

A REVIEW OF THE MANAGEMENT OF OCULAR ALLERGY

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ABSTRACT

The wide array of ocular allergy symptoms, its profound effect on the quality of life and economic burden on the sufferer, underline the need for adequate knowledge of its management options. Primary treatment algorithm includes measures to reduce allergen exposure while medication such as antihistamines, vasoconstrictors and mast-cell stabilisers remain the mainstay management of ocular allergy. Severe cases of ocular allergy may require corticosteroids or immunotherapy.

INTRODUCTION

Traditionally, ocular allergy has been defined as a group of type I and type IV hypersensitivity-mediated ocular surface diseases that include seasonal allergic conjunctivitis (SAC), perennial allergic conjunctivitis (PAC), atopic keratoconjunctivitis (AKC), vernal keratoconjunctivitis (VKC), contact dermatitis conjunctivitis (CDC) and contact lens-induced papillary conjunctivitis (CLPC).¹ However, IgE and non IgE-mediated mechanisms are involved in the development of ocular allergic diseases.² In 2001, the European Academy of Allergy and Clinical Immunology (EAACI)³ suggested a new classification that distinguishes between allergic and non-allergic hypersensitivity reactions, with allergic diseases being further divided into IgE- and non IgE-mediated hypersensitivities (Table I). The triggering event is the contact of the causative allergen with the conjunctival mucosa and ocular allergy is typically a type 1 IgE-mediated hypersensitivity reaction with cell-mediated Th-2 involvement in some types. SAC and PAC are IgE-mast cell mediated hypersensitivity reactions and are triggered mainly by pollen and dust mites respectively.² Both SAC and PAC are comorbidities of rhinitis and asthma⁴ and are seldom followed by permanent visual loss.¹ However, the symptoms of SAC and PAC can lead to a significant reduction in quality of life for the patients and their families.⁵ AKC and VKC are characterised by chronic inflammation with T-cell infiltration and can potentially cause severe visual complications.⁶ CLPC represents chronic inflammation of the tarsal conjunctiva by mechanical trauma such as contact lenses and ocular prosthetics, with the induction of alterations in local inflammatory mediators.⁷

Ocular allergy is often underdiagnosed and undertreated until it reaches severe levels due to various reasons.⁸ For

example, some patients may seek attention for concomitant atopic disease (i.e. asthma, allergic rhinitis, urticaria, or eczema) and the clinician who is managing those comorbid conditions may overlook the patient's ocular manifestations,⁹ contributing to suboptimal management of patients with ocular allergy. The International Study of Asthma and Allergies in Childhood study (ISAAC)¹⁰ has reported allergic conjunctivitis as rhinitis associated with itchy eyes (allergic rhinoconjunctivitis) and not isolated ocular symptoms.¹¹ Although available prevalence data usually address ocular symptoms such as rhinoconjunctivitis, up to 40% of the population in developed countries have been reported to experience symptoms of ocular allergy.¹¹ The ISAAC study reported that the prevalence of ocular allergy in developing countries was low but did not assess the prevalence of isolated allergic conjunctivitis. However, the prevalence of allergic conjunctivitis has been reported to be 7.3% in children between 5 and 17 years of age in Nigeria,¹² 7.9% in Gambia,¹³ and 9.1% in Ghana.¹⁴ Recent hospital based studies in Nigeria suggest that the prevalence of allergic conjunctivitis is as high as 32%¹⁵ and 42%,¹⁶ suggesting that this is a widespread visual health challenge, affecting people of all ages.

DIAGNOSIS

Ocular allergy is usually diagnosed based on the findings from the patient's history and clinical examination, particularly with a personal or family history of systemic allergic diseases.¹⁷ These characteristic features are important for the clinician to know because they may require different management strategies.

HISTORY

An accurate diagnosis of ocular allergy requires a thorough medical history to elicit characteristic signs and symptoms,



Figure 1: Seasonal and perennial allergic conjunctivitis: mild chemosis and hyperaemia of the palpebral and bulbar conjunctiva

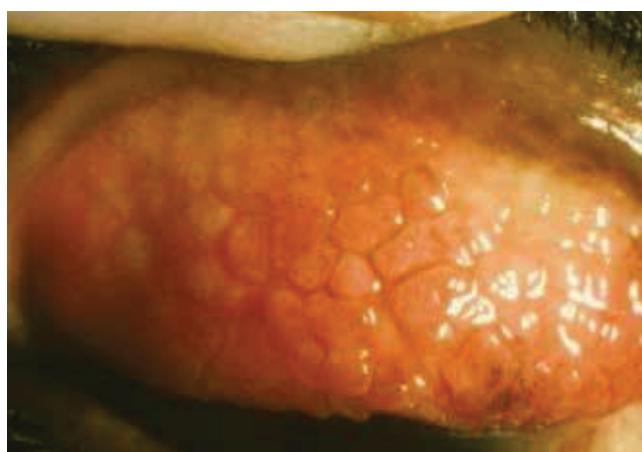


Figure 2: Vernal keratoconjunctivitis: giant papillae of the upper tarsal conjunctiva which can be seen easily by 'flipping' the upper eyelid

the offending agent, the presence of autoimmune and other allergic disorders and medication use for controlling allergy.¹⁷ The clinical presentations include itching, burning, stinging, redness, and swelling/chemosis. Tearing, redness and itching are the most common symptoms and a diagnosis of allergic conjunctivitis should be considered if any patient presents with a chief complaint of itching, together with red, irritated eyes.¹⁸ Itching, particularly aggravating in the nasal quadrant, is the hallmark symptom of ocular allergy. Patients with blepharitis, dry eye and irritative, non-allergic conjunctivitis

may also complain of itching that is localised to the eyelids or periorbital skin.¹⁷ Most patients with ocular allergy will also have nasal symptoms (nasal itching, congestion or a runny nose) because the nasal and ocular mucosal tissues react to allergens in a similar way.¹⁷ Allergic conjunctivitis is associated with a watery discharge, which may sometimes contain a small amount of mucus, making a stringy or mucoid discharge. The mucoid discharge can lead clinicians to make an erroneous diagnosis of bacterial conjunctivitis.¹⁷

TABLE I: DIFFERENTIATING FEATURES OF VARIOUS ALLERGIC EYE DISEASES^{2,5,20}

	SAC	PAC	VKC	AKC	CDC	CLPC
HISTORY OF ATOPY	Rhinitis Asthma	Rhinitis Asthma	Variable	Rhinitis Asthma Dermatitis	Variable	Variable
ALLERGIC MECHANISM	IgE-mediated	IgE-mediated	IgE- and non IgE-mediated	IgE- and non IgE-mediated	Non IgE-mediated	Non-allergic
PRESENTATION	Intermittent	Persistent	Persistent ± intermittent exacerbations	Chronic	Chronic ± intermittent exacerbations	Persistent
PREDOMINANT CELL TYPE	Mast cell Eosinophil	Mast cell Eosinophil	Lymphocytes Eosinophil	Lymphocytes Eosinophil	Lymphocytes	Lymphocytes Eosinophil
VISION INVOLVEMENT	Minimal	Minimal	Mild	Severe	Minimal	Minimal
SEASON	Spring, Autumn	Perennial	Spring, Autumn or perennial	Any	No	Any
DISCHARGE	Clear mucoid	Watery	Stringy mucoid	Stringy mucoid	Watery	Clear white/ mucous
CHEMOSIS	+	+	±	±	-	±
CONJUNCTIVA	Follicles and/or papillae	Follicles and/ or papillae	Giant papillae	Papillae ± fibrosis	±Hyperaemia Follicles	Giant papillae
CORNEA	-	-	Superficial punctate keratitis ± Ulcer ± Vernal plaque	Superficial punctate keratitis Ulcer, Plaque, Opacities, neovascularisation	-	Rare
EYELIDS	Oedema	± Oedema	Oedema Pseudoptosis	Eczema + meibomitis blepharitis	Erythema, eczema	-
LIMBUS	-	-	± Thickened + Trantas dots	± Thickened ± Trantas dots	-	Hyperaemia
ITCH	+	+	++	++	+	++
GRITTIINESS	±	±	±	±	-	+



Figure 3: Atopic keratoconjunctivitis: chemotic eyelid skin with a fine sandpaper-like texture

A history of medication can explain an incomplete clinical picture of allergy in a patient with active disease and identify an underlying cause for problems with dry eye or contact lens discomfort.¹⁷ For example, patients who are using an oral histamine medication may not have prominent itch, but may be suffering from the ocular drying effects of those medications. Asking specifically about agents purchased without a prescription is important considering a large number of clinical and experimental studies have revealed that preservatives in topical ophthalmic medications have been demonstrated to produce effects from inflammation or hypersensitivity to permanent cytotoxic effects involving all structures of the eye.¹⁹

CLINICAL EXAMINATION

The examination of patients with suspected ocular allergy should involve the inspection of the eyelids, conjunctiva and cornea. SAC and PAC are the most common forms of ocular allergies.^{2,5} The signs and symptoms of PAC and SAC are the same, the only difference being the specific allergens to which the patient is allergic.^{2,5} Redness (conjunctival injection) and chemosis (conjunctival swelling) tends to be mild to moderate (Figure 1). Itching is a fairly consistent symptom of SAC and PAC and corneal involvement is rare (Table I).

The hallmark sign in VKC is giant cobblestone papillae that appear in the upper palpebral conjunctiva (Figure 2) and patients with VKC may also complain of severe photophobia.² Trantas dots appear as small gelatinous nodules at the limbus and consist of clumps of necrotic eosinophils, neutrophils and epithelial cells.⁵

The most characteristic sign of AKC is an oedematous or thickening of the periorbital skin (Figure 3). There is some overlap between the clinical features of VKC and AKC (Table I). For example, a shield ulcer, which is due to the breakdown of the epithelial barrier function, can be seen in both chronic forms of VKC and AKC.

Contact keratoconjunctivitis (CDC) is a form of contact dermatitis that involves the ocular surface, eyelids and periocular skin and can manifest in both atopic and

non-atopic individuals.² Contact lens induced papillary conjunctivitis (CLPC) is not a true allergy (the stimuli are inert substances rather than allergens) but is an inflammatory disease characterised by papillary hypertrophy of the superior tarsal conjunctiva.² The appearance of CLPC is similar to vernal conjunctivitis (Figure 2), but unlike VKC, there is no significant corneal involvement in CLPC (Table I). The differentiating features of various types of ocular allergic diseases in the form of epidemiology, history, and clinical features are summarised in Table I.

MANAGEMENT

The management of ocular allergy is aimed at inhibiting the release of mediators of allergy, controlling the inflammatory cascade and symptoms, and preventing ocular surface damage.²¹ Management involves non-pharmacologic and pharmacologic strategies to minimise the negative impact of ocular allergy on the individual's quality of life.²¹ It is, therefore, important for the clinician to identify what type of ocular allergy is present, assess the severity, comorbidity and long term risks before instituting an appropriate treatment plan.

NON-PHARMACOLOGIC MANAGEMENT

The first line treatment in most ocular allergic conditions is to identify and avoid the offending allergen.²¹ However, the identification and complete avoidance of the offending allergen is not always possible.²¹ Table II provides a summary of practical avoidance measures (which focus primarily on environmental control) for common allergens implicated in ocular allergic diseases. In addition to strategies for allergen avoidance, other non-pharmacologic interventions include the use of cold compresses, cooled preservative free artificial tears or isotonic saline.²¹ Cold compresses act as natural decongestants against non-specific irritants and are effective in mild to moderate symptoms of ocular allergy.²¹ Frequent dosing (4-8 times a day) with over-the-counter preservative free ocular lubricants, such as artificial tears, improve symptomatic relief by diluting and flushing away allergens²¹ and encouraging vasoconstriction to reduce eyelid swelling, chemosis and hyperaemia.⁸ Clinicians should advise patients with ocular allergy to use preservative free formulations to avoid any potential hypersensitivity reactions. Similarly, the refrigeration of these products is also helpful as the cold solutions are both soothing and counteract the elevated tissue temperature associated with ocular inflammation.

TOPICAL OCULAR PHARMACOLOGIC MANAGEMENT

ANTIHISTAMINES

Topical antihistamines are the most commonly used agents in the pharmacological management of ocular allergy and are available alone or in combination with vasoconstrictors.²¹ Newer generation topical antihistamines, such as emedastine, are more potent, have a longer duration and are well tolerated.²¹ The mode of action, effects, dosage and common side effects of topical antihistamines are shown in Table III.

TABLE II: PRACTICAL ALLERGEN AVOIDANCE MEASURES²¹

ALLERGEN	CONTROL MEASURES
POLLEN	Remain indoors with windows closed at peak pollen times. Wear closely fitting, wrap around style sunglasses when outdoors. Use air-conditioning, where possible. Install car pollen filter.
MOULDS	Ensure dry indoor conditions; Use ammonia to remove moulds from bathrooms and other wet spaces.
HOUSE DUST MITES	Provide adequate ventilation to decrease humidity; Wash bedding regularly at 60°C; Encase pillow, mattress and quilt in allergen impermeable covers; Use vacuum cleaner with HEPA filter; Dispose of feather bedding; Remove carpets; Remove curtains, pets and stuffed toys from bedroom.
COCKROACHES	Eradicate cockroaches with appropriate gel-type, non-volatile, insecticides; Eliminate dampness, cracks in floors, ceilings, cover food, wash surfaces, fabrics to remove allergen.
PETS	Remove pets from bedrooms or from the entire home; Vacuum carpets, mattresses and upholstery regularly; Wash pets regularly; Avoid rubbing eyes or nose after being in contact with animals; Wash hands after and clothes which have been in contact with animals.

VASOCONSTRICTORS

Naphazoline, is the most common vasoconstrictor and is also available in a higher strength by prescription.²² One to 2 drops in each affected eye, 2 to 3 times daily, are required to reach therapeutic levels.²² Caution should be taken when prescribing vasoconstrictors to patients with hypertension, cardiovascular disease, arrhythmias, diabetes mellitus, hyperthyroidism, or angle-closure glaucoma.²² They also tend to cause rebound hyperaemia or conjunctivitis medicamentosa with chronic use.²²

ANTI-HISTAMINES/VASOCONSTRICTOR COMBINATIONS

Topical antihistamines (e.g. antazoline or pheniramine) combined with a vasoconstrictor (e.g. naphazoline, tetrahydrozoline, oxymetazoline or phenylephrine) are more effective for the treatment of allergic conjunctivitis, have a quick onset and limited duration of action.⁸ However, they are contraindicated in patients with narrow anterior chamber angles as they exhibit the anti-cholinergic effect of mydriasis, which could enhance angle-closure glaucoma attack.²¹ Given the potential adverse effects, these products should be used with caution in cases with hypertension, cardiovascular disease and poorly controlled diabetes, and are recommended only for the temporary relief of itching and redness and makes them inappropriate for long-term use.²³

ANTI-HISTAMINE/MAST CELL STABILISER COMBINATIONS

New anti-allergy drugs, such as olopatadine, ketotifen,

and azelastine are potent antihistamines and also have mast cell stabilising effect and other activities.²¹ Azelastine and epinastine demonstrate mast-cell stabilising and anti-inflammatory properties and have a rapid onset of action.²⁴

MAST CELL STABILISERS

Mast cell stabilisers are preventative medications, and therefore, cannot relieve ongoing allergic reactions once histamine and other mediators have been released from mast cells.²¹ For example, sodium cromoglycate is a classic mast cell stabiliser with a relatively excellent safety profile and is suitable for long-term prophylaxis and therapeutic management of SAC, vernal keratitis, VKC and GPC.²¹ A loading dose is required, following which recommended dosing is 4 to 6 times daily at regular intervals, tapered to three to four daily when symptoms subside.²⁵ Lodoxamide tromethamine has a faster onset of action and is 2500 times more potent than sodium cromoglycate but has a maximum usage of only 4 weeks.⁸ Newer mast cell stabilisers include pemirolast potassium and nedocromil.

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)

NSAIDS have no effect on other allergic inflammatory mediators such as histamines and leukotrienes and therefore, their use in the treatment of ocular allergy is limited.²¹ Diclofenac sodium, ketorolac, indomethacin, pranoprofen may be an alternative to steroids use due to their effect on itching.²¹ NSAIDS should be used with caution in patients who have a triad of asthma, nasal polyposis and aspirin sensitivity because of their risk of causing NSAID-induced respiratory distress in this group.²¹

CORTICOSTEROIDS

Topical corticosteroids are considered most appropriate in chronic ocular allergic conditions.²¹ Loteprednol etabonate is regarded as a "soft" steroid due to its safety profile and is a treatment option for patients with allergic ocular inflammation.^{21,26} Prednisolone acetate is effective for the treatment of severe inflammatory disorders while the fluorometholone-based steroids are used to treat mild and chronic forms of ocular allergy.²⁶ Cream-based steroids such as triamcinolone and hydrocortisone are effective in the treatment of periocular inflammation in contact ocular allergy.²⁶ Steroids are associated with the development of serious ocular adverse effects (Table III) and patients who are prescribed a topical corticosteroid should therefore be carefully monitored by an ophthalmologist, and therapy should be slowly tapered over several days once the condition is under control.²²

TOPICAL OCULAR IMMUNOSUPPRESSIVES

Topical immunomodulators such as cyclosporines and tacrolimus are gaining increasing popularity in the long term treatment of severe allergic eye disease.¹ Topical cyclosporine A 0.05% is lipophilic and therefore requires to be dissolved in an alcohol-oil base, which causes ocular irritation such as burning, tearing, erythema,

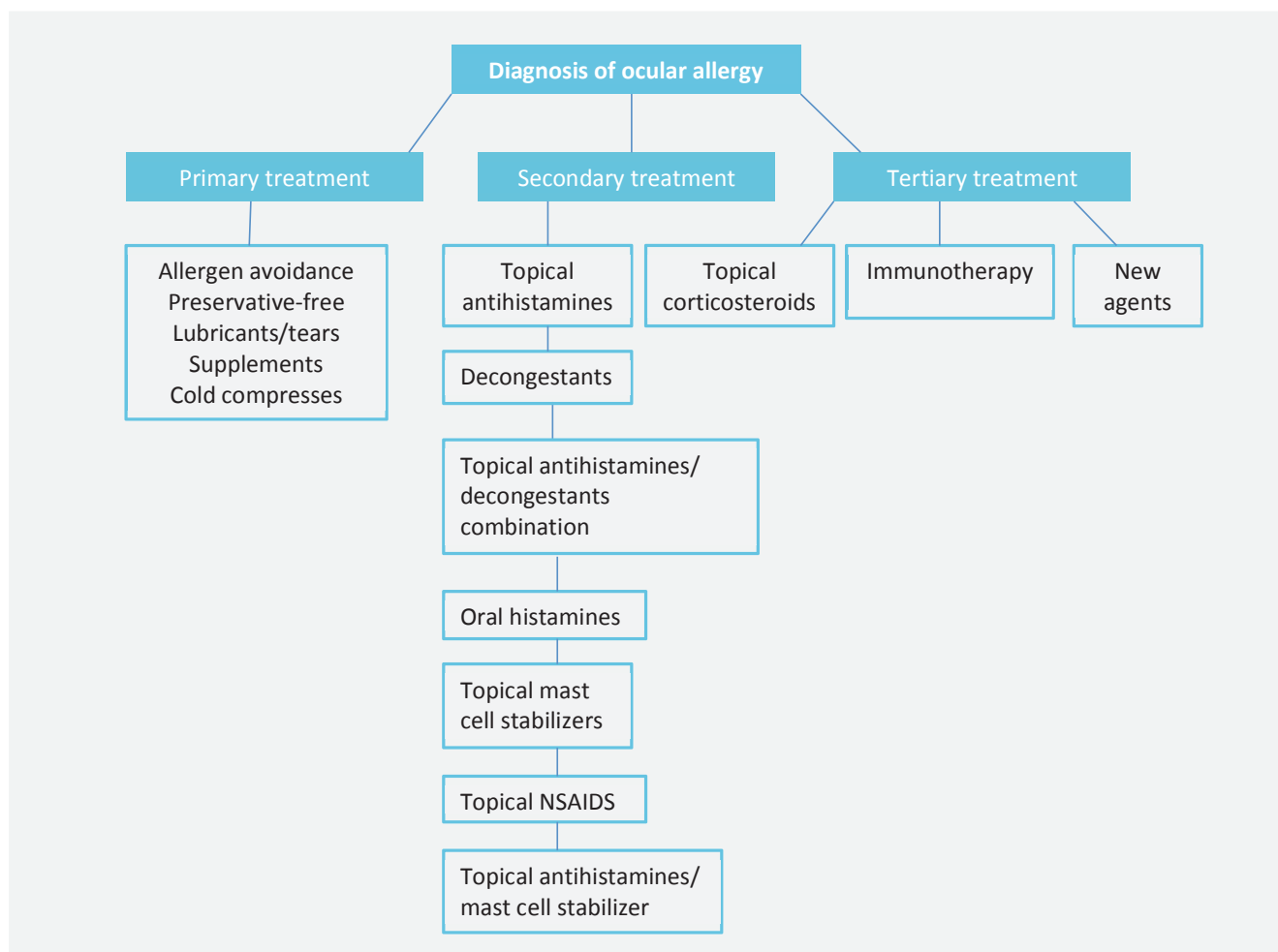


Figure 4: Stepwise approach for the treatment options of various types of allergic ocular disease^{1,17}

itching, and headaches after instillation.¹ However, these side effects are not seen with the commercially available cyclosporine A 2% because it is a neutral, hydrophobic cyclic undecapeptide metabolite of the fungus *Tolypocladium inflatum*.¹

SYSTEMIC PHARMACOLOGIC TREATMENT

ORAL ANTIHISTAMINES

Oral antihistamines are more effective when they are combined with other topical anti-allergic agents.⁵ Systemic antihistamines reduce tear production due to their anti-muscuranic action and exacerbates discomfort in the already irritated eye.⁵ They should not be used at all in the absence of systemic allergic disease, e.g., rhinoconjunctivitis and patients who are taking systemic antihistamines should be advised to use lubricants eye-drops to sooth the eyes.

SYSTEMIC IMMUNOSUPPRESSIVES

In severe cases, resistant to conventional therapy, systemic treatment with T-lymphocyte signal transduction inhibitors such as cyclosporines A or tacrolimus may ameliorate both the dermatologic and ocular manifestations.²⁷ For instance, systemic cyclosporine A, dosed 2.5 mg/kg/day in divided doses, has been successfully used for the treatment of

severe AKC and dry-eye disease.²⁷ However, potential toxicity restrict long term use of these products.²⁷

ANTI-IgE RECOMBINANT

Anti-IgE therapy used in the treatment of allergic rhinitis and asthma may have potential implications for the treatment of ocular allergy.²⁸ Humanised monoclonal antibodies against IgE such as omalizumab have been reported to be an effective treatment of moderate-to-severe allergic asthma, and for nasal and ocular symptoms of allergic rhinitis.²⁸ Williams and Sheppard²⁹ reported that five of their six patients with AKC, that they treated with once or twice monthly omalizumab injections, had a significant improvement of symptoms and only one did not show remarkable changes. Similarly, Sánchez and Cardona³⁰ reported that use of biweekly injections of omalizumab was effective in a 15-year old boy with VKC who was unresponsive to conventional therapy. Side effects include headaches, hypersensitivity, itching, runny nose, pain or tenderness around the eyes and cheekbones.²⁸

SPECIFIC ALLERGEN IMMUNOTHERAPY

This involves exposing the patient to doses of the offending allergen over time to desensitise mast cells, essentially inoculating the patient and resulting in immunity and

TABLE III: DRUGS USED FOR THE TREATMENT OF OCULAR ALLERGIC DISEASES^{2,5,17}

CLASS	EXAMPLES	MECHANISM OF ACTION	EFFECT	INDICATIONS	DOSAGE	COMMON SIDE EFFECTS
Antihistamines	Levobastine Emedastine	Histamine receptor antagonist	Relieves itching and redness	PAC, SAC, VKC, AKC	Tds-qid	Ocular burning, dry mouth, somnolence, tiredness and itching, headache (emedastine)
Vasoconstrictors	Oxymetazoline, Naphazoline	Stimulates alpha-adrenergic receptor	Decongestion	PAC, SAC	Tds	Rebound hyperaemia, follicular conjunctivitis, eczematous blepharoconjunctivitis, increase IOP
Antihistamines/ Vasoconstrictor	Pheniramine maleate/ naphazoline	Histamine receptor antagonist and decongestant	Relieves itching and redness	PAC, SAC, VKC	Qid	Conjunctival injection and chemosis, mydriasis, ocular irritation, hypersensitivity, hypertension
Antihistamine/Mast cell stabiliser	Olopatadine, Ketotifen, Epinastine, Azelastine	Histamine receptor antagonist, stabilisation of mast cell degranulation and suppression of activation and infiltration of eosinophils	Relieves itching, redness and oedema with immediate effect	SAC, VKC, AKC	Bd	Headaches (olopatadine) conjunctival injection, headache, and rhinitis (ketotifen), ocular burning, headache, bitter taste (azelastine)
Mast cell stabiliser	Sodium cromoglycate, Lodoxamide	Blocks the release of allergy mediator, chemokines and cytokines by suppressing mast cell degranulation	Used for prophylaxis	SAC, VKC, GPC	Tid-qid	Hyperaemia and blurred vision (lodoxamide). Ocular irritation and burning, stinging, and itching (rare)
NSAIDS	Ketorolac tromethamine	Inhibits prostaglandin and thromboxane synthesis by blocking the cyclooxygenase pathway	Reduces conjunctival hyperaemia and pruritus	PAC, SAC, VKC	Tds-qid	Ocular burning, stinging and itching
Corticosteroids	Loteprednol etabonate, Prednisolone acetate, Dexamethasone	Suppresses migration of polymorphonuclear leukocytes and reverses capillary permeability	Reduces inflammation and cellular infiltrates	Severe allergic diseases	Bd-qid	Cataract, glaucoma, infections, delayed wound healing
Oral antihistamines	Cetirizine, Loratadine, Ebastine, Levocetirizine	H1 receptors antagonists and inhibits ICAM1 and PAF	Reduces pruritus, oedema vasodilatation	Severe allergic conditions	Od, bd	CNS and GIT effects (with 1st generation), dry eye (especially with 2nd generation)
Immunosuppressive	Cyclosporin, Tacrolimus	Cyclosporine inhibits eosinophil infiltration. Tacrolimus blocks T-cells action	Relieves signs and symptoms and reduces steroid use	AKC, VKC	Tds	Burning during instillation

Od = once a day, Bd = two times a day, Tds = three times a day, Qid = four times a day, ICAM = intercellular adhesion molecule, PAF = platelet factor, CNS = central nervous system, GIT = gastrointestinal tract

a decrease in the amount of pharmacotherapy needed.^{25,31} Specific allergen immunotherapy treatment has been shown to be more effective than topical and oral medications in the control ocular allergy symptoms.³² Sublingual immunotherapies have better safety profiles and significantly reduce symptoms in patients with ocular allergy.³³ Reported adverse effects of specific allergen immunotherapy include increased local reactions, anaphylactic reaction and serum sickness (rare).³³ These symptoms can usually be eliminated by adjusting the dosage.³³ However, studies on allergen immunotherapy have predominantly been about rhinoconjunctivitis and have not differentiated the different types and severity of ocular allergy. The authors have acknowledged the deficiencies with the data available for their meta-analysis.³³

Common ocular allergy drugs, their mode of action and effects, indications, dosage and adverse effects, used in

various types of ocular allergy are summarised in Table III and the step by step treatment algorithm is illustrated in Figure 4.

CONCLUSION

Ocular allergy remains a growing public health problem in Africa and many other countries. Environmental factors including changing climatic conditions and extent of pollution (which comes along with urbanisation) may contribute to the increasing prevalence of the condition in Africa. It has also been reported that one of the most commonly seen entities in HIV/AIDS patients is allergic conjunctivitis.³⁴ Therefore, when a patient with no previous history of ocular allergies presents with new-onset allergic conjunctivitis, it is important for the clinician to rule out underlying HIV. The choice of ocular allergy treatment depends on the severity of the symptoms. The use of non-pharmacological management is not always adequate so anti-allergic medications may become necessary to prevent

and alleviate symptoms. Currently available medications such as antihistamines, vasoconstrictors, mast cell stabilisers, NSAIDs, steroids, and others provide safe and effective management of most cases of ocular allergy. Familiarity with topical ocular and non-ocular pharmacologic treatment,

systemic pharmacologic treatments and immunotherapy can result in significant benefits for patients with ocular allergies.

DECLARATION OF CONFLICT OF INTEREST

The author declares no conflict of interest.

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