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Review

A review of non-pharmacological and pharmacological management of seasonal and perennial allergic conjunctivitis

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ABSTRACT

Allergic eye disease encompasses a group of hypersensitivity disorders which primarily affect the conjunctiva and its prevalence is increasing. It is estimated to affect 8% of patients attending optometric practice but is poorly managed and rarely involves ophthalmic assessment. Seasonal allergic conjunctivitis (SAC) is the most common form of allergic eye disease (90%), followed by perennial allergic conjunctivitis (PAC; 5%). Both are type 1 IgE mediated hypersensitivity reactions where mast cells play an important role in pathophysiology. The signs and symptoms are similar but SAC occurs periodically whereas PAC occurs year round. Despite being a relatively mild condition, the effects on the quality of life can be profound and therefore they demand attention. Primary management of SAC and PAC involves avoidance strategies depending on the responsible allergen(s) to prevent the hypersensitivity reaction. Cooled tear supplements and cold compresses may help bring relief. Pharmacological agents may become necessary as it is not possible to completely avoid the allergen(s). There are a wide range of anti-allergic medications available, such as mast cell stabilisers, antihistamines and dual-action agents. Severe cases refractory to conventional treatment require anti-inflammatories, immunomodulators or immunotherapy. Additional qualifications are required to gain access to these medications, but entry-level optometrists must offer advice and supportive therapy. Based on current evidence, the efficacy of anti-allergic medications appears equivocal so prescribing should relate to patient preference, dosing and cost. More studies with standardised methodologies are necessary elicit the most effective anti-allergic medications but those with dual-actions are likely to be first line agents.

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1. Allergy and allergic eye disease

Allergic eye disease is the ocular manifestation of allergy, where the body produces an over-reaction or hypersensitivity to normally harmless substance known as allergens. The prevalence of allergy in Europe is between 15 and 20% [1] and is expected to increase with estimates up to 50% by 2015 [2,3]. Although genetics plays an important role in susceptibility, the increase in prevalence is reported to be the result of improved hygiene practices [4] and increased antibiotic use [5] as part of modern lifestyle [6], in addition to environmental factors such as increased air pollution, climate change and increased planting and importation of allergenic plant species [7–9].

Of those who suffer from allergy, approximately 20% experience a form of ocular allergy [10,11]. The prevalence of ocular allergy in patients attending optometric practice in the UK has been estimated at 8% [12]. Allergic eye disease is the umbrella term for a group of distinct clinical entities, typically confined to

the conjunctiva, and includes seasonal allergic conjunctivitis (SAC), perennial allergic conjunctivitis (PAC), vernal keratoconjunctivitis (VKC) and atopic keratoconjunctivitis (AKC) [13–15]. Other allergic eye conditions include contact allergy to topical medication such as anti-glaucoma agents [16–18], microbial allergy such as phlyctenulosis caused by hypersensitivity to tuberculo-protein [19], and giant papillary conjunctivitis (GPC) which represents the chronic inflammation of the tarsal conjunctiva by mechanical stimuli such as contact lenses and ocular prosthetics [10,13,14,20]. With increasing knowledge of the pathophysiology/underlying mechanisms of allergic eye disease, there has been a rapid and large increase in the number of pharmacological anti-allergic medications available for treatment [21]. However, several authors have pointed out that ocular allergies have been under-diagnosed, under-treated in particular SAC where the ocular symptoms fall under the umbrella of seasonal hay fever which may underestimate its true prevalence [22–24]. A recent study by Wolffsohn et al. highlights the current poor management of ocular allergies in the UK, where patients often self-medicate and rarely undergo an ophthalmic examination [12]. Due to the increasing prevalence of allergy, allergic eye disease is becoming more common and combined with its impact on the quality of life and inadequate management, it is important

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for practitioners to identify these patients in order to manage them appropriately.

Given that SAC and PAC are the most common forms of allergic eye disease, they are more likely to be encountered in optometric practice. AKC is often associated with atopic co-morbidities such as asthma (87%) and eczema (95%) and requires multi-disciplinary management, although only 25–42% of patients have AKC in atopic dermatitis [15]. In addition VKC is very rare, affecting less than 1% of allergic eye disease cases and along with AKC they are likely to be managed in the hospital eye service under close supervision due to topical steroid therapy, sight threatening potential and concomitant atopic disease in AKC [15,25,26]. Therefore this article will discuss the pathophysiology and management of SAC and PAC with respect to non-pharmacologic and pharmacologic interventions available to the optometrist from entry level to the therapeutically qualified.

2. Seasonal and perennial allergic conjunctivitis

The most common form of allergic eye disease is SAC constituting 90% of cases, followed by PAC at 5% [24]. SAC occurs on a seasonal basis, often as part of seasonal rhinoconjunctivitis (hay fever) and is most frequently caused by grass, tree and weed pollens and outdoor moulds which peak at different times of the year [24,26]. PAC occurs year round and is caused by house dust mites, animal dander, insects and indoor moulds [26]. Signs and symptoms of SAC typically develop on a gradual basis but can also develop suddenly following contact with the offending allergen [15,24]. They include itching, tearing, eyelid oedema and conjunctival hyperaemia, chemosis and papillary reaction and the severity often varies with pollen counts [22]. Signs and symptoms of PAC are similar to SAC but are milder and chronic in nature and may have seasonal exacerbations [24,27]. Although the signs of symptoms of SAC and PAC are relatively mild, the impact of allergic eye disease on the quality of life can be profound [28], affecting daily activities, productivity at work, school performance and even on an economic level [29–31]. Complications of SAC are limited to severity of presentation and linked to steroid use in cases refractory to conventional treatment [32–34]. Currently there is no cure for SAC or indeed for any allergy, so treatment is aimed at preventing and alleviating symptoms, but immunotherapy shows promise [21].

3. Pathophysiology

Both SAC and PAC are IgE-mast cell mediated hypersensitivity reactions, divided into two phases with the mast cell playing a central role [35,36]. The reaction involves a very complex series of immunological events coordinated by various mediators initiated by an allergen [37,38]. An allergen such as pollen reacts with specific IgE antibodies bound to a sensitised mast cell, triggering cross linkage of the IgE molecules and an influx of calcium ions into the mast cell. This causes the mast cell to degranulate and release preformed inflammatory mediators such as histamine which cause the signs and symptoms associated with the early phase response in sensitised individuals [15,37]. The early phase response is immediate and lasts clinically for 20–30 min [39].

Mast cell degranulation also initiates a series of cellular and extracellular events which lead to the late phase response, including production of prostaglandins, thromboxanes and leukotrienes derived from arachidonic acid. Mast cells also release cytokines and chemotactic factors which induce the production of IgE form B-cells, enhance production of Th2-lymphocytes, attract eosinophils and activate vascular endothelial corneal and conjunctival cells to release chemokines and adhesion molecules. The chemokines and adhesion molecules mediate the infiltration of

eosinophils, basophils, neutrophils and Th2-lymphocytes to the site of inflammation and coupled with the newly formed mediators and sustained mast cell activation they result in the late phase response [26,37,40]. This may occur 3–12 h after the initial reaction [35] and symptoms can continue up to 24 h [41]. The year round symptoms associated with PAC are the result of chronic mast cell activation and Th2-lymphocyte infiltration [26,39].

4. Non-pharmacological management

The most important and most effective step in treating allergic eye disease is avoiding the offending allergen to prevent the hypersensitivity reaction from being triggered, but this necessitates the identification of the offending allergen and complete avoidance is not always possible [21,42,43]. In SAC a detailed history is essential as knowledge of the period of time of year symptoms occur can allow identification using a pollen calendar to some extent but peak levels of common causative pollens often overlap. However, effective measures for allergen avoidance in SAC and PAC are based upon control of the environment. Given that pollens are the main cause of SAC, preventative measures include limiting outdoor activity during the symptomatic period, closing windows and using air conditioning when in a car or indoors, avoid touching/rubbing eyes after being outdoors, wash hands after being outdoors and wearing close fitting or wrap around style sunglasses when outdoors [42,44]. As PAC can affect the patient all year round, more thorough avoidance measures are necessary. Dust mite levels in the home can be reduced by using and regularly replacing protective pillow, mattress and duvet covers; washing bedding regularly at least at 60 °C; vacuum and damp dust entire house on weekly basis; reduce humidity to between 35 and 50% and remove or regularly clean carpets, upholstery, curtains and any other areas that gather dust [44–46]. Animal dander can be reduced by eliminating all pets/animals from the home or keep them outdoors; regular vacuuming; minimising exposure to areas that gather animal dander; avoid touching animals; washing hands and avoid eye touching/rubbing after contact with animals; and washing all clothes that have come into contact with animals [44,47,48]. Washing hair before going to bed can help remove any allergens trapped in the hair and prevent transfer to the pillow. Table 1 provides a summary of practical avoidance measures for common allergens implicated in SAC and PAC.

Other non-pharmacological interventions include the use of cold compresses, cooled preservative free artificial tears or saline, which help to wash out the allergens in the conjunctiva and encourage vaso-constriction of the blood vessels to reduce eyelid swelling, chemosis and hyperaemia [21,24,49]. In addition, the artificial tears may act as a barrier to the pollen allergens to prevent the hypersensitivity response [26]. Although there is a lack of evidence regarding their efficacy, their use appears plausible and these measures should be encouraged as supportive therapy, where they can be used between topical anti-allergic doses when symptoms persist.

5. Pharmacological management

Despite implementing these avoidance measures, complete avoidance is not always possible so use of anti-allergic medication may become necessary to prevent and alleviate symptoms. With increased knowledge of the pathophysiology of the hypersensitivity reaction in SAC and PAC over the years, there has been a rapid increase in the number of anti-allergic medications that target the immunological cells and inflammatory mediators involved in the allergic expression [10,21,50]. Ophthalmic anti-allergic medications include topical mast cell stabilisers,

Table 1
Practical allergen avoidance measures.

Allergen	Control measures
Pollen and outdoor moulds	Limit outdoor activities during symptomatic period Monitor pollen levels using internet and media broadcast resources to plan outdoor activities Avoid rubbing eyes and nose and wash hands after being outdoors Wear closely fitting wrap around style sunglasses when outdoors Close windows and use air conditioning when in a vehicle and doors leading outside when in the home
House dust mites	Use protective pillow, mattress and duvet covers Regularly wash bedding at 60 °C (at least) Vacuum and damp dust entire house on a weekly basis Remove or regularly clean carpets, upholstery, curtains and any other areas or objects that can gather dust Use a de-humidifier to reduce humidity in the home to between 35% and 50%
Animal dander	Avoid contact with animals Keep pets outdoors or none at all Regularly vacuum the home and clean areas that gather animal dander Avoid rubbing eyes or nose after being in contact with animals Wash hands after and clothes which have been in contact with animals

antihistamines, antihistamine–vasoconstrictor combinations and dual action agents with mast cell stabilising and antihistaminic properties [11,39]. However the availability of these agents to an optometrist depends upon the level of training, qualifications and competence received. Registration as an optometrist at entry level permits the use of a limited formulary of medications, including all general sale and pharmacy only (P-only) medicines but only some prescription only medicines (POMs) under the Medicines Exemptions Act. Optometrists may take up further study to extend the range of medicines they can use, currently at three levels of therapeutic training. Additional supply (AS) training extends the number of POMs available under the Medicines Exemptions Act to treat common ocular surface disorders and includes all currently available topical anti-allergic medicines. Supplementary prescribing (SP) status allows optometrists to prescribe any medication, however they must only prescribe medicines they are competent in using and according to an agreed management plan with an independent prescriber. Independent prescribing (IP) status also allows the optometrist to prescribe any medication providing they are competent with its use but formulate a management plan independently.

5.1. Mast cell stabilisers

The mast cell stabilisers indicated for the treatment of allergic conjunctivitis include sodium cromoglycate 2%, nedocromil 2% and lodoxamide 0.1% and have demonstrated efficacy in alleviating the signs and symptoms of SAC and PAC compared to placebo [51–54]. Mast cell stabilisers work by preventing the degranulation of the sensitised mast cells thus inhibits the release of inflammatory mediators and repressing the type 1 hypersensitivity reaction [10,50]. This action results from preventing the calcium ion influx into the mast cell after antigen stimulation [10,11]. As mast cell stabilisers act on the mast cell before degranulation occurs, they will have no effect on the inflammatory mediators once they have been released [26]. Therefore mast cell stabilisers require a loading time

of 10–14 days before symptoms are known to occur and are used topically as prophylactic agents [21,26].

Sodium cromoglycate has an excellent safety profile with the only adverse effect being transient burning and stinging sensation upon application [55] and is suitable for long term prophylaxis of allergic eye disease [11,21,56]. Nedocromil is also well tolerated and has a more rapid onset of action compared to sodium cromoglycate [52] but has maximum duration of usage of 12 weeks, making it unsuitable for long term treatment required in PAC and can leave an unpleasant taste in the mouth following application [55]. Lodoxamide, like nedocromil, has a faster onset of action than sodium cromoglycate and is also more potent [57]. However, lodoxamide has the potential to cause a wide range of adverse effects including hyperaemia and blurred vision and has maximum usage of only 4 weeks [55]. Only sodium cromoglycate 2% (maximum size 10 mL) and lodoxamide 0.1% is available for sale and supply by entry level optometrists as they are classed as P-only medicines in these concentrations and pack sizes. Sodium cromoglycate 2% is also available in preservative free single use form, making it appropriate in cases where patients experience a preservative reaction. Access to nedocromil 2% and other formulations of sodium cromoglycate and lodoxamide requires additional therapeutic qualifications (minimum AS level). Both sodium cromoglycate and lodoxamide require four times daily dosing whereas nedocromil requires only twice daily dosing [55]. However, Collum et al. demonstrated that 4% sodium cromoglycate used twice daily was similar to 2% sodium cromoglycate used four times daily [58].

5.2. Antihistamines

The most common agent used in the pharmacological management of allergic conjunctivitis is antihistamines and are available for use alone or in combination with vasoconstrictors. Antihistamines are competitive antagonists of histamine receptors (H1 and H2) on effector cells in the conjunctiva and eyelids [11,59]. When stimulated by the main preformed mediator histamine, H1 receptors cause capillary dilation and increased vascular permeability which results in symptoms of itching and localised oedema typical of the hypersensitivity reaction [10,37]. Therefore binding of these receptors by antihistamine the inflammatory events normally initiated by histamine are prevented [43,50]. However, only H1 antihistamines are available for ocular application. The antihistamine–vasoconstrictor combination drug Otrivine-Antistin contains the antihistamine antazoline 0.5% and the sympathomimetic vasoconstrictor xylometazoline 0.05% [55]. There appears to be no clinical trials in the scientific literature on the efficacy of this agent in allergic conjunctivitis, but a study by Miller and Wolf [60] showed antazoline combined with the vasoconstrictor naphazoline was effective in allergic conjunctivitis. Other ophthalmic preparations include azelastine hydrochloride 0.05% and emedastine hydrochloride 0.05%, which also demonstrate efficacy in alleviating symptoms in SAC with good safety profiles [61–63]. Azelastine is considered a dual action medication as it also demonstrates mast-cell stabilising and anti-inflammatory properties [64] and is also suitable for PAC [65] owing to maximum treatment duration of 6 months and twice daily dosing [55]. Adverse effects of azelastine are limited to mild transient irritation and bitter taste but emedastine can cause a variety of side effects including blurred vision, keratitis and corneal infiltrates [55].

Antazoline, combined with the vasoconstrictor xylometazoline (Otrivine-Antistin) is the only antihistamine available to entry level optometrists as it is available to the public, whereas the others require additional therapeutic training (minimum AS level). The vasoconstrictors xylometazoline and naphazoline are sympathomimetics (adrenergic agonist) which stimulate adrenergic receptors causing capillary constriction and reduced blood flow and

therefore reduce hyperaemia, chemosis and eyelid swelling [66]. Naphazoline, either (Mucine irritation & redness relief) alone or in combination with witch hazel (a plant with reported astringent properties [67]) is also available for public purchase (Optrex Blood-shot Eye Drops) but there is no evidence in the scientific literature regarding the efficacy of the combination product or demonstrable astringent capability in allergic conjunctivitis. Investigators have shown that naphazoline combined with an antihistamine (antazoline or pheniramine) is effective in treating allergic conjunctivitis in clinical trials and conjunctival challenge models [68–70] but these combinations are not available in the UK. Although studies have shown that antihistamine–vasoconstrictor combinations are more effective than either alone [60,71], long term use is not recommended owing to potential adverse effects such as rebound hyperaemia [32,66]. They are contraindicated in those with narrow anterior chamber angles as the sympathomimetic vasoconstrictor component exhibits the anti-cholinergic effect of mydriasis. In addition, they should be used with caution in those with heart disease, high blood pressure and diabetes due to potential systemic absorption [21]. Given the potential adverse effects caution should be exercised with these agents and are only indicated for short term relief (up to 7 days) [55].

Oral antihistamines should be considered alongside topical agents in SAC where it is associated with seasonal hay fever as the nose and throat are also affected in this condition [49,66]. First generation oral antihistamines may cause systemic side effects including those which affect the central nervous and gastrointestinal systems, but second generation oral antihistamines have been developed to overcome these shortcomings [66]. Despite the development of second generation non-sedating antihistamines, they are not as safe or effective as topically applied agents in treating allergic conjunctivitis [66,72,73] and can cause drying of mucous membranes such as the conjunctiva, which may exacerbate symptoms and counter the washing action of the tears from removing allergens from the ocular surface [74]. However, several studies have demonstrated improved efficacy when they are combined with topical anti-allergic agents [75–77]. The oral antihistamines acrivastine (Benadryl Allergy Relief), cetirizine (Zirtek; Benadryl Once a Day) and loratadine (Claritin) are non-proprietary medicines available for public consumption [55] and can therefore be sold and supplied to patients by entry level optometrists but must be competent in their use. Other oral antihistamines can only be prescribed by optometrists with SP in accordance with an agreed management plan with an independent prescriber (likely to be the patient's GP) or independently with IP status but again they must be competent with their use, acknowledging contraindications, potential interactions and adverse effects.

5.3. Dual action medications

The dual action anti-allergic topical medications azelastine hydrochloride 0.05%, epinastine hydrochloride 500 mg/mL, olopatadine hydrochloride 1 mg/mL and ketotifen fumarate 250 mg/mL combine both mast cell stabilising and antihistaminic properties and have demonstrated good efficacy and safety in treating SAC compared to placebo [62,78–81] and can therefore have the advantage as both a prophylactic to prevent mast cell degranulation and a therapeutic agent to bring about symptomatic relief following the onset of symptoms [26]. Optometric access to any of these agents also requires therapeutic qualifications (minimum AS level). Only azelastine 0.05% is indicated for both PAC and SAC but all medications only require twice daily dosing [55]. Although uncommon, these medications may cause a variety of ocular and systemic adverse effects [55]. Table 2 provides a summary of the medications available in the UK to treat allergic conjunctivitis.

6. Severe allergic conjunctivitis

In severe SAC and PAC and cases unresponsive/refractory to conventional anti-allergic medications described above, anti-inflammatory agents may be necessary such as non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids [24,39,49]. The efficacy of the NSAIDs ketorolac trometamol 0.5% and diclofenac sodium 0.1% in treating allergic conjunctivitis has been demonstrated in several studies [82,83]. Only diclofenac 0.1% has been licensed for use as treatment for SAC in the UK. NSAIDs work by preventing the formation of prostaglandins responsible for itching by blocking the cyclooxygenase pathway in the hypersensitivity response [26]. Corticosteroids however reduce inflammation by a variety of actions. They suppress the activation, recruitment and production of late phase inflammatory mediators; increase the availability of histaminases (enzymes which break down histamine); prevent histamine production in mast cells; inhibit T-cell activity and reduce the permeability of conjunctival blood vessels [26]. Corticosteroids should only be used in the short-term as pulse therapy until the allergic response is under control, at which point steroid use is slowly tapered and eventually stopped [21,24,26]. Treatment with corticosteroids requires careful monitoring owing to the potential increase in intraocular pressure and cataract formation [32,84]. The newer corticosteroid loteprednol etabonate however is a “softer” agent with an improved safety profile for treatment in severe SAC [34,85,86]. In addition, immunomodulators such as cyclosporine are gaining increasing popularity in the long term treatment of severe allergic eye disease as an alternative to topical steroid therapy, particularly in VKC steroid responders [87,88]. Topical NSAIDs and corticosteroids are only available to therapeutically trained optometrists, with the exception of diclofenac sodium which is available at AS level. In severe, persistent cases of allergic conjunctivitis and those with systemic allergic associations, referral to an allergologist/immunologist may be necessary to initiate immunotherapy. It is a well established therapy with proven efficacy in a range of allergic conditions including allergic conjunctivitis [89–91]. Here, small doses of the offending allergen identified by skin prick and conjunctival provocation tests are given over time to desensitise mast cells, essentially inoculating the patient [21].

7. Allergic conjunctivitis and contact lens wear

Although it is often stated that best practice is to cease contact lens wear until signs and symptoms have resolved completely (owing to potential binding of allergens to the lens surface therefore prolonging exposure) [26,92], most studies have recommended changing the lens material, wearing regime, cleaning regime, replacement frequency switching or to daily disposables for patients with allergic conjunctivitis [92–94]. In a recent placebo controlled, conjunctival airborne allergen challenge model Wolffsohn and Emberlin [94] demonstrated significant improvement in and reduced duration of symptoms and signs with daily disposable lens wear suggesting a barrier effect by the contact lens to airborne allergens. Modern anti-allergic agents have made possible to maintain contact lens wear in mild to moderate cases of allergic conjunctivitis as they have the advantage of twice daily dosing [95]. The dual action agents and nedocromil can be applied before lens insertion and after removal to overcome the need to abandon contact lens wear completely during a hypersensitivity episode depending on symptom severity and providing the cornea is not involved [95,96]. A study by Brodsky et al. [97] has shown increased wearing time and comfort following use of olopatadine prior to contact lens insertion.

Table 2

Topical ophthalmic medications available for the treatment of allergic conjunctivitis in the UK.

Medication class	Name	Formulation	Optometrist availability
Mast cell stabiliser	Sodium cromoglycate (non-proprietary)	Sodium cromoglycate 2%	Entry level but in maximum pack size of 10 mL
	Catacom (Moorfields Pharmaceuticals)	Sodium cromoglycate 2% single use	At least AS level
	Rapitol (Sanofi-Aventis)	Nedocromil sodium 2%	At least AS level
	Alomide (Alcon)	Lodoxamide 0.1%	Entry level
Antihistamine	Otrivine-Antistin (Novartis)	Antazoline sulphate 0.5% and xylometazoline hydrochloride 0.05% eye drops	Entry level
	Emadine (Alcon)	Emedastine hydrochloride 0.05%	At least AS level
Dual action	Opatanol (Alcon)	Olopatadine Hydrochloride 1 mg/mL	At least AS level
	Optilast (Meda)	Azelastine hydrochloride 0.05%	At least AS level
	Relestat (Allergan)	Epinastine Hydrochloride 500 µg/mL	At least AS level
	Zaditen (Novartis)	Ketotifen fumarate 250 µg/mL	At least AS level
NSAID	Voltarol ophtha multidose (Novartis)	Diclofenac sodium 0.1%	At least AS level
	Voltarol ophtha (Novartis)	Diclofenac sodium 0.1% single use	At least AS level
Vasoconstrictor	Murine irritation and redness relief (Prestige Brands)	Naphazoline Hydrochloride 0.012%w/v	Entry level (pharmacy only medicine)
	Optrex bloodshot eye drops (Reckitt Benckiser)	Naphazoline hydrochloride 0.01% (w/v) and Witch Hazel (Hamamelis water) 12.5% (v/v)	Entry level (pharmacy only medicine)

8. Medication choice

It is clear that there is a wide range of anti-allergic available to manage SAC and PAC from entry level to independent prescribing therapeutic status. Importantly no topical mast cell stabiliser or antihistamine medications have been shown to be superior to the other in terms of efficacy and onset of action, although topical antihistamines provided relief sooner [54]. Interestingly, there appears to be no studies in the scientific literature examining the safety and efficacy of mast cell stabilisers and antihistamines in combination versus use alone and placebo where the results may prove useful to entry level optometrists who have access to few anti-allergic agents. Despite their clinically plausible supportive role, there is also a lack of evidence regarding the relative efficacy non-pharmacological therapies such as tear supplements/lubricants and cold compresses in relieving the signs and symptoms of allergic conjunctivitis. However, the dual action agents may prove to be the agent of choice in SAC as it permits the use of one medication and twice daily dosing which simplifies the treatment regimen and encourages compliance. Recent studies comparing the efficacy of dual action agents have shown conflicting results. Borazan et al. [98] compared the efficacy of olopatadine, ketotifen, epinastine, emedastine and the steroid fluorometholone in an environmental model and found no significant difference between the anti-allergic medications but they were all superior to the steroid. However, Lanier et al. [99] and Mah et al. [100] showed olopatadine superior to epinastine in conjunctival challenge models, but these conflicting results may be due to the different methodologies employed. It is important to appreciate that conjunctival challenge models are considered the gold standard in determining the efficacy of anti-allergic medications as they replicate the hypersensitivity reaction of the conjunctiva in a physiologically accurate and controlled manner [101–103]. However, the concentration of the allergen used in these studies is several hundred to a thousand times greater than normally experienced by the conjunctiva and does not reflect the constant exposure of the allergen as a single dose is applied to simulate allergic conjunctivitis. Therefore despite the advantage of simulating and controlling the hypersensitivity response of the conjunctiva the conjunctival challenge model does not represent true allergen exposure.

In other conjunctival challenge model studies olopatadine is also found to be superior to the dual action medications azelastine [104], ketotifen [105], the antihistamine levocabastine [106] and the mast cell stabiliser sodium cromoglycate [107]. In contrast, olopatadine was similar to nedocromil in treating PAC in a study by Alexander et al. [108] and D'Arienzo et al. [109] found no significant difference between the efficacy of emedastine and ketotifen. Reviews of

a variety of anti-allergic medications by Borazan et al. [98] and Figus et al. [110] comparing dual action agents, antihistamines and mast cell stabilisers have also found no significant difference in efficacy in patients with signs and symptoms of allergic conjunctivitis. In light of the conflicting findings, further research using conjunctival challenge models comparing anti-allergic agents are necessary to determine most effective agents for SAC and PAC. Indeed, there is a need to standardise clinical trials to allow meaningful comparisons between the plethora of anti-allergic medications and aid meta-analyses of their efficacy [111]. Based on current evidence, the choice of which drug to prescribe should therefore relate to the frequency of applications, cost and patient preference in addition to contraindications and potential interactions, rather than onset of action [54].

9. Summary

SAC and PAC are the most common types of allergic eye disease, and the prevalence of allergy is expected to increase rapidly. Currently allergic eye disease is not well managed and the prevalence of ocular allergy may be underestimated. Despite SAC and PAC being relatively mild, they can significantly affect the quality of life including economic impacts. Knowledge of the causes, signs and symptoms of SAC and PAC is essential in addition to a sound understanding of the different classes of medications used in treatment for successful management. SAC and PAC are both type 1 IgE mediated hypersensitivity reactions where the mast cell plays a prominent role. Binding of the allergen to the IgE molecules on sensitised mast cells causes the mast cell to degranulate and release inflammatory mediators which cause the signs and symptoms of allergic conjunctivitis. The management of SAC and PAC involves both non-pharmacologic and pharmacologic interventions. In all presentations, a detailed history is essential for differential diagnosis and may help to identify the offending allergen. Allergen avoidance measures are the best method of preventing a hypersensitivity reaction and should be encouraged alongside any topical therapy. The use of cooled artificial tears, saline or cold compresses should be considered as adjunct therapy in the self-management of SAC and PAC or between doses of pharmacologic agents but further study is required to demonstrate efficacy and clarify their role.

It is likely that at some stage that topical anti-allergic medication will be necessary as it is often not possible to completely avoid the offending allergen. With increasing knowledge of the pathophysiology and immunological mechanisms of allergic eye disease a wide variety of agents have been developed that target the cells and inflammatory mediators in the hypersensitivity reaction. Both mast cell stabiliser and anti-histamines have good safety profiles

and proven to be significantly more effective compared to placebo. Pure mast cell stabilisers such as sodium cromoglycate should be used prior to the onset of symptoms particularly in the long term management of PAC but it has no effect on the inflammatory mediators following mast cell degranulation. Antihistamines can be used to bring about symptomatic relief in SAC as they competitively and reversibly block H1 receptors from binding with histamine, a potent inflammatory mediator. Topical ophthalmic agents containing vasoconstrictors are limited to certain patient populations owing to their anticholinergic effects and can only be used in the short term. Oral antihistamines should be considered alongside topical anti-allergic medication where multiple organs are affected as in hay fever. Studies comparing the efficacy of mast-cell stabilisers and antihistamine have found no significant difference in treating allergic conjunctivitis but antihistamines have a faster onset of action. However, dual action anti-allergic medications which combine both mast cell stabilising and antihistaminic properties such as olopatadine and epinastine have been shown to be superior to pure mast cell stabilisers and antihistamines in some studies, but similar efficacy in others. They also have the advantage of twice daily dosing, but only azelastine is indicated for the long term treatment of PAC. However, more studies with consistent methodologies are needed to elicit the most effective anti-allergic medications.

Severe cases of SAC and PAC are rare but may require the use of topical NSAIDs and pulsed steroid therapy to achieve control of the disease. Patients contraindicated for corticosteroid therapy may be treated with topical immunomodulating agents. Persistent, severe and multisystem allergic disease refractory to conventional treatment should be referred for immunotherapy. In addition a variety of strategies can be employed to maintain contact lens wear in mild to moderate cases of allergic conjunctivitis but ceasing wear until resolution remains the best solution.

Rather than the onset of action the choice of which agent to use should be based upon indications, contraindications, potential interactions and adverse effects of the medication; frequency of application; patient preference and cost in addition to optometrist competence. Entry level optometrists have access to few anti-allergic medications but must play a vital role in providing advice and supportive therapy. Although only available to therapeutically trained optometrists, dual action medications are likely to become the first line pharmacologic agent of choice in treating SAC and PAC. They demonstrate both prophylactic and therapeutic uses and fewer applications which serve to encourage patient compliance with treatment and offer patient convenience.

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