

Treatment of seasonal allergic conjunctivitis with ophthalmic corticosteroids: in search of the perfect ocular corticosteroids in the treatment of allergic conjunctivitis

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Purpose of review

Corticosteroids are an effective short-term treatment option for seasonal allergic conjunctivitis (SAC). Their use has been limited due to their side effects and has led to the development of modified 'soft', 'smart' ophthalmic corticosteroid formulations that retain their anti-inflammatory mechanism of action with an improved safety profile.

Recent findings

Similar to the development of the prodrug concept for the nose and lung that led to the development of ciclesonide, a chloromethyl-ester group substitution at the carbon-20 (C-20) position of the traditional corticosteroid has led to the development of a family of potential ophthalmic corticosteroids including loteprednol etabonate that has demonstrated similar efficacy to the C-20 ketone corticosteroids in the treatment of the signs and symptoms of ocular allergies, but less likely to induce elevations in intraocular pressure (IOP) or the formation of cataracts. The C-20 ester corticosteroid, loteprednol etabonate has been designed to be rapidly converted to an inactive, nontoxic metabolite, thus minimizing adverse effects, and loteprednol etabonate (0.2%) is currently the only ophthalmic corticosteroid specifically developed for and approved by the Food and Drug Administration for treatment of SAC.

Summary

The development of modified or soft, smart corticosteroids such as loteprednol etabonate provides an avenue for expanding the treatment of the inflammation associated with signs and symptoms in patients with chronic forms or severe acute exacerbations of allergic conjunctivitis. Modified corticosteroids are an effective and well tolerated option for the short-term treatment of the inflammation and signs and symptoms associated with SAC.

Keywords

C-20 esters, loteprednol etabonate, seasonal allergic conjunctivitis, smart ophthalmic corticosteroids, soft corticosteroids

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Introduction

About 15–40% of the global population is affected by allergic conjunctivitis in response to seasonal allergens such as pollens, animal dander, and other environmental antigens [1–3]. Seasonal allergic conjunctivitis (SAC) is associated with different severities of symptoms such as redness, periocular itching (pruritus), tearing (epiphora), burning, stinging, photophobia and swollen or dry eyes [1,2]. The redness and itching of the eyes are the pathognomonic symptoms associated with allergic conjunctivitis [2,4]. Depending on severity of these symptoms, patients with ocular allergies experience discomfort that may affect their quality of life significantly by reducing their productivity and restricting their daily activities

like reading or spending time outdoors [1]. A study [5] conducted in the UK found that patients with SAC had a 2.3-h reduction in productive time every week during allergy season. Another study [1] conducted in the USA found that 17% of patients with ocular allergy symptoms were unable to perform simple daily tasks. In fact, the estimated annual cost for each patient with SAC in Spain was approximately equivalent to 470 US dollars [6].

Following the first exposure of a genetically predisposed individual to a novel allergen, the impact of allergenic pollen, for example, which lands on the conjunctiva leads to the activation of a cascade of immune responses involving T-lymphocytes, neutrophils, macrophages and toll-like receptors (TLRs) that are responsible for

presentation of symptoms in SAC patients [7,8]. T-cell activation leads to production of cytokines that regulate immunoglobulin E (IgE) synthesis and eosinophil proliferation [7]. Activated T-cells also interact with B-lymphocytes in the local lymph nodes, resulting in release of additional cytokines [8]. B-cell activation leads to secretion of allergen-specific IgE-class immunoglobulins that bind to high-affinity IgE receptors on mast cells and basophils, thereby activating the immune cells to initiate an allergic response when re-exposed to the same allergenic pollen [7–9]. Histamine is the primary mediator involved in ocular allergic response, but other proinflammatory mediators, such as prostaglandins and leukotrienes synthesized by mast cells, can also cause the late-phase allergic response implicated in symptoms of SAC [10–12]. Although activation of the H₁ and H₂ histamine receptors in the conjunctiva are primarily responsible for the majority of the ocular allergic reaction in the early phase [11,13,14], other proinflammatory mediators, such as prostaglandins and leukotrienes synthesized by mast cells, are the primary mediators of the persistent late-phase allergic response and its associated symptoms of SAC [10–12]. Nonspecific induction of matrix metalloproteinases (MMPs) are divided into four groups according to substrate specificity – collagenases, gelatinases, stromelysins, and the membrane-type MMPs – and are mainly synthesized by connective tissue cells, granulocytes, and monocyte macrophages that are also involved in many critical physiological and pathologic processes, including inflammation in the conjunctival tissue [12].

Treatment of seasonal allergic conjunctivitis

The current treatment options for SAC include nonpharmacologic management by avoiding the offending allergen and using cold compresses to reduce the associated heat and swelling initially [15]. If adequate relief of symptoms is not achieved, pharmacologic therapies by either systemic or topical treatment options are used (Table 1) [16].

The primary treatment options include ocular surface-lubricating agents such as saline solution or artificial tears to help remove the allergens from the ocular surface and minimize exposure [16]. Some artificial tears provide relief by lubrication of the ocular surface, and adding wetting and/or viscosity agents to saline solution [17]. Ointments or time-released tear replacements, used at night, are a longer-lasting alternative for lubricating the ocular surface [16,18]. These agents do not treat the underlying cause of allergic response or inflammation, so their use is limited to mild SAC [19]. Topical decongestants, antihistamines, mast cell stabilizers, nonsteroidal anti-inflammatory drugs (NSAIDs), and corticosteroids are among available pharmacologic treatments for

SAC [2,15,16,18–20]. Most of these are associated with limitations and side effects when used alone or in combination with each other (Table 1). Topical decongestants can reduce symptoms of SAC through vasoconstriction via α -adrenoreceptor stimulation [16] but do not reduce allergic response since they do not antagonize mediators of inflammation [15,18,21] and prolonged use of topical decongestants leads to rebound hyperemia or conjunctivitis medicamentosa [22,23]. Antihistamines block only the histamine-induced symptoms of SAC [13] but may also have some general anti-inflammatory effects [20] that can potentially lead to development of sensitivity or aggravation of allergic response [21]. When an antigen binds the IgE and cross-links it, the degranulation of mast cells leads to vasodilation, vascular permeability and bronchial constriction. Mast cell stabilizers are therefore most effective when used prophylactically to prevent the onset of allergic conjunctivitis [13,24]. Although mast cell stabilizers are generally well tolerated, there have been reports of transient burning or stinging upon application [2,15]. Due to their complementary mechanisms of action, antihistamines and decongestants are often used in combination in a single product [18,22], although this combination therapy has associated side effects and a shorter duration than either agent alone [20]. The most commonly prescribed multiple-action combination agents work through their antihistamine and intrinsic mast cell-stabilizing activities and potentially through additional, although minor, anti-inflammatory effects [17,18]. These combination agents are generally well tolerated and can be used for a longer time with minimal side effects [18,25]. Most NSAIDs act as non-selective inhibitors of the enzyme cyclooxygenase (COX) that catalyze the formation of prostaglandins and thromboxane from arachidonic acid. One ocular NSAID, ketorolac, is currently approved for SAC treatment for the control of pruritus [17,24,25], but it may cause associated stinging and burning [13,17,24]. Ketorolac 0.4% had greater anti-inflammatory effects than diclofenac and loteprednol etabonate 0.5% in an animal model of inflammation ($P < 0.001$) [26].

Corticosteroids have been the cornerstone of treatment for various allergic disorders including asthma, atopic dermatitis, and allergic rhinitis. Topical corticosteroids have also been reported to be the most effective in the treatment of severe and chronic forms of ocular allergy [27], providing effective relief of a broad range of symptoms of ocular inflammation [2,15–17,19,20,22,24,25]. Corticosteroids exert rapid anti-inflammatory effects within 6 h of application via interactions with glucocorticoid receptors [28]. The corticosteroid–glucocorticoid receptors combination enters the nucleus in which it controls synthesis of several proteins, including one that inhibits the enzyme phospholipase A₂ which regulates arachidonic acid, a key late-phase mediator of

Table 1 Current pharmacologic treatment options for SAC and associated side effects

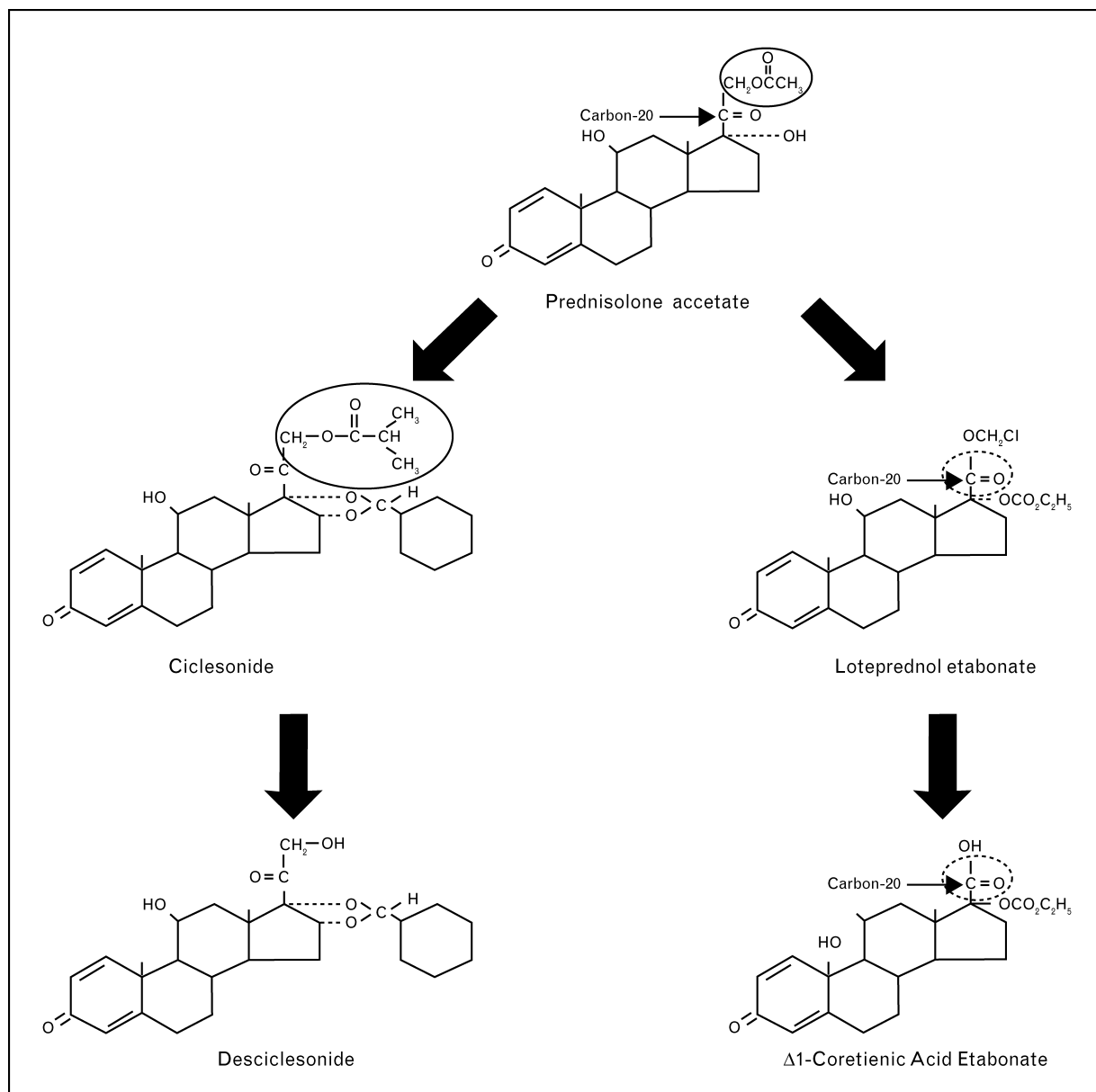
Class	Mechanism of relief for SAC signs and symptoms	Side effects
Ocular surface-lubricating agents (including saline/artificial tears, ointments, and time-release tear replacements)	Dilution of antigens Removal of antigens from ocular surface No direct efficacy on allergic mediators	Chronic use may be associated with problems due to effect of the preservatives
Topical decongestants	Vasoconstriction via α -adrenoreceptor stimulation Reduced redness and edema	Prolonged use or discontinuation can lead to conjunctiva medicamentosa
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
Topical antihistamines	Similar to systemic antihistamines with localized effect	Irritation Increased sensitivity Aggravated allergy Severe side effects with older agents
Mast cell stabilizers	Prevent degranulation of mast cells Prevent release of inflammatory mediators Decreased redness, hyperemia, itching, and irritation	Minimal tolerability concerns due to stinging and burning upon instillation
Antihistamine/decongestants	Inverse agonists of histamine receptors and vasoconstriction via α -adrenoreceptor Reduced itching, redness, and edema	Irritation Possible conjunctiva medicamentosa
Antihistamine/mast cell stabilizers	Inverse agonists of histamine receptors and mast-cell-stabilizing activity Providing relief of redness, hyperemia, itching, and irritation	Stinging, burning Distinctive bitter taste Headache Cold symptoms
Nonsteroidal anti-inflammatory drugs (NSAIDs)	Block cyclooxygenase and production of prostaglandins Reduced itching	Discomfort upon instillation Including stinging and burning
Ketone 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 Possible systemic effects
Ester corticosteroids	General anti-inflammatory effects Attenuation of activity of inflammatory cells Reduction of most ocular signs and symptoms of SAC	Compared to ketone corticosteroids Reduced elevation of intraocular pressure Reduced incidence of glaucoma Reduced risk of cataract formation

SAC, seasonal allergic conjunctivitis.

inflammation. However, systemic corticosteroids have been associated with multiple systemic side effects [e.g. osteoporosis, cataracts, growth failure, hypothalamic-pituitary-adrenal (HPA) axis suppression] that have reduced their use. Topically applied corticosteroids were introduced as safer options with improved therapeutic margins. The efficacy and safety of topically applied corticosteroids depend on pharmacokinetic and pharmacodynamic properties (e.g. systemic and topical bioavailability, deposition, receptor binding, residence time, and clearance). Manipulation of these properties has led to newer topical agents with progressively improved therapeutic margins. However, prolonged use of some of these topical agents at high doses can still be associated with certain local and serious adverse events such as cataract formation and glaucoma. Specifically, ophthalmic steroids may be associated with serious side effects, including increase in intraocular pressure (IOP), glaucoma, cataracts, delayed wound healing, susceptibility to infection, systemic suppression of the HPA axis and increased cardiovascular risks [29–35]. Most of the ophthalmic corticosteroids have a ketone group that is located at the C-20 position (Fig. 1) [25], which has been

implicated with formation of cataracts [33]. Ketone corticosteroid protein adducts form in ocular lenses and correlate with the development of cataracts, indicating the possibility that corticosteroid–protein adduct formation may play a role in cataract formation with long-term glucocorticoid therapy [34,35]. The formation of Schiff base intermediates between the C-20 ketone position of ketone corticosteroids and the lens protein results in subsequent oxidation of the lens material and eventual development of stable cataract-forming corticosteroid–protein adducts [33,34]. The marked opacification that developed in the lenses with the ketone corticosteroid prednisolone were absent with nonketone corticosteroids [34]. Topically administered corticosteroids have reduced systemic adverse events [36–39], but ocular side effects may still exist [31]. As a result, guidelines recommend that their use be limited to more severe cases of SAC only [15,16,19,20,24,25].

Advancing the search for the ‘perfect corticosteroid’ with optimized pharmacokinetic and pharmacodynamic profiles has been the thrust of research of the past 40 years for all forms of allergic disorders [29,30,37,38]. That has led

Figure 1 Chemical structures of prednisolone acetate, ciclesonide and loteprednol etabonate, and their metabolites

The change of the ketone from an ester at carbon-20 position has led to the development of loteprednol etabonate. Ciclesonide is an inactive parent compound activated by esterases to an active metabolite, desciclesonide and the esterification of des-CIC at the carbon-21 position leads to reversible lipid conjugates of des-CIC that represent a pool of active drug available for sustained long-term activity.

to the discovery of the soft corticosteroids. Soft corticosteroids are topical corticosteroids with a low rate of side effects in relation to their anti-inflammatory potency [36]. The soft drug retrometabolic drug design approach has been utilized as a means of delivering these potent anti-inflammatory agents close to their site of action while reducing the degree of systemic exposure and thus limiting or eliminating the associated systemic and local side effects [40]. In addition, the search for a once-daily formulation to enhance patient compliance is also important in the 'search for the perfect corticosteroids'. Whereas

many soft corticosteroids have failed to progress to the clinical realm, there are two that have come to be used in allergic disorders with various degrees of success. Loteprednol etabonate, (0.2%), a soft steroid that is converted to an inactive metabolite is the only Food and Drug Administration (FDA) ophthalmic agent developed and approved for SAC and is also being examined in clinical trials for its effects on airway inflammation. Ciclesonide, a prodrug corticosteroid, is activated by esterases to an active metabolite, desciclesonide (des-CIC). The esterification of des-CIC at the carbon-21 position leads to

Table 2 Ophthalmic ketone and ester corticosteroids

C-20 ketone corticosteroids	Prednisolone, Betamethasone, Dexamethasone, Difluprednate, Fluorometholone, Medrysone, Rimexolone
C-20 ester corticosteroid	Loteprednol etabonate
Modified non C-20 ester corticosteroids being researched	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

LE is the only C-20 ester corticosteroid available for treatment. Data from [36,42,43].

reversible lipid conjugates of des-CIC that represent a pool of active drug available for sustained long-term activity. Ciclesonide has demonstrated efficacy without side effects in a once-daily formulation for the treatment of asthma and allergic rhinitis [41]. These drugs represent a significant step forward in the topical treatment of allergic inflammatory diseases [33,41]. Ciclesonide is a prodrug that is enzymatically hydrolyzed at the C-21 to a pharmacologically active metabolite, C21-desisobutyrylciclesonide (des-ciclesonide or RM1) following application to the bronchial or nasal mucosa. Des-ciclesonide has anti-inflammatory activity with affinity for the glucocorticoid receptor that is 120 times higher than the parent compound [33,41].

New corticosteroids in the treatment of seasonal allergic conjunctivitis

Several classes of corticosteroids that are ester-based soft or smart corticosteroids have been studied (Table 2) [36,42,43]. The various potential ester corticosteroid candidates have resulted in one that has been clinically developed and approved for the treatment of allergic conjunctivitis, loteprednol etabonate (Fig. 1). Loteprednol etabonate is an ester corticosteroid structurally similar to prednisolone, but was designed with a 17 β -chloromethyl ester at the C-20 position in order to be hydrolyzed to an inactive carboxylic acid moiety [40,43]. Loteprednol etabonate is a Δ 1-corticenic acid etabonate

derivative of the prednisolone metabolite Δ 1-corticenic acid. This structural modification ensures that loteprednol etabonate undergoes predictable hydrolysis to an inactive metabolite and has limited systemic absorption [32,42]. As a result, loteprednol etabonate is a 'soft' or 'smart' corticosteroid which is active in the ocular tissues in which it is needed and becomes inactive shortly thereafter [33,44]. Similar to ketone corticosteroids, loteprednol etabonate exerts its anti-inflammatory effects by binding to the glucocorticoid receptor. With loteprednol etabonate it is now possible to treat ocular allergic conditions with reduced side effect of elevated IOP (Table 3) [33,34,45–48,49,50^{••},51–53].

Loteprednol etabonate is a safer alternative to C-20 ketone corticosteroids as it was first developed using a retrometabolic drug design by substituting the ketone at the C-20 position of prednisolone acetate with an ester group (Fig. 1) [33], making loteprednol etabonate less cataractogenic than ketone corticosteroids [34,38]. Loteprednol etabonate is the only C-20 ester ophthalmic corticosteroid developed specifically for and approved by the US FDA for the treatment of SAC. Similar to ketone corticosteroids, loteprednol etabonate acts via glucocorticoid receptors and interactions with immune cells to produce anti-inflammatory effects [43,54]. Loteprednol etabonate provides effective reductions in signs and symptoms of several other types of ocular, inflammatory conditions such as giant papillary conjunctivitis

Table 3 Side effects of ketone vs. ester ophthalmic corticosteroids

Clinical manifestation	Ophthalmic corticosteroids		References
	Ester	Ketone	
Glaucoma	No significant association with glaucoma	Dexamethasone [60–66% were low responders (IOP $\leq$ 20 mmHg); 30–33% were moderate responders (IOP 21–30 mmHg); 4–6% were high responders (IOP $>$ 30 mmHg)]	[45,46]
Elevated IOP	No significant IOP elevation	IOP elevation by medrysone, fluoromethalone, and dexamethasone phosphate	[47]
		1.0% rimexolone in patients responding to corticosteroids	[48,49,50 ^{••} ,51–53]
Cataract	No opacification with the nonketolic analog	Prednisolone-associated lens opacification and protein adducts	[34]
		Formation of Schiff bases between the steroid C-20 ketone group and nucleophilic groups results in stable amine-linked adducts	[33]

IOP, intraocular pressure.

(GPC) [55–57], anterior uveitis [54,58] and postoperative inflammation following cataract surgery [59,60]. Thus, the safety and efficacy of loteprednol etabonate have been evaluated in several clinical trials for control of ocular inflammation.

Well tolerated and effective prophylaxis of the signs and symptoms of SAC was demonstrated in a randomized, double-masked, placebo-controlled study [61] by loteprednol etabonate 0.5% ophthalmic solution. Loteprednol etabonate provided lasting relief in a conjunctival provocation test (CPT) study [62] of ocular allergy, with remarkable improvement in redness after 8 h, even though the itching was not significantly improved at that point. At days 14 and 28 of dosing, all concentrations of loteprednol etabonate resulted in marked improvement of both redness and itching [62]. Overall all loteprednol etabonate concentrations were well tolerated, and no IOP elevations greater than 4 mmHg were observed. Loteprednol etabonate (0.5%) administered prophylactically for 6 weeks prior to the onset of the allergy season in patients with SAC was evaluated for efficacy and safety ($n = 293$) [61]. The composite and individual scores for itching and bulbar conjunctival injection during peak pollen counts were significantly better for loteprednol etabonate ($P \leq 0.001$) relative to placebo [61]. None of the loteprednol etabonate-treated patients experienced an IOP increase greater than 10 mmHg, whereas two placebo-treated patients did [61]. In another study, efficacy of lower concentration loteprednol etabonate (0.2%) in patients with signs and symptoms of SAC was evaluated in two similar studies ($n = 133$ and $n = 135$, respectively) [63,64]. In both studies, loteprednol etabonate had a greater effect on bulbar conjunctival injection and itching than placebo ($P < 0.001$ and $P = 0.008$). In addition, the safety profiles of the two treatment groups were similar, with no patient experiencing elevated IOP in the first study [63,64], and only one patient in each treatment group experiencing an IOP elevation greater than 10 mmHg in the second study [63,64].

A conjunctival allergen challenge (CAC) study evaluated the efficacy of loteprednol etabonate 0.2%, the antihistamine/mast cell stabilizer olopatadine hydrochloride 0.1%, and placebo in the relief of ocular itching and redness following allergen challenge [65]. Results showed clinically and statistically significant ($P \leq 0.05$) improvements in relief of itching and prevention of redness with olopatadine compared with loteprednol etabonate 0.2% and placebo during the early phase of the allergic response, up to 30 min following allergen challenge [65]. This may suggest that corticosteroids do not provide an advantage in the acute phase (within 30 min) of the allergic response. In a more recent 35-day study comparing loteprednol etabonate 0.2% to olopa-

tadine hydrochloride 0.1% for the treatment of allergic conjunctivitis in 60 patients, loteprednol etabonate was found more efficacious than olopatadine in reducing the ocular surface disease index (OSDI) [66^{••},67,68]. Other parameters assessed included visual acuity, biomicroscopy, fluorescein corneal staining, applanation IOP and tear production with Schirmer's test. Loteprednol etabonate was chosen as the preferred medication for the treatment of SAC by more patients than olopatadine ($P < 0.05$) [66^{••}]. The CAC study only examined the early-phase reaction and not the late phase, in which corticosteroids show greatest efficacy [65], so such differences in results were not unexpected.

Compared with ketone corticosteroids, the C-20 ester corticosteroids such as loteprednol etabonate show a markedly improved safety profile [69] and therefore offer advantages for the treatment of SAC (Table 3) [25]. As mentioned before, since a ketone in the C-20 position has been implicated in cataract development, loteprednol etabonate is expected to be less cataractogenic than ketone corticosteroids [25,33,69]. Additionally, loteprednol etabonate has less of a tendency to elevate IOP [49,50^{••},58], even in corticosteroid responders [51] or with long-term use likely due to its rapid metabolism to inactive metabolites [70]. However, long-term use of any topical steroid in the nose or eye has not been studied prospectively.

With the projected climate change over the next 25–50 years and its impact on increasing pollen count, ocular allergies are expected to increase. As a result, SAC may be chronic and persistent in some patients and may require therapies over a prolonged period of time [18,52,71]. The long-term safety of loteprednol etabonate 0.2% for the treatment of SAC or perennial allergic conjunctivitis (PAC) was examined in a retrospective review of 159 patients who used loteprednol etabonate at least once a day for more than a year [52]. There were no recorded corticosteroid-induced adverse events such as posterior subcapsular opacification detected via slit-lamp examinations and no incidences of corticosteroid-induced elevation of IOP that exceeded 4 mmHg [52]. Although not clinically significant, a statistically significant ($P = 0.017$) increase in IOP by an average of 1.89 mmHg was detected in a cohort of patients whose last visit occurred at 30 months [52]. There was no record of new lenticular opacity or significant worsening of previously existing cataract [52]. Overall, the study showed that loteprednol etabonate 0.2% has an excellent safety profile for long-term treatment of SAC or PAC, but routine monitoring of IOP and slit-lamp examinations were recommended as the studies were limited to 1 year [52]. Multiyear studies have not been performed with ophthalmic steroids.

Allergic conjunctivitis is often linked to allergic rhinitis and requires cotreatment. The major symptoms of conjunctivitis such as burning and itching eyes and lacrimation are the same as for allergic rhinitis. Ciclesonide is a corticosteroid in development for allergic rhinitis that has been shown to be well tolerated and effective in seasonal allergic rhinitis and perennial allergic rhinitis (PAR) trials of up to 6 weeks in duration and has been shown to be well tolerated and effective for the long-term treatment of PAR, with no evidence of tachyphylaxis [72]. The combined administration of ciclesonide and at least one antihistamine for the treatment of allergic rhinitis with allergic conjunctivitis has been successful [73].

Conclusion

Designed based on the 'inactive metabolite' concept, the C-20 ester corticosteroid loteprednol etabonate can be used as a well tolerated ophthalmic anti-inflammatory drug. By design, the metabolism of loteprednol etabonate follows a predicted biotransformation pathway, thus unwanted systemic and local side effects are avoided. The C-20 ester-based corticosteroids such as loteprednol etabonate can block the allergic response via specific and nonspecific anti-inflammatory effects, including binding to glucocorticoid receptors and interactions with immune cells, similar to ketone corticosteroids [54]. Compared with ketone corticosteroids, however, the C-20 esters are less likely to induce elevations in IOP [49,50,51, 52,58,74] or cause cataract. The removal of the ketone group at the C-20 position of the molecule is expected to reduce the cataractogenic effects of the corticosteroid drug. Safety studies showed no worsening of lens opacity with long-term use of loteprednol etabonate 0.2% [52,69]. Due to an excellent efficacy and safety profile, C-20 esters such as loteprednol etabonate are effective short-term treatment options for SAC. In fact, the 0.2% dose of loteprednol etabonate has all the anti-inflammatory advantages of a corticosteroid, but almost no corticosteroid-induced side effects [52,63,64]. Currently, loteprednol etabonate is the only C-20 ester topical ophthalmic corticosteroid that was developed specifically for and approved for the treatment of SAC [22,25] and should be included in the treatment algorithm of patients with acute severe exacerbations of SAC or for the chronic persistent forms. However, long-term use of the soft ophthalmic steroid has not been studied for more than a year and if used should be monitored in concert with an ophthalmologist. Other similar therapies under clinical investigation involving the subspecialty of allergy and immunology and ophthalmology will assist in the improvement of care for patients with ocular allergy (given below) and would further promote the development of treatment options thus improving the therapeutic outcomes for all patients with SAC.

Allergy and ophthalmology consultation (for persistent moderate-to-severe clinical allergic ocular complaints; at the patient's request, in accordance with physician's treatment plan):

- (1) To an ophthalmologist
 - (a) Any patient using ocular steroids for more than 2 weeks should be monitored for increased IOP, persistent ocular complaint, presence of ciliary blush suggesting uveitis
 - (b) The patient should then be considered for treatment with topical or systemic corticosteroids
- (2) To an allergists/clinical immunologist
 - (a) Patient should be evaluated for presence of systemic atopy (eczema, rhinitis, sinusitis, asthma)
 - (b) Patient should be considered for systemic immunomodulation (immunotherapy)
 - (c) Subsequently the patient should undergo systemic assessment of an autoimmune process

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 513).

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