Allergy: Understanding The Role of Inflammation

The benefits of multi-action topical allergy remedies deserve to be more widely known, both in ophthalmology and in general medicine.

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OPHTHALMOLOGIC TREATMENT of allergic conjunctivitis has focused understandably on the eye alone, without always approaching the disorder more appropriately as a conjunctivo-rhinitis syndrome. The number of patients with allergic rhinitis who also report ocular symptoms ranges from more than 75 percent,[1,2] to more than 93 percent during pollen season.[3]

Conjunctivitis may also be more common in younger patients and may be at least as severe as the reported rhinitis symptoms.[3] Even though both ocular and nasal symptoms show the greatest reactivity to the same allergens (cockroach, dust mite, perennial rye and ragweed),[4] cutaneous reactivity measurements suggest that the population with allergic conjunctivitis is distinct from those with allergic rhinitis and may be at least fourfold greater than those with only nasal symptoms.[5] Nonetheless, there is a frequent association between rhinitis and conjunctivitis, well-known among ophthalmologists, and the current availability of multi-action topical therapies for direct treatment of allergic conjunctivitis makes this an opportune time to reinforce our understanding of the underlying inflammatory steps in conjunctivitis and why these latest treatment strategies deserve to be more widely known both within and outside of ophthalmology.

Why Topicals

Topical medications are crucial for compliance and effective treatment of ocular allergies.

General physicians often treat ocular allergies as an adjunct to allergic rhinitis, with the expectation that an oral antihistamine or nasal treatment will be effective. Systemic antihistamines, however, do not adequately manage allergic conjunctivitis, measured as a significant drop in ocular itching, compared to a topical ophthalmic solution.[6] Moreover, oral antihistamines may be associated with systemic side effects such as dry mouth and drowsiness, although newer systemic antihistamines have been developed to attempt to decrease the impact of these side effects.[7] Significantly, the standard for managing allergic rhinitis—intranasal corticosteroids—may have an impact on associated ocular allergies and is presently under investigation as a possible class effect with an unclear mechanism of action.[8-10]

Direct topical application of ophthalmic medication is clearly the more effective way to treat ocular allergy.[11] In fact, even though intranasal medication appears to be clinically limited in treating conjunctival symptoms, topical ocular medications can have a secondary effect on nasal symptoms.[8] More than 90 percent of rhinitis patients may have ocular allergic symptoms and are likely to show a significant improvement in their quality of life by topical treatment of their ocular inflammation in addition to the nasal component.[8,11] Not surprisingly, without appropriate topical treatment of the allergic eye, there is a good chance the patient will seek over-the-counter treatment.

Complex Pathways

Allergic conjunctivitis reflects inflammatory mechanisms involving multiple factors.

Ocular itching, burning sensation, hyperemia and water discharge (usually bilateral) are the well-known key symptoms of typical early-phase (acute) allergic conjunctivitis.[12,13] The symptoms are the consequence of ocular mast-cell degranulation and histamine release into extra-cellular fluid.[14]

Figure 1 identifies the complex pathways of mediators released after antigen binding to IgE-sensitized mast cells fol-

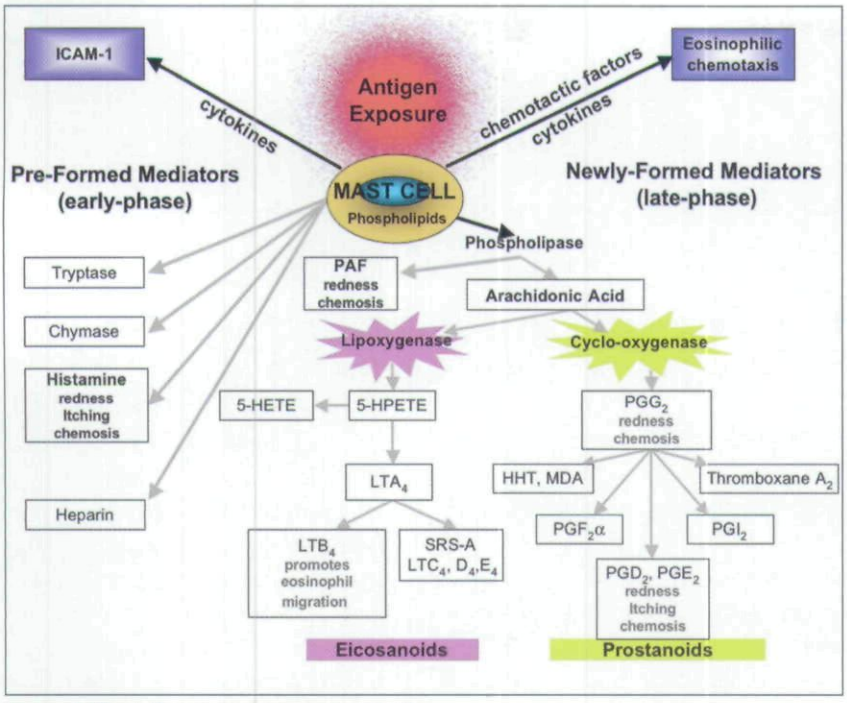

Figure 1. The inflammatory cascade. [16-18, 19-29]

lowing antigen exposure. Release of preformed histamine, in turn, is directly responsible for the classic symptoms of itching, hyperemia, tearing and chemosis.[15] At the same time, intracellular calcium increases and leads to the activation of phospholipase A_2, which promotes the synthesis of such prostanoids as prostaglandins D_2 and E_2 as well as the eicosanoid leukotrienes B_4, C_4 and D_4. Taken together, these factors are referred to as "newly formed" mast-cell mediators.[14] Tryptase, a neutral protease, is concentrated in mast cell secretory granules and is elevated in tears of patients with active ocular allergy. Tryptase is therefore considered to be a sensitive marker in diagnosing and following the pharmacologic effects of anti-allergy medications.[16,17] Although its function is not well-understood, physiological levels of tryptase lead to a dose-dependent release of IL-8 and may therefore play a role in promoting granulocyte chemotaxis in ocular allergic inflammation.[17]

A second serine-protease, chymase, is also found along with tryptase in MCTC mast cells, and while its precise role is also uncertain, it, too, may promote leukocyte infiltration during inflammation.[18]

Figure 2 shows the time course of key inflammatory mediators following antigen exposure. Concentration of the primary early-phase mediator, histamine, peaks in tears between 15 to 20 minutes after antigen exposure.[14] Tryptase peaks at about the same time, making it a specific marker for early-phase histamine release from mast cells.[30] Work on chymase has not focused on ocular allergy, but studies on allergen-induced skin epithelium suggest a biphasic role for the protease: a histamine-dependent early-phase role and a leukocyte-dependent late-phase response.[31]

By itself, histamine does not induce late-phase reactions and inflammatory cell infiltration.[14] Intercellular adhesion molecule (ICAM-1) expression on conjunctival epithelial cells is also upregulated as a result of mast-cell release of tumor necrosis factor alpha (TNF-a), indicative of the multi-action, central role of mast cells in the progression of mediator release from the early to the late phase.[32] ICAM-1 expression increases during the late-phase reactions and correlates with leukocyte infiltration.[14]

Eosinophil infiltration is facilitated by the expression of ICAM-1 and occurs in 25 percent of seasonal allergic conjunctivitis (SAC) and in up to 84 percent of perennial allergic conjunctivitis (AC), a less-common variant of SAC that occurs throughout the year.[13] Histamine release undergoes a second peak with the late-phase, but as Figure 2 shows, tryptase does not increase during late-phase reactions, suggesting that other leukocytes, probably basophils, are the source of late-phase histamine.[14]

Treating Multiple Phases

To treat ocular allergies, medications must block several pathways involved with both early and late phase inflammatory reactions.

Conjunctival tissue has between 5 and 6x103 mast cells per mm^3, which extrapolates to millions of mast cells in the human eye.[14] The number of mast cells also increases with exposure to

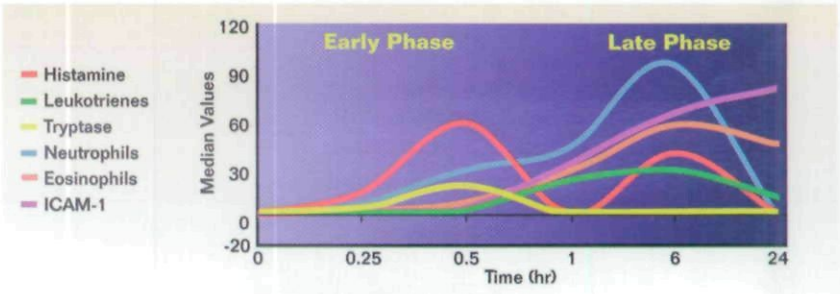

Figure 2. Time course of selected inflammatory mediators.

Table 1. Antihistamine/Mast Cell Stabilizer Medications [35-44, 46]

	Azelastine HCl 0.05% (Optivar)	Epinastine HCl 0.05% (Elestat)	Ketotifen fumarate 0.25% (Zaditor)	Olopatadine HCl 0.1% (Patanol)	Olopatadine HCl 0.2% (Pataday)
Indication	Relief of itching associated with allergic conjunctivitis	Relief of itching associated with allergic conjunctivitis	Temporary prevention of itching of the eye caused by allergies	Signs and symptoms of allergic conjunctivitis	Relief of itching associated with allergic conjunctivitis
Dosage	one drop each affected eye twice a day	one drop each affected eye twice a day (age 3 and older)	one drop each affected eye every eight to 12 hours	one drop each affected eye every six to eight hours	one drop each affected eye once a day
Adverse Effects	Transient sting (~30%), headache (~15%), bitter taste (~10%)	Cold symptoms (~10%), URI (~10%)	Headache (~10 to 25%), conjunctival injection (~10 to 25%), rhinitis (~10-25%)	Cold syndrome (~10%), pharyngitis (~10%)	Cold syndrome (~10%), (~10%), pharyngitis
Early Phase					
Antihistamine	X	X	X	X	X
Mast Cell Stabilizer	X	X	X	X	X
Late Phase					
PAF Inhibition	X				
Eosinophil Inhibition	X		X		X
ICAM Down Regulation	X		X		
Leukotriene Inhibition	X				

allergen.[14] In view of the large numbers of cells involved and the difficulty of any pharmacological agent fully affecting them, ophthalmologists agree that no single eye drop formulation will successfully inhibit the entire complement of mast cells from releasing early-phase histamine along with the mediators of the transition from early- to late-phase reactions. This explains the importance of having topical medications that block as many individual mediators as possible, including leukotrienes, platelet-activating factor (PAF) and chemokines while also functioning as an antihistamine.

The most potent approach to modulating the inflammation associated with chronic allergic conjunctivitis, when other therapies are ineffective, includes topical corticosteroids.[13] Topical corticosteroids, however, are associated with increased risk of adverse ocular effects that may include increased intraocular pressure, posterior subcapsular cataracts, and potential exacerbation of viral and/or fungal infections. Corticosteroids require that patients be monitored (including tonometry). Corticosteroids also show a slower initial onset of action when compared to antihistamines.[13,33] Not surprisingly, corticosteroids for intranasal use remain recommended only as a prescription medication because of the potential for adverse effects.[33] Fortunately, several newer therapeutic approaches have been developed that both rapidly stabilize mast cell release of histamine and inhibit a broad array of downstream mediators of inflammation for long-lasting efficacy without the risks of steroids.[7]

New Approaches

Current treatment options for allergic conjunctivitis should include topical ocular medications that combine inhibition of more than one inflammatory pathway.

Our recent understanding of mast cell pathophysiology underlies the new approaches for the treatment of ocular allergies.[34] Multiple-action pharmacological agents offer improved care because they can rapidly relieve early-phase allergic reactions as well as diminishing the late-phase reactions that are seen in more than 50 percent of patients with allergic conjunctivitis.[7] Table 1 presents an overview of the action of five currently available combination antihistamine/mast cell stabilizing agents that can meet the separate symptomatic demands of treating allergic conjunctivitis often found in association with allergic rhinitis.[35-39]

Evidence has accrued over the last 15 years for the multiple actions of these medications at several points in the gen-

eration of inflammatory mediators described in Figure 1. For example, the multi-functional azelastine HCl, a selective inhibitor of histamine H1-receptor, has been shown to have a dose-dependent inhibition of intra- and extracellular platelet-activating factor (PAF) from macrophages,[40,41] an inhibitory effect on leukotriene C_4 production,[42] as well as down-regulating ICAM-1 expression on epithelial conjunctival cells.[43] Importantly, the various multiple-action medications including azelastine, epinastine, ketotifen and olopatadine that are now used for the treatment of allergic conjunctivitis may also have some clinical impact on vasomotor conjunctivitis (perennial chronic conjunctivitis), although significant work still needs to be done to identify the best treatment modalities for chronic nonallergic noninfectious conjunctivitis.[44] The nasal counterpart of vasomotor conjunctivitis is vasomotor rhinitis and, of these agents, only azelastine is approved for the treatment of vasomotor rhinitis.

In allergic conjunctivitis, the inflammatory cascade is complex and multifaceted. Eye-care specialists focus on conjunctivitis while non-eye care specialists who treat allergic rhinoconjunctivitis often overlook the necessity for separate, direct ophthalmological intervention. Primary health-care providers need to be aware of dedicated topical anti-inflammatory agents specifically used for conjunctivitis and, at the same time, be aware of the potential hazards of oral antihistamines or oral and inhaled corticosteroids on the eye.[45] For instance, higher doses and longer duration of exposure to inhaled corticosteroids are associated with an increased risk of cataracts[47,48] and there is also an association of elevated intraocular pressure or glaucoma in patients being treated with inhaled corticosteroids.[49,50] All of the medications shown in Table 1 provide rapid relief for allergic conjunctivitis because they inhibit the early-phase step of the inflammatory cascade, blocking the histamine H1-receptor. Of these, azelastine, ketotifen and olopatadine also inhibit eosinophil migration, which may also play a role in the late phase of the inflammatory cascade. Azelastine inhibits eosinophil migration while also reducing the production of leukotrienes C_4 and D_4 and reducing expression of ICAM-1 thus demonstrating late-phase efficacy and showing clinical activity when inhibiting multiple mediators in the late phase.[45,51]

In conclusion, the more pathways of the inflammatory cascade a medication can block, while maintaining a good safety profile, the more effective the treatment of the patient should be.

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steer adaptive immunity away from the Th2-bias). TLR2, 4, and 5 ligands seem to be less promising for allergic disease therapy because of their Th2 preference, though.

Ultimately, an improved understanding of TLRs in relation to ocular allergy may lead to new immunotherapies that will enable us to reverse allergic hypersensitivities.

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