



Immunomodulators for conjunctivitis

Punchama Pacharn and Pakit Vichyanond

Purpose of review

Allergic conjunctivitis is an IgE-mediated inflammatory of conjunctiva. Despite the fact that histamine is a major mediator in this condition, use of topical antihistamines often gives only temporarily relief. Therapeutic agents aiming at inflammatory cascades of the disease are desirable particularly in cases with prolonged and severe allergic conjunctivitis. The article reviews these new treatment armamentariums with regard to their mechanism of actions and clinical efficacy.

Recent findings

Some second generation of antihistamines demonstrated anti-inflammatory properties such as inhibition of histamine release from mast cells as well as interference with the production cytokines and adhesion molecules from cord blood and conjunctival mast cells. Among these agents, ketotifen, epinastine and olopatadine are agents of major interest and are thus reviewed. Cromolyn, nedocromil, topical corticosteroids and immunotherapy, especially sublingual immunotherapy, are among other modes of therapy examined. Finally, the review focuses on cyclosporine A and tacrolimus, immunomodulators that have been extensively studied in the therapy of severe conjunctivitis such as atopic and vernal keratoconjunctivitis with promising results.

Summary

Several immunomodulatory options are currently available for treatment of allergic conjunctivitis. These therapeutic availabilities bring about a better therapeutic outcome for patients with allergic conjunctivitis, particularly those on the severe end of the spectrum.

Keywords

allergic conjunctivitis, cyclosporine A, loteprednol, olopatadine, tacrolimus

INTRODUCTION

The rising prevalence of allergic rhinoconjunctivitis among children as evident through worldwide collaborative studies such as the International Study of Asthma and Allergies in Childhood (ISAAC) study is so alarming. It has been estimated that up to 30% of children between the ages of 7 and 14 years are suffering from this once believed to be a trivial disease [1]. Eye symptoms could occur up between 30 and 50% among these children [2] and could lead to poor quality of life [3]. Thus, treatment for conjunctivitis should deserve adequate attention as for rhinitis.

Classic symptoms of allergic conjunctivitis include eye itching, irritation, tearing and to a certain degree, photophobia. These symptoms vary between patients due to varying degree of sensitivity to offending allergens, level of allergen exposure, seasonality and co-factors such as pollution, weather (temperature and humidity), infection and other unknown stimuli. Physical signs of allergic conjunctivitis also vary from mild to classic

hyperemia, swelling of conjunctiva and surrounding eye lids. On the severe end of the condition, that is, in vernal keratoconjunctivitis (VKC) and atopic keratoconjunctivitis (AKC), follicles and giant papilla are seen along with involvement of cornea (punctate keratitis to corneal ulcer). In this review, we will be focusing on various treatments aiming at modulating immune response in allergic conjunctivitis. Despite the fact that topical antihistamine yields a direct effect on antagonizing histamine – the major mediator causing allergic conjunctivitis – some of the newer antihistamines possess some

Division of Allergy and Immunology, Department of Pediatrics, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

Correspondence to Pakit Vichyanond, MD, Professor of Pediatrics, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand. Tel: +66 81 407 1589; fax: +66 2 381 8940; e-mail: pakitiv@gmail.com

Curr Opin Allergy Clin Immunol 2013, 13:550–557

DOI:10.1097/ACI.0b013e328364d86a

KEY POINTS

- Newer topical antihistamine eye drops possess anti-inflammatory activities suitable to be used as controllers for allergic conjunctivitis, both of seasonal and perennial types.
- Newer topical 'soft' steroids are associated with less incidence of increased intraocular pressure.
- Allergen immunotherapy, particularly SLIT, has been shown to alleviate symptoms of allergic conjunctivitis.
- Severe forms of allergic conjunctivitis include VKC and AKC. Although distinctively, VKC can be differentiated from classical AKC, the two conditions share several overlapping presenting symptoms/signs and pathological findings.
- Topical cyclosporine A and tacrolimus are newer immunomodulators found to be effective in treating VKC and AKC. Their use may be extended to less severe forms of conjunctivitis in the future.

immunomodulatory effects and thus will be discussed as well.

VERNAL AND ATOPIC KERATOCONJUNCTIVITIS

Vernal keratoconjunctivitis and AKC are the most severe forms of allergic conjunctivitis (giant papilla conjunctivitis caused by contact lens use is not within the context of this review). These two conditions, once thought to be rare, are becoming more commonly observed in ophthalmology and in allergy clinics. An earlier study [4] among Italian population estimated prevalence of VKC to be between 5.8 and 7.8 per 100 000. A later study [5] among six European countries estimated an even higher prevalence of 1.1–10.5 per 10 000 inhabitants. Although cases of classic VKC and AKC can be easily diagnosed and differentiated from one another, in certain cases, these two conditions share overlapping clinical features. For instance, a large number of VKC patients also suffer from atopic dermatitis [6], whereas cases of AKC, despite being described as being common in older population, can be observed in the young [7]. Attempts to study tears' function and surface cytology study demonstrated certain differences between the two conditions [8]. In spite of these similarities and disparities, AKC and VKC are being treated with similar groups of medications. Efforts to immunomodulate on-going pathogenesis of these conditions are of interest and will be reviewed together in this study.

CORTICOSTEROIDS

Corticosteroids are the most effective anti-inflammatory drugs available for clinical use to date. The anti-inflammatory actions of corticosteroids are derived through its complex interaction with cytoplasmic glucocorticoid receptor element (GRE) followed by trans-activation of RNA polymerase culminating in changes in the production of effector cytokines and chemokines. Productions of several pro-inflammatory cytokines such as IL-1, IL-4, IL-5 and TNF- α are directly 'repressed' by corticosteroids [9]. In addition, corticosteroids also decrease expression of adhesion molecules such as ICAM-1, VCAM-1 and VLA-4 [9]. Results of such molecular interference from corticosteroids to an on-going allergic reaction is a decrease in numbers of eosinophils (perhaps through induction of apoptosis and lesser extent trans-endothelial migration), neutrophils, mast cells and lymphocytes at the site of inflammation.

In contrast to treatment of inflammation at other organ systems, ocular tissue, particularly the ocular surface, is available for topical application of corticosteroids. This leads to high tissue concentration and decreased side effects. Several types of topical corticosteroids have been formulated and approved for ophthalmic use (prednisolone, triamcinolone, fluorometholone and dexamethasone). However, the use of these agents is not without side effects. Perhaps, the most important side effect of ocular steroids is increase in ocular pressure (IOP) with subsequent development of glaucoma [10]. In the classic study in normal population by Armaly [11], only one-third were susceptible to IOP after a 4–6-week use of topical steroids. Thus, application of these agents requires close monitoring of IOP within 2–4 weeks of therapy to avoid the development of glaucoma [12]. Recent introduction of newer 'soft' corticosteroids with the alteration of the ketone structure to ester at carbon C20 of the corticosteroid structure has led to a marked decrease in this side effect in both IOP and cataract formation [13[¶]]. Examples of these compounds are loteprednol and ciclesonide. Loteprednol etabonate is an ester corticosteroid that is converted to an inactive metabolite – Delta1-cortienic acid etabonate – with limited systemic absorption [13[¶]]. Loteprednol 0.2% was administered prophylactically in a group of patients with seasonal allergic conjunctivitis for 6 weeks with no IOP observed among treated patients [14]. A retrospective long-term use (1 year) of loteprednol among patients with seasonal and perennial allergic conjunctivitis also showed IOP to be no greater than 4 mmHg [15]. Loteprednol is thus a preferred topical steroid for conjunctivitis.

However, study of loteprednol among patients with VKC and AKC is not available.

CROMOLYN AND NEDOCROMIL

Disodium cromoglycate (cromolyn) is a khellin-derivative chromone introduced for use as non-steroidal anti-inflammatory agent in bronchial asthma. Altounyan demonstrated the action of cromolyn in blocking allergen-induced asthma on himself [16]. The drug was widely used in the 1970–1980s as a preventive agent (currently categorized as ‘controller’), particularly in childhood asthma. However, its popularity waned after a meta-analysis study by Tasche *et al.* [17] failed to support its efficacy [17,18]. Nedocromil, another chromone, is a pyraquinolone with a proposedly improved efficacy than cromolyn, although this was not later proven to be true [19]. Both cromolyn and nedocromil block mast cell mediator release primarily through the blocking of the calcium influx after cell stimulation [20]. In addition, chloride efflux through cell membrane can also be blocked by nedocromil and cromolyn [21]. The effect of these intracellular activities leads to interference of various cell activities such as mast cell mediator release, activation of epithelial cell and neuronal cells. Similarly to cromolyn, nedocromil was also subjected to a large investigational trial in asthma, particularly in childhood asthma. Despite a beneficial effect in short-term study, result of a long-term study of nedocromil was not as promising [22].

Through earlier encouraging results in asthma, both cromolyn and nedocromil were introduced as topical solutions for treatment of ocular allergy. Cromolyn was found to be effective in treating seasonal allergic conjunctivitis [23]. Cromolyn 4% solution was found to be more effective than 2% solution [24]. However, limitation of ophthalmic cromolyn is that it has to be applied four times per day. In fact, nedocromil 2% solution applied twice daily was found to be as effective as cromolyn 2% solution applied four times daily [25]. By increasing concentration of cromolyn to 4%, a satisfactory effect was obtained with twice-daily application [26]. Both drugs were tried in patients with VKC with more effective results attained with the use of nedocromil eye drops [27,28]. Moreover, at 22 weeks of treatment, improvement of severe conjunctivitis sign of VKC such as pannus, papilla and keratitis was improved with nedocromil treatment only [28]. In an extensive review of experience with nedocromil, it was found to be effective in seasonal, perennial and VKC with four times daily application being more efficient than twice daily [29]. Surprisingly,

the effect of nedocromil was noted to be as rapid as 15 min in this review.

DUAL-ACTING AGENTS

Topical antihistamines such as antazoline have been a drug of choice for treatment of allergic conjunctivitis in the past. They provide faster onset of action with better relief of eye symptoms than with systemic antihistamine [30]. In addition, systemic antihistamines can exacerbate dry eye [31], whereas the topical antihistamines have a less drying effect [30,32]. However, their use is limited by a relative short duration of effect and thus requiring frequent applications up to four times daily.

Within the past two decades, dual-acting agents possessing both antihistaminic effect and antiallergic effect, such as ketotifen, azelastine, epinastine, bepotastine, alcaftadine and olopatadine, have become popular armamentarium for treating allergic conjunctivitis. In this review, ketotifen, epinastine and olopatadine will be highlighted.

Ketotifen

Ketotifen, a benzocycloheptathiophene compound, has been used in the treatment of bronchial asthma in Europe and Asia for a long time as a controller [33–35]. Its use was superseded by more potent newer inhaled corticosteroids (budesonide and fluticasone) and antileukotriene compounds (montelukast and zafirlukast). However, its strong antihistaminic effects and antiallergic activity make it quite suitable for topical treatment for allergic conjunctivitis. Ketotifen was found to be more potent than conventional antihistamines such as brompheniramine and chlorpheniramine in inhibiting histamine-induced vascular permeability of conjunctiva when challenged with histamine [36]. Using IgE-sensitized human conjunctival mast cell and later challenged with anti-IgE, ketotifen at concentration of 10^{-10} to 10^{-4} mol/l was shown to block the release of histamine and tryptase by 90% [37]. Using a similar approach, Galatowicz *et al.* [38] were able to show that ketotifen inhibited histamine release in a dose-dependent fashion in cord blood stem cell-derived mast cell system activated with anti-IgE. Moreover, production of TNF- α and IL-5 was inhibited by ketotifen in this system. Clinically, ketotifen 0.025% eye drops were shown to be more effective for seasonal allergic conjunctivitis than desloratadine tablet alone [39]. Ketotifen was also shown to be effective in preventing symptoms of allergic conjunctivitis using conjunctival allergen challenge model [40], as well as in pollen allergen challenge chamber [41]. Perhaps,

heterogeneity of mast cells in various tissues, the combined effects of ketotifen in the eyes and a higher-concentration drug attained locally in the eye could explain the differential effect from ketotifen for eyes and lungs.

Epinastine

Epinastine is a multi-action agent possessing potent H1 and H2-receptor antagonist, mast cell-stabilizing properties and anti-inflammatory actions [42]. Epinastine not only inhibits activation of neutrophils and eosinophils [43,44] but also interferes with CD4+ T-cell signaling, and thus decrease of TH2 cytokine production [45].

In a conjunctival allergen challenge model, epinastine reduced multiple symptoms and signs of allergic conjunctivitis compared with vehicle. It has prompt onset (3 min) and a long duration of action (>8 h). The tolerability of epinastine was not different from vehicle [46,47].

Epinastine has an excellent safety profile. Its average maximal plasma concentration was only 0.04 ± 0.014 ng/ml after 7 days of b.i.d. dosing [42]. Local side effects were minor (such as burning sensation – 8%, folliculitis – 3%, eye redness – 1% and itching – 1%). However, when compared with other antihistamine/mast cell-stabilizing agents, 0.05% epinastine was more comfortable than azelastine and ketotifen. None of these agents caused significant ocular drying [48]. Systemic side effect such as headache, rhinitis, sinusitis and pharyngitis were found in about 1–3%, which was similar to baseline [42].

Epinastine 0.05% ophthalmic solution was approved by the US Food and Drug Administration (US-FDA) for twice-daily treatment of ocular allergies. However, no data about the usage in severe form of ocular allergy such as AKC or VKC are available.

Olopatadine

Olopatadine is a topical H1-selective antagonist and mast cell-stabilizing agent. Other than the antihistaminic activity, it also has anti-inflammatory properties such as inhibition of cytokine secretion [49], inhibition of TNF- α release from human conjunctival mast cell [50], with a subsequent decrease in ICAM-1 expression [51] and thereby a decrease in chemotaxis of inflammatory cells such as eosinophils. The 0.1% formulation has been approved for the treatment of allergic conjunctivitis [52]. Olopatadine has a rapid onset (within 20 min), with at least 8 h duration of action [53,54].

The efficacy of olopatadine has been compared to the other multiple-action agents. In a

conjunctival challenge model, 0.1% olopatadine was more efficacious and more comfortable than 2% nedrocromil in reducing the itching associated with allergic conjunctivitis [55]. In addition, olopatadine is more effective in controlling itching, redness and chemosis when compared with 0.05% epinastine in conjunctival allergen challenge model [56].

The comparative efficacy and tolerability between olopatadine and ketotifen has been extensively investigated. Olopatadine (0.1%) was shown to be superior to ketotifen (0.05%) in reducing ocular symptoms and signs of seasonal allergic conjunctivitis in a 2-week clinical study [57] and was more superior to ketotifen (0.025%) in a conjunctival challenge model [58]. In a force-choice study [59], olopatadine was preferred over ketotifen. Surprisingly, in a 3-week old, real world study [60], 0.025% ketotifen was assessed to be more effective than 0.1% olopatadine in treating seasonal allergic conjunctivitis by both patients and investigators. No significant differences in ocular comfort and tolerability were found between the groups in this study.

The 0.2% preparation with an extended duration of action up to 24 h has recently been released. With such property, this new preparation can be used once daily with equal effectiveness to the twice-daily 0.1% preparation [61]. As such, increasing compliance can be anticipated. There were only few studies about using olopatadine in severe forms of ocular allergy. Corum *et al.* [62] showed that 0.1% olopatadine not only relieved symptoms and signs of VKC but also reduced the number of goblet cells in conjunctiva. However, it has no effect on papillae formation, which is one of the main problems in VKC patients. Moreover, most VKC patients in this study had only mild to moderate symptoms; therefore the use of olopatadine in severe VKC will need to be further evaluated.

IMMUNOTHERAPY

Because allergic conjunctivitis usually accompanies allergic rhinitis, most of the studies of allergen immunotherapy were conducted in patients with symptoms of both organ systems. As a consequence, ocular symptoms were shown to be improved together with rhinitis symptoms. Interestingly, Del Prete *et al.* [63] using local ocular immunotherapy pretreated with cromolyn demonstrated that patients improved in both subjective and objective symptoms after 1 year of immunotherapy. Sublingual immunotherapy (SLIT) has been recently becoming a popular choice over subcutaneous immunotherapy (SCIT), particularly in Europe.

Calderon *et al.* [64^{***}] recently published meta-analysis results of SLIT for allergic conjunctivitis. SLIT not only improved patients' eye symptoms (red eyes, itching, watery eyes) but also increased allergen threshold. Most interestingly, a model of experimental allergic conjunctivitis in BALB/C mice (with dust mite – Der f) together with SLIT treatment was recently reported. In this study, Liu *et al.* [65[•]] succinctly demonstrated that SLIT not only reduced conjunctivitis symptoms (scratching, lacrimation) and signs (hyperemia and edema of conjunctiva) but also attenuated inflammatory changes and also eosinophil influx in the challenged conjunctiva.

Allergen immunotherapy has not been systematically evaluated in severe forms of ocular allergy, such as in atopic AKC or VKC. However, recently, SLIT has been shown to be effective for patients with atopic dermatitis [66,67]. Moreover, topical allergen (dust mites) has been shown to produce changes compatible with AKC in mouse model [68]. It is therefore conceivable that immunotherapy may have therapeutic effect in a subset of patients with AKC. Moreover, VKC and AKC have been shown to develop in patients receiving bone marrow transplant with affected donors [69]. This indicates that AKC and VKC are, in part, systemic diseases and may require a systemic therapy to alleviate the conditions.

CYCLOSPORINE A AND TACROLIMUS FOR CONJUNCTIVITIS

In general, standard treatment for AKC and VKC includes topical antihistamines, mast cell stabilizer and NSAIDs (Table 1) [70]. However, the efficacy of these drugs is, at times, not satisfactory, particularly among those with moderate-to-severe forms of the diseases [78]. Topical corticosteroids are often needed to treat exacerbations and to control severe symptoms. However, there are patients who are steroid-resistant or who become steroid-dependent. Among these patients, serious ocular complications such as glaucoma, cataract or secondary bacterial infection are major considerations [10,78,79].

Recent findings suggested that the pathogenesis of AKC and VKC are T-cell-related [6,80[•]]. Therefore, the immunomodulatory agents such as topical cyclosporine or topical tacrolimus (FK-506) have been sought as treatment for those with moderate-to-severe disease. The main actions of both agents are inhibition of T-cell activation and inhibition of release of IgE-dependent mediators and cytokines from mast cells and other related cells [81]. Furthermore, cyclosporine A (CsA) inhibits proliferation and cytokine production from conjunctival fibroblasts [82], the cell of which could play a central role in the induction and amplification of ocular allergic inflammation. Such vicious

Table 1. Summarized major reports using CsA and tacrolimus in VKC and AKC patients

First author	Medication	Design	N	Comment
Secchi <i>et al.</i> (1990) [71]	2% CsA in castor oil	DBPC for 4–9 months	11 VKC	Significantly improved symptoms and signs, except giant papillae
Pucci <i>et al.</i> (2002) [72]	2% CsA in olive oil	DBPC for 2 weeks, open for 4 months	24 VKC	Significantly improved symptoms and signs, except giant papillae
Spadavecchia <i>et al.</i> (2006) [73]	1.25% CsA vs. 1% CsA	1.25% CsA DBPC for 2 weeks, open for 3.5 months, then 1% CsA open for 4 months	20 VKC, 32 VKC	No significant difference between the two concentrations
Kilic and Gurler (2006) [74]	2% CsA in preservative free artificial tear	DMPC for 14 weeks	20 VKC	No side effect
Ohashi <i>et al.</i> (2010) [75 ^{***}]	0.1% Tacrolimus ophthalmic suspension	DMPC for 4 weeks	41 AKC, 15 VKC	Significantly improved symptoms and signs, include giant papillae
De Smedt <i>et al.</i> (2012) [76 [•]]	2% CsA vs. 0.1% dexamethasone	DMPC for 4 weeks	366 VKC	No significant difference in signs and symptoms between groups
Labcharoenwongs <i>et al.</i> (2012) [77 [•]]	0.1% Tacrolimus vs. 2% CsA in olive oil	DMPC for 8 weeks, then open for 4 weeks	24 VKC	No significant difference in symptoms and signs between groups

AKC, atopic keratoconjunctivitis; CsA, cyclosporine A; DBPC, double-blind, placebo-controlled trial; DMPC, double-masked, placebo-controlled trial; VKC, vernal keratoconjunctivitis.

cycling of inflammatory loop could lead to a consequent development of giant papillae and corneal disorders in individuals with VKC and AKC [83].

Topical cyclosporine A

Two per cent CsA ophthalmic emulsion is an effective and well tolerated drug for treatment of severe VKC [71,72,84]. However, most studies [71,72,84] demonstrated little effect on papillary hyperplasia. Both CsA and topical corticosteroids reduced symptoms and signs after 4 weeks of use without significant differences between groups [76[■]]. In addition, Pucci *et al.* [72] demonstrated that level of eosinophil cationic protein (ECP) and peripheral blood eosinophil counts significantly decreased after 4 months' use of 2% CsA.

Side effects of topical CsA are generally mild. There were no significant changes in kidney or liver enzymes when patients were observed after 7 years of use [85]. Most patients reported burning sensation that could affect compliance [71,72]. Lower concentrations of CsA, such as 0.1 and 0.05%, were studied and were associated with reduced local side effects [86,87]. However, efficacy from these lower CsA preparations was variable. Akpek *et al.* [86] reported that patients with steroid-resistant AKC had improved symptoms and signs after using 0.05% topical cyclosporine for 4 weeks. However, their results contradicted those from the study by Daniell *et al.* [87], which showed that 0.05% topical CsA had no benefit over placebo as a steroid-sparing agent in patients with AKC and VKC. A study by Spadavecchia *et al.* [73] used topical CsA at higher concentrations (1 and 1.25%) among VKC patients and demonstrated improvements with no statistically significant differences between these two concentrations. However, mild ocular burning sensation was still observed in this study.

The type of delivery vehicle could also affect the burning sensation in the eyes from CsA. Most studies with reported burning sensation side effect used olive, maize or castor oil as a delivery vehicle [71,72,88]. Kilic and Gurler [74] used 2% CsA in preservative free artificial tear among 20 patients with VKC for 14 weeks. They demonstrated a reduction of symptoms and signs, including tarsal conjunctival papillary hypertrophy scores, without any burning sensation side effect.

Tacrolimus

Tacrolimus (FK-506) is a macrolide antibiotic with potent immunomodulatory properties [89].

Vichyanond *et al.* [90] reported the results of an open study in 10 patients with recalcitrant VKC using 0.1% tacrolimus ophthalmic ointment. Satisfactory results were observed after 4 weeks of use, with only transient stinging effect. The absorption of tacrolimus at the end of the fourth week was minimal (0.29 ng/ml). No serious side effects were observed among this group of patients with intermittent to continuous use of the agent for 3 years [91]. Most recently, Ohashi *et al.* [75[■]] reported the result of treatment of severe conjunctivitis with 0.1% tacrolimus ophthalmic suspension, prepared as an isotonic aqueous suspension using polyvinyl alcohol as a dispersive agent. Significant improvement of symptoms and signs including giant papillae and corneal involvement was observed within 4 weeks' therapy [75[■]]. However, ocular irritation was still observed in 42% of the patients. Therefore, CsA and tacrolimus eye suspension with suitable dispersive agents are a major consideration for severe conjunctivitis in the future.

The efficacy of 0.1% tacrolimus ophthalmic ointment and 2% CsA eye drops was compared in 24 VKC patients using double-masked comparison technique [77[■]]. Both were effective in treatment of VKC, but adverse effects from cyclosporine were more prominent than from tacrolimus. Therefore, a study with larger sample size and with a longer period of follow-up is needed to investigate the difference between the two drugs. Table 1 shows important clinical trials using cyclosporine and tacrolimus in treated AKC and VKC patients.

CONCLUSION

Recent developments in the understanding of pathogenesis of allergic conjunctivitis have led to better selections of therapeutic agents. Newer breakthrough in the use of immunomodulators will lead to a better therapeutic outcome among patients with severe allergic conjunctivitis.

Acknowledgements

We are truly indebted to a significant research contribution from Professor Panida Kosrirukwongs from the Department of Ophthalmology, Faculty of Medicine Siriraj Hospital. We thank our patients and their families for their participation in our on-going research in VKC.

Conflicts of interest

There are no conflicts of interest.

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. 584).

1. Ait-Khaled N, Pearce N, Anderson HR, *et al*. Global map of the prevalence of symptoms of rhinoconjunctivitis in children: the International Study of Asthma and Allergies in Childhood (ISAAC) Phase Three. *Allergy* 2009; 64:123–148.
2. Björkstén B, Clayton T, Ellwood P, *et al*. Worldwide time trends for symptoms of rhinitis and conjunctivitis: phase III of the International Study of Asthma and Allergies in Childhood. *Pediatr Allergy Immunol* 2008; 19:110–124.
3. Smith AF, Pitt AD, Rodríguez AE, *et al*. The economic and quality of life impact of seasonal allergic conjunctivitis in a Spanish setting. *Ophthalmic Epidemiol* 2005; 12:233–242.
4. Leonardi A, Busca F, Motterle L, *et al*. Case series of 406 vernal keratoconjunctivitis patients: a demographic and epidemiological study. *Acta Ophthalmol Scand* 2006; 84:406–410.
5. Bremond-Gignac D, Donadieu J, Leonardi A, *et al*. Prevalence of vernal keratoconjunctivitis: a rare disease? *Br J Ophthalmol* 2008; 92:1097–1102.
6. De Smedt S, Wildner G, Kestelyn P. Vernal keratoconjunctivitis: an update. *Br J Ophthalmol* 2013; 97:9–14.
7. Ebihara N, Ohashi Y, Uchio E, *et al*. A large prospective observational study of novel cyclosporine 0.1% aqueous ophthalmic solution in the treatment of severe allergic conjunctivitis. *J Ocul Pharmacol Ther* 2009; 25:365–372.
8. Hu Y, Matsumoto Y, Dogru M, *et al*. The differences of tear function and ocular surface findings in patients with atopic keratoconjunctivitis and vernal keratoconjunctivitis. *Allergy* 2007; 62:917–925.
9. Schleimer RP. Pharmacology of glucocorticoids in allergic disease. In: Adkinson NF Jr, Bochner BS, Busse WW, *et al*, editors. Middleton's allergy, principles and practice, 7th ed. China: Elsevier Inc; 2009. pp. 1549–1574.
10. Camahan MC, Goldstein DA. Ocular complications of topical, peri-ocular, and systemic corticosteroids. *Curr Opin Ophthalmol* 2000; 11:478–483.
11. Armaly MF. Statistical attributes of the steroid hypertensive response in the clinically normal eye. I. The demonstration of three levels of response. *Invest ophthalmol* 1965; 4:187–197.
12. Kersey JP, Broadway DC. Corticosteroid-induced glaucoma: a review of the literature. *Eye (Lond)* 2006; 20:407–416.
13. Bielory BP, Perez VL, Bielory L. Treatment of seasonal allergic conjunctivitis with ophthalmic corticosteroids: in search of the perfect ocular corticosteroids in the treatment of allergic conjunctivitis. *Curr Opin Allergy Clin Immunol* 2010; 10:469–477.

A comprehensive review on newer topical steroids for ophthalmic use, particularly on loteprednol.

14. Dell SJ, Shulman DG, Lowry GM, Howes J. A controlled evaluation of the efficacy and safety of loteprednol etabonate in the prophylactic treatment of seasonal allergic conjunctivitis. Loteprednol Allergic Conjunctivitis Study Group. *Am J Ophthalmol* 1997; 123:791–797.
15. Ilyas H, Slonim CB, Braswell GR, *et al*. Long-term safety of loteprednol etabonate 0.2% in the treatment of seasonal and perennial allergic conjunctivitis. *Eye Contact Lens* 2004; 30:10–13.
16. Howell J. Roger Altounyan and the discovery of cromolyn (sodium cromoglycate). *J Allergy Clin Immunol* 2005; 115:882–885.
17. Tasche MJ, Uijen JH, Bernsen RM, *et al*. Inhaled disodium cromoglycate (DSCG) as maintenance therapy in children with asthma: a systematic review. *Thorax* 2000; 55:913–920.
18. van der Wouden JC, Uijen JH, Bernsen RM, *et al*. Inhaled sodium cromoglycate for asthma in children. *Cochrane Database Syst Rev* 2008; CD002173.
19. Parish RC, Miller LJ. Nedocromil sodium. *Ann Pharmacother* 1993; 27:599–606.
20. Janssen LJ, Wattie J, Betti PA. Effects of cromolyn and nedocromil on ion currents in canine tracheal smooth muscle. *Eur Respir J* 1998; 12:50–56.
21. Alton EW, Norris AA. Chloride transport and the actions of nedocromil sodium and cromolyn sodium in asthma. *J Allergy Clin Immunol* 1996; 98:S102–S105; discussion S5–S6.
22. Sridhar AV, McKean M. Nedocromil sodium for chronic asthma in children. *Cochrane Database Syst Rev* 2006; CD004108.
23. Glazer I, Leventon G. Topical treatment of hay fever with disodium cromoglycate (DSCG) solution. *Int Arch Allergy Appl Immunol* 1975; 49:125–128.
24. Vakil DV, Ayiomamitis A, Nizami RM. Treatment of seasonal conjunctivitis: comparison of 2% and 4% sodium cromoglycate ophthalmic solutions. *Can J Ophthalmol* 1984; 19:207–211.
25. Leino M, Ennevaara K, Latvala AL, *et al*. Double-blind group comparative study of 2% nedocromil sodium eye drops with 2% sodium cromoglycate and placebo eye drops in the treatment of seasonal allergic conjunctivitis. *Clin Exp Allergy* 1992; 22:929–932.
26. Leino M, Montan P, Nja F. A double-blind group comparative study of ophthalmic sodium cromoglycate, 2% four times daily and 4% twice daily, in the treatment of seasonal allergic conjunctivitis. *Allergy* 1994; 49:147–151.

27. el Hennawi M. A double blind placebo controlled group comparative study of ophthalmic sodium cromoglycate and nedocromil sodium in the treatment of vernal keratoconjunctivitis. *Br J Ophthalmol* 1994; 78:365–369.
28. Verin PH, Dicker ID, Mortemousque B. Nedocromil sodium eye drops are more effective than sodium cromoglycate eye drops for the long-term management of vernal keratoconjunctivitis. *Clin Exp Allergy* 1999; 29:529–536.
29. Kjellman NI, Stevens MT. Clinical experience with Tilavist: an overview of efficacy and safety. *Allergy* 1995; 50:34–38; 14–22; discussion.
30. Mah FS, O'Brien T, Kim T, Torkildsen G. Evaluation of the effects of olopatadine ophthalmic solution, 0.2% on the ocular surface of patients with allergic conjunctivitis and dry eye. *Curr Med Res Opin* 2008; 24:441–447.
31. Ousler GW, Wilcox KA, Gupta G, Abelson MB. An evaluation of the ocular drying effects of 2 systemic antihistamines: loratadine and cetirizine hydrochloride. *Ann Allergy Asthma Immunol* 2004; 93:460–464.
32. Ousler GW 3rd, Workman DA, Torkildsen GL. An open-label, investigator-masked, crossover study of the ocular drying effects of two antihistamines, topical epinastine and systemic loratadine, in adult volunteers with seasonal allergic conjunctivitis. *Clin Ther* 2007; 29:611–616.
33. Warner JO, Goldsworthy SJ. Ketotifen in childhood allergic disease. *Clin Allergy* 1982; 12 (Suppl):21–27.
34. Grant SM, Goa KL, Fitton A, Sorkin EM. Ketotifen. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in asthma and allergic disorders. *Drugs* 1990; 40:412–448.
35. Schwarzer G, Bassler D, Mitra A, *et al*. Ketotifen alone or as additional medication for long-term control of asthma and wheeze in children. *Cochrane Database Syst Rev* 2004; CD001384.
36. Yanni JM, Stephens DJ, Parnell DW, Spellman JM. Preclinical efficacy of emedastine, a potent, selective histamine H1 antagonist for topical ocular use. *J Ocul Pharmacol* 1994; 10:665–675.
37. Schoch C. In vitro inhibition of human conjunctival mast-cell degranulation by ketotifen. *J Ocul Pharmacol Ther* 2003; 19:75–81.
38. Galatowicz G, Ajayi Y, Stern ME, Calder VL. Ocular antiallergic compounds selectively inhibit human mast cell cytokines in vitro and conjunctival cell infiltration in vivo. *Clin Exp Allergy* 2007; 37:1648–1656.
39. Crampton HJ. Comparison of ketotifen fumarate ophthalmic solution alone, desloratadine alone, and their combination for inhibition of the signs and symptoms of seasonal allergic rhinoconjunctivitis in the conjunctival allergen challenge model: a double-masked, placebo- and active-controlled trial. *Clin Ther* 2003; 25:1975–1987.
40. Abelson MB, Chapin MJ, Kapik BM, Shams NB. Efficacy of ketotifen fumarate 0.025% ophthalmic solution compared with placebo in the conjunctival allergen challenge model. *Arch Ophthalmol* 2003; 121:626–630.
41. Horak F, Stubner P, Ziegler R, *et al*. Onset and duration of action of ketotifen 0.025% and emedastine 0.05% in seasonal allergic conjunctivitis: efficacy after repeated pollen challenges in the vienna challenge chamber. *Clin Drug Investig* 2003; 23:329–337.
42. Trattler WB, Luchs J, Majumdar P, Elestat (epinastine HCl ophthalmic solution 0.05%) as a therapeutic for allergic conjunctivitis. *Int Ophthalmol Clin* 2006; 46:87–99.
43. Fukuishi N, Kan T, Hirose K, *et al*. Inhibitory effect of epinastine on superoxide generation by rat neutrophils. *Jpn J Pharmacol* 1995; 68:449–452.
44. Kohyama T, Takizawa H, Akiyama N, *et al*. A novel antiallergic drug epinastine inhibits IL-8 release from human eosinophils. *Biochem Biophys Res Commun* 1997; 230:125–128.
45. Kanai K, Asano K, Watanabe S, *et al*. Epinastine hydrochloride antagonism against interleukin-4-mediated T cell cytokine imbalance in vitro. *Int Arch Allergy Immunol* 2006; 140:43–52.
46. Abelson MB, Gomes P, Crampton HJ, *et al*. Efficacy and tolerability of ophthalmic epinastine assessed using the conjunctival antigen challenge model in patients with a history of allergic conjunctivitis. *Clin Ther* 2004; 26:35–47.
47. Whitcup SM, Bradford R, Lue J, *et al*. Efficacy and tolerability of ophthalmic epinastine: a randomized, double-masked, parallel-group, active- and vehicle-controlled environmental trial in patients with seasonal allergic conjunctivitis. *Clin Ther* 2004; 26:29–34.
48. Torkildsen GL, Ousler GW 3rd, Gomes P. Ocular comfort and drying effects of three topical antihistamine/mast cell stabilizers in adults with allergic conjunctivitis: a randomized, double-masked crossover study. *Clin Ther* 2008; 30:1264–1271.
49. Yanni JM, Weimer LK, Sharif NA, *et al*. Inhibition of histamine-induced human conjunctival epithelial cell responses by ocular allergy drugs. *Arch Ophthalmol* 1999; 117:643–647.
50. Cook EB, Stahl JL, Barney NP, Graziano FM. Olopatadine inhibits TNF α release from human conjunctival mast cells. *Ann Allergy Asthma Immunol* 2000; 84:504–508.
51. Cook EB, Stahl JL, Barney NP, Graziano FM. Olopatadine inhibits anti-immunoglobulin E-stimulated conjunctival mast cell upregulation of ICAM-1 expression on conjunctival epithelial cells. *Ann Allergy Asthma Immunol* 2001; 87:424–429.
52. Wade L, Bielory L, Rudner S. Ophthalmic antihistamines and H1-H4 receptors. *Curr Opin Allergy Clin Immunol* 2012; 12:510–516.
53. Abelson MB. Evaluation of olopatadine, a new ophthalmic antiallergic agent with dual activity, using the conjunctival allergen challenge model. *Ann Allergy Asthma Immunol* 1998; 81:211–218.

54. Abelson MB, Spitalny L. Combined analysis of two studies using the conjunctival allergen challenge model to evaluate olopatadine hydrochloride, a new ophthalmic antiallergic agent with dual activity. *Am J Ophthalmol* 1998; 125:797–804.
 55. Butrus S, Greiner JV, Discepolo M, Finegold I. Comparison of the clinical efficacy and comfort of olopatadine hydrochloride 0.1% ophthalmic solution and nedocromil sodium 2% ophthalmic solution in the human conjunctival allergen challenge model. *Clin Ther* 2000; 22:1462–1472.
 56. Lanier BQ, Finegold I, D'Arienzo P, et al. Clinical efficacy of olopatadine vs. epinastine ophthalmic solution in the conjunctival allergen challenge model. *Curr Med Res Opin* 2004; 20:1227–1233.
 57. Aguilar AJ. Comparative study of clinical efficacy and tolerance in seasonal allergic conjunctivitis management with 0.1% olopatadine hydrochloride versus 0.05% ketotifen fumarate. *Acta Ophthalmol Scand Suppl* 2000; (230):52–55.
 58. Berdy GJ, Spangler DL, Bensch G, et al. A comparison of the relative efficacy and clinical performance of olopatadine hydrochloride 0.1% ophthalmic solution and ketotifen fumarate 0.025% ophthalmic solution in the conjunctival antigen challenge model. *Clin Ther* 2000; 22:826–833.
 59. Artal MN, Luna JD, Discepolo M. A forced choice comfort study of olopatadine hydrochloride 0.1% versus ketotifen fumarate 0.05%. *Acta Ophthalmol Scand Suppl* 2000; (230):64–65.
 60. Ganz M, Koll E, Gausche J, et al. Ketotifen fumarate and olopatadine hydrochloride in the treatment of allergic conjunctivitis: a real-world comparison of efficacy and ocular comfort. *Adv Ther* 2003; 20:79–91.
 61. Abelson MB, Gomes PJ. Olopatadine 0.2% ophthalmic solution: the first ophthalmic antiallergic agent with once-daily dosing. *Expert Opin Drug Metab Toxicol* 2008; 4:453–461.
 62. Corum I, Yeniad B, Bilgin LK, Ilhan R. Efficiency of olopatadine hydrochloride 0.1% in the treatment of vernal keratoconjunctivitis and goblet cell density. *J Ocul Pharmacol Ther* 2005; 21:400–405.
 63. Del Prete A, Loffredo C, Carderoli A, et al. Local specific immunotherapy in allergic conjunctivitis. *Acta Ophthalmol (Copenh)* 1994; 72:631–634.
 64. Calderon MA, Penagos M, Sheikh A, et al. Sublingual immunotherapy for treating allergic conjunctivitis. *Cochrane Database Syst Rev* 2011; CD007685.
- A recent meta-analysis of SLIT on symptoms and signs of allergic conjunctivitis.
65. Liu LL, Guo DD, Liang QX, et al. Sublingual immunotherapy for experimental allergic conjunctivitis in a murine model induced by *Dermatophagoides farinae* allergen. *Int Arch Allergy Immunol* 2013; 161:205–212.
- An amazing animal model demonstrating effect of SLIT on experimental allergic conjunctivitis caused from house-dust mites.
66. Cadario G, Galluccio AG, Pezza M, et al. Sublingual immunotherapy efficacy in patients with atopic dermatitis and house dust mites sensitivity: a prospective pilot study. *Curr Med Res Opin* 2007; 23:2503–2506.
 67. Pajno GB, Caminiti L, Vita D, et al. Sublingual immunotherapy in mite-sensitized children with atopic dermatitis: a randomized, double-blind, placebo-controlled study. *J Allergy Clin Immunol* 2007; 120:164–170.
 68. Hara Y, Shoji J, Hori S, et al. Evaluation of eosinophilic inflammation in a novel murine atopic keratoconjunctivitis model induced by crude *Dermatophagoides farinae* antigen. *Allergol Int* 2012; 61:331–338.
 69. Tabbara KF, Nassar A, Ahmed SO, et al. Acquisition of vernal and atopic keratoconjunctivitis after bone marrow transplantation. *Am J Ophthalmol* 2008; 146:462–465.
 70. Mantelli F, Santos MS, Petitti T, et al. Systematic review and meta-analysis of randomised clinical trials on topical treatments for vernal keratoconjunctivitis. *Br J Ophthalmol* 2007; 91:1656–1661.
 71. Secchi AG, Tognon MS, Leonardi A. Topical use of cyclosporine in the treatment of vernal keratoconjunctivitis. *Am J Ophthalmol* 1990; 110:641–645.
 72. Pucci N, Novembre E, Cianferoni A, et al. Efficacy and safety of cyclosporine eyedrops in vernal keratoconjunctivitis. *Ann Allergy Asthma Immunol* 2002; 89:298–303.
 73. Spadavecchia L, Fanelli P, Tesse R, et al. Efficacy of 1.25% and 1% topical cyclosporine in the treatment of severe vernal keratoconjunctivitis in childhood. *Pediatr Allergy Immunol* 2006; 17:527–532.
 74. Kilic A, Gurler B. Topical 2% cyclosporine A in preservative-free artificial tears for the treatment of vernal keratoconjunctivitis. *Can J Ophthalmol* 2006; 41:693–698.
 75. Ohashi Y, Ebihara N, Fujishima H, et al. A randomized, placebo-controlled clinical trial of tacrolimus ophthalmic suspension 0.1% in severe allergic conjunctivitis. *J Ocul Pharmacol Ther* 2010; 26:165–174.
- A study of a novel preparation of aqueous preparation of topical tacrolimus in severe conjunctivitis.
76. De Smedt S, Nkurikiye J, Fonteyne Y, et al. Topical ciclosporin in the treatment of vernal keratoconjunctivitis in Rwanda, Central Africa: a prospective, randomised, double-masked, controlled clinical trial. *Br J Ophthalmol* 2012; 96:323–328.
- A study on a large number of VKC patients treated with topical CsA from Africa.
77. Labchareonwongs P, Jirapongsananuruk O, Visitsunthorn N, et al. A double-masked comparison of 0.1% tacrolimus ointment and 2% cyclosporine eye drops in the treatment of vernal keratoconjunctivitis in children. *Asian Pac J Allergy Immunol* 2012; 30:177–184.
- The most recent study on the comparison of topical CsA with topical tacrolimus.
78. Bonini S, Lambiasi A, Marchi S, et al. Vernal keratoconjunctivitis revisited: a case series of 195 patients with long-term follow-up. *Ophthalmology* 2000; 107:1157–1163.
 79. Tabbara KF. Ocular complications of vernal keratoconjunctivitis. *Can J Ophthalmol* 1999; 34:88–92.
 80. Guglielmetti S, Dart JK, Calder V. Atopic keratoconjunctivitis and atopic dermatitis. *Curr Opin Allergy Clin Immunol* 2010; 10:478–485.
- An excellent review on AKC.
81. Schreiber SL, Crabtree GR. The mechanism of action of cyclosporin A and FK506. *Immunol Today* 1992; 13:136–142.
 82. Leonardi A, DeFranchis G, Fregona IA, et al. Effects of cyclosporin A on human conjunctival fibroblasts. *Arch Ophthalmol* 2001; 119:1512–1517.
 83. Fukuda K, Kumagai N, Fujitsu Y, Nishida T. Fibroblasts as local immune modulators in ocular allergic disease. *Allergol Int* 2006; 55:121–129.
 84. Gupta V, Sahu PK. Topical cyclosporin A in the management of vernal keratoconjunctivitis. *Eye (Lond)* 2001; 15:39–41.
 85. Pucci N, Caputo R, Mori F, et al. Long-term safety and efficacy of topical cyclosporine in 156 children with vernal keratoconjunctivitis. *Int J Immunopathol Pharmacol* 2010; 23:865–871.
 86. Akpek EK, Dart JK, Watson S, et al. A randomized trial of topical cyclosporin 0.05% in topical steroid-resistant atopic keratoconjunctivitis. *Ophthalmology* 2004; 111:476–482.
 87. Daniell M, Constantinou M, Vu HT, Taylor HR. Randomised controlled trial of topical cyclosporin A in steroid dependent allergic conjunctivitis. *Br J Ophthalmol* 2006; 90:461–464.
 88. Hingorani M, Moodaley L, Calder VL, et al. A randomized, placebo-controlled trial of topical cyclosporin A in steroid-dependent atopic keratoconjunctivitis. *Ophthalmology* 1998; 105:1715–1720.
 89. de Paulis A, Cirillo R, Ciccarelli A, et al. FK-506, a potent novel inhibitor of the release of proinflammatory mediators from human Fc epsilon RI+ cells. *J Immunol* 1991; 146:2374–2381.
 90. Vichyanond P, Tantimongkolsuk C, Dumrongkigchaiporn P, et al. Vernal keratoconjunctivitis: result of a novel therapy with 0.1% topical ophthalmic FK-506 ointment. *J Allergy Clin Immunol* 2004; 113:355–358.
 91. Pacharn P, Visitsunthorn N, Jirapongsananuruk O, Vichyanond P. Vernal keratoconjunctivitis (VKC) treated with 0.1% FK-506 ophthalmic ointment result of three years follow-up. *J Allergy Clin Immunol* 2007; 119:S153.