

Seasonal and Perennial Allergic Conjunctivitis

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Received: April 1, 2009; Accepted: April 7, 2009; Revised: April 13, 2009

Abstract: Seasonal and perennial allergic conjunctivitis are IgE-mediated, hypersensitivity ophthalmic conditions characterized by ocular pruritus, epiphora, and hyperemia. Proper diagnosis is usually made clinically based on history and physical examination. Diagnostic procedures are rarely necessary. Non-pharmacological measures, such as environmental modification and proper eye care, should be considered for all patients with allergic conjunctivitis. Pharmacological interventions may also be required. Milder cases can be treated with short-term topical ophthalmic therapy such as a decongestant/antihistamine combination, a mast cell stabilizer, or a multi-action agent. Moderate to severe cases may require longer usage of the above agents or the addition of an oral antihistamine. Refractory cases may necessitate the use of topical ophthalmic corticosteroids and/or immunotherapy. Despite all the available therapeutic agents, there continues to be a constant need to discover more effective ways to treat seasonal and perennial allergic conjunctivitis. This review article also discusses recent patents related to the field.

Keywords: Seasonal and perennial allergic conjunctivitis, ocular pruritus, epiphora, hyperemia, pharmacotherapy, immunotherapy.

INTRODUCTION

Ocular allergy is a common hypersensitive disorder. The disorder can be divided into several categories, namely, seasonal allergic conjunctivitis (SAC), perennial allergic conjunctivitis (PAC), atopic keratoconjunctivitis, vernal keratoconjunctivitis, and giant papillary conjunctivitis [1,2]. This paper will focus mainly on SAC and PAC as they represent the majority of all ocular allergy cases [3]. Both SAC and PAC generally occur in response to the contact of circulating airborne allergens with the ocular mucosal surface, leading to IgE-mediated hypersensitivity reactions. These may manifest as ocular pruritus, erythema, and tearing.

EPIDEMIOLOGY

SAC and PAC are the most common forms of ocular allergy [3,4]. In one study, over 90% of the ocular allergies are related to either SAC or PAC [4]. The exact prevalence of SAC and PAC is difficult to ascertain, as there is no specific criteria for defining the problem [5]. To further complicate the matter, many studies provided prevalence data on "allergic rhinoconjunctivitis", a similar and related allergic condition involving both the eyes and the nose. Very few studies provided similar data on the isolated involvement of the eyes. Nevertheless, recent studies showed that allergic conjunctivitis might affect up to 40% of the adult population in the United States [6,7]. There is a paucity of such data in the pediatric population, with most studies concentrating on children with both nasal and ocular symptoms. In a worldwide study, the prevalence of rhinocon-

junctival symptoms was 14.6% for children 13-14 years of age [8]. In general, industrialized countries report higher allergy prevalence [2].

SAC and PAC share some similarities but differ in their timing, duration, and respective triggers. SAC is characterized by an acute to subacute onset and a more periodic duration, with a seasonality pattern closely linked to the type of allergen present in the air, particularly pollens. Ocular symptoms tend to be more severe between May and August [6]. In general, tree pollens cause symptoms in the spring, grass pollens in the summer, and weed pollens in the fall [9].

PAC occurs less commonly than SAC [4]. PAC is more chronic in nature, often lasting for the entire year. The severity of the symptoms is usually milder than those of SAC. Dust mites, animal dander, feathers, and mold are the most common airborne allergens implicated [9].

PATHOGENESIS

SAC and PAC are both IgE-mediated hypersensitivity conditions, involving an acute-phase as well as a late-phase response [3,9-15]. On exposure of the conjunctiva to an aeroallergen, the aeroallergen is taken up by antigen-presenting cells (e.g. Langerhans cells and dendritic cells) in the conjunctiva, processed, and presented to T lymphocytes, setting up the sensitization process. The resultant inflammatory mediators induce the production of the allergen-specific IgE antibodies by B lymphocytes.

The acute phase reaction begins with the conjunctival re-exposure to the same aeroallergens and the binding of these antigens to the previously formed IgE antibodies. The resultant antigen-antibody complexes then interact with the mast cells, which are concentrated in the substantia propria of the conjunctiva. These mast cells play a key role and can

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increase substantially in allergic conjunctivitis. In one study, the mast cell number increased by 61% when comparing patients with SAC to normal subjects [12]. This process causes the degranulation of these cells with immediate release of performed chemical mediators including vasoactive amines such as histamine, proteoglycans (e.g. heparin), and proteases (e.g. tryptase and chymase) [10, 13]. Histamine, in particular, induces vasodilation and increases vascular permeability and mucous secretions, resulting in symptoms such as ocular pruritus, erythema, and tearing. The acute-phase reactions typically subside within 30 to 60 minutes. In addition to the release of preformed mediators, activated mast cells generate *de novo* mediators such as lipid mediators (e.g. prostaglandins and leukotrienes) and cytokines (e.g. interleukins and tumor necrosis factors α (TNF α)), some of which may be partially responsible for the late phase reaction [10].

Late-phase reactions generally occur several hours later with an influx of inflammatory cells, including neutrophils, lymphocytes, eosinophils, mast cells, basophils, and adhesion molecules such as ICAM-1 [11,14,16,17]. This phase can prolong the symptoms experienced by the patients. In a review [16] of multiple studies, 33 to 100% of the patients, upon receiving conjunctival provocation tests, had late phase reactions approximately 4 to 24 hours after the early phase reaction.

CLINICAL MANIFESTATIONS AND EVALUATION

Symptomatology

The symptoms of both SAC and PAC are very similar [3,9,14,18]. Ocular/peri-ocular pruritus is pathognomonic [3]. Other symptoms may include conjunctival burning, stinging, tearing, eyelid swelling, and photophobia. Some patients report gritty, foreign body sensations in the eyes. Most patients have bilateral involvement, with one eye worse than the other in some cases. Features of other allergic or atopic co-morbidities such as allergic rhinitis, atopic dermatitis, and asthma may coexist.

The onset, duration, seasonality, and periodicity of the symptoms can help confirm the diagnosis of SAC and provide clues as to the possible triggers involved. Questions about household environment and pets can provide information about the potential causes of PAC. Allergic conjunctivitis may have significant impact on general health and well-being. One study found that patients with SAC had impaired quality of life based on the validated Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) [19]. Affected areas included sleep disturbance, emotional effects, and effects on daily activities. Another scale used was the National Eye Institute (US) Visual Functioning Questionnaire 25 (VFQ-25). This validated questionnaire, which included items such as ocular pain, color vision, peripheral vision, near vision, and distance vision, had been used extensively to measure quality of life for a wide number of eye conditions. In this study, SAC was also associated with poorer perception of health and negative economic impact.

Physical Findings

The clinical examination should include both the peri-ocular and the ocular regions [3,9,14,18]. Initial screening of visual acuity is important. The conjunctiva may demonstrate hyperemia and chemosis [3,9,14,18]. Peri-orbital edema is a sign of acute ocular allergy. Lid edema and papillary hypertrophy along the tarsal conjunctival surface may sometimes occur [14]. Dark circles under the eyes, as a result of venous congestion, can sometimes be seen.

DIFFERENTIAL DIAGNOSIS

Vernal keratoconjunctivitis is a chronic bilateral ocular inflammatory process characterized by intense ocular itching, foreign body sensation, photophobia, and tearing [2, 18]. It generally affects children and young adolescents. Physical examination often shows giant papillae (up to 8mm in diameter) on the tarsal conjunctiva, white fibrinous discharge, yellow-white dots on the conjunctiva/limbus, Dennie's line, or corneal ulcers [2, 18]. Atopic keratoconjunctivitis is an ocular manifestation of atopic dermatitis [18]. The condition is characterized by intense ocular itching, burning, and tearing. Physical examination may show lid eczema. Complications may include chronic blepharitis and cataract formation [2, 18]. Giant papillary conjunctivitis is a chronic immune response to long-term exposure to foreign bodies (e.g. contact lenses) in the eyes [2, 18]. Affected patients may present with mucoid eye discharge, itchy foreign body sensation in the eyes, and conjunctival redness [18].

Bacterial and viral conjunctivitis must be ruled out. Conjunctival hyperemia is a common finding. Other important clues include the absence of pruritus, the presence of signs and symptoms of other upper respiratory infections (e.g. pharyngeal involvement, fever, enlarged lymph nodes), and the more acute nature of the conditions. A purulent ophthalmic discharge and a velvety, beef-red conjunctiva suggest a bacterial cause [14]. Other entities that can present as "red eyes", such as scleritis, uveitis, glaucoma, and corneal abrasion should also be part of the differential diagnosis. Scleritis is accompanied by scleral injection and ocular pain while uveitis presents with ciliary injection around the limbus. Narrow-angle glaucoma can present with pain, a sluggish or fixed papillary response, and visual impairment. Corneal abrasion is characterized by ocular pain, tearing, photophobia, and decreased vision. The abrasion can be detected by instilling fluorescein dye and inspecting the cornea using a blue-filtered light. In the pediatric population, Kawasaki disease, a self-limiting, vasculitic disease, can present as a non-exudative conjunctivitis. Other signs pointing toward this diagnosis include oral mucosal changes, desquamation of the peripheral extremities, polymorphous rash, and cervical lymphadenopathy.

DIAGNOSTIC STUDIES

The majority of allergic conjunctivitis can be diagnosed with a careful history and a thorough physical examination.

Most of the diagnostic procedures are performed either for confirmation of doubtful cases or for academic/research purposes [3,9,14]. Conjunctival scrapings can be used for the diagnosis of allergic conjunctivitis. The eye is usually treated with a topical ophthalmic anesthetic such as tetracaine. Conjunctival sampling from the inner lower lid can then be taken, spread and stained on a glass slide. The discovery of eosinophils in the conjunctival sample is indicative of allergic conjunctivitis. Up to 80% of patients with allergic conjunctivitis will have positive findings. The absence of eosinophils should prompt the clinician to repeat sampling as eosinophils may situate deep in the conjunctiva. Purulent ophthalmic discharge should be sent for culture.

Ocular provocation tests can be performed by instilling an allergen-containing solution into the conjunctival sac [14, 20]. Post-provocation reproduction of the patient's symptoms and signs helps to identify the offending allergens.

MANAGEMENT

The management of both SAC and PAC are quite similar and involve both non-pharmacological measures and pharmacologic modalities.

Non-Pharmacological Measures

All patients with SAC and PAC should consider non-pharmacological measures. These interventions may include environmental modification through the identification to avoid primary triggers and general eye care using eye lubricant, proper contact lens care, and eye compresses [3, 9, 14]. They are mainly based on expert opinion and consensus.

Environmental Modification

The avoidance of triggers and allergens is the mainstay of the management [3, 9, 14]. Strategies possibly effective for SAC prevention include avoiding outdoor activities during high pollen times, keeping house and car windows closed during peak seasons, and using indoor air conditioner and air filtering systems.

For the prevention of PAC, indoor allergens can be minimized by using physical barriers (e.g. covers for mattress, pillows, and beddings), by minimizing reservoirs (e.g. old carpet, upholstery, and plush toys), and by reducing allergen load (e.g. washing pillows and mattresses). If animal dander is the trigger, contact with any pet or visitation to any home with pets should be minimized.

General Eye Care

Decreased tear production or increased tear evaporation can contribute to the symptoms of gritty feeling in the eyes, pruritus, pain, and photophobia [18,21-23]. Certain medications, such as antihistamines, antipsychotics, and anticholinergics, can lead to dryness in the eyes [24-26]. Therefore, the reduction in the use of these medications is part of the management for SAC and PAC. Eye lubricants, which contain saline and other components such as methylcellulose, can be invaluable for relieving the symptoms of allergic conjunctivitis by keeping the ocular surface moist and by potentially diluting the tear levels of allergen and mediators. Frequent applications up to six times daily of

these artificial tears can be effective. Numerous brands of ocular lubricants are available and their choices are based on effectiveness on the individual and patient preference. Cold compresses and sterile irrigation can also be used to provide further relief of the pruritus often seen with allergic conjunctivitis [3,9].

Contact lenses, particularly the soft ones, can increase allergen accumulation by disallowing proper tear exchange underneath the lenses. They may also contribute to tear film insufficiency by permitting greater tear evaporation from the lens. Contact lens wear during allergic episodes can increase irritation to the eyes [27]. Preservatives, such as thimerosal and sorbate, in contact lens solutions can further sensitize the eyes.

Pharmacotherapy

Patients with SAC and PAC who do not find non-pharmacological measures alone adequate or practical may resort to pharmacotherapy [3,9,14]. There are several major classes of medications currently available for the management of allergic conjunctivitis: decongestants, antihistamines, mast cell stabilizers, multi-action agents, and corticosteroids Table 1. For milder cases, short-term usage of topical ophthalmic product such as a decongestant/antihistamine combination, a mast cell stabilizer, or multi-action agent will suffice. The choice of products depends on individual patient's response and tolerability as well as the practitioner's familiarity with the products. Moderate to severe cases may require longer usage of the above agents or the addition of an oral antihistamine. Refractory cases may sometimes necessitate the use of topical corticosteroid and/or immunotherapy.

Table 1. Pharmacotherapy for SAC and PAC

Decongestants (Topical)	Naphazoline, tetrahydrozoline, oxymetazoline, phenylephrine
Antihistamines (Oral)	First generation: chlorpheniramine, diphenhydramine, hydroxyzine, pheniramine Newer generation: loratadine, desloratadine, fexofenadine, cetirizine
Antihistamines (Topical)	First generation: pheniramine Newer generation: levocabastine, emedastine
Mast cell stabilizers (Topical)	Sodium cromoglycate, lodoxamide, pemirolast
Multi-action agents (Topical)	Nedocromil, olopatadine, ketotifen, azelastine, epinastine
Non-steroidal anti-inflammatory drugs (Topical)	Ketorolac, diclofenac
Corticosteroid (Ophthalmic)	Prednisolone, dexamethasone, loteprednol Other ophthalmic corticosteroid not mentioned: rimexolone, fluorometholone, medrysone

Decongestants

Topical decongestants are generally adrenergic agonists that act as vasoconstrictors. Agents such as naphazoline, tetrahydrozoline, oxymetazoline, and phenylephrine, provide short-term symptomatic relief by reducing edema and erythema [28-31]. These vasoconstrictive agents are usually packaged with topical antihistamines [e.g. pheniramine] as combination products and their combined effect is generally considered more effective than either one alone [31-33]. The usual recommendation is the instillation of one to two drops up to four times daily during acute episodes. Adverse reactions are uncommon for short-term usage. The most common side effect is local burning [34]. One of the more recognized drawbacks of topical decongestant is conjunctival inflammation after prolonged use [30]. One study identified several patterns of conjunctival inflammation after daily decongestant use for a median of three years. The most common pattern was a pharmacologically induced conjunctival hyperemia upon sudden withdrawal of the vasoconstrictor after prolonged use. All patterns of conjunctival inflammation generally resolved after a median time of 4 weeks [34].

Antihistamines

In the conjunctiva, histamine activates both H₁ and H₂ receptors, leading to local vasodilation, increased vascular permeability, and pruritus. Antihistamines, both systemically and topically, are used for the management of SAC and PAC [25]. First generation oral antihistamines, such as chlorpheniramine, diphenhydramine, hydroxyzine, and pheniramine, have been useful in reducing histamine related effects; however, they are non-selective and cause significant drowsiness [25,35,36]. They also cause a number of unwanted anticholinergic side effects such as dryness of the nose and mouth, constipation, and altered mental state, particularly in the elderly [37]. Furthermore, they can lead to dry eyes, which would complicate the symptoms of allergic conjunctivitis [30].

Second generation oral antihistamines are more specific for the H₁ receptors [35]. Multiple studies reported clinical effectiveness with their use in allergic conjunctivitis [38-43]. Furthermore, they can be used to treat coexisting allergic rhinitis. However, terfenadine and astemizole can cause serious cardiovascular events, including QT prolongation, torsades de pointes, and cardiac dysrhythmia, particularly in patients with underlying cardiac diseases or serious hepatic impairment [35,44]. Terfenadine and astemizole were withdrawn from the US market in the late 1990s. The newer agents, such as loratadine, desloratadine, fexofenadine, and cetirizine, do not induce these cardiotoxic effects. They are also less lipophilic than their first generation counterparts and, thus, cross the blood-brain barrier poorly, thereby minimizing their sedative effect [36]. Due to their better safety profile, these medications have mostly replaced the first generation oral antihistamines for ocular allergies. These medications also seem to be effective and safe in children [45]. In general, however, oral antihistamines should not be used as monotherapy but, rather, as adjuncts to topical therapy due to their slower onset of action and their less direct site of action. Several studies demonstrated better results with combined oral and topical therapy [9,46-48].

As mentioned before, topical antihistamine is widely available as combination products with topical decongestant. These topical over-the-counter products usually contain first generation antihistamines that may be more irritating to the eyes and, due to their non-selective nature and anticholinergic effect, may potentially lead to unwanted photophobia and blurred vision. They may also produce a mydriatic effect that would make them contraindicated in narrow-angle glaucoma. Although rapid in onset, often faster than that of oral antihistamines, they have very short duration of action, usually lasting only two hours [9,30].

Newer generation topical antihistamines are more effective and tolerable. Levocabastine, often given as a 0.05% solution up to four times daily, is a specific H₁ antagonist that produces a more rapid onset and a longer duration of action [30]. Some studies demonstrated the effectiveness of levocabastine in relieving ocular symptoms [49-51]. Levocabastine was shown to be at least as effective as mast cell stabilizers, such as sodium cromoglycate [52-54] and lodoxamide [55], and multi-action agent, such as nedocromil [56]. This medication exerts little systemic effect as only a small amount of the drug is absorbed systemically. The most common side effect is local stinging and burning.

Emedastine, another selective topical antihistamine, is generally given as a 0.05% solution up to four times daily. In several trials, emedastine, when compared to levocabastine, seemed to be more effective [57-60]. There are also studies showing that emedastine was better in reducing pruritus and erythema than other agents, such as loratadine [47] and nedocromil [61], and was at least equivalent in efficacy to ketotifen, a multi-action agent [30,62]. The most common side effect for emedastine is headache.

Mast Cell Stabilizers

Mast cell stabilizers exert their effects by inhibiting the antigen-induced degranulation process of the mast cells, preventing the exocytosis of preformed mediators that eventually lead to SAC and PAC. They have no effect on already-synthesized and released inflammatory mediators [30]. As such, mast cell stabilizers are more effective if started early and used prophylactically. Their onset of action is much slower, often taking two to three days. The requirement for frequent administration at four times daily reduces compliance in patients [30]. They are all well tolerated and safe. The classic example is sodium cromoglycate. Other agents in the same family include lodoxamide and pemirolast.

Sodium cromoglycate, available as a 4% solution, usually acts slowly and requires two to five days of frequent administration, up to four to six times daily, before onset of symptom relief occurs. It also requires two weeks for maximal effect. The medication is effective in the relief of allergic symptoms, such itching and tearing [63-70]. When compared to multi-action agents, sodium cromoglycate appeared to be similar in efficacy to azelastine [67] but inferior to ketotifen [68]. In one study comparing with olopatadine, sodium cromoglycate was comparable in reducing ocular itchiness and redness at 4 hours but significantly less effectiveness at 42 days [69]. The major adverse effect is local burning/stinging [30].

Lodoxamide, available as a 0.1% solution, is 2500 times more potent than cromoglycate in preventing the release of mediators from mast cells [14,30]. One randomized, placebo-controlled trial in patients with allergic conjunctivitis showed that patients on lodoxamide for 4 weeks had significantly fewer symptoms of pruritus, photophobia, tearing, and swelling than patients on cromoglycate [67]. In a head-to-head trial with levocabastine, both medications appeared to be equal in effectiveness and safety [55].

Pemirolast, available as a 0.1% solution, is 100 times more potent *in-vitro*, than sodium cromoglycate [30]. It was significantly better than placebo in reducing ocular symptoms [71]. Pemirolast was similar effectiveness in symptom improvement when compared bromofenac [72], a non-steroidal anti-inflammatory drug (NSAID), and nedocromil [73]. A clinical trial showed that pemirolast could be used effectively as a twice daily versus a four times daily regimen [74]. This can potentially improve compliance.

Multi-Action Agents

There are several medications in this class of topical therapy characterized by inhibition of allergy by multiple pathways. Most of the available agents, including nedocromil, olopatadine, ketotifen, azelastine, and epinastine, involve mainly the combined antihistaminic, anti-inflammatory, and mast cell stabilizing action [30]. Many of them also inhibit the expression of ICAM-1, an adhesion molecule required for the infiltration of inflammatory cells. In general, all of these medications are well tolerated.

Nedocromil has originally been classified as a pure mast cell stabilizer, similar to sodium cromoglycate. However, recent evidence showed that nedocromil has other activities, such as its inhibitory effects on H_1 receptors, tumor necrosis factor α , and inflammatory cells (e.g. eosinophils and neutrophils) [14,30,75]. Placebo-controlled studies demonstrated the ability of nedocromil to reduce pruritus in allergic conjunctivitis, particularly in SAC [76-80]. It was postulated that nedocromil can act more rapidly than sodium cromoglycate because of its added anti-inflammatory action [75]. However, there was no difference in clinical outcome in a head-to-head study comparing nedocromil with sodium cromoglycate for SAC [81]. Nedocromil can be given as a 2% solution on a twice-daily basis.

Olopatadine possesses inhibitory activity against H_1 receptors and inflammatory lipid mediators [30, 82, 83]. It also has mast cell stabilization capability [30, 82, 83]. Placebo-controlled studies demonstrate significant clinical improvement with the use of olopatadine [84-86]. When compared to other medications in conjunctival allergen challenge models, olopatadine was shown to be superior than other multi-action agents, including nedocromil [87], ketotifen [88] and azelastine [89], and ketorolac [90]. Clinical trials also showed that olopatadine was more effective in reducing ocular symptoms than nedocromil [91] and sodium cromoglycate [69]. The medication, originally available as a 0.1% solution for twice daily administration, has been marketed recently as a 0.2% solution for once daily administration to enhance compliance [92-94].

Ketotifen, given as a 0.025% solution in a twice-daily dosing regimen, acts on several different pathways. It is a

non-competitive H_1 antagonist, a mast cell stabilizer, an inhibitor of leukotriene formation, and an inhibitor of eosinophils [30]. Ketotifen was found to be superior in the relief of ocular symptoms, particularly pruritus and hyperemia, when compared to placebo and cromoglycate [95]. On the other hand, when compared head to head with olopatadine, the current literature exhibited mixed results [96-98].

Azelastine interferes with calcium influx in mast cells, inhibits H_1 histamine receptor, reduces eosinophil chemotaxis, and inhibits platelet-activating factor [14,30]. Azelastine is available as a 0.05% solution for twice daily administration. Azelastine, when compared to placebo, appeared to be more effective in patients with PAC [99, 100] and SAC [101, 102]. Azelastine seemed to be similar in effectiveness when going head-to-head against sodium cromoglycate [67] and levocabastine [103]. One study indicated that azelastine was less effective in the management of pruritus when compared to olopatadine [89].

Epinastine, a combined H_1 and H_2 antagonist and mast cell stabilizer, can be used for the prevention of pruritus in allergic conjunctivitis [14,30,104]. Epinastine can be given as a 0.05% solution twice daily. The medication has a very rapid onset of action with long lasting effects (at least 8 hours) [105]. Several studies compared epinastine to other agents. Epinastine was similar to levocabastine in the ability to reduce ocular pruritus and hyperemia. [106]. When compared to olopatadine, epinastine appeared to be less effective [107, 108]. The medication is well tolerated and is not associated with any higher adverse events than placebo [104].

Non-Steroidal Anti-Inflammatory Drugs (NSAID)

Ketorolac and diclofenac act by binding to the cyclooxygenase thereby blocking prostaglandin synthesis [14,30]. Topical application of these medications is effective in relieving symptoms of ocular pruritus and hyperemia in allergic conjunctivitis [109-111]. Both medications are generally well tolerated, with local stinging and burning being the most common side effects [30]. Compared to corticosteroids, ketorolac and diclofenac do not mask ocular infection, affect wound healing, increase intraocular pressure, or contribute to cataract formation [30].

Corticosteroids

Corticosteroids act mainly on the inflammation pathway. By inhibiting phospholipase A, corticosteroids block the synthesis of both prostaglandins and leukotriene from arachidonic acid. They also prevent the production of inflammatory proteins at the nuclear transcription level [30]. Two commonly used ophthalmic corticosteroids include prednisolone and dexamethasone. Corticosteroids are strong anti-inflammatory medications and, when instilled into the eyes, can cause potentially serious side effects such as increased intraocular pressure, cataracts, and infections of the cornea and conjunctiva [14,30]. In general, topical corticosteroids are reserved for more persistent and/or severe cases of allergic conjunctivitis [14].

Loteprednol, a newer generation corticosteroid for ophthalmic use, has been shown to be effective for allergic conjunctivitis [112, 113] and, because it is broken down

quickly into inactive metabolites, has a less propensity to increase intraocular pressure [114]. A retrospective review showed that loteprednol was safe to use for over 12 months in patients with SAC and PAC [115]. Nevertheless, ophthalmic corticosteroid use requires constant monitoring and is contraindicated in patients with infectious ocular diseases.

Immunotherapy

Immunotherapy should be considered for patients who do not respond to conventional pharmacotherapy [116]. Allergen immunotherapy involves a process of introducing allergens in increasing doses over extended periods of time to individuals in order to slowly enhance tolerance to the allergens. Studies have also shown that subcutaneous immunotherapy is effective in reducing conjunctival symptoms with resultant better quality of life, and reduced the need for medication use [117-119]. One study has even demonstrated that children who have had pollen immunotherapy for seasonal rhinoconjunctivitis had a reduction in the future development of asthma [120]. On the other hand, a recent systematic review of immunotherapy in children and adolescents with allergic rhinoconjunctivitis did not find conclusive evidence for positive effects from immunotherapy [121]. Currently, there is a lack of evidence for the use of immunotherapy as the primary therapeutic modality in allergic conjunctivitis.

CURRENT & FUTURE DEVELOPMENTS

Most cases of SAC and PAC can be effectively treated with a combination of non-pharmacological measures and pharmacological modalities. Nevertheless, there are a number of patients who do not respond to these therapies. As such, there is a constant need for research on novel medical agents with different mechanism of action. Compliance has always been an issue in the management of SAC and PAC. Most medications require at least twice daily administration. Some patents of new agents, such as a once-daily formulation would simplify the treatment regimen. Olopatadine has been available as a 0.1% solution for twice daily administration. Recently, a 0.2% solution has been made available for only once daily administration [92-94].

The more novel treatment approach is the use of intranasal steroid, such as fluticasone, mometasone, budesonide, flunisolide, and beclomethasone, for the management of allergic conjunctivitis as ocular symptoms may be part of the manifestation of a general IgE-mediated allergic reaction or allergic rhinoconjunctivitis [122-127]. A meta-analysis of nine clinical trials (n=648) showed that intranasal steroids produced similar results as topical antihistamines in the treatment of ocular symptoms [128]. The mechanism of action behind intranasal steroids on the allergic eye is not fully understood. It has been postulated that reflux of medication via the nasolacrimal route, improved drainage in the nasolacrimal duct, and systemic immune effects might be responsible [122].

Recently, Marx and Muller disclosed the use of a combination of ciclesonide and an antihistamine in a nasal spray for the treatment of allergic rhinoconjunctivitis [129]. Ciclesonide, a novel corticosteroid prodrug, is converted into its active metabolite, desisobutryl-ciclesonide, by the

mucosal esterases in the respiratory tract. Such combination may potentially provide both prolonged and immediate symptom relief and allow for lower doses of each component to produce beneficial effects [130].

Another area that is creating some interest is the use of recombinant DNA technology to produce allergen specific immunotherapy vaccines [131]. In a two-year, randomized, double-blinded, placebo-controlled study of patients with rhinoconjunctivitis (n=134), recombinant birch pollen vaccine was safe and effective in treating birch pollen allergy and induced a highly specific immune response [131].

Topical tacrolimus has been found to be in the management of intractable PAC and vernal keratoconjunctivitis [132]. Tacrolimus works by binding to a cytoplasmic immunophilin. The complex inhibits the activity of calcineurin to dephosphorylate the transcription factor required to activate IL-2 gene transcription, thereby suppressing cytokine production by the T-cells [132]. In a pilot study involving 20 patients (mean age 10.8 years, range 6-26), there was significant improvement in conjunctival score after 8 weeks of application of the tacrolimus 0.03% ointment into the conjunctival sacs [132]. Adverse events were limited to local burning in one patient.

Cyclosporin is an immunomodulator that has been long used for various conditions such as rheumatoid arthritis and organ transplantation. It may have an effect in inhibiting the antigen processing and presentation to T lymphocytes. Recently, cyclosporin was found to be effective in the treatment of patients with severe allergic keratoconjunctivitis and vernal keratoconjunctivitis [133, 134]. No trial has been done on patients with steroid-dependent SAC and PAC; however, these studies may potentially provide grounds for the further investigation.

Activated mast cells, as found in allergic conjunctivitis, can produce and release TNF α , a cytokine that serves to activate endothelial cells to recruit eosinophils and other inflammatory cell types at the site of immediate hypersensitivity reactions, giving rise to the late-phase of the allergic response and sustained inflammation. An anti-TNF α drug is any agent that decreases, interferes, or blocks the activity of TNF α . It can potentially help in the relief of the symptoms of allergic conjunctivitis. Possible agents currently available include etanercept, a soluble receptor fusion protein that binds to soluble TNF to neutralize its activity, infliximab, a chimeric monoclonal antibody that binds both soluble and membrane-bound TNF, and adalimumab, a human monoclonal antibody with binding properties similar to infliximab. Recently, Yanni *et al.* disclosed an ophthalmic formulation comprising a TNF inhibitor and an H₁ receptor antagonist to treat patients with allergic conjunctivitis [135]. Such compound may provide both immediate and long-term relief of allergic conjunctivitis [135].

New targets for the treatment of SAC and PAC are constantly being found. One example is the acidic mammalian chitinase (AMCase) [136]. This protein was previously found to be increased in the lung tissues of asthmatic patients. Recently, authors from one study found that levels of AMCase were significantly increased in patients with

SAC and vernal keratoconjunctivitis when compared to healthy subjects [136]. One early study on rabbits showed that the uveitis induced by ophthalmic lipopolysaccharide instillation was associated with significant increases in the tear levels of AMCase [137]. When topical administration of known AMCase inhibitors, such as caffeine and allosamidin, were used, significant reduction in AMCase activities were observed [137].

CONFLICT OF INTEREST

Dr. Wong, Dr. Barg, and Dr. Leung have disclosed no relevant financial relationship.

ACKNOWLEDGEMENT

The authors have received no external funding for the preparation of this article.

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