M, Giles K, McDowall A. T-cell integrins: More than just sticking points. J Cell Sci 2003;116(Pt 23):4695-705.
14. Marlin SD, Springer TA. Purified intercellular adhesion molecule-1 (ICAM-1) is a ligand for lymphocyte function-associated antigen 1 (LFA-1). Cell 1987;51:813-9.
15. Grakoui A, Bromley SK, Sumen C, Davis MM, Shaw AS, Allen PM, *et al.* The immunological synapse: A molecular machine controlling T cell activation. Science 1999;285:221-7.
16. Perez VL, Pflugfelder SC, Zhang S, Shojaei A, Haque R. Lifitegrast, a novel integrin antagonist for treatment of dry eye disease. Ocul Surf 2016;14:207-15.
17. Zhong M, Gadek TR, Bui M, Shen W, Burnier J, Barr KJ, *et al.* Discovery and development of potent LFA-1/ICAM-1 antagonist SAR 1118 as an ophthalmic solution for treating dry eye. ACS Med Chem Lett 2012;3:203-6.
18. Zhong M, Hanan EJ, Shen W, Bui M, Arkin MR, Barr KJ, *et al.* Structure-activity relationship (SAR) of the a-amino acid residue of potent tetrahydroisoquinoline (THIQ)-derived LFA-1/ICAM-1 antagonists. Bioorg Med Chem Lett 2011;21:307-10.
19. Zhong M, Shen W, Barr KJ, Arbitrario JP, Arkin MR, Bui M, *et al.* Discovery of tetrahydroisoquinoline (THIQ) derivatives as potent and orally bioavailable LFA-1/ICAM-1 antagonists. Bioorg Med Chem Lett 2010;20:5269-73.
20. Semba CP, Swearingen D, Smith VL, Newman MS, O'Neill CA, Burnier JP, *et al.* Safety and pharmacokinetics of a novel lymphocyte function-associated antigen-1 antagonist ophthalmic solution (SAR 1118) in healthy adults. J Ocul Pharmacol Ther 2011;27:99-104.
21. Semba CP, Torkildsen GL, Lonsdale JD, McLaurin EB, Geffin JA, Mundorf TK, *et al.* A phase 2 randomized, double-masked, placebo-controlled study of a novel integrin antagonist (SAR 1118) for the treatment of dry eye. Am J Ophthalmol 2012;153:1050-60.e1.
22. Sheppard JD, Torkildsen GL, Lonsdale JD, D'Ambrosio FA Jr., McLaurin EB, Eiferman RA, *et al.* Lifitegrast ophthalmic solution 5.0% for treatment of dry eye disease: Results of the OPUS-1 phase 3 study. Ophthalmology 2014;121:475-83.
23. Tauber J, Karpecki P, Latkany R, Luchs J, Martel J, Sall K, *et al.* Lifitegrast ophthalmic solution 5.0% versus placebo for treatment of dry eye disease: Results of the randomized phase III OPUS-2 study. Ophthalmology 2015;122:2423-31.
24. Shire's OPUS-3 Phase 3 Trial with Lifitegrast Meets Primary and Key Secondary Endpoints, Significantly Reducing Patient-Reported Symptoms for Dry Eye Disease. Available from: https://www.shire.com/newsroom/2015/october. [Last accessed on 2016 Jul 12].
25. Donnenfeld ED, Karpecki PM, Majmudar PA, Nichols KK, Raychaudhuri A, Roy M, *et al.* Safety of lifitegrast ophthalmic solution 5.0% in patients with dry eye disease: A 1-year, multicenter, randomized, placebo-controlled study. Cornea 2016;35:741-8.
26. Savjani KT, Gajj ar AK, Savjani JK. Drug solubility: Importance and enhancement techniques. ISRN Pharm 2012;2012:195727.
27. Shire Resubmits New Drug Application for Lifitegrast to US FDA. Available from: https://www.shire.com/newsroom/2016/january. [Last accessed on 2016 Jul 22].