
Review Article

Management of seasonal allergic conjunctivitis: guide to therapy

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ABSTRACT.

Seasonal allergic conjunctivitis (SAC) is an inflammatory response of the conjunctiva triggered by exposure to seasonal allergens. Treatment options for SAC include artificial tears, antihistamines, decongestants, mast cell stabilizers, nonsteroidal anti-inflammatory drugs, dual antihistamine/mast cell stabilizers, immunotherapy and corticosteroids. Topical, intranasal and systemic formulations of corticosteroids have traditionally provided the most effective relief of the inflammation and signs and symptoms associated with severe, acute exacerbations of SAC. However, steroid-induced ocular and systemic side-effects have limited the prescribing of these agents. This limitation of traditional corticosteroids led to the development of modified corticosteroids that retain the anti-inflammatory mechanism of action of traditional corticosteroids with a much-improved safety profile because of their rapid breakdown to inactive metabolites after exerting their activity. The development of one such novel corticosteroid, loteprednol etabonate (LE), led to the insertion of an ester (instead of a ketone) group at the carbon-20 (C-20) position of the basic corticosteroid structure. Clinical trials assessing this C-20 ester corticosteroid have demonstrated similar efficacy to C-20 ketone corticosteroids in the prevention or treatment of the signs and symptoms of SAC but with a greatly improved safety profile, as the C-20 ester corticosteroid is less likely to elevate intraocular pressure. In addition, the ketone at the C-20 position has been implicated in the formation of cataract, while nonketolic corticosteroids do not form Schiff base intermediates with lens proteins, which is a common first step in cataractogenesis. The clinical relevance of the C-20 ester corticosteroid class, as modelled by LE, is that they provide both effective and safe treatment of the inflammation associated with SAC and relief of its signs and symptoms. Loteprednol etabonate offers a well-tolerated treatment option for patients with debilitating acute exacerbations as well as chronic forms of the disease.

Key words: allergic rhinitis – C-20 ester corticosteroid – C-20 ketone corticosteroid – loteprednol etabonate – seasonal allergic conjunctivitis

Introduction

Allergic conjunctivitis, an inflammatory response of the conjunctiva to allergens such as pollens, animal dander and other environmental antigens, affects 15–40% of the population (Alexander et al. 2005; Singh & Bielory 2007a,b; Bielory & Friedlaender 2008). More than half of allergic conjunctivitis cases are classified as seasonal, or intermittent (<4 weeks in duration), allergic conjunctivitis (SAC) (Ono & Abelson 2005; Bielory 2007; Bielory & Friedlaender 2008). Seasonal allergic conjunctivitis, together with perennial, or persistent (>4 weeks in duration) allergic conjunctivitis (PAC), makes up about 95% of ocular allergy cases in the United States (Butrus & Portela 2005). However, reported rates of SAC incidence vary in the rest of the world (Bielory et al. 2007), as ocular allergy is often classified as rhinoconjunctivitis because of the common concurrence of allergic rhinitis and allergic conjunctivitis (Bielory 2006). Most cases of SAC occur during the spring and autumn when levels of seasonal allergens (i.e. pollens) are elevated (Chambless & Trocme 2004). In contrast, PAC generally occurs in response to environmental allergens (e.g. animal dander and dust mites) that are present through the year and is generally more chronic in nature (Bielory 2000; Chambless & Trocme

2004; Stahl & Barney 2004; Singh & Bielory 2007a,b; Bielory 2008).

Signs and symptoms associated with SAC include redness, periocular itching (pruritus), tearing (epiphora), burning, stinging, photophobia, watery discharge and swollen or dry eyes in differing degrees of severity with variable duration (Alexander et al. 2005; Bielory & Friedlaender 2008). Of these, redness and itching are the most consistent symptoms of allergic conjunctivitis (Ono & Abelson 2005; Bielory & Friedlaender 2008). The pathognomonic symptom is itching, without which the ocular condition is likely not ocular allergy (Ono & Abelson 2005). These SAC-related symptoms occur following a cascade of inflammatory responses when a sensitized individual is exposed to an allergen. This allergic cascade includes the release of a number of preformed and newly synthesized inflammatory mediators, such as histamine, leukotrienes and prostaglandins, as well as activation and recruitment of inflammatory cells to the site of allergen exposure (Bielory & Friedlaender 2008).

Ocular symptoms associated with allergic rhinitis are considered under-diagnosed and under-treated. Similar to ocular allergy, allergic rhinitis is recognized as imposing a substantial burden of disease, including health-related quality of life and economic impact on allergy patients (Alexander et al. 2005).

As a result of the discomfort from ocular symptoms, patients with ocular allergies may limit or completely restrict daily activities including reading, computer use and going outside (Alexander et al. 2005). In a UK study, patients with SAC reported a mean reduction of 2.3 hr of productive time per week during the allergy season (Pitt et al. 2004). A US study found that 17% of patients with ocular allergy symptoms were unable to perform daily tasks when symptoms were present (Alexander et al. 2005). The loss of productivity impacts costs; for example, in Spain, the total annual cost per patient of SAC was estimated to be approximately €350 (Smith et al. 2005). Thus, although SAC is generally not sight-threatening, patients' discomfort because of its signs and symptoms can have a significant impact on morbidity, quality of life

and productivity or working time (Dell et al. 1998).

Pathophysiology of Seasonal Allergic Conjunctivitis

The presentation of allergic signs and symptoms results from a cascade of immune responses following the first exposure of a genetically predisposed individual to a novel allergen through a process called sensitization (Pearlman 1999; Broide 2007). Neutrophils and macrophages recognize antigens by cell surface receptors that are specific for allergen structures or patterns. Toll-like receptors (TLRs) are a family of innate immune receptors that enable the host immune system to recognize and respond to antigens by triggering the earliest immune responses that lead to inflammation (Chang et al. 2006). TLR stimulation of antigen-presenting cells also leads to the activation and priming of antigen-specific naive T cells (Chang et al. 2006). Antigen presentation causes the T cells to produce cytokines that, in turn, regulate the synthesis of immunoglobulin E (IgE) and eosinophil proliferation (Broide 2007). Activated T cells interact with B lymphocytes that have encountered the same allergen (Pearlman 1999), and this interaction results in the release of additional T-helper cytokines, especially interleukin (IL)-4 (Pearlman 1999). B-cell activation leads to the production of allergen-specific IgE-class immunoglobulins that bind to high-affinity IgE receptors present on mast cells and basophils (Pearlman 1999; Broide 2007). As a result, the immune cells become 'primed' to initiate the allergic response upon re-exposure to the same allergen (Pearlman 1999; Bielory 2000; Broide 2007).

Upon exposure of the ocular surface to an allergen to which an individual has become sensitized, the interaction between an allergen and allergen-specific IgE receptors found on conjunctival mast cells results in the activation of mast cells, which undergo a process known as mast cell degranulation (Bielory 2006; Leonardi et al. 2007). The inflammatory mediators that have been implicated in contributing to the signs and symptoms

of SAC include the presynthesized mediator histamine that triggers the early phase of the allergic response, as well as the newly synthesized (*de novo*) prostaglandins, leukotrienes and other inflammatory mediators that cause a separate, secondary inflammatory cascade known as the late-phase allergic response (Fig. 1) (Bielory 2006; Leonardi et al. 2007). Histamine acts via multiple subtypes of the histamine receptor, although only H₁ and H₂ receptors have been identified in the conjunctiva (Bielory et al. 2001). The majority of the ocular allergic reaction occurs via activation of H₁ receptors (Bielory et al. 2001) by histamine, which elevates intracellular inositol phosphate, which, in turn, increases intracellular calcium and leads to the symptom of pruritus as well as the processes of inflammatory cytokine secretion and cascade (Bielory & Ghafoor 2005). In addition, activation of H₂ receptors causes some indirect responses via vasodilation (Bielory & Ghafoor 2005) that result in ocular redness (Bhargava et al. 1998). Additional downstream effects of histamine binding to H₁ and H₂ receptors in the conjunctiva include hyperaemia, oedema, fibroblast cell proliferation, cytokine secretion and increased micro-vascular cell permeability (Bielory & Ghafoor 2005).

The presence of proinflammatory mediators, prostaglandins and leukotrienes in the tear fluid is associated with the itching, redness, watering and mucous discharge that occur with SAC (Bielory 2006). Prostaglandins contribute to the increase in micro-vascular permeability that causes ocular surface hyperaemia, amplifies the pruritogenic effects of histamine as well as stimulates goblet cell discharge that leads to mucus hypersecretion (Woodward et al. 1995). In addition, prostaglandin-2 also stimulates eosinophil infiltration, leading to further inflammation as part of the late phase of the allergic reaction (Bhargava et al. 1998). Leukotrienes are found in high concentrations in tear fluid following allergen exposure along with prostaglandins to enhance vascular permeability and oedema formation and with histamine to contribute to enhanced vascular permeability (Woodward et al. 1989; Abelson 1998). Matrix metalloproteinases (MMPs) that degrade all components

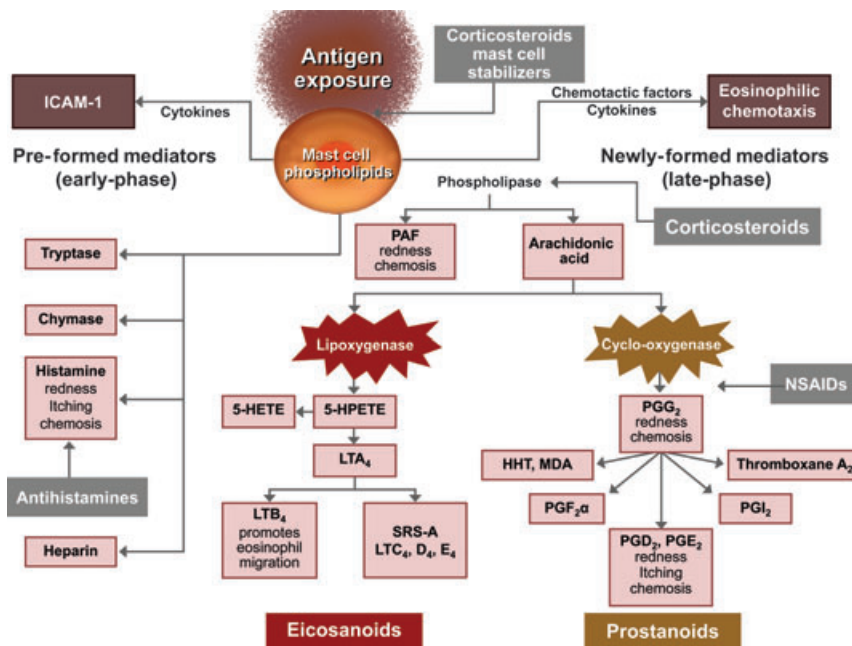


Fig. 1. Early phase and late phase of the allergic response of allergic conjunctivitis and sites of action for different treatments. ICAM-1 = intercellular adhesion molecule-1, PAF = platelet-activating factor, SRS-A = slow-reacting substance of anaphylaxis, PG = prostaglandin; LT = leukotriene, HETE = hydroxyeicosatetraenoic acid, HPETE = hydroperoxyeicosatetraenoic acid, MDA = malonyldialdehyde, HHT = heptadecatrienoic.

of the extracellular matrix are involved in inflammation related to eosinophil migration during allergic inflammation and have been found in high concentration in tears of patients with SAC (Leonardi et al. 2007).

Allergic conjunctivitis is characterized by the infiltration of inflammatory cells into the conjunctiva in approximately 25–43% of patients with SAC (Bielory et al. 2001). This infiltration of inflammatory cells into the conjunctiva occurs because of release of inflammatory mediators such as tumour necrosis factor alpha (TNF α), which up-regulates adhesion molecules such as intercellular adhesion molecule (ICAM)-1 (Leonardi 2002). Similarly, the cytokine IL-4 plays a key role in continued inflammation during the late phase of the ocular allergic response through the promotion of T-cell growth, induction of IgE production from B cells, up-regulation of adhesion molecules and regulation of T-helper type 2 (Th2) cell differentiation (Leonardi et al. 2006, 2007). IL-4 also promotes eotaxin expression and secretion from corneal stromal keratocytes and conjunctival fibroblasts, which preferentially attracts eosinophils (Leonardi

et al. 2006, 2007). Activation of these cells causes the release of additional inflammatory mediators and the propagation of the inflammatory response (Pearlman 1999). A higher proportion of conjunctival infiltration of cellular components is present in the common form of SAC compared with allergic rhinitis (Bielory 2000).

Management of Seasonal Allergic Conjunctivitis

Current therapies for the relief of the signs and symptoms associated with SAC include nonpharmacological management as well as pharmacological therapies (Table 1) (American Academy of Allergy, Asthma & Immunology 2000). When adequate relief of SAC signs and symptoms is not achieved by nonpharmacological therapies, topical or systemic pharmacological therapies are initiated (Table 1) (Bielory 2002a,b).

The initial treatment options for SAC are saline solution or artificial tears to physically irrigate, dilute and remove the allergens from the ocular surface (Bielory 2002a,b). If these fail to provide adequate relief, higher

viscosity formulations, including ointments or time-released tear replacements, may be used (Bielory 2002a,b). Many treatment options for other types of allergies such as allergic rhinitis may also provide a benefit in allergic conjunctivitis (American Academy of Allergy, Asthma & Immunology 2000; Wallace et al. 2008). Additional pharmacological treatment options include topical decongestants, antihistamines, mast cell stabilizers, nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids (American Academy of Allergy, Asthma & Immunology 2000; Bielory 2002a,b; American Academy of Ophthalmology 2003; Bielory & Friedlaender 2008; Wallace et al. 2008).

Ocular surface lubricating agents

As irrigation of the ocular surface facilitates removal of allergens, saline solutions and artificial tears help to achieve one of the primary principles of allergy management by minimizing exposure of the ocular surface to allergens (American Academy of Allergy Asthma & Immunology 2000; Bielory 2002a,b). In addition, some types of artificial tears provide relief through the lubrication of the ocular surface via a combination of saline solution with a wetting and viscosity agent (Bielory et al. 2007). If tear substitutes do not provide sufficient relief of mild SAC, ointments or time-released tear replacements, used at night, provide a longer-lasting option, delivering ocular surface lubrication while the patient sleeps (Bielory 2002a,b). These agents neither treat the underlying allergic response (Bielory et al. 2007) nor modify the activity of any of the mediators of inflammation, so their use is limited to mild SAC (Wallace et al. 2008).

Topical decongestants

Topical decongestants reduce some signs and symptoms of SAC through vasoconstriction via α -adrenoreceptor stimulation (Bielory 2002a,b). This action results in the reduction of hyperaemia, chemosis and ocular redness through the constriction of blood vessels supplying the eye (Barney & Graziano 2003). There is also some amelioration of ocular itching associated with the use of topical decongestants (American Academy of Allergy,

Table 1. Current pharmacological treatment options for seasonal allergic conjunctivitis (SAC) and associated side-effects (select list).

Class	Mechanism of relief for SAC signs and symptoms	Side-effects	Examples
Ocular surface lubricating agents (including saline/artificial tears, ointments and time-release tear replacements)	Dilution of antigens, removal of antigens from ocular surface, no direct efficacy on allergic mediators	Chronic use may be associated with problems because of effect of the preservatives, only provide temporary relief, ineffective for moderate and severe forms of SAC	Cellulose derivatives; dextran 70; gelatin; liquid polyols; polyvinyl alcohol and povidone; demulcents (carboxymethylcellulose sodium, hydroxypropyl methylcellulose)
Topical decongestants	Vasoconstriction via α -adrenoreceptor stimulation, reduced redness and oedema	Prolonged use or discontinuation can lead to conjunctivitis medicamentosa, toxic, follicular reactions, contact dermatitis, rebound redness, dilation, intolerance to the drug and masking of signs and symptoms of SAC; contraindicated in narrow angle glaucoma because of mydriatic effect	Emedastine, levocabastine, cyclopentamine, ephedrine, phenylephrine, tetrahydrozoline hydrochloride, naphazoline hydrochloride
Systemic antihistamines	Inverse agonists of histamine receptors Blocking endogenous histamine Reducing histamine-induced ocular signs and symptoms, particularly itching	Ocular dryness, sedation, possible systemic side-effects including cardiotoxicity	Promethazine, hydroxyzine, or alimemazine, cetirizine, loratadine, chlorpheniramine
Topical antihistamines	Similar to systemic antihistamines with localized effect	Local irritation, increased sensitivity, aggravated allergy, severe side-effects with older agents	Diphenhydramine hydrochloride, mepyramine or pyrilamine, olopatadine, ketotifen, azelastine
Mast cell stabilizers	Prevent degranulation of mast cells Prevent release of inflammatory mediators Decrease redness, hyperaemia, itching and irritation	Minimal tolerability concerns because of stinging and burning upon instillation, works best when started before symptoms occur	Cromolyn sodium, lodoxamide, pemirolast sodium, ketotifen, nedocromil
Antihistamine/decongestants	Inverse agonists of histamine receptors plus vasoconstriction via α -adrenoreceptor, reduced itching, redness and oedema	Irritation, possible conjunctivitis medicamentosa, take longer to relieve symptoms, sedation, excitability, dizziness or disturbed co-ordination, effect may last only a few hours, mydriatic effect	Naphazoline/pheniramine maleate
Antihistamine/mast cell stabilizers	Inverse agonists of histamine receptors plus mast-cell-stabilizing activity, providing relief of redness, hyperaemia, itching and irritation	Stinging, burning, distinctive bitter taste, headache, cold symptoms, take longer to relieve symptoms, sedation, excitability, dizziness or disturbed co-ordination, effect may last only a few hours	Olopatadine, ketotifen, azelastine, bepotastine, epinastine
Nonsteroidal anti-inflammatory drugs (NSAIDs)	Block cyclooxygenase and production of prostaglandins, reduced itching	Discomfort upon instillation, stinging and burning	Ketorolac, diclofenac, nevanac
Corticosteroids	General anti-inflammatory effects, attenuation of activity of inflammatory cells, reduction of most ocular signs and symptoms of SAC	Increased intraocular pressure, glaucoma, cataract formation, delayed wound healing	Loteprednol etabonate, prednisolone, fluorometholone

Asthma & Immunology 2000). As with artificial tears, topical decongestants do not reduce the allergic

response, because they do not antagonize any of the mediators of allergic inflammation (American Academy of

Allergy, Asthma & Immunology 2000; Bielory 2002a,b; Wallace et al. 2008). Prolonged use of topical deconges-

tants as well as the discontinuation of these agents following prolonged use can lead to rebound hyperaemia ('*conjunctivitis medicamentosa*') (Spector & Raizman 1994; Barney & Graziano 2003). To minimize this potential side-effect, exposure to topical decongestants should be limited through less frequent dosing or shorter treatment durations (Meyer 2006).

Antihistamines

Antihistamines act via histamine receptor antagonism to block the inflammatory effects of endogenous histamine and to prevent or relieve the signs and symptoms of SAC that are associated with histamine (Bhargava et al. 1998). In addition, some topical antihistamines may have general anti-inflammatory effects that occur because of the prevention of the late phase of the allergic response (The Medical Letter 2007). Most antihistamines employed in the treatment of allergy are inverse agonists of the H₁ receptor subtype, although some agents may have affinity for other subtypes (Bielory et al. 2004; Bousquet et al. 2008).

Systemic antihistamines may be used to control the symptoms of rhinoconjunctivitis, but these agents may have only partial efficacy for ocular symptoms (Bhargava et al. 1998; Butrus & Portela 2005; Bielory & Friedlaender 2008). In addition, the use of systemic antihistamines may potentially lead to side-effects, including sedation, ocular drying and cardiotoxicity (Bhargava et al. 1998; Butrus & Portela 2005; Bielory & Friedlaender 2008). As a result, systemic antihistamines are not usually recommended for the treatment of SAC unless it is accompanied by other rhinoconjunctivitis symptoms (Butrus & Portela 2005).

As an alternative to systemic antihistamines, several formulations of topical antihistamines are available (Bhargava et al. 1998; Butrus & Portela 2005). Because these agents are applied directly to the ocular surface, they offer more efficient localized delivery of the drug to the site of allergic inflammation and provide more rapid relief of SAC than systemic antihistamines (Butrus & Portela 2005). Topical application of antihistamines can be irritating to the

eye and can potentially lead to sensitivity reactions and aggravation of allergic responses (Bielory 2002b). In addition, older topical antihistamines may nonspecifically bind to other ocular receptor types, such as the muscarinic receptors, potentially leading to adverse side-effects including ciliary muscle paralysis, mydriasis, photophobia and angle closure glaucoma (Bielory 2002b) and may preferentially exacerbate dry eye (tear film dysfunction) that may coexist with ocular allergy.

Immunotherapy

Allergic rhinitis treatment with allergen immunotherapy has prevented progression of other atopic conditions (Bielory & Mongia 2002). For allergic patients who had asthma and rhinoconjunctivitis when exposed to animal dander [Fel d-1 allergen (International Union of Immunological Societies nomenclature), the major allergen produced by the domestic cat, (*Felis catus*)], immunotherapy improved the overall symptoms of rhinoconjunctivitis, decreased the use of allergy medications and required a 10-fold increase in the dose of allergen to induce a positive reaction after 1 year of immunotherapy with the specific cat allergen (Alvarez-Cuesta et al. 1994). Symptom assessment postchallenge for ragweed-sensitive patients treated for at least 2 years with specific ragweed immunotherapy demonstrated that ragweed immunotherapy significantly reduced symptoms of allergic rhinitis but had no significant effect on ocular symptoms (Donovan et al. 1996). The effect of immunotherapy specific for Japanese cedar (*Cryptomeria japonica*) pollinosis had reduced the daily total symptom severity not only in cedar but also in the cross-allergenic Japanese cypress (*Chamaecyparis obtusa*) pollination season, but not significantly (Ito et al. 1997). Thus, immunotherapy has been shown to have an important role in the 'long-term' control of rhinoconjunctivitis, although it has not been proven for allergic conjunctivitis.

Mast cell stabilizers

Mast cell stabilizers prevent the degranulation of mast cells and the release of preformed inflammatory

mediators, as well as the synthesis of additional inflammatory mediators (Butrus & Portela 2005). As a result, mast cell stabilizers provide relief from SAC by preventing both the early and late phases of the allergic response (Butrus & Portela 2005). Mast cell stabilizers reduce hyperaemia, itching and irritation, although efficacy in SAC varies among different agents (Bhargava et al. 1998; Barney & Graziano 2003). Mast cell stabilizers are most effective when administered prior to the triggering of the allergic reaction and should therefore be used prophylactically (Bhargava et al. 1998; Butrus & Portela 2005), although patients may notice some improvements in SAC signs and symptoms within 24–48 hr if they are used following exposure to the allergen (Bielory & Friedlaender 2008). Mast cell stabilizers require a long loading period, during which they must be applied routinely for several weeks for optimal prophylactic benefit (Butrus & Portela 2005). As a result of this required long regular dosing before exposure to seasonal allergens, patient compliance may decrease (Butrus & Portela 2005). Topical mast cell stabilizers are generally safe and have minimal ocular side-effects, although there may be some tolerability concerns, because transient burning or stinging may occur upon application (American Academy of Allergy Asthma & Immunology 2000; Bielory & Friedlaender 2008).

Topical antihistamine/decongestant agents

As antihistamines and decongestants have different but complementary mechanisms of action, these agents are often combined into a single product that can have better efficacy than either agent alone (Barney & Graziano 2003; Wallace et al. 2008). However, these agents generally have a shorter duration of action in addition to the side-effects associated with decongestants and antihistamines, such as rebound hyperaemia with continued use (The Medical Letter 2007). Therefore, unless daily dosing can be reduced, use of these agents should be limited to <10 days to minimize the potential for side-effects such as

conjunctivitis *medicamentosa* (Wallace et al. 2008).

Topical antihistamine/mast cell stabilizer agents

Some multiple-action agents provide relief of SAC through the inhibition of mast cell degranulation as well as competitive binding of the H₁ receptor to block histamine binding (Bielory et al. 2007; Wallace et al. 2008). These agents have a rapid onset of antihistamine action, usually within minutes following application, and therefore improve patient compliance compared with pure mast cell stabilizer agents (Bielory et al. 2007; Wallace et al. 2008). There are several drugs with antihistamine and mast cell stabilizing activities that generally provide relief of the itching associated with SAC (Bielory 2008). As a result of these attributes, the dual action products are currently the most commonly prescribed group of agents for ocular allergy (Barney & Graziano 2003). These multiple-action agents are generally well tolerated and can be used for longer-term treatment of SAC; side-effects are generally mild and include headache, cold-like symptoms, burning, stinging and possible transient bitter taste (Bielory 2008; Wallace et al. 2008).

Nonsteroidal anti-inflammatory agents

Nonsteroidal anti-inflammatory drugs block the cyclooxygenase enzyme and the production of prostaglandins from arachidonic acid (Fig. 1) (Bhargava et al. 1998). Because of this mechanism of action, NSAIDs reduce mucus secretion, cellular infiltration, erythema and chemosis, which results in the relief of ocular itching, although some improvement in conjunctival hyperaemia and inflammation and swollen eyes may also be seen (American Academy of Allergy, Asthma and Immunology 2000; Butrus & Portela 2005; Bielory 2006; Bielory et al. 2007; Bielory 2008). One ocular NSAID, ketorolac tromethamine, is currently approved for the control of pruritus associated with SAC (Butrus & Portela 2005; Bielory et al. 2007; Bielory 2008). NSAIDs may cause discomfort upon instillation, including stinging and burning, and may therefore decrease patient compliance (Bhargava et al. 1998; Butrus & Por-

tela 2005; Bielory et al. 2007). Ulcerative keratolysis has occurred as a serious complication associated with ocular application of a generic ophthalmic formulation of diclofenac sodium.

Corticosteroids

The most effective therapeutic agents in the treatment of SAC and allergic rhinitis are corticosteroids, as they manage all the various facets of allergic symptoms (Leonardi 2002). Following binding to glucocorticoid receptors (GRs), corticosteroids modulate protein synthesis through the regulation of transcription and indirectly by modifying the activity or half-life of transcription factors and mRNA (Belvisi & Hele 2003). Corticosteroids thus reduce allergic inflammation through changes in the circulation and migration of pro-inflammatory cells and by modifying functions of these cells (Schacke et al. 2002). Corticosteroids exert rapid anti-inflammatory effects via interactions with cellular membranes, nongenomic effects that are mediated by cytosolic GRs, and interactions with membrane-bound GRs (Stahn et al. 2007).

Because topical corticosteroids provide effective relief of a broad range of signs and symptoms of ocular inflammation, these agents are considered an effective acute treatment option for SAC (American Academy of Allergy, Asthma & Immunology 2000; Bielory 2002a,b; American Academy of Ophthalmology 2003; Barney & Graziano 2003; Butrus & Portela 2005; Bielory et al. 2007; Bielory 2008; Bielory & Friedlaender 2008). Topical ophthalmic corticosteroids can be prescribed in lower doses to produce equal or greater local drug concentrations with negligible systemic adverse events (i.e. suppression of the hypothalamic-pituitary-adrenal axis, negative cardiovascular and metabolic effects) (Carnahan & Goldstein 2000; Schacke et al. 2002) compared with systemic corticosteroids (McGhee et al. 2002), although there is the potential for ocular side-effects (Carnahan & Goldstein 2000). However, topical corticosteroids are not commonly used, because of a fear of associated ocular side-effects, such as increases in intraocular pressure

(IOP), induction or exacerbation of glaucoma (Fig. 2), formation of cataracts, delayed wound healing and increased susceptibility to infection or superinfections (McGhee et al. 2002).

The propensity of topical corticosteroids to induce adverse effects depends, in part, on the structure, dose and duration of treatment (McGhee et al. 2002). In addition, the development of increases in IOP and glaucomatous changes with the use of corticosteroids may vary depending on whether or not the patient is a 'steroid responder' (Carnahan & Goldstein 2000; McGhee et al. 2002; Holland et al. 2009). Following daily administration of topical corticosteroids for 4–6 weeks, approximately 5% of the population have been defined as 'high responders', with an increase in IOP > 15 mmHg, and about one-third of the population are 'moderate responders', with an increase in IOP of between 6 and 15 mmHg (Armaly 1965; McGhee et al. 2002; Jones & Rhee 2006). The mechanism of IOP elevation has been proposed to occur through corticosteroid-induced increases in resistance to aqueous outflow in the trabecular meshwork through a variety of mechanisms (Tripathi et al. 1999; Jones & Rhee 2006).

As a result of these side-effects associated with corticosteroids, most guidelines recommend that their use be limited to more severe SAC that is not controlled by other treatments and that these agents be used in pulse fashion for as short a duration as possible (American Academy of Allergy, Asthma & Immunology 2000; Bielory 2002a,b; American Academy of Ophthalmology 2003; Butrus & Portela



Fig. 2. Glaucomatous optic atrophy secondary to corticosteroid-associated glaucoma with habitual topical ketone corticosteroid use in persistent allergic conjunctivitis.

Table 2. Current corticosteroid treatment options for seasonal allergic conjunctivitis.

Carbon-20 (C-20) ketone corticosteroids	Prednisolone, betamethasone, dexamethasone, difluprednate, fluorometholone, medrysone, rimexolone
C-20 ester corticosteroid	Loteprednol etabonate
Experimental non-C-20 ester corticosteroids	N-substituted 3- or 4-(aminomethyl)benzoate 21-esters of hydrocortisone, HYC 141, Thiol ester corticosteroids, RS-85095 and RS-21314, 3-[(4-methylpiperazin-1-yl)methyl]benzoate ester of hydrocortisone

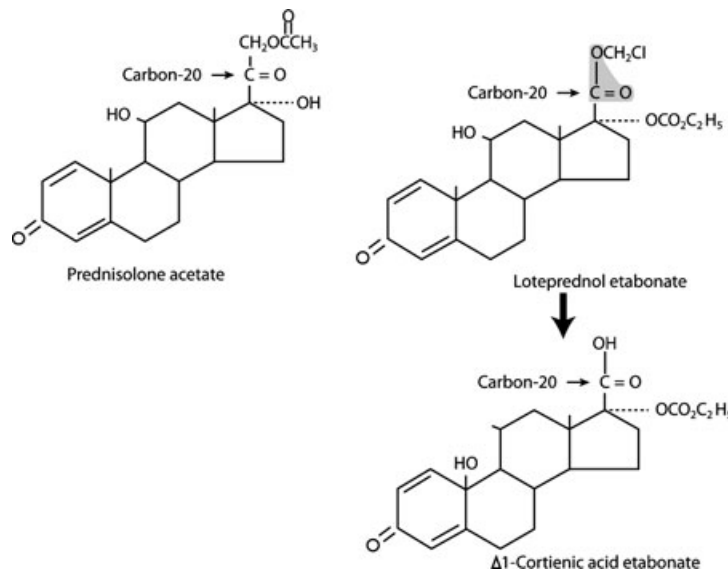


Fig. 3. Chemical structure of the corticosteroid prednisolone acetate with a ketone at the carbon-20 (C-20) position, and chemical structure of loteprednol etabonate (LE) with the ester group substitution at the carbon-20 position. LE is metabolized to Δ1-cortienic acid etabonate.

2005; Bielory 2008). This limitation led to the development of a novel corticosteroid using retrometabolic drug design, which allowed for the delivery of these corticosteroids to their site of action while limiting side-effects (Table 2). Whereas many such ophthalmic agents developed have not yet reached the clinical realm, one such corticosteroid, LE, has been studied

and approved for use in the treatment of SAC in most major markets throughout the world. Loteprednol etabonate is an ester corticosteroid structurally similar to ketone corticosteroids, but with a 17β-chloromethyl ester at the carbon-20 (C-20) position instead of a ketone. (Fig. 3) Specifically, LE is the 17β-chloromethyl ester of Δ1-cortienic acid etabonate, a

derivative of the prednisolone metabolite Δ1-cortienic acid. This allows LE to be active at its site of action and subsequently undergo predictable hydrolysis to inactive carboxylic acid metabolites by naturally occurring ocular esterases, resulting in reduced side-effects of elevated IOP (Table 3) (Armaly 1965; Mindel et al. 1980; Manabe et al. 1984; Bartlett et al. 1993a; Urban & Dreyer 1993; Leibowitz et al. 1996; Ilyas et al. 2004; Bodor & Buchwald 2005; Holland et al. 2008; White et al. 2008; Holland et al. 2009). In addition, the C-20 ketone group on corticosteroids is associated with the formation of cataracts through the development of Schiff base intermediates via an interaction between the C-20 ketone group and lysine residues of proteins (Manabe et al. 1984; Bodor & Buchwald 2005). Schiff base formation is followed by a Heyns rearrangement, resulting in stable amine-linked adducts that cause destabilization of protein structure, allowing further modifications and the development of cataract (Bodor & Buchwald 2005). Nonketolic corticosteroids, such as LE, do not form Schiff base intermediates and hence do not lead to cataract formation through this mechanism. Long-term head-to-head comparisons are necessary to fully determine the differences in cataractogenic effects between C-20 ester and C-20 ketone corticosteroids.

Loteprednol etabonate is the only topical corticosteroid to date specifically studied in patients with signs and symptoms of SAC prior to obtaining marketing approval (Barney & Graziano 2003; Bielory 2008). In two multicentre, randomized, double-masked, placebo-controlled studies

Table 3. Ketone versus ester ophthalmic corticosteroid side-effect profiles (Armaly 1965; Mindel et al. 1980; Manabe et al. 1984; Bartlett et al. 1993b; Urban & Dreyer 1993; Leibowitz et al. 1996; Ilyas et al. 2004; Bodor & Buchwald 2005; Holland et al. 2008; White et al. 2008; Holland et al. 2009).

Clinical manifestation	Ophthalmic corticosteroids	
	Ester	Ketone
Elevated intraocular pressure (IOP)	No significant IOP elevation	IOP elevation by prednisolone acetate, medrysone, fluoro-methalone, rimexolone and dexamethasone. For dexamethasone, 60–66% of subjects are low responders (IOP ≤ 20 mmHg); 30–33% are moderate responders (IOP 21–30 mmHg); and 4–6% are high responders (IOP > 30 mmHg)
Cataract	No lens opacification with nonketolic corticosteroids	Ketone corticosteroids are associated with lens opacification, through protein adduct formation Formation of Schiff base intermediates between the steroid C-20 ketone group and nucleophilic groups on lens protein followed by Heyns rearrangement result in stable amine-linked protein adducts

($n = 133$ and $n = 135$, respectively), treatment with LE 0.2% ophthalmic solution administered four times daily resulted in a significant reduction in the severity of bulbar conjunctival injection and itching compared to placebo ($p < 0.001$ and $p \leq 0.008$) (Dell et al. 1998; Shulman et al. 1999). The safety profile of LE was similar to that of placebo, with no patients experiencing elevated IOP in the first study and only one patient in each group experiencing an IOP elevation (≥ 10 mmHg) in the second study (Dell et al. 1998; Shulman et al. 1999). In addition, LE 0.5% ophthalmic solution was shown to be effective and well tolerated in the prophylaxis of the signs and symptoms of SAC without IOP elevation in a randomized, double-masked, placebo-controlled study ($n = 293$) (Dell et al. 1997). Loteprednol etabonate also provided lasting relief in a conjunctival provocation test study of ocular allergy, with improvement in redness after 8 hr (Abelson et al. 1998). At days 14 and 28 of dosing, all concentrations of LE (0.1%, 0.2% and 0.3%) resulted in significant ($p < 0.05$) improvement of both redness and itching (Abelson et al. 1998). The long-term safety of LE (0.2%) for the treatment of SAC or PAC was examined in a retrospective review of 159 patients who used LE at least once a day for more than a year (Ilyas et al. 2004). There were no reports of posterior subcapsular opacification or IOP elevations exceeding 4 mmHg (Ilyas et al. 2004).

Conclusion

Seasonal allergic conjunctivitis affects a large proportion of the population. Discomfort because of signs and symptoms affects patients' quality of life and productivity imparting a significant economic burden. Nonpharmacological therapies utilized in the treatment of SAC are aimed at minimizing exposure to the antigen on the ocular surface, while pharmacological treatments such as antihistamines, mast-cell stabilizers or NSAIDs, target preformed (early phase) mediators or newly formed (late phase) mediators of the allergic response. Corticosteroids affect multiple facets of the allergic response and are therefore

considered the most effective pharmacological agents in the treatment of SAC. However, because of significant side-effects, most guidelines recommend their use be limited to more severe SAC, not controlled by other treatments. The recent development of C-20 ester corticosteroids may warrant revision of the guidelines. C-20 ester corticosteroids, modelled by LE, are as effective as traditional corticosteroids but are significantly less likely to induce elevations in IOP (Bartlett et al. 1993a; Asbell & Howes 1997; Friedlaender & Howes 1997; Loteprednol Etabonate Postoperative Inflammation Study Group 2 1998; Novack et al. 1998; Loteprednol Etabonate US Uveitis Study Group 1999; Novack 2002; Ilyas et al. 2004; Holland et al. 2008; White et al. 2008; Holland et al. 2009), while the replacement of the ketone group at the C-20 position with an ester is expected to reduce the cataractogenic effects of these corticosteroids (Manabe et al. 1984).

The predicted increase in pollen count because of climate change over the next several years may result in a concomitant increase in ocular allergies. As a result, SAC may become chronic and persistent in more patients and may require treatments over prolonged periods of time (Chambless & Trocme 2004; Ilyas et al. 2004; Wallace et al. 2008). Data obtained with C-20 ester corticosteroids suggest that these novel corticosteroids should be considered in the treatment algorithm of both patients with acute exacerbations of SAC and in patients with chronic and persistent forms. However, further long-term safety and efficacy studies are needed. Additional selectively targeted therapies, including immunotherapy, are under clinical investigation for the treatment of ocular allergy and may lead to improvement of therapeutic outcomes and better management of patients suffering from SAC.

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