

# Comparative Study Between The Effectiveness And Associated Adverse Effects Of Olopatadine And Alcaftadine When Used In Treating Allergic Conjunctivitis In A Tertiary Eye Care Centre Of Northern India

Dr. Wahegurupal Singh<sup>1</sup>, Dr. Mohan Lal Pandey<sup>2\*</sup>, Ms. Kiran Rana<sup>3</sup>, Dr Kamiya Chugh<sup>4</sup>,

<sup>1</sup>Pg Resident, Department of Ophthalmology Maharishi Markandeshwar Institute of Medical Science And Research, Mullana, Ambala

<sup>2</sup>Professor, Department of Ophthalmology Maharishi Markandeshwar Institute Of Medical Science And Research, Mullana, Ambala

<sup>3</sup>Assistant Professor, Nursing M.M College of Nursing, Mullana, Ambala

<sup>4</sup>Pg Resident Department of Community Medicine Maharishi Markandeshwar Institute of Medical Science And Research, Mullana, Ambala

\*Corresponding Author- Dr. Mohan Lal Pandey

\*Professor, Department of Ophthalmology Maharishi Markandeshwar Institute Of Medical Science And Research, Mullana, Ambala,

Email Id--Mlpandey23@Gmail.Com

DOI: 10.47750/pnr.2022.13.510.463

## Abstract

**Background:** Since the last decade, there has been an exponential rise in the allergic disorders<sup>1</sup>.The highly prevalent ocular condition in clinical ophthalmology is ocular allergy. There are numerous factors contributing to its aetiology, including genetics, pollution of the air, exposure to the pets, etc. Since, a huge percentage of population requires the treatment of allergies, the treatment costs have increased<sup>3</sup>.Ocular conjunctivitis eventually causes blindness, if it remains untreated and unattended.

**Methods:** The study was an observer-masked, randomized, prospective, parallel-group study. Signs and symptoms were graded using Total Ocular Symptom Scoring System (TOSS). All patients aged between 18 and 60 years belonging to either gender, with mild-to-moderate allergic conjunctivitis presenting to outpatient department. The statistical analysis was done using software OPenEPi and SPSS version 20.

**Results:** Alcaftadine(0.25%) drops shows good final outcome with less adverse effects. Both the drugs are safe and effective in treating allergic conjunctivitis, but it was seen that alcaftadine appears to be superior to olopatadine (0.1%) in reducing the signs and symptoms associated allergic conjunctivitis.

**Conclusion:** Once daily alcaftadine 0.25 % eye drop showed better outcome than twice daily olopatadine 0.1 % eye drop in relieving symptoms of allergic conjunctivitis at both 1 week and 1 month follow up. Both eye drops were found to be safe and effective.

**Keywords:** Alcaftadine, Olopatadine, Allergic conjunctivitis.

## INTRODUCTION

Since the last decade, there has been an exponential rise in the allergic disorders<sup>1</sup>.The highly prevalent ocular condition in clinical ophthalmology is ocular allergy. There are numerous factors contributing to its aetiology, including genetics, pollution of the air, exposure to the pets, etc <sup>2</sup>. Since, a huge percentage of population requires the treatment of allergies, the treatment costs have increased<sup>3</sup>. Ocular conjunctivitis eventually causes blindness, if it remains untreated and unattended.

Allergic conjunctivitis comprises of perennial allergic conjunctivitis (PAC), seasonal allergic conjunctivitis (SAC), vernal keratoconjunctivitis (VKC), and atopic keratoconjunctivitis (AKC). SAC and PAC have different clinicopathological features from AKC and VKC. Still, both of them have common markers of allergy<sup>4</sup>. Ocular allergies constitutes of giant papillary conjunctivitis (GPC), which is being associated with contact lenses or ocular prosthesis. Still, it is not wise to consider them as culprit of actual allergic diseases, but they need to come to an immediate attention and be treated by ophthalmologists in association with experts of contact lenses<sup>5</sup>.

This disease is multifactorial in origin and the exact etiology remains unknown. However combination of factors like climatic changes, exposure to allergen, atopic dermatitis, genetic predisposition, and foreign bodies on the ocular surface like contact lenses, prostheses, cyanoacrylate glue and sutures may contribute to its prevalence. Recording the clinical

findings is the first step in diagnosing the cases of allergic conjunctivitis, but laboratory tests are usually used as an adjunct in supporting the diagnosis<sup>6</sup>. Skin testing is the other test that is helpful for determining specific allergens, which can be done by scratch tests or by injecting the allergen intra dermally. There is wide application of in-vitro tests for IgE antibodies for specific allergens. Intrinsic and extrinsic forms can be distinguished by allergic tests and this would further be helpful in the treatment<sup>7</sup>

The gold standard and the primary therapy is to avoid the allergen. The first line defence role is being played by artificial tears by inhibiting the portal of entry of foreign particles into the ocular surface. Anti-allergic medications including mast cell stabilizers, the antihistaminics and combination drugs may be used. The H<sub>1</sub> topical levocabastine hydrochloride is efficacious in reducing the inflammation of ocular surfaces on its topical administration to the eye<sup>8,9</sup>. These topical antihistaminics do not have any action on rest of the pro-inflammatory mediators and leukotrienes. Also their prolonged use can be irritating to the eyes<sup>10</sup>

### Alcaftadine

Preliminary data in the literature regarding alcaftadine [6, 11-dihydro-11-(1-methyl-4-piperidinylidene)-5H-imidazo [2, 1-b] [3] benzazepine-3-carboxaldehyde] have concluded that this drug has antihistamine properties various in vivo models. In guinea pig models, it showed alleviation of eosinophilic infiltration in allergic conjunctivitis<sup>28</sup>.

### Olopatadine

This compound is tricyclic consisting of various mechanisms of action against multiple allergic conditions. It is an antagonist for H<sub>1</sub> receptor and is also a mast cell stabilizer, having anti-inflammatory properties. Europe, Japan, and the United States have licensed the sale of Olopatadine as an ophthalmic solution.

## MATERIAL AND METHOD

The study was an observer-masked, randomized, prospective, parallel-group study conducted at the Department of Ophthalmology, at Maharishi Markandeshwar Institute of Medical Sciences and Research, Mullana, Ambala, Haryana. We took an approval for the study from the institutional ethical committee. Clinical signs and symptoms were used to diagnose allergic conjunctivitis. Signs and symptoms were graded using Total Ocular Symptom Scoring System (TOSS). All patients aged between 18 and 60 years belonging to either gender, with mild-to-moderate allergic conjunctivitis presenting to outpatient department between 2021 and 2022 were included after obtaining written informed consent. Those patients satisfying the inclusion criteria will be recruited.

### Inclusion criteria

- Patients who were diagnosed clinically as allergic conjunctivitis.
- Both males and females
- Patients presenting with signs and symptoms of allergic conjunctivitis.
- Those who have signed the informed consent.
- Patients prepared to follow up all visits.

### Exclusion criteria

- Pregnant women who are nursing.
- Patients who have history of an ocular herpetic infection
- Patient who are on any other topical drug therapy for ocular pathology like blepharitis, meibomitis or dry eye.
- Patient who are on steroidal therapy
- Patients on antihistamines within 7 days prior the trial initiation
- Patients infected with bacterial, fungal, viral, and protozoan ocular infection.
- Subjects with contact lenses.
- Allergic to any of the study medications, that could affect safety or trial parameters.
- Scheduled to undergo any ocular surgery or refractive surgery during study period.

Each patient has signed a consent in their regional language before they were admitted to study. Patients' data was collected using a case proforma and by personal interview, Patients were filtered out according to the data provided. Once the patient was selected for the study, a detailed clinical history of the patients was carried including the duration of AC complaint. After detailed history was obtained, through clinical examination of the patients was carried out in accordance with the department procedures. Visual insight of the patients were tested using Snellen's chart. First patient was examined on torch light, then detailed examination was performed on slit lamp with and without lid eversion of both eyes. Focus of examination was on tarsal and bulbar conjunctiva, limbus and cornea. Upon assessment, the presence or absence of papillae were noted and if papillae are present then size of the papillae were measured. The conjunctiva were examined for presence of any hyperaemia, chemosis and scarring. The limbus were examined for the presence of any limbal oedema or tranta spots. Cornea was examined for presence of SPK, epithelial erosions, ulcers, or keratoconus. Finally, eyelids were then examined for position, oedema, margin, and discharge. All of the above findings were graded. The symptoms were recorded at 15 min, followed by 1 day, 1 week and subsequently at 1 month. Ocular findings were recorded at baseline, 1 week and 1 month. Total ocular symptom scoring system (TOSS) was assessed at baseline, day 0,7,14 and 21. The data collected was tabulated in Excel sheet and statistical analysis was done using software OPenEPi and SPSS

version 20. We applied “t” test for quantitative data and for qualitative data, we applied “Chi Square test”. P value was calculated and value <0.05 was considered significant.

## RESULT

The present study was done on 100 patients coming to Ophthalmology OPD who had allergic conjunctivitis. This 100 patients then were further divided into 2 groups randomly. Group I- 50 patients were treated with Olopatadine 0.1% eyedrops and Group II- 50 patients were treated with Alcaftadine 0.25% eyedrops. The mean age for I group was 41.0 years and for II group was 41.8 years. Total number of male in group I were 35 and 32 in group II and total number of female were 15 and 18 respectively. The present study shows that among group I majority were farmers and among group II majority were clerk. It was seen that most common symptom among both group was redness of eye, followed by watering and discharge etc. Majority of cases had past history of allergic conjunctivitis. Among all the family 10 cases and 12 cases had positive family history among group I and group II respectively. Mean systolic blood pressure was 126.4±6.4mm Hg in I group and 124.5±4.9 mm of Hg in II group. Mean diastolic blood pressure was 79.4±4.2mmHg in I group and 80.6±3.9 mm of Hg in II group. Mean random blood sugar was 189.2±33.2 and 1010.6±326.6 mm of Hg among group I and group II respectively. Table 1 and Table 2. Shows symptoms when on treatment for both group I and II where seen to be decreased on each follow up, but it was seen that group II showed rapid decrease as compared to group I. On ocular examination most common finding was presence of papillae followed by discharge etc. The signs when observed during ocular examination at follow up group II showed rapid decrease in findings as compared to group I. Table 3. shows Total ocular symptom score was less in group II, statistical significance was seen at 7<sup>th</sup> day, 14<sup>th</sup> day and 21<sup>st</sup> day. Statistical significance was seen for conjunctival hyperaemia score. The Visual acuity was decreased more in group I than group II. In present study, adverse effects were comparatively increased in group I than group II. Figure 1. shows final outcome group II patients were more satisfied than group I. p value 0.04 shows statistical significance.

**Table 1.** Symptoms when on treatment for group I

Symptoms	At 15 min	At 1 <sup>st</sup> day	At 1 <sup>st</sup> week	At 1 <sup>st</sup> month
Redness	45	43	42	41
Watering/ discharge	42	40	38	36
Foreign body sensation	40	38	36	35
Itching	35	33	32	32
Photophobia	32	28	26	25
Poor Overall comfort	18	15	15	14

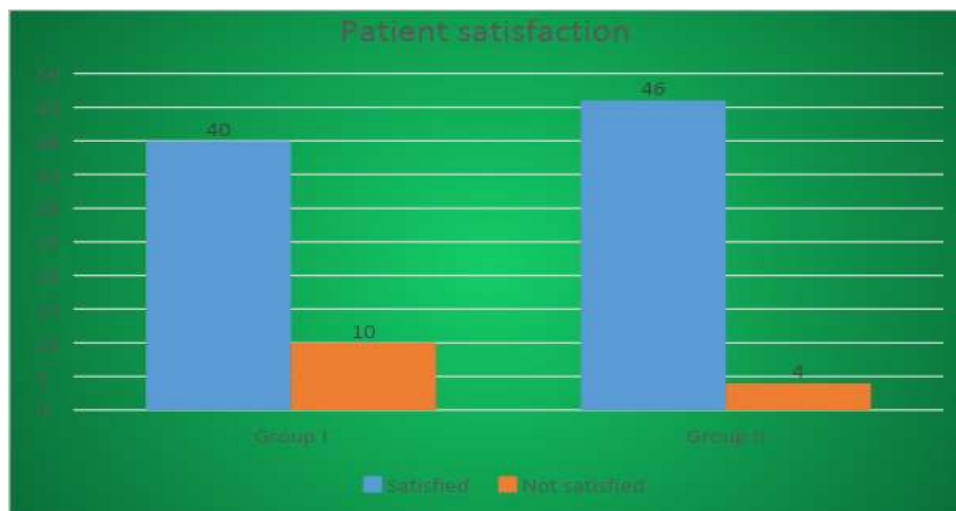
**Table 2.** Symptoms when on treatment for group II

Symptoms	At 15 min	At 1 <sup>st</sup> day	At 1 <sup>st</sup> week	At 1 <sup>st</sup> month
Redness	40	35	28	25
Watering/ discharge	38	32	25	16
Foreign body sensation	35	31	27	21
Itching	41	35	28	18
Photophobia	28	22	14	11
Poor Overall comfort	15	11	8	3

**Table 3.** Total ocular symptom score

Total ocular symptom score	Group I		Group II		P value
	The mean	SD	The mean	SD	
0 <sup>th</sup> day	8.1	0.93	7.9	1	0.2
7 <sup>th</sup> day	6.1	0.7	5.5	1.1	<0.001*
14 <sup>th</sup> day	3.6	0.9	2.7	0.8	<0.001*
21 <sup>st</sup> day	0.5	0.5	0.3	0.4	0.02*

**Figure 1.** Shows final outcome group II patients were more satisfied than group I. p value 0.04 shows statistical significance



## DISCUSSION

Present study shows age distribution where, among both group majority had age less than 30 years and average age for I group was 41.0 years and for II group was 41.8 years. Study by Sanjeev Kumar et al<sup>(128)</sup> showed that among all groups majority had age 30 or less than 30 years. Mean age was 29.3 years for alcaftadine and 29.45 years for olopatadine group. Study by Ayyappanavar S et al<sup>(133)</sup> showed that mean age in I group was 28.66 years and II group was 28.66 years. Hiroshi Nakatani et al<sup>(134)</sup> showed that mean age among I group was 33.2 years and II group was 38.7 years.

Present study shows that among I group majority were farmers and among II group majority were clerk. It was seen that most common symptom among both group was redness of eye, followed by watering and discharge etc. Sanjeev Kumar et al<sup>(128)</sup> had majority of males. Study by Ayyappanavar S et al<sup>(133)</sup> showed that majority were males among both groups. Even Hiroshi Nakatani et al<sup>(134)</sup> showed male preponderance. Present study showed majority of cases had past history among both groups. 10 cases had positive family history in I group and II group had 12 cases.

Study by Sanjeev Kumar et al<sup>(128)</sup> showed that as compared to olopatadine, alcaftadine is more beneficial for decreasing symptoms of allergic conjunctivitis, and showed statistical significance ( $p = 0.0007$ ). Donshik et al.<sup>(130)</sup> stated that all these three medications provided relief of allergic conjunctivitis symptoms. McLaurin EB, et al<sup>(132)</sup> also observed that patients on Alcaftadine presented with lesser mean itch than those on olopatadine. Present study showed total ocular symptom score was II group, statistical significance was seen at 7<sup>th</sup>, 14<sup>th</sup> and 21<sup>st</sup> day. Study by Sanjeev Kumar et al<sup>(128)</sup> showed that mean for I group was 8.41 and for II group was 8.25 and statistical significance was seen at 14<sup>th</sup> day. Study by Ayyappanavar S et al<sup>(133)</sup> showed that mean TOSS in I group was 7.68 and in II group was 7.65 and statistical significance was seen for 14<sup>th</sup> day. Present study showed statistical significance for conjunctival hyperaemia score and significant reduction was seen among alcaftadine group. Study by Sanjeev Kumar et al<sup>(128)</sup> showed that statistical significance was seen at 14<sup>th</sup> day, whereas present study showed for all follow up. Study by Ayyappanavar S et al<sup>(133)</sup> showed that statistical significance was not seen follow up. Hiroshi Nakatani et al<sup>(134)</sup> showed that low significance in patients treated with alcaftadine.

## REFERENCES

1. Barbee RA, Kaltenborn W, Lebowitz MD, Burrows B. Longitudinal changes in allergen skin test reactivity in a community population sample. *J Allergy Clin Immunol.* 1987;79:16–24
2. Leonardi S, delGiudiceMiraglia M, La Rosa M, Bellanti JA. Atopic disease, immune system, and the environment. *Allergy Asthma Proc.* 2007;28(4):410–417.
3. Friedlander MH. Ocular Allergy. *Curr Opin Allergy Clin Immunol.* 2011;11(5):477–482.
4. Bielory L, Frohman L. Allergic and immunologic disorders of the eye. *J Allergy Clin Immunol.* 1992;86:1–20.
5. Leonardi A, Motterle L, Bortolotti M. Allergy and the eye. *ClinExp Immunol.* 2008;153:17–21
6. Krachmer JH, Mannis MJ, Holland EJ, editor. St Louis: Mosby Elsevier; 2011. Seasonal and perennial allergic conjunctivitis; pp. 570–571
7. Friedlander MH. Ocular Allergy. *Curr Opin Allergy Clin Immunol.* 2011;11(5):477–482.
8. Stokes TC, Feinberg G. Rapid onset of action of levocabastine eye-drops in histamine-induced conjunctivitis. *ClinExp Allergy.* 1993;23:791–794.
9. Donshik PC, Pearlman D, Pinnas J, Raizman MB, Tauber J, Tinkelman D, Walters TR. Efficacy and safety of ketorolac tromethamine 0.5% and levocabastine 0.05%: a multicenter comparison in patients with seasonal allergic conjunctivitis. *Adv Ther.* 2000;17:94–102.
10. Leonardi S, Marchese G, Marseglia GL, La Rosa M. Montelukast in allergic diseases beyond asthma. *Allergy Asthma Proc.* 2007;28(3):287–291
11. Abelson MB, Paradis A, George MA, Smith LM, Maguire L, Burns R. Effects of Vasocon-A in the allergen challenge model of acute allergic conjunctivitis *Arch Ophthalmol.* 1990;108:520–524.
12. Mishra GP, Tamboli V, Jawla J, Mitra AK. Recent patents and emerging therapeutics in the treatment of allergic conjunctivitis. *Recent Pat Inflamm Allergy Drug Discov.* 2011;5:26–36
13. Woerly G, Loiseau S, Loyens M, Schoch C, Capron M. Inhibitory effects of ketotifen on eotaxin-dependent activation of eosinophils: Consequences for allergic eye diseases. *Allergy.* 2003;58:397–406.
14. Nabe M, Miyagawa H, Agrawal DK, Sugiyama H, Townley RG. The effect of ketotifen on eosinophils as measured at LTC4 release and by chemotaxis. *Allergy Proc.* 1991;12:267–271
15. Canonica GW, Ciprandi G, Petzold U, Kolb C, Ellers-Lenz B, Hermann R. Topical azelastine in perennial allergic conjunctivitis. *Curr Med Res Opin.* 2003;19:321–329.

16. Bielory L, Lien KW, Bigelsen S. Efficacy and tolerability of newer antihistamines in the treatment of allergic conjunctivitis. *Drugs*. 2005;65:215–228.
17. Kari O, Saari KM. Updates in the treatment of ocular allergies. *J Asthma Allergy*. 2010;3:149–158
18. Spector SL, Raizman MB. Conjunctivitis medicamentosa. *J Allergy Clin Immunol*. 1994;94:134–136
19. Dell SJ, Lowry GM, Northcutt JA, Howes J, Novack GD, Hart K. A randomized, double-masked, placebo-controlled parallel study of 0.2% loteprednol etabonate in patients with seasonal allergic conjunctivitis. *J Allergy Clin Immunol*. 1998;102:251–255.
20. Comstock TL, Decory HH. Advances in corticosteroid therapy for ocular inflammation: loteprednol etabonate. *Int J Inflam*. 2012. Epub 2012 Mar 28.
21. Noon L, Cantab BC. Prophylactic inoculation against hay fever. *Lancet*. 1911;1:1572–1574
22. Moller C, Dreborg S. Cross-reactivity between deciduous trees during immunotherapy. I. In vivo results. *Clin Allergy*. 1986;16:135–143.
23. Andersen NH, Jeppesen F, Schiøler T, Osterballe O. Treatment of hay fever with sodium cromoglycate, hyposensitization, or a combination. *Allergy*. 1987;42:343–351
24. Winther L, Malling HJ, Moseholm L, Mosbech H. Allergen-specific immunotherapy in birch- and grass-pollen-allergic rhinitis. I. Efficacy estimated by a model reducing the bias of annual differences in pollen counts. *Allergy*. 2000;55(9):818–826.
25. Leonardi S, Vitaliti G, Marsiglia GL, Caimmi D, Lionetti E, del Miraglia Giudice M, Salpietro C, Spicuzza L, Ciprandi G, La Rosa M. Function of the airway epithelium in asthma. *J Biol Regul Homeost Agents*. 2012;26:41–48.
26. Durham SR, Walker SM, Varga EM, Jacobson MR, O'Brien F, Noble W, Till SJ, Hamid QA, Nouri-Aria KT. Long-term clinical efficacy of grass-pollen immunotherapy. *N Engl J Med*. 1999;341:468–475.
27. Broide DH. Immunomodulation of allergic disease. *Annu Rev Med*. 2009;60:279–291.
28. Mizutani, N., Aoki, Y., Nabe, T., Ishiura, M., Yoshino, S., Takagaki, H., and Kohno, S. Effect of TA-270, a novel quinolinone derivative, on antigen-induced nasal blockage in a guinea pig model of allergic rhinitis. *Eur. J. Pharmacol*. 602:138–142, 2009.
29. Amir, S. Naloxone improves, and morphine exacerbates, experimental shock induced by release of endogenous histamine by compound 48/80. *Brain Res*. 1984;297:187–190, 1984
30. Torres, R., Gri fols, J., Marco, A., and de Mora F Sensitization of naive beagles by intradermal injection of an ascaris antigen: induction of a model of skin allergy. *Immunopharmacol. Immunotoxicol*. 2006;28:697–702, 2006.
31. Nonaka H, Ishii A, and Kase H. Effect of KW-4679, a novel antiallergic agent, on histamine H1 receptor. *Jpn J Pharmacol* 61(suppl 1):87, 1993 (Abs O-83).
32. Leonardi A, De Dominicis C, Motterle L. Immunopathogenesis of ocular allergy: a schematic approach to different clinical entities. *Curr Opin Allergy Clin Immunol*. 2007;7(5):429–35
33. Butrus S, Greiner JV, Discepolo M, Finegold I. Comparison of the clinical efficacy and comfort of olopatadine hydrochloride 0.1% ophthalmic solution and nedocromil sodium 2% ophthalmic solution in the human conjunctival allergen challenge model. *Clin Ther*. 2000 Dec;22(12):1462-72
34. Katelaris CH, Ciprandi G, Missotten L, Turner FD, Bertin D, Berdeaux G; International Olopatadine Study Group. A comparison of the efficacy and tolerability of olopatadine hydrochloride 0.1% ophthalmic solution and cromolyn sodium 2% ophthalmic solution in seasonal allergic conjunctivitis. *Clin Ther*. 2002 Oct;24(10):1561-75.
35. Berdy GJ, Stoppel JO, Epstein AB. Comparison of the clinical efficacy and tolerability of olopatadine hydrochloride 0.1% ophthalmic solution and loteprednol etabonate 0.2% ophthalmic suspension in the conjunctival allergen challenge model. *Clin Ther*. 2002 Jun;24(6):918-29
36. Brodsky M, Berger WE, Butrus S, Epstein AB, Irkec M. Evaluation of comfort using olopatadine hydrochloride 0.1% ophthalmic solution in the treatment of allergic conjunctivitis in contact lens wearers compared to placebo using the conjunctival allergen-challenge model. *Eye Contact Lens*. 2003 Apr;29(2):113-6.
37. Spangler DL, Abelson MB, Ober A, Gotnes PJ. Randomized, double-masked comparison of olopatadine ophthalmic solution, mometasone furoate monohydrate nasal spray, and fexofenadine hydrochloride tablets using the conjunctival and nasal allergen challenge models. *Clin Ther*. 2003 Aug; 25(8):2245-67
38. Lanier BQ, Finegold I, D'Arienzo P, Granet D, Epstein AB, Ledgerwood GL. Clinical efficacy of olopatadine vs epinastine ophthalmic solution in the conjunctival allergen challenge model. *Curr Med Res Opin*. 2004 Aug;20(8):1227-33.
39. Abelson MB, Gomes PJ, Vogelson CT, Pasquine TA, Gross RD, Turner FD, Wells DT, Bergamini MV, Robertson SM. Clinical efficacy of olopatadine hydrochloride ophthalmic solution 0.2% compared with placebo in patients with allergic conjunctivitis or rhinoconjunctivitis: a randomized, double-masked environmental study. *Clin Ther*. 2004 Aug;26(8):1237-48
40. Abelson MB, Gomes PJ, Vogelson CT, Pasquine TA, Turner FD, Wells DT, Robertson SM. Effects of a new formulation of olopatadine ophthalmic solution on nasal symptoms relative to placebo in two studies involving subjects with allergic conjunctivitis or rhinoconjunctivitis. *Curr Med Res Opin*. 2005 May;21(5):683-91
41. Abelson MB, Spangler DL, Epstein AB, Mah FS, Crampton HJ. 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 Dec;32(12):1017-22
42. 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 Jan 13;5:87-93
43. 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 Mar;27(3):623-31
44. 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 Feb 8;5:77-84
45. Mahvan TD, Buckley WA, Homecker JR. Alcaftadine for the prevention of itching associated with allergic conjunctivitis. *Ann Pharmacother*. 2012 Jul-Aug;46(7-8):1025-32
46. Ackerman S, D'Ambrosio F Jr, Greiner JV, Villanueva L, Ciolino JB, Hollander DA. 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 Apr 8;6:43-52
47. Fukushima A, Ebihara N. Efficacy of olopatadine versus epinastine for treating allergic conjunctivitis caused by Japanese cedar pollen: a double-blind randomized controlled trial. *Adv Ther*. 2014 Oct;31(10):1045-58.
48. McLaurin EB, Marsico NP, Ackerman SL, Ciolino JB, Williams JM, Villanueva L, Hollander DA. Ocular itch relief with alcaftadine 0.25% versus olopatadine 0.2% in allergic conjunctivitis: pooled analysis of two multicenter randomized clinical trials. *Adv Ther*. 2014 Oct;31(10):1059-71
49. Ciolino JB, McLaurin EB, Marsico NP, Ackerman SL, Williams JM, Villanueva L, Hollander DA. Effect of alcaftadine 0.25% on ocular itch associated with seasonal or perennial allergic conjunctivitis: a pooled analysis of two multicenter randomized clinical trials. *Clin Ophthalmol*. 2015 May 2;9:765-72
50. Chigbu DI, Coyne AM. Update and clinical utility of alcaftadine ophthalmic solution 0.25% in the treatment of allergic conjunctivitis. *Clin Ophthalmol*. 2015 Jul 8;9:1215-25
51. Mizoguchi T, Ozaki M, Ogino N. Efficacy of 0.05% epinastine and 0.1% olopatadine for allergic conjunctivitis as seasonal and preseasonal treatment. *Clin Ophthalmol*. 2017 Sep 27;11:1747-1753
52. Nakatani H, Gomes P, Bradford R, Guo Q, Safyan E, Hollander DA. Alcaftadine 0.25% versus Olopatadine 0.1% in Preventing Cedar Pollen Allergic Conjunctivitis in Japan: A Randomized Study. *Ocul Immunol Inflamm*. 2019;27(4):622-631
53. Dudeja L, Janakiraman A, Dudeja I, Sane K, Babu M. Observer-masked trial comparing efficacy of topical olopatadine (0.1%), bepotastine (1.5%), and alcaftadine (0.25%) in mild to moderate allergic conjunctivitis. *Indian J Ophthalmol*. 2019 Sep;67(9):1400-1404
54. Çavdarlı C, Topcu Yılmaz P. Pupil Diameter, Corneal Thickness, and Anterior Chamber Alterations Following Topical Olopatadine Hydrochloride 0.1%: A Single-Masked Randomized Controlled Clinical Study. *J Ocul Pharmacol Ther*. 2020 Sep;36(7):540-544

55. Ayyappanavar S, Sridhar S, Kumar K, Jayanthi CR, Gangasagara SB, Rathod BLS, Preethi B, Mittal P. Comparative analysis of safety and efficacy of Alcaftadine 0.25%, Olopatadine hydrochloride 0.2% and Bepotastinebesilate 1.5% in allergic conjunctivitis. *Indian J Ophthalmol.* 2021 Feb;69(2):257-261
56. Fujishima H, Hasunuma T, Kawakita T, Sekiya T, Gomes P, Hollander DA. Efficacy of Alcaftadine 0.25% (AGN-229666) for Once-daily Prevention of Cedar-Pollen Allergic Conjunctivitis: A Phase 3 Randomized Study. *OculImmunolInflamm.* 2021 Nov 17;29(7-8):1621-1626.
57. Dr Sanjeev Kumar, Dr Kanhaiya Lal Agarwal. In allergic conjunctivitis, a comparison of the safety and effectiveness of Alcaftadine 0.25%, Olopatadine hydrochloride 0.2% and Bepotastinebesilate 1.5%. *European Journal of Molecular and Clinical Medicine (EJMCM)* 2020; &(10):44-63
58. Donshik PC, Pearlman D, Pinnas J, Raizman MB, Tauber J, Tinkelman D, et al. Efficacy and safety of ketorolac tromethamine 0.5% and levocabastine 0.05%: A multicenter comparison in patients with seasonal allergic conjunctivitis. *AdvTher.* 2000;17:94–102