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Ocular Allergy Guidelines

A Practical Treatment Algorithm

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Abstract

The treatment of ocular allergy requires a better understanding of the spectrum of clinical disorders involving various components of the immune system, and of interactions at the conjunctival surface. The immune response focuses primarily on the different levels of activity of Th2 lymphocytes and various other immune cells associated with allergic disorders, including mast cells, eosinophils, fibroblasts, and epithelial and endothelial cells.

Ocular allergic disorders include seasonal allergic conjunctivitis (SAC), perennial allergic conjunctivitis (PAC), vernal keratoconjunctivitis (VKC), giant

papillary conjunctivitis (GPC) and atopic keratoconjunctivitis (AKC), which, through immunopathological and molecular immunological techniques, can all be better appreciated as being part of a larger spectrum of an atopic disease state. In SAC, pathological changes, such as increased mast-cell activation, the presence of migratory inflammatory cells, and early signs of cellular activation at the molecular level, are minimal. In PAC, these changes are more pronounced in line with the increased duration of allergenic stimulation. In more chronic forms of allergic conjunctivitis, such as VKC in children and AKC in adults, the following changes are evident: a persistent state of mast cell, eosinophil and lymphocyte activation; noted switching from connective-tissue to mucosal-type mast cells; increased involvement of corneal pathology; and follicular development and fibrosis.

The treatment of acute and more chronic forms of allergic conjunctivitis has focused in the past on symptomatic relief of symptoms, but with a better understanding of the mechanisms involved we can now provide interventional therapeutic strategies and symptomatic relief. Our advances in the basic understanding of these conditions are providing the foundation for guidelines that improve the ocular health of patients with ocular allergies.

1. Treatment of Ocular Allergies

The birth of immunology is considered to have occurred in 1880 at the hands of Louis Pasteur. Physicians interested in the eye immediately recognised the importance of unveiling immunological mechanisms in the understanding and treatment of ocular disorders. Thus, the early links between the ophthalmologist and immunologist have evolved within the 20th century into the young specialty of 'immuno-ophthalmology' with involvement in the conjoint clinical trials to evaluate new therapeutic interventions.

The eye and its surrounding tissues are commonly involved in local and systemic immunological hypersensitivity reactions.[1,2] Conjunctivitis, especially allergic and seasonal allergic conjunctivitis (SAC), are the predominant forms that have been part of a general increase in allergic disorders seen around the world. The pharmaceutical industry has only recently embarked on a more extensive research and development programme that has generated over ten new products over the past 10 years, with prescriptions and sales increasing 10- to 20-fold during this same period of time.[3]

The treatment of ocular allergies is based largely on the important aspect of interference with the quality of life that a patient experiences; i.e. severity of symptoms.[4] Quality-of-life parameters may take up to 2½ weeks to improve during treatment. The easiest and most direct therapeutic method is placement of a 'topical' agent on the affected tissue. Several topical agents are available for the treatment and, to some degree, the prophylaxis of ocular allergy. These include vasoconstrictors, antihistamines, mast-cell stabilisers, and anti-inflammatory agents. Efficacy of these agents varies from patient to patient, and the choice of agent used will depend on the underlying health of the eye and other variables, such as drug cost, contact lens wear and potential for compliance.

The primary treatment algorithm includes avoidance of allergens, cold compresses and lubrication (figure 1). Avoidance of allergens remains the first option in the management of any ocular disorder. This mainly involves the use of environmental interventions, ranging from removal of the offending allergen source to a change of occupational venue. Cold compresses provide considerable symptomatic relief, especially from ocular pruritus.

Lubrication is another form of avoidance that primarily assists in the direct removal and dilution of allergens that may come into contact with the

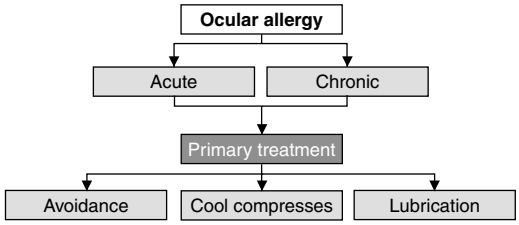

Fig. 1. Primary treatment of ocular allergy, including acute forms such as seasonal and perennial allergic conjunctivitis, and more chronic forms such as atopic and vernal keratoconjunctivitis and giant papillary conjunctivitis.

conjunctival surface. Tear substitutes, consisting of saline combined with a wetting and viscosity agent such as methylcellulose or polyvinyl alcohol ('artificial' tears), are the typical formulations that can be applied topically two to four times a day as necessary. If tear substitutes are inadequate, ointments or time-released tear replacements are commonly used at night and provide moisture to the ocular surface while the patient sleeps. Sample ophthalmic lubricants available in the US are listed in table I. In general, all ocular medications, when refrigerated, provide additional subjective relief when applied immediately in a cold state.

Secondary treatment regimens include the symptomatic use of topical agents and oral decongestants, antihistamines, and mast-cell stabilising and anti-inflammatory agents (figure 2).

1.1 Topical Decongestants

Topical decongestants act primarily as vasoconstrictors that are highly effective in reducing erythema and are widely used in combination with topical antihistamines.[5] Vasoconstrictors, such as phenylephrine and tetrahydrozoline, are sympathomimetic agents that decrease vascular congestion and eyelid oedema via α-adrenoceptor stimulation. They have no effect in diminishing the allergic response. The decongestants are applied topically, one to two drops per eye every 2 hours, up to four times a day.

Naphazoline 0.02% and tetrahydrozoline 0.05% significantly reduced baseline redness after a single use, although naphazoline produced significantly more whitening than tetrahydrozoline, and naphazoline retained its whitening ability after 10 days. Although the level of redness remained significantly below baseline for 8 hours after a single use of either vasoconstrictor, after multiple doses, the duration of action of naphazoline was reduced to only 6 hours.[6] Adverse effects of topical vasoconstrictors include burning and stinging on instillation, mydriasis, especially in patients with lighter irides, and rebound hyperaemia or conjunctivitis medicamentosa with long-term use;[7] however, short-term use for 10 days did not appear to be related to the development of conjunctivitis medicamentosa.[6] Naphazoline/antazoline 0.5%/0.05% is the only decongestant/antihistamine approved by the US Food and Drug Administration (FDA) to treat the signs and symptoms (itch and redness) of allergic conjunctivitis. The primary contraindication is narrow-angle glaucoma.

1.2 Antihistamines

1.2.1 Topical Versus Oral Antihistamines

Initially, oral antihistamines were extensively employed to systemically control the symptoms of allergic rhinoconjunctivitis. However, when such agents were studied for their effects on the eye,

Table I. Ophthalmic lubricants available in the US

Trade name (manufacturer)	Composition
AKWA Tears Ointment (Akorn)	Sterile ointment containing white petrolatum, liquid lanolin and mineral oil
Duolube (Bausch & Lomb)	Sterile ointment containing white petrolatum and mineral oil
Duratears Naturale (Alcon)	Sterile ointment containing white petrolatum, liquid lanolin and mineral oil
HypoTears (Iolab)	Sterile ointment containing white petrolatum and light mineral oil
Lacri-Lube S.O.P. (Allergan)	Sterile ointment containing 42.5% mineral oil, 55% white petrolatum, lanolin alcohol and chlorobutanol
Refresh P.M. (Allergan)	Sterile ointment containing 41.5% mineral oil, 55% white petrolatum, petrolatum and lanolin alcohol

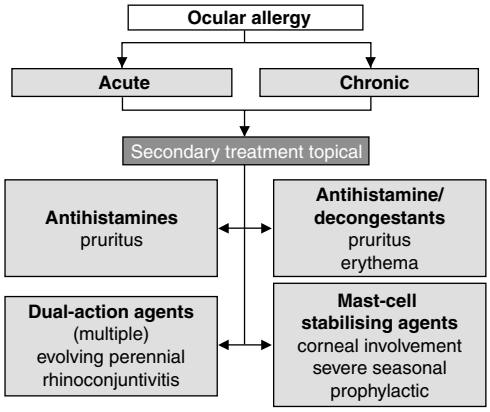

Fig. 2. Secondary treatment of acute and chronic forms of ocular allergy may include the topical use of antihistamines for pruritus, or a combination antihistamine/decongestant for the control of pruritus and erythema. Secondary treatment of the more chronic forms of ocular allergy requires the initiation of dual (multiple)-action agents. Mast-cell stabilising agents appear to have their primary indications in the treatment of corneal involvement in the most chronic forms of ocular allergy, although such agents are also used in seasonal allergic conjunctivitis and perennial allergic conjunctivitis.

they appeared in many direct comparisons with topical agents and placebo to be only as effective as placebo regarding the onset of symptom relief within 15 minutes.[8] This is exemplified in a study that compared the immediate effect of topical olopatadine with that of oral loratadine.[9,10] Therefore, an increased focus on the development of topical antihistamines has occurred during the past 12 years. However, when oral antihistamines are studied alone for their effects against ocular allergy, they clearly reflect a positive trend in some studies, although data are buried in the 'rhinoconjunctivitis' literature.

In the conjunctiva, histamine H_1 receptor stimulation principally mediates the symptom of pruritus, as seen in various binding studies, while the existence of histamine H_2 receptors has been inferred to be clinically involved in the vasodilatory aspect of the ocular allergic response.[11] Although topical antihistamines can be used alone to treat allergic conjunctivitis, combining an antihistamine with a vasoconstrictor is more effective than either agent alone.[5] The vasoconstrictors commonly used in combination with topical antihistamines are phenylephrine or naphazoline.

1.2.2 Levocabastine

Levocabastine, approved in the US in the spring of 1994, is a cyclohexyl-3-methylpiperidine derivative shown in animal models to inhibit the development of compound 48/80-induced anaphylactic shock, histamine skin reactions, passive cutaneous anaphylactic reactions and allergic conjunctivitis.[12,13] Levocabastine is a selective H_1-receptor, topical antihistamine suspension having rapid and long-lasting activity with no central nervous system effects.[14] Levocabastine has been shown to be effective in the treatment of allergic conjunctivitis when compared with placebo in clinical studies[12,15,16] and in animal models.[17-19] Although it appears to work primarily as an antihistamine affecting H_1 receptors, levocabastine has also been shown to downregulate intracellular adhesion molecules by almost half in an ocular allergen-challenge model.[20,21]

In comparative studies using a variety of clinical parameters, including the inhibition of itching, hyperaemia, eyelid swelling, chemosis and tearing, levocabastine was found to be better than sodium cromoglycate (cromolyn sodium) in an allergen-challenge model,[22] but performed less effectively than ketorolac.[23] In clinical studies of SAC, levocabastine performed as well as, or better than, sodium cromoglycate[24-26] or lodoxamide.[27] In patients with a more chronic form of allergic conjunctivitis, vernal keratoconjunctivitis (VKC), levocabastine even improved symptoms of photophobia.[28] In a conjunctival provocation study, previous treatment with levocabastine required a 10-fold increase in allergen concentration to reproduce the same symptoms. In addition, such pretreatment promoted the development of a late-phase anti-inflammatory response in the eyes of three of the 11 patients.[29,30]

1.2.3 Emedastine

Emedastine is a relatively selective blocker of H_1 receptors with no apparent effects on adrenoceptors, dopamine or serotonin receptors.[31] Emedastine has greater H_1 receptor selectivity than

mepyramine (pyrilamine), levocabastine, pheniramine, chlorphenamine (chlorpheniramine) and antazoline.[31] Relief of the signs and symptoms of allergic conjunctivitis has been demonstrated in patients treated for 6 weeks with emedastine in an environmental study, as has reduction in ocular itching when patients were challenged with antigen.[32] Comparative studies have primarily involved the use of levocabastine[32-35] and ketorolac.[36]

1.2.4 Ocular Antihistamines in Provocation Models

Some of the studies evaluating the potential of new agents in the treatment of allergic conjunctivitis have used either an *in vitro* human model or an animal model of experimental conjunctivitis,[19] that primarily measured the inhibition of histamine content in tears or the development of various levels of ocular injection. In these models, amlexanox was less effective than levocabastine, chlorphenamine or ketotifen.[37]

Human conjunctival epithelial cells express H_1 receptors[38] and, when exposed to histamine, release the pro-inflammatory cytokines interleukin (IL)-6 and IL-8.[39] Importantly, treatment of the epithelial cells with drugs that possess antagonistic properties at H_1 receptors prevents cytokine production.[40] It is interesting to note that the newer antihistamines emedastine and levocabastine are more potent than the first-generation antihistamines antazoline and pheniramine in the inhibition of histamine-stimulated cytokine synthesis in intact epithelial cells.[41] In addition, there is a growing set of newer dual-agent (multiple) antihistamines that are speculated to be more advantageous in the treatment of allergic conjunctivitis.[42]

1.3 Dual (Multiple)-Acting Agents

1.3.1 Olopatadine

Olopatadine appears to possess a dual form of action with limited mast-cell stabilising effects and H_1 receptor binding.[40,43,44] However, compared with first-generation antihistamines (antazoline and pheniramine), olopatadine was noted to inhibit cytokine secretion,[40] including the release of tumour necrosis factor (TNF)-α mediators from human conjunctival mast cells.[43-47] As with many of the dual-acting agents, olopatadine has been shown to be significantly more effective than placebo in relieving itching and redness for up to 8 hours.[48,49] In a comparative study with another multiple-acting agent, ketotifen, olopatadine faired only slightly better during a short, 2-week course of treatment[50] (table II).

1.3.2 Ketotifen

Ketotifen is a benzocycloheptathiophene agent that has been approved in the US for the treatment of allergic conjunctivitis. It has multiple mechanisms of action, possessing both mast-cell stabilising and several antimediator properties, including strong H_1 receptor antagonism and inhibition of leukotriene formation.[52,53] Ketotifen has been used as an orally active prophylactic agent for the management of bronchial asthma and allergic disorders. Ketotifen has also been shown to have pronounced antihistaminic and anti-anaphylactic properties that result in moderate-to-marked symptom improvement in most patients with atopic dermatitis, seasonal or perennial rhinitis, allergic conjunctivitis, acute or chronic urticaria, or food allergy.[54] It has been reported in several studies to have a mild stinging effect on the conjunctival surface.[50] Ketotifen is distinguished from the cromones (sodium cromoglycate and nedocromil) by a conjoint antihistaminic effect (table III).

1.3.3 Azelastine

Azelastine is a second-generation H_1 receptor antagonist which was first shown to be clinically effective in relieving the symptoms of allergic rhinitis after oral or intranasal administration.[62,63] Azelastine has been reported to inhibit the early allergic response[62,64] and histamine release from rat mast cells after antigenic and non-antigenic stimuli.[43-47,64,65] It is likely that the additional prophylactic anti-allergic properties of azelastine are partially due to inhibition of a broad array of other inflammatory mediators and important receptors for the allergic response. Indeed, the following azelastine-induced changes have been re-

Table II. *In vivo* and *in vitro* studies of the ocular effects of olopatadine (OLO)

Reference	Model/system	Method	Comparator	Parameter measured	Comments
***In vivo* studies**					
Deschenes et al.[51]	Conjunctival provocation model –db, sc, co	Pretreatment with OLO 0.1%, then allergen challenge	Ketorolac 0.5%	Ocular itching and hyperaemia in conjunctival, ciliary and episcleral vascular beds	OLO significantly reduced itching and redness and patients found it more comfortable than ketorolac up to 20 minutes
***In vitro* studies**					
Cook et al.[46]	HCMC-cadaveric	Preincubate with OLO in increasing concentrations, then challenge with anti-IgE antibody	Unchallenged controls	TNFα release in supernatant	OLO inhibited anti-IgE antibody-mediated release of TNFα from HCMC. This could contribute to the long duration of anti-allergic activity reported for the drug
Yanni et al.[40]	Primary human conjunctival epithelial cell cultures	Histamine in presence or absence of test drugs	Antazoline, emedastine, levocabastine, olopatadine and pheniramine	Phosphatidylinositol turnover and IL-6 and IL-8 secretion	OLO attenuated phosphatidylinositol turnover, and IL-6 and IL-8 secretion; Antihistaminic potency alone does not predict anti-inflammatory potential
Yanni et al.[42]	HCMC	OLO then anti-human IgE	Nedocromil pemirolast	Histamine content of supernatant, H_1 receptor binding	Only OLO exhibited significant inhibition of histamine release, and exhibited significant H_1 receptor binding OLO possesses antiallergic and antihistaminic activity
Yanni et al.[42]	Cadaveric HCMC cultures	Anti-human IgE in presence or absence of test drugs	Sodium cromoglycate	Histamine release and H_1 receptor binding activity	OLO inhibited histamine release in a concentration-dependent fashion. Only OLO exhibited significant H_1 receptor binding activity at relevant concentrations. Conclusion: OLO possesses antiallergic activity in human conjunctival mast cells and along with antihistaminic activity this suggests it will have efficacy advantages in allergic conjunctivitis over other drugs tested
Sharif et al.[43]	Monodispersed HCMC Also human conjunctival epithelial cells and other human ocular cells	OLO	Ketotifen, levocabastine, antazoline, pheniramine	Release of histamine, tryptase, and PGD_2; Histamine receptor subtype binding affinities and functional potencies were determined with ligand binding and phosphatidylinositide turnover assays, respectively	OLO inhibited release of histamine, tryptase and PGD_2 in a concentration-dependent manner; had relatively high affinity for the H_1 receptor but lower affinities for the H_2 receptors; inhibited histamine-induced phosphoinositide turnover in human conjunctival epithelial cells and other human ocular cells with non-competitive antagonist properties in these cells. Combination of mast cell mediator release inhibition and selective H_1 receptor antagonism suggests that OLO may be particularly useful in the treatment of ocular diseases
Sharif et al.[38]	Cultured human conjunctival epithelial cells, human corneal fibroblasts, transformed human trabecular meshwork cells	OLO	Levocabastine, ketotifen, antazoline, pheniramine	Ability to compete for H_1, H_2 & H_3 histamine receptors; histamine-induced phosphoinositide turnover	OLO selectivity: $H_1 > H_2 > H_3$. OLO more H_1-selective than other drugs tested. OLO antagonised histamine-induced phosphoinositide turnover in all 3 cell systems. Conclusion: OLO is high-affinity, high-potency, H_1-selective histamine antagonist
Yanni et al.[45]	HCMC	OLO	Ketotifen	Cyclooxygenase, 5-lipoxygenase, histamine	OLO did not stimulate histamine release and inhibited histamine release. OLO did not inhibit cyclooxygenase or 5-lipoxygenase

co = cross-over; **db** = double blind; **HCMC** = human conjunctival mast cells; **Ig** = immunoglobulin; **IL** = interleukin; **PG** = prostaglandin; **sc** = single centre; **TNF** = tumour necrosis factor.

Table III. Clinical and *in vitro* studies of ocular effects of ketotifen (KET)

Reference	Patients/system	Agent	Comparator	Parameter measured	Comments
Clinical studies					
Artal et al.[55]	80 allergic patients, db, mc, r	0.05% KET fumarate: one drop, one eye	0.1% OLO: one drop, other eye	'Forced choice' based on ocular comfort	100% selected OLO as the more comfortable formulation
Berdy et al.[56]	53 patients screened, 32 patients entered	KET: one drop, one eye	OLO: one drop, other eye	Conjunctival antigen challenge with measure of ocular itching, subject satisfaction, slit lamp findings, visual acuity, & ocular comfort	Of 22 pts who had a preference, 16 (73%) were more satisfied with OLO than KET
Mikuni et al.[57]	11 patients with conjunctivitis (Japanese Cedar pollinosis)	0.1% KET ophthalmic preparation		Time to effect and other clinical parameters	In 7 of 10 pts with therapeutic effect noted, time to effect was ≤3 days
Aguilar et al.[50]	80 adults with history of allergy and showing signs of allergic conjunctivitis	0.05% KET: one drop in affected eye q12h	0.1% OLO: one drop in affected eye	Clinical improvement of symptoms	OLO: 80-87.5% improved at 7 days; KET: 60-75% improved at 7 days, 67.5-75% improved at 14 days. Conclusion: OLO controlled allergic conjunctivitis symptoms and signs more rapidly and to a greater extent than KET. Stinging occurred in 23% of KET patients, not in OLO patients
Mikuni et al.[58]	10 pts with seasonal cedar pollinosis	KET 0.08% eye drops		Quantitative determination of tear fluids	Efficacy rate = 80%
Hockwin et al.[59]	372 patients	KET	Picumast	Lens transparency: Scheimpflug photography, slit lamp exams, microdensitometric analyses of film negatives after 1yr treatment	Negative for picumast or KET
Kato et al.[60]	Patients with pollinosis	KET (prophylactic treatment)	No treatment	Blood eosinophil count; serum ECP values; subjective symptoms	Serum ECP during season and post-season were significantly higher than pre-season. Significant correlation between ECP and blood eosinophil count during season. During season, all 3 parameters measured were significantly lower in KET group than in no-treatment group
Mikuni et al.[58]	Provocation testing in 10 adults	0.08% KET		Itching of the eye	80% efficacy rate
Urbanek et al.[61]	23 children with perennial allergic bronchial asthma	KET syrup/ capsules		Corticosteroid discontinuation; allergic manifestations in eyes, nose & skin	Improvement observed in 16 of 23 pts, associated with decreased allergic manifestations; corticosteroids could be discontinued in 3 of 7 pts; transient tiredness in 6 children but only one required dose reduction
***In vitro* studies**					
Sharif et al.[44]	Monodispersed human conjunctival mast cells	KET	OLO, levocabastine, antazoline, pheniramine	Release of histamine tryptase PGD_2; histamine receptor subtype binding affinities by ligand binding assay; functional potencies by phosphoinositide turnover assay	KET was less H_1 selective than OLO. Abstract focuses on OLO
Yanni et al.[45]	Human conjunctival mast cell preparation	KET	OLO	Histamine release	KET-stimulated histamine release at concentrations slightly higher than effective inhibitory concentrations; OLO did not stimulate histamine release at concentrations as high as 10 mmol/L

db = double blind; **ECP** = cationic protein; **OLO** = olopatadine; **PG** = prostaglandin; **mc** = multicentre; **q12h** = every 12 hours; **r** = randomised.

ported: inhibition of superoxide generation by neutrophils and eosinophils;[66] inhibition of leukotriene synthesis;[67-71] inhibition of TNFα secretion from rat basophilic leukaemia cells;[72,73] inhibition of IL-6 release from human leukaemic mast cells;[47-50,52-54,62-74] and downregulation of intercellular adhesion molecule (ICAM)-1 in the human conjunctiva.[75] These and various other studies have reflected an extensive array of anti-inflammatory mechanisms involved in the control of allergies and asthma. In the US, azelastine has been approved as the only antihistamine nasal spray and has recently been approved by the FDA for the treatment of allergic conjunctivitis[76] (table IV).

1.3.4 Nedocromil

Nedocromil was originally thought to be just a mast-cell stabilising agent, but it is now appreciated to have multiple actions,[100] including as an H_1 receptor antagonist with inhibitory effects on various allergic inflammatory cells, mast cells and eosinophils;[101] however, conflicting results exist regarding the inhibition of neutrophil migration by nedocromil.[102,103] In an animal model, nedocromil suppressed early and late-phase conjunctival hyperaemia and oedema, eyelid oedema and eosinophil infiltration.[104]

Topical nedocromil treatment has been shown, in an ocular allergen-challenge model, to reduce tear concentrations of histamine and prostaglandin (PG) D_2 and the number of IL-4 secreting mast cells,[21] while increasing conjunctival tolerance to the allergen.[105] In cultures, nedocromil has been shown to abolish the expression of human leucocyte antigen (HLA)-DR and to reduce ICAM-1 expression.[106] Nedocromil has also been shown to improve clinical symptoms in the control of ocular pruritus and irritation when compared with placebo in the treatment of SAC[107-112] and VKC.[113] In placebo-controlled studies, nedocromil effectively alleviated the signs and symptoms of SAC, providing relief in 80% of patients.[114,115]

The safety profile of nedocromil is similar to that of sodium cromoglycate, but nedocromil appears to be more potent in chronic ocular allergic conditions such as VKC. Nedocromil can be given just twice daily.[116] It is associated with stinging or burning of the eyes on application of the drops, and a distinctive taste once some of the agent drains into the nasolacrimal duct, in approximately 5% of the population[117] (table V).

1.4 Mast-Cell Stabilising Agents

1.4.1 Sodium Cromoglycate

Sodium cromoglycate is the prototypic mast-cell mediator. Its efficacy appears to be concentration-dependent.[122] After many years of clinical use, the possible mechanisms of sodium cromoglycate action remain unclear.[41,123,124] Sodium cromoglycate was originally approved for more severe forms of conjunctivitis [giant papillary conjunctivitis (GPC), atopic keratoconjunctivitis (AKC), VKC], but many physicians have used it for the treatment of acute SAC and perennial allergic conjunctivitis (PAC) with an excellent safety record. Some of the studies reflecting the clinical efficacy of sodium cromoglycate in SAC and PAC indicated marginal efficacy relative to placebo in clinical trials[16,125] and in some animal models.[18]

1.4.2 Lodoxamide

Lodoxamide is a mast-cell stabiliser that is approximately 2500 times more potent than sodium cromoglycate in the prevention of histamine release in several animal models.[126] Lodoxamide 0.1% has been shown to inhibit the production of leukotriene (LT) B_4 and LTC_4 in the tears of patients with GPC, compared with healthy controls, when used for 1 month.[127] In a comparative study of a topical corticosteroid, fluorometholone 0.1%, with the mast-cell stabilisers lodoxamide 0.1% and sodium cromoglycate 2% in patients with VKC, LTB_4 and LTC_4 levels were statistically significantly decreased from baseline in all treatment groups.[128] Lodoxamide is effective in reducing tryptase, histamine and the recruitment of inflammatory cells in tear fluid after allergen challenge.[129,130] In early clinical trials, lodoxamide 0.1% delivered greater and earlier relief than sodium cromoglycate in patients with more chronic forms of conjunctivitis such as VKC, including upper tarsal papillae, limbal signs (papillae, hyperae-

Table IV. Clinical and *in vitro* studies of ocular effects of azelastine (AZ)

Reference	Patients/system	Agent	Comparator	Parameter measured	Comments
Clinical studies					
Ciprandi et al.[77]	20 children with asymptomatic mite conjunctivitis	AZ preceded or followed by hyperosmolar glucose challenge to eye (10µl glucose solution ranging between 10 and 50%)	Placebo (10µl 0.03% saline albumin diluent)	Hyperaemia >2+ (grading by Abelson, Udell and Weston)	Significant reduction in non-specific conjunctival hyperreactivity compared to the placebo group ($p = 0.018$)
Ciprandi et al.[78]	20 outpatients with allergic rhino-conjunctivitis due to *Parietaria judaica* (Wall Parietary), outside the pollen season	ASCC followed by single drop AZ or by 7 days treatment with AZ	Placebo	Hyperaemia, itching, lacrimation, eyelid swelling, for EPR and LPR after ASCC; cytological assessment (no. neutrophils, eosinophils, monocytes, lymphocytes) and ICAM-1	Reduction of symptom scores during EPR and LPR ($p < 0.01$), a reduction of inflammatory cell infiltration during both EPR ($p < 0.01$) and LPR ($p < 0.01$), and a reduction of ICAM-1 expression during EPR and LPR (both $p < 0.01$)
***In vitro* studies**					
Jepsen et al.[79]	Human airway epithelia grown at the air-liquid interface	AZ, fluticasone propionate, sodium chromoglycate, ipratropium bromide, oxymetazoline	Saline	Transepithelial resistance, sodium and chloride transport, in Ussing chambers	AZ showed a significant decrease in transepithelial resistance. Conclusion: several of the common topical nasal agents alter the electrolyte transport of the nasal airway epithelia
Lippert et al.[47]	HMC-1; basophilic cells (KU812)	Histamine H_1 and H_2 receptor blockers: AZ, loratadine, cetirizine, ranitidine	Dexamethasone	TNFα, IL-3, IL-6, IL-8, GM-CSF after cells stimulated with phorbolmyristyl acetate and calcium ionophore A23187	Dose-dependent inhibition of TNFα release from HMC-1 cells, maximal effects at 10^{-12} mol/L for AZ. In blocking cytokines: TNFα > IL-8 >> IL-6 >> IL-3. No significant effect on GM-CSF. Antihistamines had no effect on calcium flux in resting or stimulated cells. Only AZ had inhibitory effect at mRNA level with KU812 cells at IL-8. Conclusion: data show distinct inhibitory patterns for different antihistamines during cytokine production from human mast cells and basophils which may contribute to antiinflammatory effects of these drugs during treatment of allergic diseases
Ventura et al.[80]	Eosinophils isolated from peripheral blood of untreated allergic subjects in acute phase, pre-incubated with different concentrations of Ca^{2+}	AZ	Budesonide	Eosinophils chemotactic activity (AZ acts *in vitro* as regulator of Ca^{2+} pump)	AZ inhibited chemotaxis in a dose-dependent fashion; AZ may exert this action by inhibiting Ca^{2+} flow into cells; budesonide may downregulate eosinophil chemotaxic capacity

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Table IV. Contd

Reference	Patients/system	Agent	Comparator	Parameter measured	Comments
Easeamuzie and Al-Hage[81]	Human blood eosinophils	AZ	Salbutamol, salmeterol, theophylline, denbufylline, sodium cromoglycate, ketotifen, dexamethasone	O^{2-}, EPO release measured in eosinophils stimulated with PAF or IL-5 (for O^{2-} release) or complement fragment (C5a) or FMLP (for EPO release)	Only theophylline and AZ were able to inhibit EPO release by both C5a and FMLP. AZ and most others inhibited PAF-induced O^{2-} release. Conclusion: Direct effects on human blood eosinophils may be stimulus-dependent and more pronounced against O^{2-} release than against degranulation
Shindo et al.[82]	Human alveolar macrophages from asthmatic and non-asthmatic patients	AZ		PAF activity detected by aggregation of washed guinea pig platelets	Preincubation with AZ caused a dose-dependent inhibition of intra- and extra-cellular PAF activity from asthmatic and non-asthmatic macrophages in the same manner
Yoneda et al.[83]	Human gingival fibroblasts	AZ	Peplomycin	Protein tyrosine phosphorylation and c-myc mRNA expression; intranuclear NF–κ B	AZ inhibits peplomycin-induced pulmonary fibrosis by contradicting the up-regulation of signal transduction
Inoue et al.[84]	Cultured normal dermal fibroblasts from same traumatic region in 3 patients and CRL-1475 cell line	AZ		PGE_2 production enhanced by IL-1 in normal fibroblasts was inhibited by AZ, but spontaneous production of PGE_2 by normal fibroblasts was slightly increased.	Results suggest that AZ either regulates synthesis of an inducible cyclooxygenase protein or inhibits PGE_2 production as an inducible cyclooxygenase inhibitor
Watanabe et al.[85]	Cultured (HUVEC)	AZ		Arachidonic acid metabolites: $PGF_{2\alpha}$, LTB4, 5-HETE	AZ treatment in vitro results in the release of smaller amounts of arachidonic acid metabolites into the medium than control HUVEC. Suggests that AZ may inhibit contraction of bronchial smooth muscle cells and reduce bronchial inflammation by suppressing the release of arachidonic acid metabolites from vascular endothelial cells
Yoneda et al.[86]	Human gingival fibroblasts and human peripheral blood lymphocytes	AZ		NF-κ B activation associated with generation of cytokines and NO, DNA, protein synthesis, generation of TNFα, IL-1β, GM-CSF, IL-6	Suppression of cytokine and NO generation by AZ results at least partially from inhibition of NF-κ B activation
Shizawaet al.[87]	Human leucocytes (calcium ionophore-stimulated)	AZ		LTB4 and LTC4	AZ inhibited release of LTB4 and LTC4
Yamada and Tajima[88]	Cultured human skin fibroblasts from normal and scleroderma patients	AZ		Cell proliferation during proliferating cell phases; collagen synthesis: Type I:III; collagen chain mRNAs: α1(I), α1(III), α1(VI), α2(VI), α3(VI)	AZ inhibited cell proliferation, and collagen synthesis, and reduced α1(I), α1(III), and α1(VI) mRNAs. Results suggest that AZ modulates collagen synthesis at the pre-translational level. Same results in normal and scleroderma patients. AZ may be useful in treatment of fibrotic disease

Konno et al.[89]	Human peripheral blood leucocytes stimulated with concanavalin A	AZ	Ketotifen, sodium cromoglycate, oxatomide	Leucocyte blastic activity, IL-2, IL-3, IL-4, IL-5	AZ caused inhibition of leucocyte activation, suppressed production of interleukins
Hojo et al.[90]	Human neutrophils and cell lysate (cell-free system)	AZ	Oxatomide, tranilast, pemirolast, repirinast, ketotifen	fMet-Leu-Phe (N-formyl-methionyl-leucyl-phenylalanine)-induced O^{2-} generation; mobilisation of $[Ca^{2+}]_i$; NADPH-oxidase activity (lysate)	AZ directly inhibited NADPH oxidase. AZ inhibited $[Ca^{2+}]_i$ mobilisation. For inhibition of O^{2-} generation: oxatomide>AZ>tranilast>pemirolast>repirinast; ketotifen not effective
Kondo et al.[91]	PBMCs from 7 patients with atopic dermatitis & sensitive to hen's egg or cow's milk. Patient age 8mo to 4yr	AZ *in vitro*	Blood from 11 non-allergic healthy children aged 9mo to 4yr	Proliferative response of PBMCs to ovalbumin measured by incorporation of ^{3}H-thymidine	Proliferative responses of PBMCs to ovalbumin are concentration-dependently inhibited by AZ in patients with atopic dermatitis. Moreover, inhibition resulted from effects of AZ on T cells
Ueta et al.[92]	Peripheral PMN and pulmonary alveolar macrophages	AZ		Respiratory burst - chemiluminescence and O^{2-}, nitroblue tetrazolium reduction activity (human PMN); inositol triphosphate, $[Ca^{2+}]i$, PKC, tyrosine phosphorylation of proteins, SOD activity, phorbolmyristyl acetate, FMLP-induced O^{2-} generation	AZ suppresses multiple signal transduction steps in respiratory burst of PMN. Suggests AZ would be useful in the prevention and treatment of reactive oxygen-associated disorders. (not clear what was done in humans and what was done in rabbits)
Hamamoto et al.[93]	PBMC and U937 cells a pro-monocytic cell line	AZ in culture		TNFα release upon stimulation by phytohemagglutinin and TPA was inhibited by AZ	Results suggest that inhibitory effect of AZ on TNFα release plays an important role in its antiallergic action in addition to inhibition and/or antagonism of histamine and leukotrienes which has been previously reported
Werner et al.[94]	Human leucocytes	AZ	Astemizole, oxatomide, masoprocol (NDGA; a 5-lipoxygenase inhibitor)	FMLP-stimulated release of elastase	AZ reduction of elastase release may contribute to anti-allergic effects. (Elastase is a proteinase involved in intestinal digestion, originally thought to be selective for elastin - a scleroprotein in connective tissue)
Hatmi et al.[95]	Human platelets	AZ		cAMP, PG-induced; platelet aggregation	AZ potentiates the PG-induced increase of cAMP content
Akamatsu et al.[96]	Human neutrophils and cell-free xanthine - xanthine oxidase system	AZ		Chemotaxis; phagocytosis; oxygen-radical generation O^{2-}, H_2O_2, OH^-	AZ inhibited phagocytosis and generation of O^{2-}, H_2O_2, OH^-. AZ did not affect neutrophil chemotaxis or reactive oxygen species in cell-free system. Suggests: AZ may exert anti-inflammatory effect by inhibiting neutrophil phagocytosis as well as oxygen radical generation at site of inflammation
Todoroki et al.[97]	Peripheral blood mono-nuclear cells from patients with bronchial asthma	AZ		Induction of dermatopagoides farinae antigen-specific IL-2 responsiveness in lymphocytes; induction of PPD antigen-specific IL-2 responsiveness	AZ suppressed induction of IL-2 responsiveness. AZ suppressed antigen-presenting adherent cells but not non-adherent responder cells (T-cell-rich fraction). Data suggest that AZ suppresses the antigen-specific lymphocyte reactions and that these effects are based on the weak suppressive effect on the antigen-presenting and/or processing pathway

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Table IV continued

mia and Trantas dots) and conjunctival discharge; lodoxamide 0.1% also improved epithelial defects seen in the chronic forms of conjunctivitis (i.e. VKC, AKC, GPC) to a greater extent than sodium cromoglycate.[131]

1.4.3 Pemirolast

Pemirolast, a pyridopyrimidine compound, is a mast-cell stabiliser that is approved in Japan for use in the treatment of bronchial asthma, allergic rhinitis, and allergic/vernal conjunctivitis.[132] Studies in animal models have shown that pemirolast could inhibit the development of allergic conjunctivitis. Its potency appears to be >100 times that of sodium cromoglycate, although in some *in vitro* models pemirolast was equivalent to sodium cromoglycate.[42]

1.5 Nonsteroidal Anti-Inflammatories

Nonsteroidal anti-inflammatories (NSAIDs) inhibit prostaglandin production. Prostaglandins, particularly PGE_2 and PGI_2, are extremely pruritogenic to the conjunctival mucosa.[133-135] NSAIDs used in the topical treatment of ocular disorders include ketorolac, diclofenac and flurbiprofen. Clinical studies have shown that topical NSAIDs significantly diminish ocular itching and conjunctival hyperaemia associated with seasonal antigen-induced, allergic conjunctivitis[136] and VKC.[137] These agents, unlike topical corticosteroids, do not mask ocular infections, affect wound healing, increase intraocular pressure, or contribute to cataract formation.

Although topical ketorolac is the only topical NSAID currently approved by the FDA for use in acute SAC, topical diclofenac may have similar features in the treatment of SAC.[138] Ketorolac has been studied in comparison with topical antihistamines, with better outcomes in some patients.[23,138-140] In a recent study comparing topical ketorolac with levocabastine, in which the medications were instilled in each eye four times daily for 6 weeks, ketorolac, followed by levocabastine and then vehicle, produced the greatest improvements in most efficacy variables. Ketorolac was significantly more effective than vehicle in reducing

Table IV. Contd

Reference	Patients/system	Agent	Comparator	Parameter measured	Comments
Little et al.[98]	Human lung tissue	AZ		cAMP, cGMP in anti-IgE- and calcium ionophore (A23187)-stimulated lung tissue	AZ inhibits stimulated histamine release from human lung tissue *in vitro* but does not alter nucleotide content
Kikawaet al.[99]	Whole blood of paediatric asthma patients	AZ		CPAS that characterises the biosynthesis and inhibition of LTB4, LTC4, LTD4, and LTE4 in calcium ionophore-stimulated whole blood	AZ added *in vitro* caused a dose-dependent inhibition of calcium ionophore-stimulated LTB4 and LTE4 production with an IC_{50} of 10 μmol/L. (In this system, LTC4 converts to LTE4 at 80 min, at this time LTE4 and LTB4 reached plateau)

5-HETE = 5-hydroxyeicosatetraenoic acid; **ASCC** = allergen specific conjunctival challenge; **cAMP** = cyclic adenosine monophosphate; **cGMP** = cyclic guanine monophosphate; **CPAS** = computerised photodiode-array spectrophotometer; **EPO** = eosinophil peroxidase; **EPR** = early phase reaction; **FMLP** = formyl-methionyl-leucyl-phenylalanine; **GM-CSF** = granulocyte-monocyte colony-stimulating factor; **HMC-1** = human leukaemic mast cells; **HUVEC** = human umbilical vein endothelial cells; **IC_{50}** = concentration to inhibit 50%; **ICAM** = intercellular adhesion molecule; **Ig** = immunoglobulin; **IL** = interleukin; **LPR** = late phase reaction; **LT** = leukotriene; **NADPH** = nicotinamide adenine dinucleotide phosphate; **NDGA** = nordihydroguaiaretic acid; **NF-κB** = nuclear factor κ B; **NO** = nitric oxide; **O^{2-}** = superoxide anion; **OH^{-}** = hydroxy radical; **PAF** = platelet activating factor; **PBMC** = peripheral blood mononuclear cells; **PG** = prostaglandin; **PKC** = protein kinase C; **PMN** = polymorphonuclear leukocytes; **PPD** = purified protein derivative; **SOD** = siperoxide dismutase; **TNF** = tumour necrosis factor; **TPA** = 12-O-tetratecanoyl-phorbol-13-acetate.

Table V. Clinical and *in vitro* studies of ocular effects of nedocromil (NED)

Reference	Patients/system	Agent	Comparator	Parameter measured	Comments
Clinical studies					
Alexander et al.[118]	28 pts with PAC and previous OLO experience; co	NED 2% 2x/day for 1 wk	OLO 0.1% 2x 1day for 1wk	Light sensitivity scores among other parameters	Light sensitivity scores were significantly lower with nedocromil (p = 0.0125)
Tabbara et al.[119]	24 pts w/ severe VKC; db, r	NED 2%	FMI 0.1%	Ocular surface temperature and other ocular parameters	Significant decrease in ocular surface temperature seen with FMI compared with NED (p = 0.03)
Bailey et al.[120]	45 pts with contact lens-associated papillary conjunctivitis; 6 wk, db, comparative	NED eye drops unpreserved 2%	Placebo	Tear IgE levels; serum IgE levels; signs and symptoms; mucus found on upper tarsal surface	NED group showed a significant (p < 0.02) difference (improvement) in mucus by end of study. No significant difference seen for tear or serum IgE between 2 treatment groups
Bonini et al.[113]	20 symptomatic patients with VKC; db, r, pc	NED 2% for 6 wk	Placebo	In tears the number of: neutrophils, eosinophils, lymphocytes	Significant reduction in number of neutrophils, eosinophils and leucocytes seen in tear fluid of pts on NED
Elegant et al.[121]	Review of multiple studies	NED		QoL	Paper reviews practical issues regarding incorporation of a QoL measure into a trial
***In vitro* studies**					
Yanni et al.[40]	Human conjunctival mast cells; human skin mast cells	NED; sodium chromoglycate	OLO	Human mast cell stabilising activity in connective tissue type, tryptase/chymase containing, human conjunctival mast cells; human skin mast cell degranulation	Lack of mast cell stabilising activity for NED and sodium chromoglycate. OLO was most effective. Lack of human mast cell degranulation with NED and sodium chromoglycate
Diebold et al.[106]	Human conjunctival epithelial cells-primary cultures; Chang conjunctival cells; above incubated with or without IL-1β and/or INFγ	NED10^{-5} mol/L		ICAM-1; HLA-DR	Addition of NED resulted in complete abolition of HLA-DR expression and notable reduction in ICAM-1 expression in primary cultures and Chang cells
Yanni et al.[42]	Monodispersed suspension of partially purified human conjunctival mast cells from cadaver challenged with anti-human IgE	NED	OLO; pemirolast; sodium chromoglycate	Histamine content of cell supernatants; H_1 receptor binding	OLO inhibited histamine release in concentration-dependant fashion. Only OLO exhibited significant H_1 receptor binding activity at relevant concentrations. NED inhibited histamine release only at lowest concentration tested with 1 min exposure time

co = crossover; **db** = double-blind; **FMI** = fluorometholone; **HLA** = human leucocyte antigen; **ICAM** = intercellular adhesion molecule; **Ig** = immunoglobin; **IL** = interleukin; **INF** = interferon; **OLO** = olopatadine; **PAC** = perennial allergic conjunctivitis; **pc** = placebo-controlled; **QoL** = quality of life; **r** = randomised; **VKC** = vernal keraconjunctivitis.

mean itching scores, palpebral and bulbar hyperaemia, and oedema.[23] It appears that it may take up to 2 weeks of ketorolac treatment to have an effect in an experimental model of contact lens induced conjunctivitis.[141] The concern of NSAID-induced asthma does not appear to be a problem, except in patients that have the triad of asthma, nasal polyposis and aspirin sensitivity.[142]

1.6 Tertiary Treatment

The tertiary treatment of ocular allergy should be considered, using more potent immunomodulatory properties, when topically administered medications such as mast-cell stabilising agents, dual (multiple)-action agents, antihistamines and vasoconstrictors are ineffective. Such tertiary therapy commonly includes mild topical corticosteroids, immunotherapy and experimental treatments (figure 3).

1.6.1 Topical Corticosteroids

Administration of topical corticosteroids may be associated with localised ocular complications, including increased intraocular pressure, viral infections and cataract formation. Two 'modified' corticosteroids have therefore recently been investigated for their efficacy in allergic conjunctivitis: rimexolone is a derivative of prednisolone that is quickly inactivated in the anterior chamber of the eye thus improving the efficacy while decreasing the safety concerns (such as increased ocular hypertension); and both low-dose (0.2%) and high-dose (0.5%) loteprednol etabonate are highly effective as prophylaxis against, and in the acute treatment of, allergic conjunctivitis.[143-150]

1.6.2 Immunotherapy

Immunotherapy was used for the primary treatment of allergies, including spring 'catarrh', before the discovery of antihistamines and other pharmacological agents. In fact, in the first report of immunotherapy used against allergy, 'the patient's resistance during experiments of pollen extracts to excite a conjunctival reaction' was measured.[151]

Immunotherapy involves the administration of suspected allergenic proteins, in various formulations, primarily as a subcutaneous injection but also directly onto the mucosae of the conjunctiva, gastrointestinal tract or nose. In intraocular inflammatory disorders, specifically in the inhibition of experimental autoimmune uveitis, such proteins have included retinal antigens,[152-155] S-antigen[152,156-161] and interphotoreceptor retinoid-binding protein.[152,162-164]

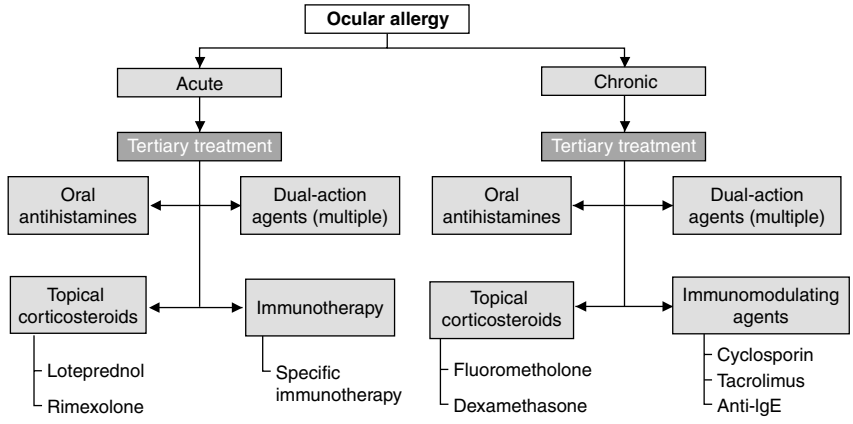

Fig. 3. Tertiary treatment of acute and chronic forms of ocular allergy requires discerning use of interventional strategies that include topical corticosteroids, allergen immunotherapy focusing on specific allergens, and oral immunomodulatory agents. **IgE** = immunoglobulin E.

Although initial studies of allergen immunotherapy did not specifically address ocular allergy symptoms in a separate manner,[165] more recent clinical studies have started to identify the following in separate categories: improvement in ocular signs and symptoms;[166-169] and increased tolerance to allergens in the conjunctival provocation test.[170,171] Interestingly, when specific allergen immunotherapy was instituted in adults and children with multiple allergies, the treatment was both effective and specific to the allergens in season.[170,172-175] The level of circulating pollen had to be a minimum of 20 to 30 pollen grains/m^3 for the efficacy of grass immunotherapy to be appreciated.[175]

Experimentally, allergic conjunctivitis has been suppressed by oral administration of the offending allergen in animal models, with a concomitant decrease in the development of allergen-specific immunoglobulin (Ig)E.[176] Experimental, topical applications of allergen,[177] or immunostimulatory sequence oligodeoxynucleotides,[178] have predominantly decreased the late-phase inflammatory response. Alternative forms of immunotherapy, such as sublingual immunotherapy, that are considered experimental have also been attempted in the treatment of seasonal and perennial rhinitis. Results included a statistical decrease in ocular symptoms,[179,180] in some cases without any changes in rhinitis symptoms, thus reflecting that ocular rather than nasal symptoms may be more sensitive to treatment with allergen immunotherapy.[181]

1.6.3 Experimental Pharmacotherapeutic Interventions

N-acetyl-aspartyl glutamic acid (NAAGA), a dipeptide, is another mast-cell stabiliser. In double-blind studies, NAAGA 4.9% demonstrated some efficacy in the control of allergic conjunctivitis, although, in a comparative study, it appeared not to be as useful as lodoxamide.[182-184] This was confirmed in other studies: in patients with VKC, NAAGA 6.0% did not perform as well as lodoxamide;[185] and in patients with GPC, NAAGA 6.0% was equivalent to placebo.[186] However, in animal studies, NAAGA appears to have a better effect on vascular permeability, as measured by Evans Blue extravasation, than either lodoxamide or sodium cromoglycate.[187]

Amlexanox, an azoxanthone derivative recently developed as an ocular anti-allergic drug, has shown limited antihistaminic properties in guinea-pig models of allergic conjunctivitis.[17-19,37]

Acetylcysteine is commercially available as a 10% solution, which has been useful as a mucolytic agent to decrease the tenacity of the ocular exudative process in VKC. Refrigerated acetylcysteine is stable for 96 hours, but the cysteine-residue odour can be quite objectionable to patients. Other forms of membrane-forming conjunctivitis (e.g. Ligneous conjunctivitis) have been experimentally treated with topical heparin, α-chymotrypsin and corticosteroids: preliminary results revealed improved outcomes with all three treatments.[188]

2. General Considerations of Ophthalmic Medications

2.1 Routes of Administration

The most common route of administration of a drug for ocular use is topical; i.e. drugs are applied directly to the ocular surface via drops, solutions or ointments. Such administration is noninvasive and offers several advantages: these include ease of administration; rapid drug delivery to, and drug absorption at, the site of action; and a decreased risk of systemic adverse effects. The effect of a topical eye drop is dependent on various factors, including drop size, size and health of the conjunctival surface, patient compliance and delivery technique.

The average volume of an ophthalmic drop, 10μl, is approximately equal to the total volume of the conjunctival sac, which already contains 10μl of tears. Once one exceeds the capacity of the conjunctival sac, excess fluid will spill over the edge of the eye lid or will be drained via the punctum into the nasolacrimal system. Absorption of any ocularly administered drug through the nasal or pharyngeal mucosa has the potential to produce

systemic adverse effects. Topical application to the conjunctival surface also has the potential to produce ocular irritation and reflex tearing. Such excess tearing can further dilute, and facilitate the elimination of, a topically administered drug, thereby decreasing its therapeutic effect. The type of formulation of topical agents can also determine ocular penetration, contact time and therapeutic effect. Agents that have a longer contact time with the ocular surface, such as viscous preparations, ointments, gels and lipid-soluble drops, can provide greater drug absorption into ocular tissues.

The underlying health of the conjunctiva and corneal epithelium determines the extent to which an ocularly administered drug will be absorbed into the eye. The ocular penetration of any drug is enhanced when the epithelium is inflamed, irregular, traumatised or ulcerated. Since most ocular allergic conditions affect the epithelial surface of the conjunctiva, increased drug penetration into the cornea has the potential to decrease the therapeutic effect of the drug and may also increase the irritant effect of the preservative.

2.2 Ocular Drug Formulations

Solutions and suspensions are the most common formulations of ocular medications. These formulations contain various inactive ingredients, including preservatives, viscosity and tonicity components, antioxidants, wetting agents and buffers. Preservatives are added to control the growth of micro-organisms that may be introduced into the solution accidentally. Some of these preservatives can stain contact lenses or have a high incidence of hypersensitivity reactions.

Ocular ointments are ideal for prolonging the contact time of the drug with the eye. However, ointments can cause blurred vision; patients should therefore be informed of the possibility of a temporary decrease in, or blurring of, vision. Drugs formulated in ocular gels also have a prolonged contact time with the eye. Often patients use multiple ocular medications: in such cases, they should be advised to administer eye drops at least 5 minutes apart to allow adequate drug-tissue contact time and to prevent one drug from diluting the other; when using a solution and ointment, the solution should be administered before the ointment, since an ointment can retard the entry of subsequent ocular drops.

3. Future Developments

The future treatment of ocular allergy will focus on potent steroid-sparing agents that control the immune response of the conjunctival surface, or on the development of combination products that have multiple effects, including antihistaminic, antioxidative and mast-cell stabilising.

Cyclosporin, a fungal antimetabolite, has been shown to decrease the clinical signs and symptoms of conjunctivitis in the chronic forms VKC and AKC.[189-191] Topical cyclosporin inhibits various mediators and the development of mast-cell mediated allergic conjunctivitis.[192-195] Being lipophilic, cyclosporin must be dissolved in an alcohol-oil base, which directly causes ocular irritation (i.e. burning, tearing, erythema and itching) and headache. Thus, new delivery systems will be required before the commercial use of cyclosporin, although systemic cyclosporin has been used for the treatment of severe AKC and keratoconjunctivitis sicca.[196-203]

Tacrolimus (FK-506), a macrolide antibiotic with potent immunomodulatory properties, has been effective in the treatment of various immune-mediated ocular diseases, such as corneal graft rejection, keratitis, scleritis, ocular pemphigoid, and uveitis. Tacrolimus acts primarily on T lymphocytes to inhibit the production of lymphokines, particularly IL-2, as well as IL-3, IL-5, TNFα, and interferon-γ. Tacrolimus blocks the degranulation of mast cells and the activation of several mast-cell cytokines such as IL-3 and IL-5.[204-209]

A change on the horizon of ocular allergy is expected regarding the current dependence on the topical delivery of ocular agents such as solutions, suspensions and ointments. Liposomal drug delivery has been shown to increase therapeutic activity with decreased toxicity. Compounds encased in liposomal, microscopic capsules have a greater

penetrating effect into the cornea, aqueous and vitreous humour, and conjunctiva.[210] Alfadex (alpha-cyclodextrin), a cyclic oligosaccharide, is another new carrier which has also shown increased ocular penetration and decreased ocular toxicity.[211,212]

Cytokine antagonists are becoming an increasing area of interest as possible treatments for ocular allergy. The antagonism of cell-cell interactions, through blockade of various cellular adhesion molecules or their ligands, may offer novel therapeutic strategies to modulate inflammatory responses. Since cellular adhesion molecules such as ICAM-1 play a critical role for the homing-in and migration of the various polymorphonuclear cells involved in inflammation, it is evident that such adhesion molecules are likely targets for immunomodulatory therapeutic intervention. Topical application of blocking antibodies to ICAM-1, lymphocyte function-associated antigen-1, IL-1 receptor antagonist, and soluble-form P-selectin glycoprotein ligand-1, has a profound inhibitory effect on the development of antigen-induced conjunctivitis in animal models.[213-215]

Anti-IgE therapy for ocular disorders was initially reported with human IgE pentapeptide and was thought to herald a new era of immunomodulatory therapy; however, clinical trials reflected limited therapeutic value.[216,217] More recently, anti-IgE therapy was evaluated for the treatment of allergic rhinitis and asthma, and perhaps could also be considered for allergic conjunctivitis, since the IgE–mast cell interface remains critical to the development of all common forms of ocular allergy.[218,219]

4. Conclusions

Ophthalmologists, allergists and other eye-care specialists are recognising that the treatment of patients with ocular allergy is often challenging and that it is becoming even more important to work together when treating patients with moderate-to-severe ocular allergic symptoms that have not responded to initial treatment.

Thus, during the past 15 years, 'Guidelines for the Treatment of Ocular Allergy' have evolved to include a substantial armamentarium based on an ever-expanding understanding of the conjunctival inflammatory response. Thoughtful therapeutic strategies against the various forms of allergic conjunctivitis can be provided to control ocular inflammation, and produce symptomatic relief in patients with ocular allergies, with minimal adverse effects and with the sparse use of topical corticosteroids. The future holds promise for additional advances with steroid-sparing immunomodulatory agents, especially in the more severe and chronic forms of ocular allergy.

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