New Strategies in the Diagnosis and Management of Ocular Allergy

Identifying allergens and teaching patients how to avoid or reduce their exposure can be a helpful first step.

BY GREGG J. BERDY, MD

Ocular allergy accounts for a large number of patients' visits to ophthalmologists. Although the disorder may have an impact on the skin and periocular tissue, the conjunctiva is more commonly affected. Ocular allergy encompasses a spectrum of diseases characterized by antigen-specific immunoglobulin E (IgE) and T-helper type 2 lymphocyte-mediated hypersensitivity. Allergic disorders may have overlapping signs and symptoms, but each has its own pathognomonic characteristics that are useful in determining the specific diagnosis. By understanding the pathophysiology of allergic conjunctivitis, physicians can choose the appropriate therapy by which to control their patients' allergic responses (Figure) and accompanying symptoms and signs of disease.

PATHOPHYSIOLOGY

Seasonal allergic conjunctivitis is the prototype of ocular allergy, and it begins as an antigen-IgE antibody interaction on the surface of conjunctival mast cells.[1] Exposure of airborne allergens to sensitized IgE-coated mast cells is the initiating stimulus.

The exogenous allergen binds two separate IgE molecules, creating a dimer formation.[2,3] This bridging of IgE molecules induces the activation of mast cell membrane-associated enzymes, leading to the initiation of a biochemical cascade that ultimately causes a release of granules into the extracellular space.[4-10]

The sentinel role of histamine in the acute allergic response has been well established.[11,12] The identification of histamine receptors (both histamine 1 and 2)[13,14] has permitted investigators and clinicians to better understand its role in human allergic diseases. The conjunctival epithelial surface contains both receptor subtypes, with each receptor's controlling a specific response to histamine. Stimulation of the H1 receptor causes ocular itching,[15,16] whereas stimulation of the H2 receptor produces vasodilation of conjunctival vessels.[17] Histamine is only one of several mediators of inflammation that are implicated in the etiology of allergic disease.

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EPIDEMIOLOGY

According to a survey of the National Family Opinion, Inc., database of 200,000 American households, 31.5% of the population (approximately 79.5 million Americans) has ocular/nasal symptoms seven or more times per year.[18] The survey also reported that approximately 14.5 million Americans

have physician-diagnosed seasonal allergic rhinitis/conjunctivitis. In studies of patients with pollen allergy, ocular symptoms occur in approximately 75% of patients with rhinitis.[19]

According to a nationwide random sample of Americans with rhinoconjunctivitis (N = 312) who completed the Rhinoconjunctivitis Quality of Life Questionnaire, the condition leads to a significant decline in the general health status of sufferers compared with healthy controls (n = 96).[20] Another survey included 481 random American households containing a person afflicted with rhinoconjunctivitis. It revealed that 19% of the respondents who were being treated by a physician for ocular/nasal symptoms stopped seeing him or her because they believed that "effective treatments are not available."[21]

OCULAR ALLERGIC DISEASE

Patients with seasonal allergic conjunctivitis (SAC) or perennial allergic conjunctivitis (PAC) present with complaints of red, itching, tearing, and burning eyes.[22,23] These symptoms are nonspecific for diagnosis; therefore, to make a differential diagnosis, the clinician must examine the entire patient. SAC and PAC are often accompanied by symptoms of allergic rhinitis: a runny and itchy nose, scratchy and itchy soft palate, and itchy ear canal. These symptoms of rhinitis often accompany symptoms of allergic conjunctivitis, because the allergens and the pathophysiology of the diseases are similar.[24]

Ocular symptoms may have a seasonal onset (ie, SAC), occurring in the spring when the levels of grass and tree pollen peak or in the fall when the levels of weed pollen peak. PAC is chronically manifested and may be caused by an allergy to dust mites, feathers, or animal dander. Upon examination, the patients' eyelids usually appear edematous and erythematous, and the conjunctiva has mild to moderate chemosis with injection of the bulbar and tarsal conjunctiva. A ropey, mucosal discharge may be apparent. Itching is the most important symptom for a differential diagnosis.

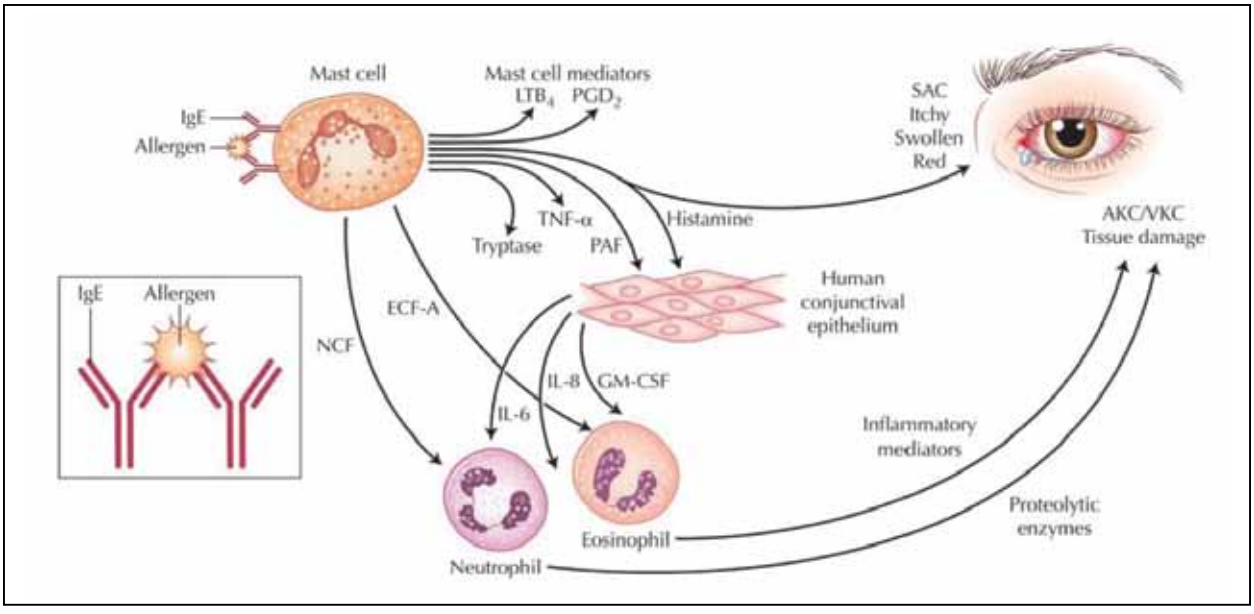

Figure. Diagram of the allergic cascade. Allergen exposure in a sensitized individual causes bridging of IgE molecules, which initiates a biochemical cascade and results in mast cell degranulation with the release of preformed mediators, including histamine, tryptase, ECF-A, NCF, and PAF. Degranulation of mast cell and eosinophil membranes release arachidonic acid, which is metabolized via the cyclooxygenase and lipoxygenase pathways to prostaglandins and leukotrienes, causing vasodilation and mucous production. These mediators of inflammation trigger allergic responses of itching, redness, and chemosis of the conjunctival tissue and attract eosinophils and neutrophils to the site. These cells, in turn, contain inflammatory mediators, which exacerbate and promulgate the response. In more chronic diseases, such as VKC and AKC, individuals have T-lymphocyte regulatory dysfunction, leading to chronic inflammation. (Reproduced with permission from Berdy GJ, Berdy SS. Ocular allergic disorders: disease entities and differential diagnoses. *Current Allergy and Asthma Reports*. 2009;9:297-303.)

Abbreviations: AKC, atopic keratoconjunctivitis; ECF-A, eosinophil chemotactic factor of anaphylaxis; GM-CSF, granulocyte-macrophage colony-stimulating factor; IgE, immunoglobulin E; IL, interleukin; LTB4, leukotriene B4; NCF, neutrophil chemotactic factor; PAF, platelet-activating factor; PGD2, prostaglandin D2; SAC, seasonal allergic conjunctivitis; TNF-alpha, tumor necrosis factor alpha; VKC, vernal keratoconjunctivitis.

If the eye does not itch, then the problem is not ocular allergy. It should be noted that itching can be a sign of dry eye disease, but that condition is not accompanied by other seasonal symptoms and has a different ocular corneal staining pattern with vital dyes than allergic conjunctivitis.[25]

SAC and PAC are characterized by an antigen-specific IgE mast cell-mediated response.[26] In a sensitized individual, the allergen binds to IgE-coated mast cells in the conjunctiva, causing mast cell degranulation and a release of inflammatory mediators. Together, these mediators produce itching, redness, and chemosis of the conjunctiva—the so-called triple response to allergen exposure. Recent studies have demonstrated the role of certain conjunctival dendritic cells (antigen-presenting cells) in the pathophysiology of ocular allergy.[27-30] Nonetheless, the histamine response continues to be an important contributor to the early phase of the allergic reaction, as mentioned previously.

CHOICES FOR TREATMENT

A variety of nonprescription and prescription therapies are available. Identifying the allergen and teaching patients how to avoid or reduce their exposure via control of their environment can be a beneficial first step. Application of topical artificial tears can dilute the antigen load and prevent the allergens from interacting with the mast cells in the conjunctiva. Cold compresses can be used as an adjunct to decrease itching. Allergen-specific immunotherapy may be effective, and novel methods of administration are being developed to improve safety and compliance.[31-33] Prescription pharmaceuticals are the mainstay of treatment, and topical ophthalmic medications give optimal symptomatic control.

During the past 4 years, three prescription products in the antihistamine-mast cell stabilizer class have been introduced. They are olopatadine 0.2% ophthalmic solution (Pataday; Alcon Laboratories, Inc.), bepotastine besilate 1.5% ophthalmic solution (Bepreve; Ista Pharmaceuticals, Inc.), and alcaftadine 0.25% ophthalmic solution (Lastacaft; Allergan, Inc.).

Olopatadine is a useful adjunct for the treatment of allergic conjunctivitis in adults and children 3 years of age and older. The results from clinical trials of up to 12 weeks' duration demonstrate that this agent effectively relieves ocular itching with once-daily use.[34] In one study, olopatadine was significantly more effective than placebo at reducing ocular itching at all time points for both the onset of action and the 16-hour allergen challenge. The drug was also significantly more effective than placebo in the reduction of conjunctival redness, chemosis, and eyelid swelling.[35] In results from two patient-reported outcome studies, significantly more individuals reported being very satisfied with olopatadine's speed of relief and comfort than with azelastine 0.05% (Optivar; Meda Pharmaceuticals, Inc.).[36]

Bepotastine besilate has been available for the past 2 years and is indicated for twice-daily dosing in adults and children 2 years of age and older. This antihistamine-mast cell stabilizer has a high specificity for the histamine 1 receptor.[37-39] In two well-controlled conjunctival allergen challenge studies, bepotastine demonstrated rapid and sustained reductions in ocular itching, the primary endpoint.[40,41] These decreases were clinically and statistically significant at a majority of time points.[42] Also of interest was the observation that the drug produced statistically and clinically significant reductions in a prespecified secondary endpoint, the Non-Ocular Composite Symptom score, incorporating nasal congestion, rhinorrhea, ear/palate itching, and nasal itching.[43]

Alcaftadine is the newest entry onto the market for the treatment of allergic conjunctivitis, and the drug offers multiple mechanisms of action (data on file with Allergan, Inc.). In the agent's pivotal FDA clinical trials, 97% of subjects treated with alcaftadine reported minimal itching 3 minutes after the product's instillation, and 87% reported minimal itching 16 hours after instillation.[44] With its rapid onset of action and extended duration of itching control through 16 hours with one drop, alcaftadine addresses patients' needs for effective relief of symptoms. The drug has an excellent safety profile, with less than 4% of treated subjects in the pivotal trials reporting adverse ocular events. Alcaftadine is the only once-daily allergy drop to be both pregnancy category B and approved for use in pediatric patients as young as 2 years of age.

CONCLUSION

With 4.7 million prescriptions filled annually in the United States for allergic conjunctivitis medications[45] and undoubtedly some multiple of that purchased as over-the-counter treatments, ocular allergy affects a large number of patients. Although effective treatments have been available for some time, there has always been a trade-off between efficacy, duration of action, and convenience. The unique clinical profile of the drugs that combine an antihistamine and a mast cell stabilizer helps to address shortcomings of older treatments.

The question of which ophthalmic allergy drop is most effective and truly provides patients with the best

full-day itching control is an important one. In the next few months, several clinical studies will be released, including the results of a randomized, masked, controlled trial evaluating these drugs in a head-to-head protocol. ■

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