Loteprednol Etabonate Suspension 0.2% Administered QID Compared With Olopatadine Solution 0.1% Administered BID in the Treatment of Seasonal Allergic Conjunctivitis: A Multicenter, Randomized, Investigator-Masked, Parallel Group Study in Chinese Patients

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ABSTRACT

Background: Seasonal allergic conjunctivitis (SAC) is caused by seasonal allergens and usually manifests as ocular itching and bulbar conjunctival injection (redness). Treatment options for SAC include corticosteroids and dual-acting antihistamine and mast-cell stabilizers.

Objective: Our objective was to compare the efficacy and tolerability of loteprednol etabonate (LE), a C-20 ester-based corticosteroid, with those of olopatadine, a dual-acting antihistamine mast-cell stabilizer, in Chinese patients.

Methods: This was a multicenter, randomized, investigator-masked, parallel group study. Patients with acute SAC experiencing grade 4 ocular itching and grade 2 or higher bulbar conjunctival injection received either LE suspension 0.2% QID at 4-hour intervals or olopatadine solution 0.1% BID at 6- to 8-hour intervals bilaterally for 15 days. Primary efficacy end points included the change from baseline (CFB) in ocular itching and bulbar conjunctival injection at day 15. The primary analysis tested the noninferiority of LE suspension 0.2% to olopatadine solution 0.1%. Tolerability outcomes included the incidence of adverse events (AEs), biomicroscopy findings, visual acuity, and intraocular pressure.

Results: A total of 300 patients were randomly assigned, and 293 were included in the per-protocol population (LE, n = 147; olopatadine, n = 146). Mean (SD) CFB at day 15 in the LE and olopatadine treatment groups, respectively, was −3.74 (0.47) and −3.28 (0.91) for ocular itching and −1.91 (0.52) and −1.71 (0.59) for bulbar conjunctival injection. The 95% CI for the differences in CFB in ocular itching (−0.59 to −0.27) and bulbar conjunctival injection (−0.27 to −0.08) was less than the prespecified noninferiority limit of 0.3. Treatment differences in CFB were significantly better with LE compared with olopatadine for both end points ($P \leq 0.0006$). Ocular AEs were few and similar between treatment groups. There were no clinically significant biomicroscopy or visual acuity findings, and no patient experienced a clinically significant increase in intraocular pressure (≥10 mm Hg).

Conclusion: Results of this investigator-masked study with Chinese patients suggest LE suspension 0.2% was noninferior to olopatadine solution 0.1% for the treatment of SAC. Both LE suspension 0.2% and olopatadine solution 0.1% were well tolerated. ClinicalTrials.gov identifier: NCT01435460. (*Clin Ther*. 2012;34:1259–1272) © 2012 Elsevier HS Journals, Inc. All rights reserved.

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INTRODUCTION

The conjunctiva, or mucous membrane component of the ocular surface, is continually exposed to a variety of airborne antigens[1] that can lead to inflammation, often termed *allergic conjunctivitis*. The incidence of allergic conjunctivitis varies from 15% to 40% in the population.[2–4] Based on the presentation, allergic conjunctivitis can be classified as seasonal allergic conjunctivitis (SAC), perennial allergic conjunctivitis (PAC), atopic keratoconjunctivitis, vernal keratoconjunctivitis, or giant papillary conjunctivitis.[5] The most frequently encountered of these are SAC and PAC, with >95% of the ocular allergy cases being classified as one of these conditions.[6] Although SAC is usually an acute or subacute manifestation characterized by peaks of signs and symptoms such as ocular itching, dryness, burning, redness, and pain, patients with PAC can experience these symptoms year round.[7]

Topical antihistamine mast-cell stabilizers and corticosteroids are both effective in treating symptoms associated with allergic conjunctivitis, but they differ in their mechanisms of action. Antihistamine mast-cell stabilizers work by competitively blocking histamine binding to H_1 receptors and inhibiting mast-cell degranulation. Corticosteroids work at the molecular and cellular level; they bind with receptors and stimulate the synthesis of those proteins that regulate multiple aspects of the anti-inflammatory response, as well as modulate the mast-cell response by inhibiting mediators that induce mast-cell proliferation and recruitment.[7] They also increase histaminase stores, thereby reducing levels of available histamine, and down-regulate expression of histamine receptors.[8–10] However, their use has been limited due to concerns about unwanted side effects, such as increased intraocular pressure (IOP), cataract formation, and vulnerability to infection.[5]

Olopatadine hydrochloride is a dual-acting selective histamine H_1 receptor antagonist and mast-cell stabilizer,[11–13] and loteprednol etabonate (LE) is a C-20 ester corticosteroid. LE differs from other corticosteroids in that the C-20 ketone position of the traditional prednisolone structure is replaced by an ester. After exerting its effects, LE is rapidly converted into an inactive metabolite.[14] This, in turn, results in fewer IOP elevations compared with older corticosteroids.[15,16] In addition, the lack of a ketone at the C-20 position precludes formation of Schiff base intermediates with lens protein, considered a first step in cataractogenesis.[17] Both olopatadine hydrochloride ophthalmic solution 0.1%* and LE ophthalmic suspension 0.2%† have been reported to be effective and well tolerated in randomized controlled studies in SAC.[18–22]

Our study evaluated the efficacy and tolerability of LE suspension 0.2% compared with olopatadine hydrochloride solution 0.1% for the temporary relief of signs and symptoms of SAC in a population of Chinese patients. In addition to providing comparative efficacy for 2 distinct classes of drugs used in the treatment of patients with SAC, our study was also conducted, in part, to meet regulatory requirements for registration of LE suspension 0.2% in China.

METHODS

Study Design

This randomized, single-masked, active-controlled, parallel group study (Clinicaltrials.gov identifier: NCT 01435460) included 7 clinical centers in China. Patients with SAC were enrolled from August 2010 through April 2011. All patients randomly assigned were Chinese. The study was conducted in accordance with Good Clinical Practice as described in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Harmonized Tripartite Guidelines for Good Clinical Practice 1996, China State Food and Drug Administration's Good Clinical Practices, applicable local regulations, and the Declaration of Helsinki.[23–25] The protocol was approved by the Medical Ethics Committees of the Eye Nose and Throat Hospital of Fudan University and the First Affiliated Hospital of Medical School of Zhejiang University. All patients provided written informed consent at screening (see Supplemental Figure in the online version at http://dx.doi.org/10.1016/j.clinthera.2012.04.024).

Included in this study were patients aged 18 years or older who were diagnosed with acute SAC with grade 4 (severe) ocular itching and grade 2 or higher (ie, moderate to severe) bulbar conjunctival injection (red-

*Trademark: Patanol® (S.A. Alcon-Couvreur N.V., Puurs, Belgium).

†Trademark: Alrex® (Bausch + Lomb, Rochester, New York).