A Comparative Study of Efficacy of Alcaftadine 0.25 % and Olopatadine 0.2 % in Allergic Conjunctivitis

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ABSTRACT

BACKGROUND

Allergic conjunctivitis is one of the commonly found clinical conditions in ophthalmology practice. Diagnostic features consist of itching, redness and swelling of conjunctiva. Cornea is rarely involved. The physiologic basis of allergy is mast cell degranulation releasing histamine and other pro-inflammatory mediators. Mast cells release histamine which is responsible for early acute phase of allergies and pro-inflammatory mediators like prostaglandins, leukotrienes etc. which are responsible for the late phase. Activation of H1 receptors on conjunctival neurons causes itching while that of H1 and H2 receptors on vascular endothelium is responsible for vasodilation (appearing as redness) and endothelial swelling. Itching and inflammation are caused by response of H4 receptors on immune and inflammatory cells. Olopatadine is an H1 receptor antagonist and mast cell mediator release inhibitor. It is available as 0.1 % formulation used twice daily, and 0.2 % and 0.7 % formulations, both used once daily. Alcaftadine has high affinity and specificity for H1 and H2 receptors, and moderate affinity for the H4 receptors. It is an inverse agonist of H1, H2 and H4 receptors and also acts as mast cell stabiliser. Thus, antihistaminic effect relieves the early phase and mast cell stabilisation relieves the late phase of ocular allergic response. Both have become the most important therapy for allergic conjunctivitis.

METHODS

This was a prospective, observer-masked, single centre clinical trial conducted at outpatient department of ophthalmology, S.N. Medical College, Agra, from February 2018 to July 2019. Subjects with allergic conjunctivitis (n = 136) were registered for a prospective study and followed up for two weeks. Subjects were randomised using computer generated random number tables into one of the two treatment groups: alcaftadine 0.25 % eye drop and olopatadine 0.2 % eye drop. In this study, efficacy of the drug was taken as mean reduction in severity score of the subjects evaluated at one week and two weeks follow up.

RESULTS

Patients treated with alcaftadine 0.25 % eye drop showed comparatively early alleviation of signs and symptoms in comparison to patients treated with olopatadine 0.2 % eye drop. Alcaftadine 0.25 % treated subjects experienced significantly higher mean reduction in severity score than olopatadine 0.2 % treated subjects at every follow up visit; after 1 week ($p = 0.0205$) and after 2 weeks ($p = 0.0475$). No adverse effects were reported with either drug.

CONCLUSIONS

Once daily alcaftadine 0.25 % eye drop showed higher efficacy than once daily olopatadine 0.2 % eye drop in relieving signs and symptoms of allergic conjunctivitis at both one week and two weeks follow up. Both treatment arms were found to be safe and effective.

KEYWORDS

Allergic conjunctivitis, Olopatadine, Alcaftadine

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DOI: 10.18410/jebmh/2020/642

How to Cite This Article:
Sen S, Yadav HK, Singh P. A comparative study of efficacy of alcaftadine 0.25 % and olopatadine 0.2 % in allergic conjunctivitis. J Evid Based Med Healthc 2020; 7(52), 3153-3158. DOI: 10.18410/jebmh/2020/642

Submission 13-07-2020,
Peer Review 20-07-2020,
Acceptance 14-11-2020,
Published 28-12-2020.

BACKGROUND

Allergic conjunctivitis is one of the commonly found clinical conditions in ophthalmology practice. Various factors are responsible like genetics, air pollution in cities, pet animals, and early childhood exposure. Numerous types of ocular allergy are seasonal allergic conjunctivitis (SAC), perennial allergic conjunctivitis (PAC), vernal keratoconjunctivitis (VKC), atopic keratoconjunctivitis (AKC) and giant papillary conjunctivitis (GPC). SAC and PAC are the most common among all.

SAC is usually caused by pollens. PAC is caused by perennial allergens. SAC and PAC are characterized by redness, itching, and conjunctival swelling. Cornea is rarely involved.[1] In vernal keratoconjunctivitis, ocular symptoms include severe itching, redness, photophobia, swelling, and ropy discharge. Ocular signs include giant papillae, trantas dots and shield ulcers which heal by forming an anterior stromal opacity. In AKC, e czematous lesions may be present anywhere on the body including eyelids which are itchy. Other features present are chemotic eyelid skin, giant papillae, conjunctival scarring and trantas dots. These patients may develop atopic cataract. Contact allergy is a type-IV delayed hypersensitivity reaction caused by allergens like poison ivy and oak, nickel, neomycin, latex, atropine and its derivatives. It is generally associated with itching. Giant papillary conjunctivitis is caused by use of contact lens,[1] by immune or mechanical mechanisms.

Mast cells release histamine which is responsible for early acute phase of allergies and pro-inflammatory mediators like prostaglandins, leukotrienes etc. which are responsible for the late phase.[2] Activation of H1 receptors on conjunctival neurons causes itching[3] while that of H1 and H2 receptors on vascular endothelium is responsible for vasodilation (appearing as redness) and endothelial swelling.[4,5] Itching and inflammation is caused by response of H4 receptors on immune and inflammatory cells.[6,7,8]

Topical ophthalmic anti-histamines are the primary choice of treatment for ocular allergy. Both olopatadine and alcaftadine are dual action anti-allergic agents i.e. antihistamines and mast cell stabilizers and therefore have become the most important therapy for allergic conjunctivitis.

Olopatadine

Olopatadine is an H1 receptor antagonist and mast cell mediator release inhibitor.[9] It's available as 0.1 % formulation used twice daily, and 0.2 % and 0.7 % formulations, both used once daily. All preparations are well tolerated and there is virtually no systemic absorption after ocular application.[10]

Alcaftadine

Alcaftadine is a tricyclic piperidine aldehyde compound. It's metabolized to a carboxylic acid form in body. Its empirical formula is $C_{19}H_{21}N_3O$ and chemical name is 6, 11-dihydro-11- (l-methyl-4-piperidinylidene) -5H-imidazo [2,1-b][3] benzazepine-3-carboxaldehyde (CAS No 147084-10-4).[11,12] It has high affinity and specificity for H1 and H2 receptors[12] and moderate affinity for the H4 receptors. It's an inverse agonist of H1, H2 and H4 receptors and also acts as mast cell stabilizer. Thus, antihistaminic effect relieves the early phase and mast cell stabilization relieves the late phase of ocular allergic response.[13]

Ocular alcaftadine and its metabolite attain their maximum serum concentration at 15 minutes and 1 hour of use respectively.[12,14] Both become undetectable after 3 hours and 12 hours respectively.

METHODS

This was a prospective, observer masked, single centre clinical trial conducted at outpatient department of ophthalmology, S.N. Medical College, Agra, from February 2018 to July 2019. Approval was taken from the ethics committee of our institute (IEC number 2017/26/TH/Ophthalmology) and adhered to the principles of the declaration of Helsinki. Informed consent was obtained from all the participants.

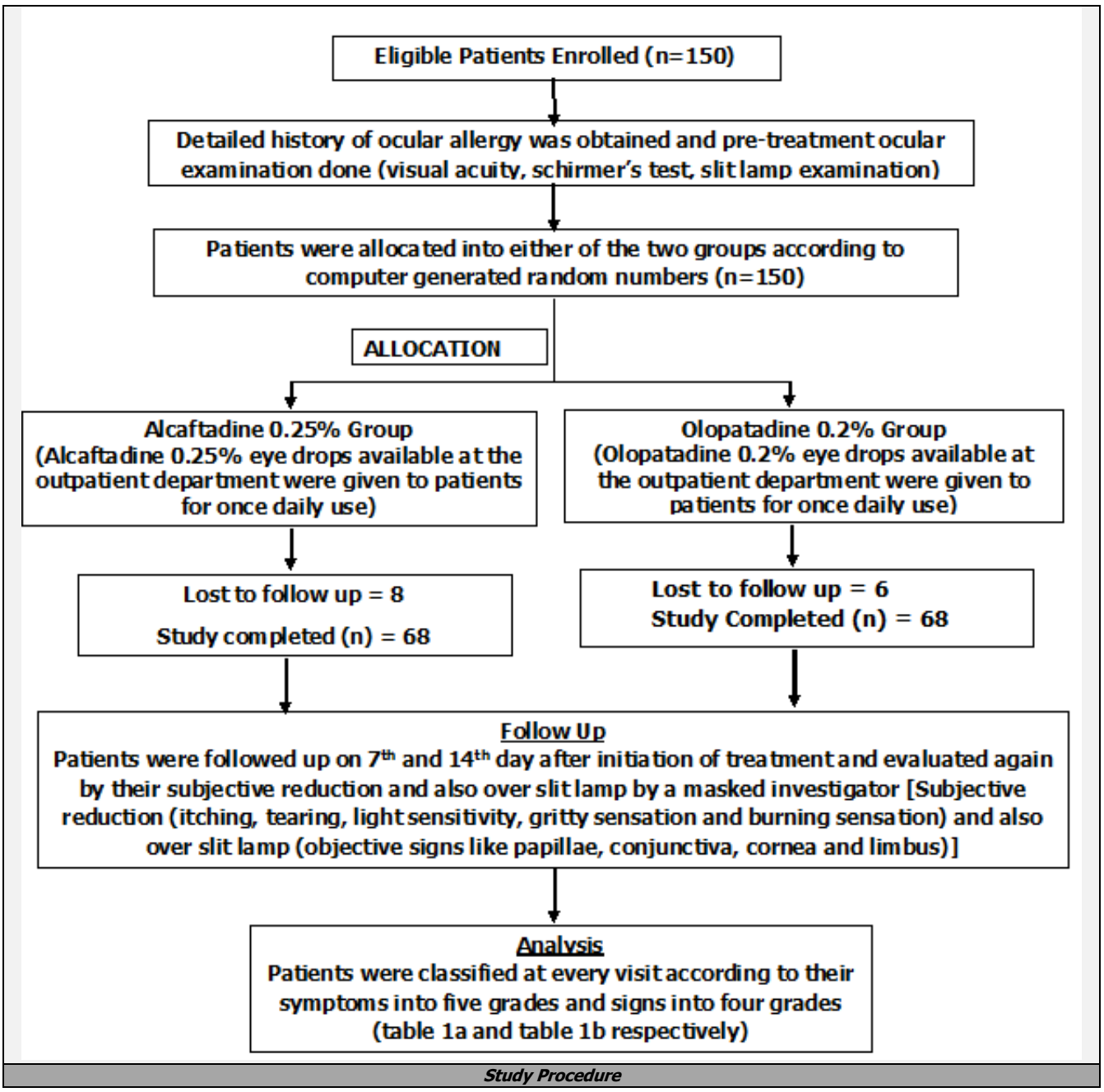
Study Eligibility Criteria

Key inclusion criteria included subjects' age more than 18 years having a positive history of ocular allergies and having a best corrected visual acuity of 6 / 12 or better in each eye. Subjects should have no history of wearing contact lens for at least three days before and during the study period.

Key exclusion criteria included subjects who have undergone any ocular surgical intervention within three months; subjects who have used aspirin, or related products, or H1-antagonist antihistamines within 72 hours; corticosteroids or mast cell stabilising drugs within 14 days, and immunotherapeutic agents; subjects who used any other topical eye drops (including ocular lubricants) other than the drugs under study within 72 hours; or subjects who used any investigational medications or devices within 30 days of the study; or patients with known hypersensitivity to olopatadine and alcaftadine including benzalkonium chloride which is used as preservative in the ophthalmic solutions were excluded. Pregnancy and lactation were also exclusion criteria of the study.

Clinical Grading Systems

Grading system for clinically classifying the patient into different categories, was structured with reference to suggested grading systems by dos Santos et al.,[15] Uchio et al.[16] and Atzin Robles-Contreras et al.[17]



Study Procedure

	0 None of the Time	1 Some of the Time	2 Half of the Time	3 Most of the Time	4 All of the Time
Itching					
Tearing					
Light sensitivity					
Gritty sensation					
Burning sensation					

Table 1a. Evaluation of Grade of Subjective Symptoms Severity

Primary Outcome

Reduction in total severity score at subsequent visits was taken as primary outcome of drug and efficacy was measured as mean difference between severity score at two different visits for all the patients in that treatment group.

Statistical Analysis

Data analysis was done using Microsoft Excel and GraphPad statistical calculator. Descriptive data were presented as mean and standard deviation for quantitative data and frequency for qualitative data. Tests of significance included independent t-test for quantitative data (age distribution, severity score and reduction in severity score in both treatment groups) and chi-squared test for qualitative data (sex distribution in both treatment groups and number of patients improved by either drug in mild and moderate category). All p-values were two-tailed at a significance level of 0.05. Total severity score was calculated at each visit and categorised as mild: 1 – 9, moderate: 10 – 18, moderately severe: 19 – 27 and severe: 28 - 36.

Grade/ Level	1 Mild	2 Moderate	3 Moderately Severe	4 Severe
Papillae	Micro: < 0.3 mm	Macro: 0.3 – < 0.5 mm	Cobblestone: 0.5 - < 1 mm + / - fibrosis	Giant: ≥ 1mm
Conjunctiva	Hyperaemia	Hyperaemia + partial conjunctival swelling	Hyperaemia +diffuse thin chemosis	Hyperaemia + cyst like chemosis / scar
Cornea	Sectoral SPKs	Diffuse SPKs	Shield ulcer or erosion of epithelium	Keratoconus with or without central leucoma, conjunctival-ization of cornea encroaching on visual axis
Limbus (limbal oedema / trantas dots)	< 1 / 2 of limbal circumference affected	1 / 2 or > 1 / 2 of limbal circumference affected		

Table 1b. Evaluation of Grade of Objective Signs Severity

RESULTS

150 patients were enrolled out of whom 14 were lost to follow up and 136 patients completed the study. 68 patients received alcaftadine 0.25 % eye drop and 68 patients received olopatadine 0.2 % eye drop. Mean age of alcaftadine 0.25 % treated group was 25 ± 5.62 years and that of olopatadine 0.2 % treated group was 25.9 ± 6.4 years. Number of males in alcaftadine treated group and olopatadine treated group are 56 and 54 respectively and number of females are 12 and 14 respectively. Male female ratio was 4.67:1 and 3.86:1 respectively in the two groups.

	Alcaftadine 0.25 %	Olopatadine 0.2 %	P-Value
Age in Years (Mean ± SD)	25 ± 5.62	25.9 ± 6.74	0.40
Male	56	54	0.66
Female	12	14	

Table 2. Patient Demographics in Two Treatment Groups

In alcaftadine 0.25 % treated group, at the time of presentation, mild, moderate, moderately severe and severe cases were 36 (52.94 %), 28 (41.18 %), 4 (5.88 %) and 0 (0 %) respectively. Similarly, in olopatadine 0.2 % treated group, at the time of presentation, mild, moderate, moderately severe and severe cases were 52 (76.47 %), 12 (17.65 %), 4 (5.88 %) and 0 (0 %) respectively.

In alcaftadine 0.25 % group, after 1 week of treatment, out of 36 patients in mild category, 10 (27.78 %) patients recovered or improved. Out of 28 patients in moderate category, 24 (85.71 %) patients improved and out of 4 patients in moderately severe category, all 4 (100 %) patients improved. In olopatadine 0.2 % group, after 1 week of treatment, out of 52 patients in mild category, 12 (23.08 %) patients recovered or improved. Out of 12 patients in moderate category, 8 (66.67 %) patients improved and out of 4 patients in moderately severe category, all 4 (100 %) patients improved.

On comparing the subjective and objective response after 1 week of treatment, results of alcaftadine 0.25 % treated group are better in mild and moderate cases, as compared to olopatadine 0.2 % treated group but the difference is statistically not significant (p = 0.616 and 0.343 respectively).

After 2 weeks of treatment, there is an increase in number of cases responding favourably in both groups. In alcaftadine 0.25 % group, after 2 weeks of treatment, out of 36 patients in mild category, 32 (88.89 %) patients recovered or improved. Out of 28 patients in moderate category, all 28 patients (100 %) improved. 22 (78.57 %) patients improved to mild category and 6 (21.43 %) patients recovered. Out of 4 patients in moderately severe category, all 4 (100 %) patients improved. In olopatadine 0.2 % group, after 2 weeks of treatment, out of 52 patients in mild category, 31 (59.62 %) patients recovered or improved. Out of 12 patients in moderate category, all 12 patients (100 %) improved. 6 (50.0 %) patients improved to mild category and 6 (50.0 %) patients recovered. Out of 4 patients in moderately severe category, all 4 (100 %) patients improved. Results of alcaftadine 0.25 % treated group are better in mild cases as compared to olopatadine 0.2 % treated group and the difference is found to be statistically significant (p = 0.005), but there is no significant difference in moderate and moderately severe category after 2 weeks of treatment.

Table 3 shows distribution of mean severity scores for all patients in both treatment groups at time of presentation and after 1 week and 2 weeks of treatment. Mean severity scores at presentation in both alcaftadine and olopatadine group were comparable with no significant difference (p-value = 0.136, statistically not significant). Both the drugs showed downward shift in mean severity score which was greater in alcaftadine treated group than in olopatadine treated group.

Time of Assessment	Alcaftadine 0.25 %	Olopatadine 0.2 %	P-Value
At Time of Presentation	9.26 ± 4.96	8 ± 4.84	0.136
After 1 Week	4.03 ± 3.57	3.85 ± 3.58	
After 2 Weeks	0.88 ± 1.36	1.06 ± 1.52	

Table 3. Mean Severity Scores of Alcaftadine 0.25 % Treated Group and Olopatadine 0.2 % Treated Group at the Time of Presentation, after 1 Week and after 2 Weeks

Treatment Groups	At 1 Week Mean Reduction ± SD	At 2 Weeks Mean Reduction ± SD
Alcaftadine 0.25 % (n = 68)	5.235 ± 2.456	8.382 ± 4.176
Olopatadine 0.2 % (n = 68)	4.147 ± 2.933	6.941 ± 4.397
P Value	0.0205*	0.0475*

Table 4. Mean Reduction in Severity Score of Alcaftadine 0.25 % Treated Group and Olopatadine 0.2 % Treated Group after 1 Week and after 2 weeks

*Statistically significant at p < 0.05

Table 4 shows mean reduction in severity scores achieved in both treatment groups at 1 week and at 2 weeks of treatment. Mean reduction in severity score was higher in alcaftadine treated group at both 1 week and 2 weeks post treatment and the difference were statistically significant (p-value = 0.0205 and 0.0475 respectively).

DISCUSSION

This study is based on total 136 patients, out of which 68 patients belonged to alcaftadine 0.25 % treated group and 68 patients belonged to olopatadine 0.2 % treated group. There was no significant difference among the groups alcaftadine 0.25 % and olopatadine 0.2 % regarding mean age (25 ± 5.62 vs. 25.9 ± 6.74; p = 0.40) and sex distribution (p = 0.66). Saboo US et al. reported male preponderance (M:F ratio 6.4:1) in their study which is consistent with our study[18] (M:F in alcaftadine 0.25 % treated group = 4.67:1 and olopatadine 0.2 % treated group = 3.86:1).

Patients treated with alcaftadine 0.25 % eye drop showed comparatively early alleviation of signs and symptoms in comparison to patients treated with olopatadine 0.2 % eye drop, as evident from Table 3. In this study, mean reduction in severity score of alcaftadine 0.25 % treated subjects was significantly higher than olopatadine 0.2 % treated subjects, evident at each follow up visit; after 1 week (p = 0.0205) and after 2 week (p = 0.0475). Ackerman et al.[19] showed better results with alcaftadine 0.25 % than olopatadine 0.2 % in relief of itching in ocular allergy. In a previous study, Greiner et al. showed that alcaftadine had earlier onset of action than olopatadine, and also its effects were more sustained compared to olopatadine.[20] Ono SJ et al. in his study on murine model of allergic conjunctivitis demonstrated greater reduction of eosinophilic recruitment and higher zonula occludens stability for alcaftadine than olopatadine.[21] Contreras-Ruiz L et al., in his study on corneal epithelial barriers, suggested the cause of these observed clinical differences to be greater efficacy of alcaftadine in preventing allergen-activated disruption of the epithelial barriers.[22] In our study, at 1 week follow up, a greater proportion of mild category of alcaftadine 0.25 % treated patients achieved full recovery (severity score = 0) (27.78 %) compared with mild category of olopatadine 0.2 % treated patients (23.08 %) but the difference is statistically not significant (p = 0.616). After 2 weeks of treatment, the proportion of mild category of alcaftadine 0.25 % treated patients who achieved full recovery was significantly greater (severity score = 0) (88.89 %) as compared with mild category of olopatadine 0.2 %treated patients (59.62 %) (p = 0.005). As seen in previous studies on alcaftadine and olopatadine,[19,20,23,24] treatment with both the drugs were found to be safe and generally well tolerated, but with alcaftadine 0.25 % there is comparatively early alleviation of signs and symptoms of disease and effects are sustained.

The primary limitation of the study is its shorter time period i.e. only 2 weeks of follow up. Studies with longer follow up may reveal more insight into the long-term effects of both the drugs.

CONCLUSIONS

In our study, alcaftadine 0.25 % eye drops showed higher efficacy than olopatadine 0.2 % eye drops in relieving ocular signs and symptoms at both 1 week and 2 weeks follow up. Both drugs were found to be safe and well tolerated. Further research is required to understand the basic factors and reasons responsible for these differences in efficacy between the two treatment arms.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
Financial or other competing interests: None.
Disclosure forms provided by the authors are available with the full text of this article at jebmh.com.

REFERENCES

[1] Friedlander MH. Ocular allergy. Curr Opin Allergy ClinImmunol 2011;11(5):477-482.
[2] Church MK, McGill JI. Human ocular mast cells. Curr Opin Allergy Clin Immunol 2002;2(5):419-422.
[3] Abelson MB, Udell IJ. H2-receptors in the human ocular surface. Arch Ophthalmol 1981;99(2):302-304.
[4] Abelson MB, Loffler O. Conjunctival allergen challenge: models in the investigation of ocular allergy. Curr Allergy Asthma Rep 2003;3(4):363-368.
[5] Nakano Y, Takahashi Y, Ono R, et al. Role of histamine H(4) receptor in allergic conjunctivitis in mice. Eur J Pharmacol 2009;608(1-3):71-75.
[6] Thurmond RL, Gelfand EW, Dunford PJ. The role of histamine H1 and H4 receptors in allergic inflammation: The search for new antihistamines. Nat Rev Drug Discov 2008;7(1):41-53.
[7] Zampeli E, Thurmond RL, Tiligada E. The histamine H4 receptor antagonist JNJ7777120 induces increases in the histamine content of the rat conjunctiva. Inflamm Res 2009;58(6):285-291.
[8] Kenji O Ken-Ichi H, Toshihiko K, et al. Pharmacological, pharmacokinetic and clinical properties of olopatadine hydrochloride, a new antiallergic drug. Jpn J Pharmacol 2002;88(4):379-397.
[9] Yanni JM, Stephens DJ, Miller ST, et al. The in vitro and vivo ocular pharmacology of olopatadine (al-4943a), an effective anti-allergic/antihistaminic agent. J Ocul Pharmacol Ther 1996;12(4):389-400.
[10] Patanol prescribing information: 2017. [cited 2018 Feb 16]. FDA approved labeling and prescribing information of ophthalmic olopatadine 0.1 %.http://www.accessdata.fda.gov/drugsatfda_docs/label/2003/20688slr016_patanol_lbl.pdf.
[11] Bohets H, McGowan C, Mannens G, et al. Clinical pharmacology of alcaftadine, a novel antihistamine for the prevention of allergic conjunctivitis. J Ocul Pharmacol Ther 2011;27(2):187-195.
[12] Mahvan TD, Buckley WA, Hornecker JR. Alcaftadine for the prevention of itching associated with allergic conjunctivitis. Ann Pharmacother 2012;46(7-8):1025-1032.
[13] Namdar R, Valdez C. Alcaftadine: a topical antihistamine for use in allergic conjunctivitis. Drugs Today (Barc) 2011;47(12):883-890.

[14] Abelson MB, Smith L, Chapin M. Ocular allergic disease: Mechanisms, disease sub-types, treatment. Ocul Surf 2003;1(3):38-60.
[15] Dos Santos MS, Alves MR, de Freitas D, et al. Ocular allergy Latin American consensus. Arq Bras Oftalmol 2011;74(6):452-456.
[16] Uchio E, Kimura R, Migita H, et al. Demographic aspects of allergic ocular diseases and evaluation of new criteria for clinical assessment of ocular allergy. Graefes Arch Clin Exp Ophthalmol 2008;246(2):291-296.
[17] Robles-Contreras A, Santacruz C, Ayala J, et al. Allergic conjunctivitis: an immunological point of view. In Tech 2011.
[18] Saboo US, Jain M, Reddy JC, et al. Demographic and clinical profile of vernal keratoconjunctivitis at a tertiary eye care centre in India. Ind J Ophthalmol 2013;61(9):486-489.
[19] Ackerman S, D'Ambrosio F Jr, Greiner JV, et al. A multicenter evaluation of the efficacy and duration of action of alcaftadine 0.25 % and olopatadine 0.2 % in the conjunctival allergen challenge model. J Asthma Allergy 2013;6:43-52.
[20] Greiner JV, Edwards-Swanson K, Ingerman A. Evaluation of alcaftadine 0.25 % ophthalmic solution in acute allergic conjunctivitis at 15 minutes and 16 hours after instillation versus placebo and olopatadine 0.1 %. Clin Ophthalmol 2011;5:87-93.
[21] Ono SJ, Lane K. Comparison of effects of alcaftadine and olopatadine on conjunctival epithelium and eosinophil recruitment in a murine model of allergic conjunctivitis. Drug Des Devel Ther 2011;5:77-84.
[22] Contreras-Ruiz L, Schulze U, Garcia-Posadas L, et al. Structural and functional alteration of cornea lepithelial barrier under inflammatory conditions. Curr Eye Res 2012;37(11):971-981.
[23] Torkildsen G, Shedden A. The safety and efficacy of alcaftadine 0.25 % ophthalmic solution for the prevention of itching associated with allergic conjunctivitis. Curr Med Res Opin 2011;27(3):623-631.
[24] Abelson MB, Spangler DL, Epstein AB, et al. Efficacy of once-daily olopatadine 0.2% ophthalmic solution compared to twice-daily olopatadine 0.1% ophthalmic solution for the treatment of ocular itching induced by conjunctival allergen challenge. Curr Eye Res 2007;32(12):1017-1022.