doi.org/10.58931/cait.2023.3253

ABOUT THE AUTHOR

King Chow, MD, FRCSC

Dr. King Chow is a Royal College certified ophthalmologist with a special interest in medical and surgical management of ocular surface diseases. His practice also includes comprehensive ophthalmology, medical laser treatment of glaucoma and pterygium surgery. Dr. Chow completed an Honours Bachelor of Science degree in Human Behavioural Sciences at the University of Toronto. His undergraduate and postgraduate medical training was completed at the Schulich School of Medicine at Western University. He is a graduate of the residency program at Western University in London, Ontario. He is currently an Assistant Clinical Professor (Adjunct) in the Department of Surgery, McMaster University Waterloo Campus and a faculty member within the Department of Ophthalmology and Vision Sciences at the University of Toronto.

Affiliations:
Department of Surgery, McMaster University
Department of Ophthalmology and Vision Sciences, University of Toronto
Comprehensive Ophthalmology, Clarity Eye Institute
Mount Sinai Hospital, Toronto

TARGETED THERAPIES FOR ALLERGIC CONJUNCTIVITIS: AN OPHTHALMOLOGIST'S PERSPECTIVE

Introduction
Allergic eye disease is extremely common as the eye is sensitive to irritants due to its constant exposure to the external environment. Approximately 40% of the general population is affected by ocular allergies.[1] The majority of patients may also suffer with additional associated symptoms of allergic rhinitis, such as nasal congestion, sneeze, etc.; however, 6% may have isolated ocular symptoms.[2] In addition, there are links between ocular allergies and other allergic conditions such as asthma, food allergy and atopic dermatitis.[3] The challenge is that in addition to ocular symptoms, patients experience a substantial negative influence on their quality of life (QOL). The most common symptoms are watery and itchy eyes; redness; soreness; stinging; burning sensations; and swelling.[4] Unfortunately, as these symptoms are quite common, most patients may choose to self-medicate and many cases are undiagnosed or underdiagnosed. As a result of this, patients may not utilize the correct management strategy; this can lead to a further propagation of symptoms and a greater reduction in patients' QOL. Hence, it is crucial for patients to seek professional medical attention, while physicians must gather a comprehensive medical history and conduct relevant investigations. Additionally, the physician ought to propose the correct diagnosis and suitable treatment plan.

Anatomy of the Eye
Each component of the eye can have an impact on the patient's immune response **(Figure 1)**. The eyelids act as a barrier to allergens. The lacrimal gland and its components produce tears which help to lubricate

and protect the ocular surface. The concentration and quality of the tears is affected by any type of inflammatory response.[4] In addition, the conjunctiva and cornea are the external layers that come into contact with allergens. While there are no mast cells within these tissues, these will increase in the setting of an allergic response. The cornea is avascular, therefore it will not be directly involved; however, the influence of the patient's immune response can lead to ocular surface instability and result in blurry vision.[6] The sclera is the next layer under the conjunctiva and is composed primarily of collagen. The uvea is highly vascularized and produces aqueous humour; it is the site involved in uveitis. The retina and optic nerve complete the visual organ.

Allergic Eye Disease

There are numerous components in allergic eye disease, however, the most common consist of seasonal allergic conjunctivitis (SAC) and perennial allergic conjunctivitis (PAC), which can affect up to 15%-25% of the population. The differentiating factor between these two types of allergic eye disease is typically the periodicity or chronicity of the patient's symptoms. SAC is triggered by transitory allergens (e.g., tree pollen) while PAC is caused usually by indoor allergens (e.g., dust mites or dander).[6] Furthermore, allergic conjunctivitis (AC) can be classified as the following: atopic keratoconjunctivitis (AKC), vernal keratoconjunctivitis (VKC) and giant papillary conjunctivitis (GPC). The last entity relates primarily to physical friction as opposed to a true allergy. It can be associated with contact lens wear or other types of mechanical rubbing.

Mechanism of Disease

The immunopathophysiology of ocular allergies helps to determine their optimal treatment. Ocular allergies are mediated by both early and late phase reaction, triggered initially by allergens eliciting histamine release. This is followed by a cascade of proinflammatory mediators such as prostaglandins, leukotrienes and cytokines, with eventual eosinophil, neutrophil and macrophage involvement. All of these biochemical molecules contribute to the eventual signs and symptoms of the allergic response.[7]

Treatment Modalities

As mentioned above, in cases of allergic eye disease, the majority of patients self-diagnose and self-medicate with over-the-counter (OTC) products. Prior to this, some patients will simply use water to rinse and wash their eyes to attempt symptomatic relief. This is somewhat effective, as it does help to physically clear away allergens from the ocular surface and dilute them. Another method is allergen avoidance; however, this is sometimes difficult to achieve. Cool compresses offer temporary relief from vasoconstriction.

Antihistamines

Antihistamines are used to target a major factor in the allergic response and they are certainly one of the initial choices for treatment. Of note, clinicians must be aware of the impact of various histamine receptors and their effects. H1 and H4 receptors are primarily responsible for pruritus; H2 relates to vasodilation; and H3 receptors have an immunomodulatory effect as their release actually inhibits histamine release.[8]

A variety of topical applications are on the market, some of which are available on an OTC basis. For example, antazoline (Naphcon-A®) and pheniramine (Opcon-A®) can be easily sourced. They are helpful for the short-term relief of itchiness only and may require repeated instillations to achieve symptomatic relief. They are therefore best used in the acute or early phase of the allergic response.

In addition, oral antihistamines play a role in the treatment of the ocular response. This is due to the fact that ocular symptoms are typically accompanied by symptoms including rhinitis and sneezing, making a systemic approach helpful. In this context, the distinction between first and second generation antihistamines is noteworthy. Second generation antihistamines may be preferred due to their reduced sedative side effect profile resulting from their reduced ability to cross the blood-brain barrier.[9]

Mast cell stabilizers

These agents are best utilized on a prophylactic basis and require a loading period of several weeks prior to antigen exposure. This can lead to decreased compliance as patients do not experience the agents' maximal effect until a later time.[10] Examples of these agents are lodoxamine ([Pr]Alomide®) and sodium cromoglycate 2% ([Pr]Cromolyn®).

Dual-action topical agents

These agents offer the benefits of both antihistamines and mast cell degranulation inhibitors. Therefore, they are effective in the early phase (the antihistamine component) as well as the late phase (prophylactic mast cell stabilization) of allergic eye disease. As they can achieve good overall symptomatic relief, they are generally used as first line. There are few examples of medications in this category. One of these is olopatadine ([Pr]Patanol®) which has been used for many years with good success. It was the first dual-action agent available. In addition to its high H1 receptor affinity, it inhibits leukotriene release, adhesion molecules and cytokines.[9]

Bepotastine ([Pr]Bepreve®) is a relatively new medication, initially used orally for the treatment of allergic rhinitis, urticaria and other dermatological conditions.[11] When used topically, it has been shown to have relatively rapid onset , high affinity for the H1 receptor and a duration of up to 8 hours.[12]

Steroid eye drops

Steroid eye drops treat AC via multiple approaches: They reduce the inflammatory cytokine release, reduce mast cell proliferation and reduce the overall immune response. They are definitely the most effective agent for symptomatic relief; however, due to their potential side effects (e.g, possible increase in intraocular pressure (IOP) and potential for accelerated cataract formation) they are typically used for only a short period of time. Once symptoms have subsided, it is usually recommended that they be replaced with any of the non-steroid approaches mentioned above. In light of this, they are typically utilized in a pulsed fashion to reduce exacerbations. Ester-based steroids such as loteprednol etabonate ([Pr]Alrex® 0.2% or [Pr]Lotemax® 0.5%) are sometimes preferred as they are metabolized more efficiently and therefore produce fewer side effects than other agents.[13]

Stronger steroids, such as ketone-based prednisolone acetate 1% ([Pr]Pred Forte®), prednisolone phosphate 1% and dexamethasone 0.1% ([Pr]Maxidex®), can be used in more severe cases. Naturally, due to their stronger nature, they are also known to cause an increased incidence of side effects.

Topical immunomodulators

Topical immunomodulators are utilized in cases involving the cornea, specifically VKC and atopic keratoconjunctivitis (AKC). The most commonly-used agents are cyclosporine A and tacrolimus; their mechanism of action is T cell inactivation. Cyclosporin A 0.05% ([Pr]Restasis®) has been indicated for dry eye disease (DED) and has traditionally been used in the setting of AC as a steroid-preserving method. However, recently, cyclosporin A 0.1% ([Pr]Verkazia®) has been approved by Health Canada for the treatment of VKC in a pediatric setting (age 4 to adolescence). Cyclosporin A 0.1% contains a unique formulation in which a cationic nanoemulsion is utilized to deliver the cyclosporine onto the corneal surface. As the emulsion is positively charged, the product remains on the negatively charged corneal surface for an extended duration, allowing for improved exposure and more rapid spread of the medicine.[14] Currently available ophthalmic agents for the treatment of AC are described in **Table 1**.

Conclusion

Evolving research within the field of AC has yielded, and will continue to yield, novel and more effective modes of treatment with the objective of optimizing symptomatic relief and reducing potential side effects. In addition to improved efficacy, innovative drug delivery mechanisms will certainly lead the way toward this.

Corresponding Author:
Dr. King Chow
Email: kyc2008@gmail.com

Financial Disclosures:
Speaking Fees & Advisory Boards: Allergan/ Abbvie, Alcon, Aequus Pharma, Bausch & Lomb, Johnson & Johnson Vision, Laboratoires Théa, Santen, Shire/Novartis, SUN Pharma

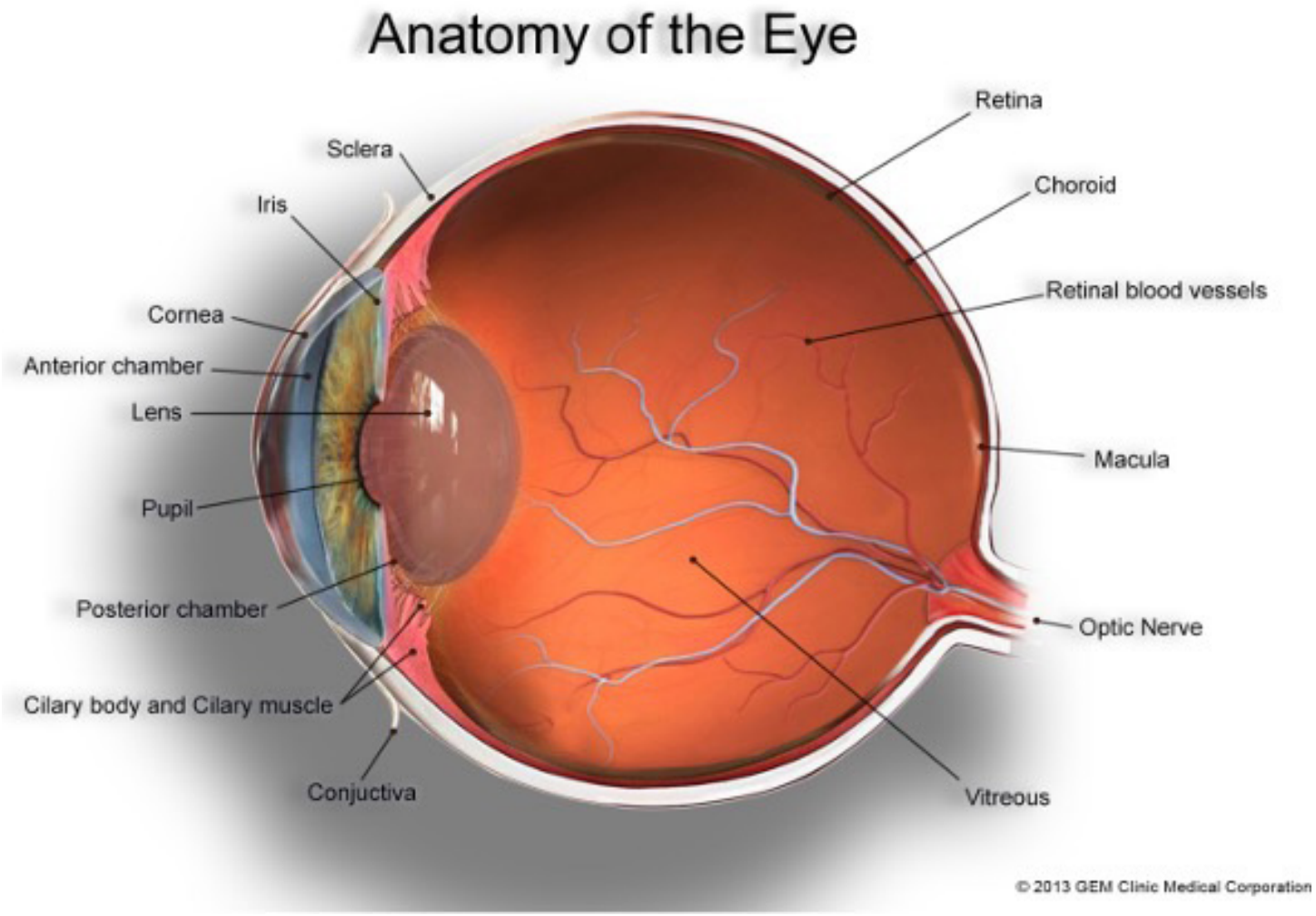

Figure 1: *Anatomy of the Eye.*

Agent (Brand name)	OTC vs. Rx	Dosing
Topical antihistamines	OTC	QID
Antazoline (Naphcon-A)	OTC	QID
Pheniramine (Opcon-A)		
Mast cell stabilizers	Rx	QID
Lodoxamide (Alomide)	Rx	QID
Cromolyn sodium 2%		
Dual activity	Rx	BID
Olopatadine 0.1% (Patanol)	Rx	QD
Olopatadine 0.2% (Pataday)	Rx	QD
Olopatadine 0.7% (Pazeo)	Rx	BID
Ketotifen 0.025% (Zatidor)	Rx	BID
Bepotastine besilate 1.5% (Bepreve)		
Steroids	Rx	BID to QID
Loteprednol etabonate 0.2% (Alrex)	Rx	BID to QID
Loteprednol etabonate 0.5% (Lotemax)	Rx	QD to QID
Fluorometholone acetate 0.1% (FML)	Rx	QD to QID
Prednisolone actetate 1.0% (Pred Forte)	Rx	QD to QID
Dexamethasone 0.1% (Maxidex)		
Topical immunomodulators	Rx	BID
Cyclosporine 0.05% (Restasis)	Rx	QID
Cyclosporine 0.1% (Verkazia)		
Non-medicated	OTC	QD to QID
Soothe allergy + dry eye (0.24% hyaluronic acid and 2% ectoine)	OTC	QD to QID
HYLO-DUAL (0.5 mg/mL hyaluronic acid and 20 mg/mL ectoine)	OTC	QD to QID
HYLO-DUAL Intense (2.0 mg/mL hyaluronic acid and 20 mg/mL ectoine)	OTC	TID to QID
Zaspray (4.5% Per-Lip complex and 0.2% hyaluronic acid)		

Table 1: *Ophthalmic agents for the treatment of AC; courtesy of King Chow, MD, FRCSC*

References

1. *Committee on Infectious Diseases. Influenza immunization for all health care personnel: keep it mandatory. Pediatrics. 2015;136(4):809-818.*
2. *Singh K, Axelrod S, Bielory L. The epidemiology of ocular and nasal allergy in the United States, 1988-1994. Journal of Allergy and Clinical Immunology. 2010;126(4):778-783.*
3. *Gradman J, Wolthers OD. Allergic conjunctivitis in children with asthma, rhinitis and eczema in a secondary outpatient clinic. Pediatric Allergy and Immunology. 2006;17(7):524-526.*
4. *Berta A, Higazy MT, Petricek I, Prost ME, Németh J. Red Eye: Differential diagnosis and management. Debrecen (HU): External Eye Disease Working Group; 2007.*
5. *Beuerman R, Mircheff A, Pflugfelder S, Stern M. The lacrimal functional unit. In: Plfugfelder S, Beuerman R, Stern M, eds. Dry eye and ocular surface disorders. New York (NY): Marcel Dekker; 2004. p. 11-39.*
6. *Barney NP, Cook EB, Stahl JL. Allergic and immunologic diseases of the eye. In: Middleton's Allergy. Philadelphia (PA): WB Saunders; 2014. p. 618-637.*
7. *Ackerman S, Smith LM, Gomes PJ. Ocular itch associated with allergic conjunctivitis: latest evidence and clinical management. Ther Adv Chronic Dis. 2016;7(1):52-67.*
8. *Kimchi N, Bielory L. The allergic eye: recommendations about pharmacotherapy and recent therapeutic agents. Curr Op Allergy Clin Immunol. 2020;20(4):414-420.*
9. – *Bielory L, Delgado L, Katelaris CH, Leonardi A, Rosario N, Vichyanoud P. ICON: diagnosis and management of allergic conjunctivitis. Annals of Allergy, Asthma & Immunology. 2020;124(2):118-134.*
10. – *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 Proceedings. 2013 May;34(3).*
11. *Williams JI, Kennedy KS, Gow JA, Torkildsen GL, Abelson MB, Gomes PJ, McNamara TR; Bepotastine Besilate Ophthalmic Solutions Study Group. Prolonged effectiveness of bepotastine besilate ophthalmic solution for the treatment of ocular symptoms of allergic conjunctivitis. J Ocul Pharmacol Ther. 2011;27(4):385-393.*
12. *Macejko TT, Bergmann MT, Williams JI, Gow JA, Gomes PJ, McNamara TR; Bepotastine Besilate Ophthalmic Solutions Clinical Study Group. Multicenter clinical evaluation of bepotastine besilate ophthalmic solutions 1.0% and 1.5% to treat allergic conjunctivitis. Am J Ophthalmol. 2010;150(1):122-127.*
13. *Ilyas H, Slonim CB, Braswell, GR, Favetta JR, Schulman M. Long-term safety of loteprednol etabonate 0.2% in the treatment of seasonal and perennial allergic conjunctivitis. Eye & Contact Lens. 2004;30(1):10-13.*
14. *Leonardi A, Doan S, Aragona P, Amrane M, Ismail D, Montero J, Bremond-Gignac D. Topical cyclosporin A cationic ophthalmic emulsion in paediatric vernal keratoconjunctivitis: pooled analysis of randomised NOVATIVE and VEKTIS trails. Eye (Lond). 2023 Aug;37(11):2320-2326.*