PharmacologyOnLine

Archives • 2021 • vol.3 • 892-901

# A REVIEW ON THE RISING ROLE OF DUAL-ACTING AGENTS IN THE MANAGEMENT OF ALLERGIC CONJUNCTIVITIS

Kothai Ramalingam*, Angela Moncy John, Anita V Reji, Anitha Benny, Arul Balasubramanian

*Department of Pharmacy Practice, Vinayaka Mission's College of Pharmacy, Vinayaka Mission's Research Foundation (Deemed to be University), Salem – 636008, Tamil Nadu, India.*
*kothaiarul@yahoo.co.in

**Abstract**

Community-acquired In this review, we examine the existing evidence that pertains to the use of dual-action agents in the symptomatic management of allergic conjunctivitis. Allergic conjunctivitis is an allergic condition of the eye that usually presents with itching, redness, swelling of eyelids, tearing, and ocular discharge. The data used to collate this review were obtained from various peer-reviewed journal articles on the dual-action drugs and their role in managing allergic conjunctivitis, PubMed using relevant MeSH terms, and also in Scopus and Google Scholar using relevant keywords All the dual-acting agents and their rising role of in the management of allergic conjunctivitis were examined and included. Opinions from practicing ophthalmologists were also incorporated in writing the review. On assessing the available literature on the various treatment strategies, the use and recommendation of dual-action agents are more frequent and effective for managing the symptoms of Allergic conjunctivitis. Dual Action Agents are recommended more as they are superior in ameliorating the ocular symptoms associate with AC rapidly and their actions persist for a longer duration. From this review, it was established that the use of dual-action agents such as olopatadine, Bepotastine Besilate, and Alcaftadine are on the rise as they provide rapid relief from ocular symptoms. Various treatment strategies are also discussed in view of identifying the popularity of Dual Acting Agents.

Key words: Allergic conjunctivitis, Mast cell stabilizers, Antihistamine, Dual action agents

## Introduction

Ocular allergy is a common immunological phenomenon that affects the majority of the population.[1] These allergic reactions can be triggered by various pollutants such as dust, smoke, and environmental agents such as pollen grass, and animal dander.[2] As a result of the interaction of such allergens with the surface of the eyes, the natural immune systems flare-up to expel the irritant as a result the following symptoms are produced: itching, redness, discharge, tearing, foreign body sensation, swollen eyelids, and corneal staining.[3] However, all of these symptoms are non-life threatening and most of them resolve when the allergen is removed from the surface of the eye. Only in some cases, these symptoms tend to persist which needs medical attention as they may affect the daily activities of the affected individuals. Most reported cases of Allergic conjunctivitis (AC) are children since they are easily noticed by the parents/caretakers. When the need for medical attention arises, the management strategies depend upon the nature and severity of the ocular symptom. In the last two decades, various therapeutic agents such as antihistamines, mast cell stabilizers, ophthalmic corticosteroids, vasoconstrictors, immuno-modulators, and dual-action agents have been introduced to manage the various symptoms of allergic conjunctivitis.[4] Of all the categories mentioned above the current trends in the management of AC revolve around the use of dual activity (Antihistamine-Mast cell stabilizing) agents as they block the H1 receptors and also prevent the further release of histamine molecules from mast cells.[5] Also, most of the drugs approved by the FDA are highly safe and effective, and they provide quick and rapid relief from symptoms and maintain their effects for a longer duration. So, these agents have found a stable and significant place in the management strategies of various types of allergic conjunctivitis.[6]

## Allergic conjunctivitis

Neonates Conjunctiva is a mucous membrane that is immunologically active and consists of epithelial and subepithelial layers. These layers encompass goblet cells, blood vessels, immune cells, non-immune cells, and Langerhans cells.[7] Allergic reactions that affect the ocular surface can be either T cell-mediated or IgE-mediated. The conjunctiva and cornea come in contact with various environmental allergens as it being the most external part of the eye.[8] There are no mast cells in normal conjunctiva, the mast cells along with other inflammatory agents reside below the superficial portion of the substantia propria. Allergic conjunctivitis, which is an inflammation of the conjunctiva caused predominantly by IgE mediated allergic reaction to external allergens which will thereby increase the tear and mast cell production in the conjunctiva.[9]

The prevalence and incidence of conjunctivitis vary according to the underlying cause, which may be influenced by the patient's age, as well as the season of the year.[10] Currently around, 40% of the global population is suffering from allergic conjunctivitis. Exposure to particulate matter less than 2.5 µm can lead to allergic reactions.[11] In India, about 25% of the population is affected by allergic conjunctivitis mainly due to the pollution in the country.[12]

### *Types of allergic conjunctivitis*

Allergic conjunctivitis is a syndrome affecting the entire ocular surface, including conjunctiva, lids, cornea, and tear film.[13] AC is instigated by the contribution of numerous factors, including genetics, air pollution in urban areas, pets, and early childhood exposure.[14] Allergic conjunctivitis can either be acute or chronic based on the periodicity or chronicity of the symptoms. The types include

- Seasonal allergic conjunctivitis (SAC)
- Perennial allergic conjunctivitis (PAC)
- Vernal keratoconjunctivitis (VKC)
- Atopic keratoconjunctivitis (AKC)
- Phlycentular keratoconjunctivitis (PKC)
- Giant papillary conjunctivitis (GPC)
- Contact or drug-induced dermatoconjunctivitis (CDC)

## Seasonal and perennial allergic conjunctivitis

Typical agents such as *Streptococcus pneumonia,*

*Haemophilus influenza, Moraxella catarrhalis, Staphylococcus aureus, Group A Streptococci, anaerobes, and gram-negative organism*

## Seasonal and perennial allergic conjunctivitis

Seasonal and perennial allergic conjunctivitis is the most common and the mildest form of ocular allergy Seasonal allergic conjunctivitis symptoms are usually prompted by transitory allergens such as tree or grass or flower pollens. Perennial allergic conjunctivitis symptoms are instigated by indoor allergens such as house dust mites, animal dander, mold spores, cockroach, or rodents.[15]

This leads to itching, tearing, watery discharge, foreign body sensation, redness, lid edema, and burning. In the majority of patients, the foreign body sensation and burning symptoms will manifest due to instability in the tear film, which is caused by Eosinophilic activation and concomitant release of inflammatory mediators.[16]

These forms of acute allergic conjunctivitis affect about 15 – 20% of the population as the smaller allergens have the potential to cause more symptoms since they can become more easily unstable.[17]

## Vernal keratoconjunctivitis (VKC) and Giant papillary conjunctivitis (GPC)

Vernal keratoconjunctivitis is a chronic inflammatory form of allergic conjunctivitis that usually affects young people living in a dry, warm climate. VKC is bilateral and characterized by seasonal or perennial symptoms that exacerbate with recurrences in 60% during spring. During aggravations, intense itching is the predominant feature, followed by photophobia, tearing, and sticky mucus discharge.[18] Vernal keratoconjunctivitis is primarily mediated by Th2 lymphocyte with over-expression of mast cells, eosinophils, neutrophils, Th2-derived cytokines, chemokines, adhesion molecules, growth factors, fibroblast, and lymphocytes. VKC can present in any of the three clinical forms: Palpebral, bulbar, and mixed. The main characteristic sign of VKC is giant papillae on the upper tarsal conjunctiva which is caused due to the involvement of IL4, IL13, and the proliferation of conjunctival fibroblasts.[19] GPC occurs mainly as a result of repetitive microtrauma caused in contact lens users.

The symptoms are usually severe like itching which can be debilitating and severe photophobia tenacious mucous discharge and lacrimation which contain high levels of IgE, mast cell mediators Histamine, leukotrienes, prostaglandins, and kinase.[20]

## Immunopathological mechanism of allergic conjunctivitis

The visual mucosa having a large surface area, thereby provides the most comprehensible sites permitting direct antigen deposition which leads to the initiation of the two phases of the allergic cascade.

AC is the only ocular disease to involve exclusively a type I allergic reaction. Th2 cells will release pro-inflammatory cytokines which include IL-3, IL-4, IL-5, IL-13 that will eventually stimulate the B cells to produce immunoglobulin E (IgE) in sensitized individuals.

The IgE become membrane-bound to mast cells and cross-link with their particular allergens which will trigger mast cell degranulation and in turn releases histamine, tryptase, and newly formed mediators like leukotrienes and prostaglandins.

There are mainly two phases to the immunopathological mechanism of allergic conjunctivitis: the early phase and late phase.[21] **The early phase** of the cascade begins within seconds to minutes after exposure to the allergens and will clinically last for about 20–30 minutes. The mast cell will release mediators during this early phase which will lead to symptoms such as pruritus, tearing, redness, itching, chemosis, papillary reaction, and watery discharge.[22]

**The late phase** of the allergic cascade begins within a few hours and one of the characteristic features of the late phase is the epithelial infiltration of inflammatory cells like neutrophils, lymphocytes, basophils, and eosinophils, which will lead to inflammation, persistent and severe symptoms, and increased possibility of tissue injury. As the reaction advances, hypersecretion of tears increases drainage through the lacrimal ducts carrying allergens directly into the nasal passage, which triggers allergic rhinitis.[23]

## Current management strategies for allergic conjunctivitis

The main aim in the management of various symptoms of allergic conjunctivitis is to reduce or to stop the allergic cascade through allergen avoidance, pharmacotherapy, immunotherapy, and patient education. Allergen avoidance is the obvious way to curb the inflammatory cascade that triggers the symptoms of AC, but the conjunctiva and cornea are widely exposed to the environment which proves to be a difficult challenge in avoiding allergens.[24] However, strategies to subside allergen exposure include removing furry pets, carpets, and other dust-filled substances from the living environment.[25] Using HEPA filters to remove airborne allergens which could trigger an allergic reaction from the office and home, is recommended for susceptible patients. Wearing protective clothing and accessories such as sunglasses and keeping vehicle windows closed while traveling to prevent allergen contact is advised.[26] Another useful method is administering OTC lubricating drops which will help boost the ocular defense mechanisms by expelling the allergens and relieving mild ocular symptoms. Allergen avoidance can only help the patient to prevent the onset of allergic reactions.[27] When the patients start showing symptoms the treatment strategy must also change depending on the severity of the symptoms and the various therapeutic options are shown in Figure 1.

## Pharmacologic approach

Various pharmacotherapeutic agents such as topical ocular decongestants, topical NSAIDs, corticosteroids, antihistamines (oral and topical), mast cell stabilizers, and the newly emerging dual-acting agents (antihistamine-mast cell stabilizers) can be used to suppress the exacerbation of allergic symptoms.[28]

Topical ocular decongestants (phenylephrine, naphazoline, tetrahydrolazine, and oxymetazoline) are adrenergic agonists that reduce redness by constricting the ocular blood vessels.[29] However, these agents are not recommended in the management of allergic conjunctivitis as they do not affect the conjunctival response to allergens thereby has no impact on itching. So topical ocular decongestants are generally used only when the patient has severe redness and no itching.

Antihistamines are the most vital part of pharmacologic agents used in managing AC symptoms. Antihistamines primarily act by inhibiting the inflammatory actions of the neurotransmitter Histamine by blocking its interaction with the H1 receptor.[30] They act as inverse receptor agonists which block the physiologic effects of histamine molecules which are yet to bind with H1 receptors thereby reducing pruritis, capillary dilation, mucosal decongestion, and other symptoms mediated by histamine.[31] Topical antihistamines (Pheniramine, antazoline, and Bepotastine Besilate) are widely preferred in managing ocular allergic symptoms because of their rapid onset of action eliciting quicker relief from itching and other symptoms.[32] Oral antihistamines (cetirizine, levocetirizine, loratadine, and desloratadine) are used less commonly as they take a longer time to act due to delayed systemic absorption as they are best used adjunctively.[33] Another major undesirable effect of oral antihistamines is they bind to receptors in unaffected tissues causing unwanted sedation, dry mouth, dry eye, and tachycardia. This is one of the greatest concerns of first-generation antihistamines. However, topical antihistamines generally do not contribute to such side effects as they do not interact with cholinergic receptors which makes them the better choice compared to oral antihistamines.

The only approved topical NSAID for treating seasonal-AC is Ketorolac tromethamine which was found serendipitously while using it in preoperative cataract care.[34]

Topical Mast cell stabilizers prevent type I hypersensitivity associated degranulation by stabilizing the mast cell membrane and thereby moderates the influx of several inflammatory cells including eosinophils, monocytes, and neutrophils.[35] Mast cell stabilizers are indicated for itching and tearing associated with allergic conjunctivitis. But since the mast-cell stabilizers take a longer time to produce the desired effects, they are rarely used in the treatment of allergic conjunctivitis. Some topical Mast-cell stabilizers (single-acting) include Pemirolast and Nedocromil which are indicated for acute allergic conjunctivitis,

whereas Cromolyn sodium and Lodoxamide are specified for chronic allergic conjunctivitis.[36] Topical ophthalmic steroids help in hindering both the early and late phases of the allergic cascade by inhibiting cell-mediated immune responses, suppressing mast cell proliferation, and obstructing the production of inflammatory chemical mediators, such as prostaglandins, leukotrienes, and platelet-activating agents. Because of their broad spectrum of activity topical steroids can be indicated for various signs and symptoms associated with allergic conjunctivitis. Steroids, in general, produce various side effects, as a result, an ester-based steroid was introduced by altering their chemical structure. Loteprednol etabonate, an ester-based steroid has a unique pharmacokinetic property that causes rapid metabolization of unbound drugs thereby reducing the risk of side effects associate with steroids (Ketone group).[37]

### Topical dual-action agents

Dual-acting antihistamine/mast cell stabilizers being the most recently developed class of agents is clinically superior in relieving both signs and symptoms associated with allergic conjunctivitis. These dual-acting agents have the combined mechanism of antihistamines and mast cell stabilizers.[28] This aids in providing the benefits of immediate relief by antihistamine and prophylactic action of mast cell stabilizers along with the inhibition of inflammatory mediators, including IL-5, PAF.[35] Anti-histamines acts by blocking the histamine receptors on blood vessels and nerves thereby helps in reducing itching and vasodilation associated with allergic conjunctivitis. Mast cell stabilizers abridge the allergic cascade by inhibiting degranulation of mast cells, inflammatory mediators, and histamine release as a result of the immune response.

Topical dual-acting agents enable the rapid onset of action by selectively inhibiting the H1 receptors and by averting the release of inflammatory mediators by mast cells. This selective inhibition of H1 receptors helps in subsiding the adverse events (lethargy, dryness) caused by other therapeutic non-selective receptor binding agents.[38] Various clinical studies have shown that dual-acting agents can be used in the treatment of allergic conjunctivitis as they effectively help in reducing itching, redness and have shown better tolerability than single-acting antihistamines. This clinical superiority of dual activity agents has made them the primary choice of treatment for AC.

The need for dual-acting agents is significant, given that the single-action agents (mast-cell stabilizers, antihistamines) lack immediate response and can cause many adverse events as they are non-selective. This in due course will cause inadequate treatment and also less patient compliance. Some of the topical dual-action agents that have been approved for therapeutic usage include ketotifen, azelastine, Epinastine, olopatadine, Bepotastine Besilate, and Alcaftadine.[21]

Olopatadine was first introduced in the late 1990s and has both H1receptor inhibiting and mast cell stabilizing property and was the first topical dual-action agent that has been approved for use. ketotifen, azelastine, Epinastine, and Bepotastine Besilate are administrated two-three times daily, whereas olopatadine and Alcaftadine are administered once daily which could be better for higher patient compliance.[39] Olopatadine inhibits histamine-dependent cytokine production along with H1 receptor blocking, this effect contributes to its improved action and makes them more effective than other antihistamines.[40]

Several studies and trials have proved that a single drop of olopatadine is much effective than a two-week course of Nedocromil (Mast-cell stabilizer). olopatadine has more patient compliance and efficacy than compared with other dual-action agents.[41]

#### *Bepotastine Besilate 1.5%*

Bepotastine Besilate 1.5% was approved by the FDA for the management of allergic conjunctivitis in the year 2009.[42] This drug targets multiple sites in early and later phases of the immunopathologic mechanisms involved in the development of various symptoms of AC.[42] Apart from managing itching in AC this drug also exhibits the potential to treat allergic rhinitis associate with AC. This drug elicits relief from the itching by blocking histamine receptors and also stabilizes the mast cells to prevent the further release of histamine. Bepotastine also inhibits the synthesis and

production of leukotrienes, platelet-activating factor (PAF), and IL-5 and also reduces the recruitment of eosinophils to the site of inflammation.[43] In multiple clinical trials, Bepotastine Besilate has shown a significant reduction of itching rapidly and maintaining it for a longer duration. Bepotastine is used to treat mild to severe symptoms of AC by administering the ophthalmic solution two to three times per day.[44] The various advantages of the dual-acting agent Bepotastine Besilate are its highly selective for H1 receptors, safety and efficacy is high, rapid onset of action, and long duration of drug effect.

Various clinical practice guidelines have been suggested in managing AC that promote the advantages of dual-action agents.

***American Optometric Association*** [45]

1. Dual-acting agents Antihistamine-Mast cell Stabilizers can be used to treat AC effectively.
2. Olopatadine may be more effective than other mast cell stabilizer agents
3. Olopatadine may be more effective than ketotifen in relieving itchiness and redness

***American Academy of Ophthalmology*** [45]

1. OTC products such as ketotifen or other vasoconstrictor agents or more effective legend AH/MCS agents can be used to treat mild allergic conjunctivitis.
2. Both acute and chronic allergic conjunctivitis can be effectively managed with Dual-action agents.

**Immunotherapy**

The use of immunomodulating agents such as calcineurin inhibitors has also found its place in the management of chronic forms of allergic conjunctivitis. These drugs provide comparable therapeutic efficacy without the side effects associated with the use of corticosteroids. Cyclosporine is a calcineurin inhibitor that suppresses the IL 2 induced TH2 cell proliferation and also inhibits the release of histamine from mast cells which consecutively suppresses the conjunctival inflammation.[46] Tacrolimus is another highly effective immunomodulator that also belongs to the class of calcineurin inhibitors which can be used in the management of chronic forms of allergic conjunctivitis.

Recombinant humanized monoclonal antibodies such as omalizumab are also used for treating allergic rhinoconjunctivitis.[47] These agents bind to the Fc portion of IgE which makes it scarce and thus preventing its immunologic mechanisms that induce inflammation. Some studies have also shown that allergen-specific immunotherapy reduces the symptomatic expression and prevents reoccurrences of ocular allergic diseases, especially for perennial allergic conjunctivitis.

**An algorithm in the management of allergic conjunctivitis**

Choosing the right therapeutic agent to manage AC can ameliorate the symptoms rapidly and provide better relief. Various clinical practice guidelines make it easy for ophthalmologists to choose the appropriate agent by providing a framework of evidence-based guidelines. The first step in managing AC is assessing the patient's symptoms and their severity.[48] The severity of ocular symptoms can be examined and categorized as mild, moderate, and severe. Severe itching and redness in the affected eye of the patient should lead the clinician to consider the possibility of a severe allergic condition. In addition to assessing ocular symptoms, the clinician must also examine the patient for non-ocular symptoms including rhinorrhea, sneezing, coughing, wheezing, and nasal congestion.[49]

After assessing the severity of the symptoms, the patients can be managed with the following strategies. Patients with mild and intermittent itching can be advised to use nonpharmaceutical measures such as lubricating ophthalmic drops and cold compression. Some OTC dual-action medication such as Bepotastine Besilate 1.5% may also be recommended. In patients with mild to severe itching, the use of dual-action agents such as Bepotastine Besilate or olopatadine is highly recommended. For patients with severe itching and redness, topical steroids such as loteprednol etabonate ophthalmic suspension 0.2% should be

recommended with other dual-action agents such as Bepotastine and olopatadine. All the patients must be asked to return for follow-ups after 10 to 14 days to assess the improvement of allergic ocular symptoms.

## Conclusion

In event that the symptoms of allergic conjunctivitis require medical attention, various therapeutic agents can be used to manage them. The star category of agents among the existing drugs are the Dual action agents as they employ two distinct mechanisms (antihistamine and Mast cell stabilization) that effectively ameliorate the various ocular allergic symptoms. Among the available dual-action agents, olopatadine and Bepotastine Besilate are two of the finest drugs that can be used in managing symptoms for mild to severe stages of the condition. Provided these drugs help the therapy achieve maximum patient compliance and medication adherence as they don't need to be administered more frequently.

## Acknowledgments

The authors are thankful to the authorities of Vinayaka Mission's Research Foundation (Deemed to be University), Salem for providing the facilities for carrying out this research.

## References

1. Mashige KP. Ocular allergy. Heal SA Gesondheid 2017;22:112–22.
2. La Rosa M, Lionetti E, Reibaldi M, Russo A, Longo A, Leonardi S, et al. Allergic conjunctivitis: a comprehensive review of the literature. Ital J Pediatr 2013;39:18.
3. James IG V, Campbell LM, Harrison JM, Fell PJ, Ellers-Lenz B, Petzold U. Comparison of the efficacy and tolerability of topically administered azelastine, sodium cromoglycate, and placebo in the treatment of seasonal allergic conjunctivitis and rhino-conjunctivitis. Curr Med Res Opin 2003;19:313–20.
4. Ridolo E, Montagni M, Caminati M, Senna G, Incorvaia C, Canonica GW. Emerging drugs for allergic conjunctivitis. Expert Opin Emerg Drugs 2014;19:291–302.
5. Carr W, Schaeffer J, Donnenfeld E. Treating allergic conjunctivitis: A once-daily medication that provides 24-hour symptom relief. Allergy Rhinol (Providence) 2016;7:107–14.
6. Mishra GP, Tamboli V, Jwala J, Mitra AK. Recent patents and emerging therapeutics in the treatment of allergic conjunctivitis. Recent Pat Inflamm Allergy Drug Discov 2011;5:26–36.
7. Alfonso SA, Fawley JD, Alexa Lu X. Conjunctivitis. Prim Care 2015;42:325–45.
8. Leonardi A, Bogacka E, Fauquert JL, Kowalski ML, Groblewska A, Jedrzejczak-Czechowicz M, et al. Ocular allergy: recognizing and diagnosing hypersensitivity disorders of the ocular surface. Allergy 2012;67:1327–37.
9. Yanni JM, Barney NP. Chapter 11 - Ocular Allergy: Clinical, Therapeutic and Drug Discovery Considerations. In: Yorio T, Clark AF, Wax MBBT-OT, editors. London: Academic Press; 2008. p. 239–74.
10. Belfort R, Marbeck P, Hsu CC, Freitas D. Epidemiological study of 134 subjects with allergic conjunctivitis. Acta Ophthalmol Scand Suppl 2000;230:38–40.
11. Mimura T, Ichinose T, Yamagami S, Fujishima H, Kamei Y, Goto M, et al. Airborne particulate matter (PM2.5) and the prevalence of allergic conjunctivitis in Japan. Sci Total Environ 2014;487:493–9.
12. Leonardi A, Castegnaro A, Valerio ALG, Lazzarini D. Epidemiology of allergic conjunctivitis: clinical appearance and treatment patterns in a population-based study. Curr Opin Allergy Clin Immunol 2015;15:482–8.
13. Bielory L, Friedlaender MH. Allergic conjunctivitis. Immunol Allergy Clin North Am 2008;28:43–58, vi.
14. Leonardi S, Miraglia del Giudice M, La Rosa M, Bellanti JA. Atopic disease, immune system, and the environment. Allergy asthma Proc 2007;28:410–7.
15. Bonini S. Atopic keratoconjunctivitis. Allergy 2004;59:71–3.
16. Leonardi A. The central role of conjunctival mast cells in the pathogenesis of ocular allergy. Curr Allergy Asthma Rep 2002;2:325–31.

17. Wong AHC, Barg SSN, Leung AKC. Seasonal and perennial allergic conjunctivitis. Recent Pat Inflamm Allergy Drug Discov 2009;3:118–27.
18. Irani AM, Butrus SI, Tabbara KF, Schwartz LB. Human conjunctival mast cells: distribution of MCT and MCTC in vernal conjunctivitis and giant papillary conjunctivitis. J Allergy Clin Immunol 1990;86:34–40.
19. Bremond-Gignac D, Donadieu J, Leonardi A, Pouliquen P, Doan S, Chiambarretta F, et al. Prevalence of vernal keratoconjunctivitis: a rare disease? Br J Ophthalmol 2008;92:1097–102.
20. Kumar S. Vernal keratoconjunctivitis: a major review. Acta Ophthalmol 2009;87:133–47.
21. Dupuis P, Prokopich CL, Hynes A, Kim H. A contemporary look at allergic conjunctivitis. Allergy, Asthma Clin Immunol 2020;16:5.
22. Vadlapudi AD, Patel A, Cholkar K, Mitra AK. Recent Patents on Emerging Therapeutics for the Treatment of Glaucoma, Age Related Macular Degeneration and Uveitis. Recent Pat Biomed Eng 2012;5:83–101.
23. Leonardi A, De Dominicis C, Motterle L. Immunopathogenesis of ocular allergy: a schematic approach to different clinical entities. Curr Opin Allergy Clin Immunol 2007;7:429–35.
24. Portnoy J, Miller JD, Williams PB, Chew GL, Miller JD, Zaitoun F, et al. Environmental assessment and exposure control of dust mites: a practice parameter. Ann allergy, asthma Immunol Off Publ Am Coll Allergy, Asthma, Immunol 2013;111:465–507.
25. Mahakittikun V, Boitano JJ, Ninsanit P, Wangapai T, Ralukruedej K. Effects of high and low temperatures on development time and mortality of house dust mite eggs. Exp Appl Acarol 2011;55:339–47.
26. Jia-Ying L, Zhao C, Jia-Jun G, Zi-Jun G, Xiao L, Bao-Qing S. Efficacy of air purifier therapy in allergic rhiniti. Asian Pacific J allergy Immunol 2018;36:217–21.
27. Sánchez-Borges M, Fernandez-Caldas E, Thomas WR, Chapman MD, Lee BW, Caraballo L, et al. International consensus (ICON) on: clinical consequences of mite hypersensitivity, a global problem. World Allergy Organ J 2017;10:14.
28. Ben-Eli H, Solomon A. Topical antihistamines, mast cell stabilizers, and dual-action agents in ocular allergy: current trends. Curr Opin Allergy Clin Immunol 2018;18:411–6.
29. Hosten LO, Snyder C. Over-the-Counter Ocular Decongestants in the United States - Mechanisms of Action and Clinical Utility for Management of Ocular Redness. Clin Optom 2020 Jul 23;12:95–105.
30. Parsons ME, Ganellin CR. Histamine and its receptors. Br J Pharmacol 2006;147:S127–35.
31. Baroody FM, Naclerio RM. Antiallergic effects of H1-receptor antagonists. Allergy 2000;55 Suppl 6:17–27.
32. Castillo M, Scott NW, Mustafa MZ, Mustafa MS, Azuara-Blanco A. Topical antihistamines and mast cell stabilizers for treating seasonal and perennial allergic conjunctivitis. Cochrane database Syst Rev 2015;6:CD009566.
33. Purohit A, Melac M, Pauli G, Frossard N. Comparative activity of cetirizine and desloratadine on histamine-induced wheal-and-flare responses during 24 hours. Ann allergy, asthma Immunol Off Publ Am Coll Allergy, Asthma, Immunol 2004;92:635–40.
34. Ballas Z, Blumenthal M, Tinkelman DG, Kriz R, Rupp G. Clinical evaluation of ketorolac tromethamine 0.5% ophthalmic solution for the treatment of seasonal allergic conjunctivitis. Surv Ophthalmol 1993;38:141–8.
35. Cook EB, Stahl JL, Barney NP, Graziano FM. Mechanisms of antihistamines and mast cell stabilizers in ocular allergic inflammation. Curr Drug Targets Inflamm Allergy 2002;1:167–80.
36. Shulman DG. Two mast cell stabilizers, pemirolast potassium 0.1% and nedocromil sodium 2%, in the treatment of seasonal allergic conjunctivitis: a comparative study. Adv Ther 2003;20:31–40.
37. Druzgala P, Wu WM, Bodor N. Ocular absorption and distribution of loteprednol etabonate, a soft steroid, in rabbit eyes. Curr Eye Res 1991;10:933–7.
38. Mauser PJ, Kreutner W, Egan RW, Chapman

RW. Selective inhibition of peripheral histamine responses by loratadine and terfenadine. Eur J Pharmacol 1990;182:125–9.
39. Ackerman S, Smith LM, Gomes PJ. Ocular itch associated with allergic conjunctivitis: latest evidence and clinical management. Ther Adv Chronic Dis 2016;7:52–67.
40. Simons FER, Simons KJ. H1 antihistamines: current status and future directions. World Allergy Organ J 2008;1:145–55.
41. Uchio E. Treatment of allergic conjunctivitis with olopatadine hydrochloride eye drops. Clin Ophthalmol 2008;2:525–31.
42. Cavet ME, Gomes PJ, Carr WW, Williams JI. Bepotastine besilate ophthalmic solution 1.5% for alleviating nasal symptoms in patients with allergic conjunctivitis. J Asthma Allergy 2018;11:29–39.
43. Kida T, Fujii A, Sakai O, Iemura M, Atsumi I, Wada T, et al. Bepotastine besilate, a highly selective histamine H(1) receptor antagonist, suppresses vascular hyperpermeability and eosinophil recruitment in vitro and in vivo experimental allergic conjunctivitis models. Exp Eye Res 2010;91:85–91.
44. Carr WW, Nayak AS, Ratner PH, Gow JA, McNamara TR, Williams JI. Efficacy of bepotastine besilate ophthalmic solution 1.5% for seasonal allergic conjunctivitis: a randomized, placebo-controlled, natural exposure, clinical trial. Allergy asthma Proc 2013;34:247–54.
45. Varu DM, Rhee MK, Akpek EK, Amescua G, Farid M, Garcia-Ferrer FJ, et al. Conjunctivitis Preferred Practice Pattern®. Ophthalmology. 2019 Jan;126(1):P94–169.
46. Kari O, Saari KM. Updates in the treatment of ocular allergies. J Asthma Allergy 2010;3:149–58.
47. Bousquet J, Wahn U, Meltzer EO, Fox H, Hedgecock S, Thomas K, et al. Omalizumab: an anti-immunoglobulin E antibody for the treatment of allergic respiratory diseases. Eur Respir Rev 2008;17:1 LP – 9.
48. Bielory L, Meltzer EO, Nichols KK, Melton R, Thomas RK, Bartlett JD. An algorithm for the management of allergic conjunctivitis. Allergy asthma Proc 2013;34:408–20.
49. Mantelli F, Lambiase A, Bonini S. A simple and rapid diagnostic algorithm for the detection of ocular allergic diseases. Curr Opin Allergy Clin Immunol 2009;9:471–6.

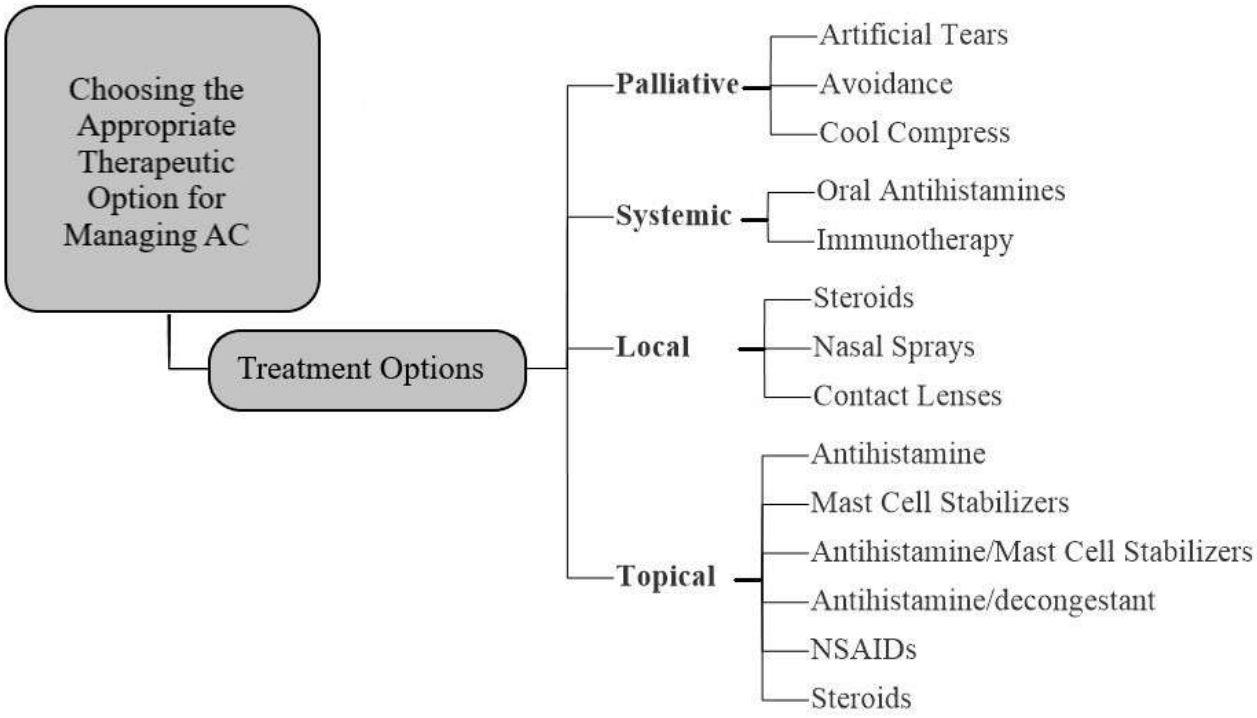


Fig 1: Appropriate therapeutic options for managing allergic conjunctivitis