

Allergic inflammation of the anterior surface of the eye

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ABSTRACT

Background: Ocular allergies affect an estimated 40% of the population, 98% of which are because of allergic conjunctivitis and includes tear film dysfunction. With the current advent of both repurposed drugs for ocular allergies, as well as novel drugs, lubricants and methods of administration, there is a need to update new treatments to optimize the care of ocular allergy patients.

Methods: An overview of mediators, clinical characteristics and management is provided in a summary format.

Results: Lubricants (best when refrigerated provide immediate relief that is short lived (several minutes) due to its dilutional effect on mediators and pollen in the tear film. Immediate and longer-term benefit occurs from different topical and oral medications – primarily histamine receptor agonists.

Conclusion: The newest prescription topical ophthalmic histamine H1 receptor antagonist (an inverse agonist) to be approved by the U.S. Food and Drug Administration in the past 10 years (U.S. NDA approved May 30, 2017) is cetirizine ophthalmic solution for the treatment of ocular itching with allergic conjunctivitis in adults and in children more than 2 years old.

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QUESTION

What are the best targeted treatments for ocular allergy, short and long term?

INTRODUCTION

Ocular allergy is a common immunologic inflammatory process of the anterior surface of the eye. It has been identified as one of the unmet needs associated with the diagnosis and management of the spectrum of allergic disorders that has gathered increased attention. Ocular allergy as a form of ocular anterior surface disease that includes tear film dysfunction (dry eye disorders) is reported to affect up to 20% of the U.S. population in the allergic rhinitis literature and up to 40% when examined in an ophthalmologic survey and, as with other allergic conditions, seems to be increasing that has significant impact on quality of life as well as being an economic burden.¹

Allergic eye disease represents one of the most common ocular conditions as it commonly in combination with rhinitis and is at times more pronounced than nasal and will

increase as the global incidence of allergy increase.² Ocular allergy symptoms can become severely debilitating, with the development of intense ocular pruritus, tearing discharge, foreign body sensation and/or grittiness (which suggest the overlap with dry eye features), and swelling.¹ It has been appreciated that up to one-third of patients are undiagnosed and undertreated, and often self-medicate with topical over-the-counter medications and lubricants. With limited guidance, most of these drugs have limited efficacy, and their overuse can lead to undesirable adverse effects, e.g., conjunctivitis medicamentosa.

QUESTION

What are the primary mediators of ocular allergy?

1. Leukotriene B4
2. Prostaglandin D₂
3. Histamine
4. Eosinophil major basic protein

Various arachidonic acid mediators of inflammation, including prostaglandin D₂, prostaglandin E₂, prostaglandin F₂-α, prostaglandin I₂, thromboxane A₂, and leukotriene B4 have been demonstrated to be increased in tear fluid compared with control tissue challenged by PBS.³ Prostaglandin I₂ has been identified as a potent pruritogenic tear fluid agent, but, in a randomized, double-blind, placebo controlled, two-way crossover study, the prostaglandin-induced prostaglandin D₂ receptor 2 (CRTH2) receptor antagonist (OC000459) seems to have more of an impact on patients with rhinoconjunctivitis.⁴

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Histamine from degranulated mast cells binds receptors (H_1 , H_2 , H_3 , and H_4) on vascular endothelial cells, neuronal fibers, goblet cells, immune cells, and conjunctival epithelium, which culminates in the clinical manifestations of allergic conjunctivitis; these include rubor (redness, erythema), tumor (periocular swelling, chemosis), dolor (itching, pruritus), and tearing. Histamine receptor agonists as selective agents that bind these receptors still remain the cornerstone of treatment of ocular allergy. Histamine receptor subtype agonists impact the various components of allergic inflammation, including altered permeability of conjunctival epithelium leading to epithelial barrier disruption; stimulation and release of adhesion molecules, chemokines, and proinflammatory cytokines; and recruitment and activation of dendritic cells leading to maturation of antigen-presenting cells and activation of CD4 T-helper type 2 lymphocytes.⁵ The eosinophil major basic protein is a common finding in the disruption of the corneal and conjunctival epithelial surfaces that are seen in corneal defects in the more chronic ocular surface disorders, associated atopic keratoconjunctivitis and vernal conjunctivitis.

CLINICAL CHARACTERISTICS AND PATHOPHYSIOLOGY

The simplest definition of allergic inflammation, in Latin, is calor, dolor, rubor, and tumor as they were defined in the first century A.D. by the Roman scholar Celsus. These assonant words refer to the heat (calor), pain (dolor) or itch because they both are conducted nerve fiber C, redness (rubor) injection, and swelling (tumor) chemosis that characterize the clinical symptoms of ocular allergic inflammation.

QUESTION

In a patient who has developed progressive ocular allergy symptoms in excess of nasal symptoms, which of the following treatments would provide the most immediate and quotidian relief?

1. Lubricants
2. Oral antihistamines
3. Intranasal steroids
4. Ophthalmic antihistamines
5. Immunotherapy

MANAGEMENT

Many patients attempt initiate management of their ocular surface with over-the-counter medications that commonly include different combinations of decongestants and antihistamines with relief of some of the milder cases, but, more commonly, patients also focus on the need to treat their nasal symptoms. A stepwise approach, beginning with nonpharmaceutical agents, *e.g.*, cold compresses, brings relative immediate relief to acute cases but does not provide any longer-term benefit. Lubricants (best when refrigerated) also provide immediate relief, which is short lived (several minutes) due to its dilutional effect on mediators and pollen in the tear film. Immediate and longer-term benefits occur from different topical and oral medications, primarily histamine receptor agonists.

However, many oral antihistamines also have the ability to bind to anticholinergic receptors, which enhances the drying effect for the nasal symptom of rhinorrhea and tearing but may accentuate the “dry eye” (tear film dysfunction) that occurs in many patients with ocular allergy (Figure 1).⁶ The maximum control is achieved with immunotherapy, which has been shown to provide the ability to

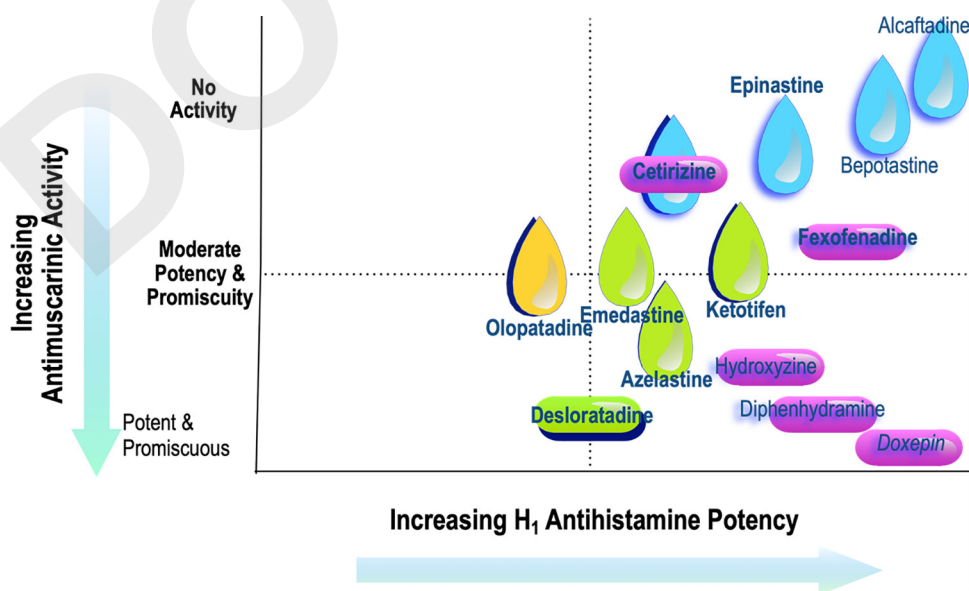


Figure 1. Comparative pharmacology of marketed antihistamines.

Table 1 Ocular lubricants that contain HPMC

Name of Lubricant	Formulation	Components	Preservative	Frequency of Use
Ocular lubricants that contain HPMC				
Contain preservatives				
GenTeal Gel	Gel	0.3% HPMC, carbopol 980	Sodium perborate	As needed
GenTeal Mild	Artificial tears	0.2% HPMC	Sodium perborate	As needed
GenTeal Moderate to Severe	Artificial tears	0.3% HPMC, 0.25% CMC	Sodium perborate	As needed
Isopto Alkaline	Artificial tears	1.0% HPMC	BAK	As needed
Isopto Plain	Artificial tears	0.5% HPMC	BAK	As needed
Isopto Tears	Artificial tears	0.5% HPMC	BAK	As needed
Lacril	Artificial tears	0.5% HPMC	Chlorobutonal	1–2 times/day
Natural Balance Tears	Artificial tears	0.4% HPMC	BAK	As needed
Nature's Tears	Artificial tears	0.4% HPMC	BAK	As needed
Rohto Hydra	Artificial tears	0.3% HPMC	Polyaminopropyl biguanide	4 times/day
Tearisol	Artificial tears	0.3% HPMC	BAK	3–4 times/day
Tears Naturale Forte	Artificial tears	0.3% HPMC, 0.1% dextran 70, 0.2% glycerin	Polyquaternium-1	As needed
Tears Naturale II	Artificial tears	0.3% HPMC, 0.1% dextran 70	Polyquaternium-1	As needed
Tears Renewed	Artificial tears	0.3% HPMC, 0.1% dextran 70	BAK	As needed
Ultra Tears	Artificial tears	0.3% HPMC	BAK	As needed
Preservative free				
GenTeal Gel	Gel	0.3% HPMC, carbopol 980	None	As needed
Lacrisert	Insert	5 mg HPMC	None	1 insert in each eye, 1–2 times/day
Tears Naturale Bion Tears	Artificial tears	0.3% HPMC, 0.1% dextran 70, zinc + bicarbonate	None	As needed
Tears Naturale Free	Artificial tears	0.3% HPMC, 0.1% dextran 70	None	As needed
Ocular lubricants that contain hyaluronic acid				
Contain preservatives				
Blink Gel Tears	Artificial tears	0.25 Polyethylene glycol 400, hyaluronic acid	SOC	As needed
Blink Tears	Artificial tears	0.25 Polyethylene glycol 400, hyaluronic acid	SOC	As needed
Freshkote PF	Artificial tears	2.7% Polyvinyl alcohol and 2.0% Povidone	None	As needed
Vizulize Dry Eyes Eye Mist	Spray	0.10% Hyaluronate	N-Hydroxymethylglycinate	Spray 4 times/day on each closed eyelid

Table 1 Continued

Name of Lubricant	Formulation	Components	Preservative	Frequency of Use
Preservative free Blink Tears	Artificial tears	0.25 Polyethylene glycol 400, hyaluronic acid	None	As needed
Hylo-Gel	Gel	0.2% Hyaluronic acid	None	3 times/day
Hylo-Comod	Artificial tears	0.1% Hyaluronic acid	None	3 times/day
Hylo-Fresh	Artificial tears	0.03% Hyaluronic acid	None	3 times/day
Ocular lubricants that contain hyaluronic acid				
Contain preservatives				
GenTeal Moderate to Severe	Artificial tears	0.3% HPMC, 0.25% CMC	Sodium perborate	As needed
Just Tears	Artificial tears	0.5% CMC	SOC	As needed
Refresh Celluvisc	Artificial tears	1.0% CMC	SOC	As needed
Refresh Liquigel	Artificial tears	1.0% CMC	SOC	As needed
Refresh Optive	Artificial tears	0.5% CMC, 0.9% glycerine	SOC	As needed
Refresh Optive Advanced	Artificial tears	0.5% CMC, 1.0% glycerine, 0.5% polysorbate	SOC	As needed
Refresh Tears	Artificial tears	0.5% CMC	SOC	As needed
Tears Again Night & Day Gel	Gel	1.5% CMC	SOC	As needed
Thera Tears	Artificial tears	0.25% CMC	Sodium perborate and phos	As needed
Preservative free				
Refresh Celluvisc	Artificial tears	1.0% CMC	None	As needed
Refresh Liquigel	Artificial tears	1.0% CMC	None	As needed
Refresh Optive	Artificial tears	0.5% CMC, 0.9% glycerine	None	As needed
Refresh Optive Advanced	Artificial tears	0.5% CMC, 1.0% glycerine, 0.5% polysorbate	None	As needed
Refresh Optive Sensitive	Artificial tears	0.5% CMC, 0.9% glycerine	None	As needed
Refresh Plus	Artificial tears	0.5% CMC	None	As needed
Thera Tears	Artificial tears	0.25% CMC	None	As needed

HPMC= Hydroxypropyl methylcellulose; CMC = carboxy methylcellulose; BAK = benzalkonium chloride; SOC = stabilized oxychloro complex.

be exposed to 10–100 concentrations in ocular challenge models.⁷ The localized targeted treatment with ophthalmic antihistamines provides the most immediate and quotidian relief.¹

QUESTION

Which ophthalmic antihistamine is a zwitterion that has a slow receptor dissociation rate, high selectivity, negligible liver enzyme interaction, low CNS penetration that contains a combination of two topical lubricants in addition to a minimal anticholinergic binding activity?

1. Olopatadine
2. Bepotastine
3. Cetirizine
4. Azelastine
5. Ketotifen

CORRECT ANSWERS

Ophthalmic antihistamines provide the most immediate and targeted therapy. In the stepwise treatment algorithm, ophthalmic antihistamines are on the first step of targeted treatment of the ocular surface.¹ All of these agents provide statistical and clinical relief from the “ocular itching,” as the basis for approval from the U.S. Food and Drug Administration. The zwitterionic cetirizine displays distinct advantages over the basic hydroxyzine in several categories, such as slow receptor dissociation rate, high selectivity, negligible liver enzyme interaction, and low CNS penetration.⁸ Cetirizine has a pH neutral formulation (pH 7.0) that contains glycerin and hydroxypropyl methylcellulose, ingredients commonly found in lubricant drops; of 30 ophthalmic lubricants, glycerin was used in 9 and hydroxypropyl methylcellulose was used in 18,⁹ which provides additional comfort on the application with mean comfort scores of <1 (Table 1).¹⁰ Of interest is that this agent was tested in two patient groups, moderate and severe allergic conjunctivitis, and was found to be clinically effective.¹¹ Ophthalmic agents that also have low antimuscarinic receptor binding include alcaftadine, bepotastine, cetirizine, and epinastine (Current Opinion in Press).

Pearls

1. Ocular allergy is commonly associated with tear film dysfunction (dry eye conditions).
 - a. Lubricants are helpful (some more than others)
 - (i) Table of ophthalmic antihistamines that contain lubricants (Table 1).⁹

- b. Consideration of ophthalmic agents with low antimuscarinic binding (Figure 1).
- c. Consideration of ophthalmic antihistamine with oral formulation proven for treatment of “allergic rhinoconjunctivitis” and urticaria.
- d. Chemosis is the swelling (or edema) of the conjunctiva, equivalent to urticaria on the conjunctival surface.

Pitfalls

1. Oral antihistamines commonly have anticholinergic effects and can accentuate the tear film dysfunction (dry eye condition) of the ocular surface.
 - a. Figure of H₁ versus muscarinic binding

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