

Topical treatment options for allergic conjunctivitis

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Allergic conjunctivitis can be classified as an acute or chronic condition. Acute allergic conjunctivitis encompasses seasonal allergic conjunctivitis and perennial allergic conjunctivitis. The more severe chronic conditions include vernal keratoconjunctivitis, acute keratoconjunctivitis and giant papillary conjunctivitis. The mainstay in the treatment of allergic conjunctivitis remains the use of topical dual-acting agents which have mast cell stabilising properties and act as antihistamines. Although corticosteroids are among the most effective agents in the treatment of allergic conjunctivitis, they can cause serious adverse effects and their use should be reserved for short-term "pulse" treatment to gain quick control of the symptoms. Topical nonsteroidal anti-inflammatory drugs can also cause corneal melting. However, their use may be considered in severe cases to reduce the use of topical steroids. Several new agents acting at newly identified targets in the inflammatory process are under investigation for the treatment of allergic conjunctivitis.

Keywords: allergic conjunctivitis, seasonal allergic conjunctivitis, perennial allergic conjunctivitis, vernal keratoconjunctivitis, acute keratoconjunctivitis and giant papillary conjunctivitis

Introduction

Acute allergic conjunctivitis is estimated to affect at least 20–40% of the population, and the incidence is increasing worldwide.¹⁻³ Increasing incidence is believed to be owing to several factors, including urbanisation, industrialisation, air pollution and climate change.⁴ Although allergen avoidance remains the initial step in the management of allergic conjunctivitis, this is often not possible considering that allergens are frequently airborne and avoiding contact with the ocular surface is difficult.^{1,3} The mainstay in the treatment of allergic conjunctivitis remains the use of topical agents as the onset of action is generally rapid, with less adverse effects.¹ This article focuses on topical treatment options when treating the acute and more severe chronic forms of allergic conjunctivitis.

Classification and pathogenesis

Allergic conjunctivitis can be classified as acute or chronic, with subcategories, as outlined in Table 1.^{1,2,5}

Table 1: The classification of allergic conjunctivitis^{1,2,5}

Acute allergic conjunctivitis	Chronic allergic conjunctivitis
<ul style="list-style-type: none"> Seasonal allergic conjunctivitis Perennial allergic conjunctivitis 	<ul style="list-style-type: none"> Vernal keratoconjunctivitis Atopic keratoconjunctivitis Giant papillary conjunctivitis

Acute allergic conjunctivitis

Acute allergic conjunctivitis is a sudden-onset type I hypersensitivity reaction, whereby an early-phase immune response associated with mast cell degranulation causes the release of histamine, tryptases, prostaglandins and leukotrienes,

which results in the rapid development of symptoms, i.e. within seconds or minutes.¹ This is followed by a late-phase immune response, involving infiltration of the basophils, eosinophils, T cells, macrophages and neutrophils into the conjunctiva approximately 6–72 hours after exposure to an antigen.^{1,2,5} The symptoms include intense periods of ocular pruritis, burning, hyperaemia, tearing, chemosis (conjunctival oedema), blurry vision and eyelid oedema, which generally resolve over a period of 24 hours.^{1,2,5}

Seasonal allergic conjunctivitis (SAC) usually develops over a period of days or weeks, and is associated with outdoor allergens which correspond to one or more specific pollen seasons. These may include tree pollen in spring, grass pollen in summer and weed pollen in late summer and autumn.^{2,5} Grass pollen may be implicated in perennial symptoms because of the long grass season in South Africa.⁶

Perennial allergic conjunctivitis (PAC) usually relates to year-round exposure to indoor allergens, such as dust mites, cigarette smoke, mould and pet dander. Symptoms tend to be chronic and mostly mild, but may wax and wane throughout the year.^{2,5}

SAC is the most commonly occurring form of allergic conjunctivitis, followed by PAC. Although its impact is mostly owing to persistence rather than severity, it can have a significant impact on quality of life and morbidity. Symptoms generally resolve with treatment and overall prognosis is favourable.^{2,5}

Chronic allergic conjunctivitis

More severe forms of allergic conjunctivitis include vernal keratoconjunctivitis (VKC), atopic keratoconjunctivitis (AKC) and giant papillary conjunctivitis (GPC).^{1,2,5}

VKC is a bilateral inflammation which usually affects boys living in warm, dry, subtropical climates with exacerbations in spring.^{2,4,7} VKC is the result of chronic lymphocyte and mast cell infiltration of the conjunctiva.⁴ Symptoms include intense ocular pruritis, copious fibrinous discharge and pseudomembrane formation on the upper lid. The development of giant cobblestone papillae on the superior tarsal conjunctiva differentiates VKC from other types of allergic conjunctivitis.^{2,4,7} VKC is often associated with a family history of atopic disease, and more than 90% of patients with VKC suffer from some concomitant atopic condition, such as asthma, atopic dermatitis or seasonal allergic rhinitis.^{5,8} Severe cases may include corneal neovascularisation, shield ulcers, corneal scarring and keratoconus.⁷

AKC is strongly associated with atopic dermatitis, and affects the lower tarsal conjunctival surface.⁹ AKC typically presents in adults aged 30–50 years of age.^{2,5} Although it is the least common ocular allergy, it is a severe, lifelong condition.⁹ Like VKC, AKC is also a chronic mast cell-mediated type I hypersensitivity disorder, and can involve the cornea, with significant visual impairment in severe uncontrolled cases.⁴ AKC can also lead to thickening and lichenification of the eyelids.²

GPC is not considered to be a true allergic condition, but rather a chronic inflammatory disease due to chronic mechanical irritation from foreign bodies, such as contact lenses, ocular sutures, ocular prostheses or ocular implants.^{2,9} It is believed that an antigen is present in predisposed individuals that stimulates the immunological reaction. A combination of type I and type IV hypersensitivity reactions result in giant papillae, more than 0.3 mm in diameter, on the superior tarsal conjunctiva.⁵ GPC differs from VKC as it has a different papillary form and also because there is an absence of corneal involvement.⁸

Treatment

Goals of treatment include a reduction in the signs and symptoms, including redness, itching, tearing, blurry vision, chemosis and eyelid oedema, to improve quality of life.^{1,4} In addition to avoiding the offending antigen, a variety of topical preparations, each targeting a different point in the inflammatory process, is available to manage the symptoms of ocular allergy.⁵

Artificial tears

First-line defences include barriers, such as the eyebrows, eyelids and eyelashes, which serve as obstacles to allergens.¹ A healthy tear film also helps by flushing out antigens and inflammatory mediators from the ocular surface, and diluting the concentration of these components in the eye.^{1,5} Tap water reduces the stability of the tear film, and the frequent use of water to wash the eyes should be avoided. Artificial tear solutions or lubricating gels alleviate symptoms, and can be used 2–4 times daily.¹⁰ If artificial tears are used more than four times daily, the use of

a preparation without preservatives is preferable.⁸ Available artificial tear preparations in South Africa, including those which are preservative free, are listed in Table 2.^{1,11-13}

Decongestants

Topical preparations containing alpha-adrenergic receptor stimulant drugs, such as phenylephrine, naphazoline, oxymetazoline and tetrahydrozoline, are indicated for ocular redness associated with minor eye irritation.¹¹ Decongestants cause vasoconstriction, resulting in immediate-onset whitening and decongestion of the eye, but have little effect on itching.^{1,4} They are contraindicated in patients with narrow-angle glaucoma and angle-closure glaucoma, and should be used with caution in patients with cardiovascular disease, diabetes and hyperthyroidism.⁴ Long-term use leads to the downregulation of alpha 1-adrenergic receptors and can lead to rebound hyperaemia and inflammation.^{1,5,14} Decongestants should be used for episodic treatment only, and for no longer than two weeks at a time.¹⁴ Although they have only been shown to be effective in the treatment of ocular allergy when used in combination with antihistamines, single-agent preparations are available over the counter, and are often used by patients for self-treatment.¹ Decongestants are often combined with antihistamines for the more effective topical treatment of ocular allergies.¹⁴

Brimonidine is a longer-acting alpha 2 agonist, and a low-dose formulation is currently under investigation for the treatment of ocular redness, with the advantage of minimum tachyphylaxis and rebound redness.¹

Antihistamines

The use of systemic antihistamines can exacerbate dry eyes, and is best avoided in patients without concurrent rhinitis or sinusitis.¹ Topical antihistamines provide rapid relief from symptoms, such as itching, tearing and oedema, and have a favourable benefit to risk ratio.¹

Three of the four histamine receptors which have been identified play a role in ocular allergy. H₁- and H₂- receptor stimulation results in pruritis, conjunctival hyperaemia, cytokine secretion, fibroblast proliferation, microvascular permeability and the production of procollagens, while H₄-receptor signalling affects cytokine and chemokine release and chemotaxis.¹ Antazoline, pheniramine maleate, emedastine and levocabastine are competitive, reversible H₁-receptor antagonists, and primarily affect the early-phase response of allergic conjunctivitis.^{1,4,5}

A topical formulation of cetirizine, a second-generation antihistamine, is currently being developed for twice-daily use in the prevention of ocular allergic itching.¹

Dual-acting antihistamines

In addition to their antihistamine effects, dual-acting agents also have a mast cell stabilising effect. As mast cell stabilisers, they prevent the degranulation of mast cells and limit the release of histamine, leukotrienes and prostaglandin D₂. As antihistamines, they competitively and reversibly block histamine receptors in

Table 2: Topical preparations for the treatment of allergic conjunctivitis in South Africa^{1,11-13}

Trade name	Active ingredient	Preservative
Artificial tears		
Spersatear [®] , Moisture Drops [®] and Viscotraan [®]	Hypromellose	Benzalkonium chloride
Murine [®] Bright & Moist Eyes	<ul style="list-style-type: none"> • Polyvinyl alcohol • Povidone 	Benzalkonium chloride Disodium acetate
Systane Ultra [®]	<ul style="list-style-type: none"> • Polyethylene glycol • Propylene glycol 	Polyquaternium
Tears Naturale [®] II	<ul style="list-style-type: none"> • Dextran • Hypromellose 	Polyquaternium
Optive [®]	Carmellose	Stabilised chlorine dioxide
Tears Naturale [®] Preservative Free	<ul style="list-style-type: none"> • Dextran • Hypromellose 	None
Cellufresh [®] , Celluvisc [®] and Refresh [®]	Carmellose	None
Duratears [®] Lubricating Eye Ointment	Anhydrous liquid lanolin	None
Oculet [®]	Povidone	None
Decongestants		
Safyr Bleu [®]	Naphazoline	Benzalkonium chloride
Oculosan [®]	<ul style="list-style-type: none"> • Naphazoline • Zinc sulphate 	Benzoxonium chloride
Oxylin [®] Liquifilm	<ul style="list-style-type: none"> • Oxymetazoline • Polyvinyl alcohol 	Benzalkonium chloride
Eye gene [®]	Phenylephrine hydrochloride	Benzalkonium chloride and disodium edetate
Prefrin [®] Liquifilm	<ul style="list-style-type: none"> • Phenylephrine hydrochloride • Polyvinyl alcohol 	Benzalkonium chloride
Universal [®] Eye Drops	<ul style="list-style-type: none"> • Phenylephrine hydrochloride • Boric acid 	Benzalkonium chloride
I-Glo [®]	<ul style="list-style-type: none"> • Phenylephrine hydrochloride • Boric acid, borax and sodium chloride 	Thiomersal
Antihistamines		
Emadine [®]	Emedastine	Benzalkonium chloride
Livostin ED [®]	Levocabastine	Benzalkonium chloride
Antihistamine and decongestant combination		
Antistin-Privin [®]	<ul style="list-style-type: none"> • Antazoline • Naphazoline 	Benzalkonium chloride
Spersallerg [®] , Gemini [®] and Oculerge [®]	<ul style="list-style-type: none"> • Antazoline • Tetryzoline 	Benzalkonium chloride
Dual-acting antihistamines/mast cell stabilisers		
Optilast [®]	Azelastine	Benzalkonium chloride
Relestat [®]	Epinastine	Benzalkonium chloride
Zaditen [®]	Ketotifen	Benzalkonium chloride
Patanol [®]	Olopatadine	Benzalkonium chloride
Mast cell stabilisers		
Alomide [®]	Lodoxamide	Benzalkonium chloride
Cromohexal [®] and Stop-Allerg [®]	Sodium cromoglycate	Benzalkonium chloride
Cromobak [®]	Sodium cromoglycate	None
Corticosteroids		
Maxidex [®] and Spersadex [®]	Dexamethasone	Benzalkonium chloride
Flucon [®] and FML [®]	Fluoromethalone	Benzalkonium chloride
Pred Mild [®] and Pred Forte [®]	Prednisolone acetate	Benzalkonium chloride
Minims Prednisolone Sodium Phosphate [®]	Prednisolone sodium phosphate	None

NSAIDs: nonsteroidal anti-inflammatory drugs

the conjunctiva and eyelids, countering the effect of histamine which has already been released.^{4,14} Dual-acting agents have a relatively rapid onset of action and a longer duration of action than single-action antihistamines.⁴ The prophylactic therapy only takes full effect after at least two weeks of treatment when the inflammation is controlled and the symptoms have subsided.¹⁴ Dual-agents include alcaftadine, azelastine, bepotastine, epinastine and olopatadine.¹ Those available in South Africa are listed in Table 2.

Mast cell stabilisers

Mast cell stabilisers act by stabilising the mast cell membranes, thereby preventing degranulation, and reducing the influx of various inflammatory agents, including eosinophils, neutrophils and monocytes.¹⁴ Mast cell stabilisers do not alleviate existing symptoms and should be used prophylactically, making these ideal for the treatment of chronic ocular allergies, such as VKC and GPC.⁵ Long-term use may also affect patient compliance, and they are now rarely used for the treatment of acute allergic conjunctivitis.⁹ Although lodoxamide was found to be much more potent than sodium cromoglycate, pemirolast was the only mast cell stabiliser which showed considerable clinical efficacy in the treatment of SAC.¹ Lodoxamide has been found to be most efficacious in the treatment of shield ulcers and epitheliopathy associated with VKC.¹ Only lodoxamide and sodium cromoglycate preparations are available on the South African market at the moment.^{11,13}

Topical nonsteroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit the cyclo-oxygenase (COX) enzymes, COX-1 and COX-2,¹⁴ thereby interfering with the prostaglandins, mediators of the late-phase allergic response.⁹ Ketorolac, flurbiprofen, indomethacin, diclofenac and nepafenac are NSAIDs that have been used topically.¹ These NSAIDs are mostly used in perioperative treatment with cataract surgery. Ketorolac is the only agent registered for the treatment of SAC in the USA.⁴ The ocular use of NSAIDs can potentially cause corneal melting, especially in patients with prior ocular surface disease,¹ and for this reason its use in acute allergic conjunctivitis should be limited to occasional use in patients who do not respond to other agents.⁴ However, the use of topical NSAIDs, such as indomethacin, ketorolac and diclofenac, has been shown to reduce ocular inflammation in VKC, and to reduce topical steroid use in these patients.⁹ Although ketorolac, diclofenac and nepafenac eyedrops are available in South Africa, none of these topical NSAIDs are currently registered for the treatment of ocular allergy.^{11,13}

Corticosteroids

Corticosteroids, such as hydrocortisone, triamcinolone, fluoromethalone, rimexalone, prednisolone and dexamethasone, are among the most potent and effective options in the treatment of allergic conjunctivitis, affecting both the early- and late-phase allergic response.^{4,9} Corticosteroids suppress mast cell proliferation, reduce inflammatory cell influx, and block the

production of all inflammatory mediators, including eosinophils, leukotrienes, prostaglandins and platelet-activating factor.^{1,9}

Unfortunately, they can also cause serious adverse events, such as increased intraocular pressure, delayed wound healing, immunosuppression, secondary infection, ptosis (steroid myopathy), mydriasis, conjunctival petechiae, cataract formation, corneal hazing, corneal and scleromalacia and the induction or exacerbation of glaucoma.^{1,5,9,13} The use of topical corticosteroids should be reserved for severe or refractory cases, and treatment limited to short-term management with careful monitoring.^{1,5,9} Rimexalone, medrysone and fluoromethalone are weaker agents with less potency in the eye and have fewer adverse effects, while prednisolone acetate and dexamethasone phosphate are more potent, but have a higher incidence of adverse effects.^{5,14}

Loteprednol etabonate is a topical corticosteroid with a novel molecular structure which may be associated with a more rapid drug metabolism and a reduction in adverse effects.¹⁴

Calcineurin inhibitors

Immunosuppressant agents, such as cyclosporine A, mitomycin C and tacrolimus, have been used as off-label alternatives to long-term treatment with corticosteroids for the treatment of VKC, AKC and GPC.^{7,9,14} Calcineurin inhibitors have been found to be effective in reducing the signs and symptoms of severe chronic ocular conditions and reduce the need for corticosteroid treatment.⁹ The topical administration of tacrolimus and cyclosporine A both inhibit T-cell activation, while cyclosporine A also inhibits eosinophil infiltration into the conjunctiva.¹

Treatment considerations

Acute allergic conjunctivitis

Patients with SAC and PAC should be counselled on avoiding the offending antigen. The use of artificial tears may be recommended to alleviate symptoms.¹⁴ Dual-acting antihistamines with mast cell stabilising effects, such as azelastine, epinastine, ketotifen and olopatadine, are the mainstay of treatment when nonpharmacological treatment has failed.⁸ Where possible, the treatment of SAC should start approximately 2–4 weeks prior to exposure to optimise effectiveness.¹⁴ Patients who fail to respond to at least three weeks of treatment with a dual-acting agent should be referred to an ophthalmologist for further management and the consideration of topical steroids.

Severe chronic allergic conjunctivitis

Vernal keratoconjunctivitis

Patients with mild forms of VKC may combine non-pharmacological treatment, such as avoiding triggers by wearing sunglasses and the application of cold compresses, with the use of a mild antihistamine and vasoconstrictor combination.⁷ This may provide limited relief and is only recommended for short-term management.⁵ NSAID eyedrops and a mast cell stabiliser may also be considered in mild cases.⁷ Mast cell stabilisers with antihistamine effects form the mainstay of treatment

in VKC.⁵ Patients with significant symptoms may eventually need treatment with topical steroids. Pulse treatment, starting with high doses of steroids, followed by rapid tapering, is recommended. Treatment should be with the lowest effective dose for the shortest possible period to avoid the development of serious adverse events, and can be repeated if necessary.⁵ Corneal shield ulcers may require treatment with an antibiotic and steroid ointment, or surgery in severe cases.⁵

Atopic keratoconjunctivitis

As for VKC, the treatment of AKC begins with avoiding environmental factors. The use of antihistamine and vasoconstrictor combination products may provide limited short-term relief. The use of mast cell stabilisers is recommended, but onset of action is long, and full efficacy is only noticed after approximately two weeks.⁵ Pulse treatment with topical steroids may be added in the initial weeks to control and alleviate symptoms. Patients may need additional systemic therapy with antihistamines to manage symptoms.

Giant papillary conjunctivitis

Removal of the foreign body responsible for the conjunctivitis is the ultimate treatment for GPC, and may be possible when these are sutures or a scleral buckle. However, patients with prosthetics or contact lenses may prefer to continue using these. Changing the contact lens care routine and switching to disposable lenses or rigid gas-permeable lenses may prevent the accumulation of proteins which can be the stimulating antigen in GPC.⁵ Pharmacological treatment with antihistamines and mast cell stabilisers can be used, with the addition of pulse treatment with steroids, where necessary.^{5,8}

Novel therapies under investigation

New targets for therapy have been identified by a better understanding of the molecular and cellular mechanisms involved in ocular allergy.⁹ Several agents are currently under investigation in phase II trials. These include:

- Selective glucocorticoid receptor agents, such as mapracorat, for ocular inflammation and allergic conjunctivitis
- Interleukin 1-receptor antagonists (EBI-005 and topical anakinra) for moderate to severe allergic conjunctivitis

- Resolvin E1, a proresolving lipid mediator
- An integrin antagonist, lifitegrast, for allergic conjunctivitis.^{1,9}

N-acetyl-aspartyl glutamic acid eyedrops have anti-inflammatory properties and have demonstrated efficacy in the treatment of VKC.⁹

Conclusion

Topical treatment using dual-acting antihistamine and mast cell stabilising agents remains the mainstay of treatment for allergic conjunctivitis. The choice and duration of treatment mainly depends on the severity, chronicity and onset of symptoms, and varies depending on the clinical diagnosis. The goals of treatment are the alleviation of symptoms and an improvement in quality of life. Allergic conjunctivitis can be managed successfully in the majority of patients.

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