

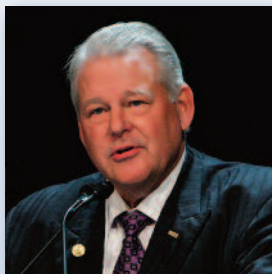
It's estimated that anywhere from 7% to 35% of individuals worldwide suffer from dry eye

This supplement is derived from an EyeWorld CME Symposium at the 2011 ASCRS•ASOA Symposium and Congress in San Diego



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Dynamics of ocular allergies and impact on optimizing the ocular surface

Edward J. Holland, M.D., professor of ophthalmology, University of Cincinnati, and director, cornea service, Cincinnati Eye Institute, remembers about 25 years ago, when Dr. Holland was a resident, **Richard L. Lindstrom, M.D.**, now adjunct professor emeritus, University of Minnesota, and founder of Minnesota Eye Consultants, Minneapolis, was already talking about the importance of ocular surface disease.

At the time, there wasn't much interest in what Dr. Lindstrom had to say about the ocular surface. "No one in the community got excited about it," said Dr. Holland. "No one wanted to treat dry eye, no one really cared about blepharitis, and allergic eye disease was left to the primary care doctors."

The attitude toward ocular surface disease has since changed; ophthalmologists now realize the significance of the

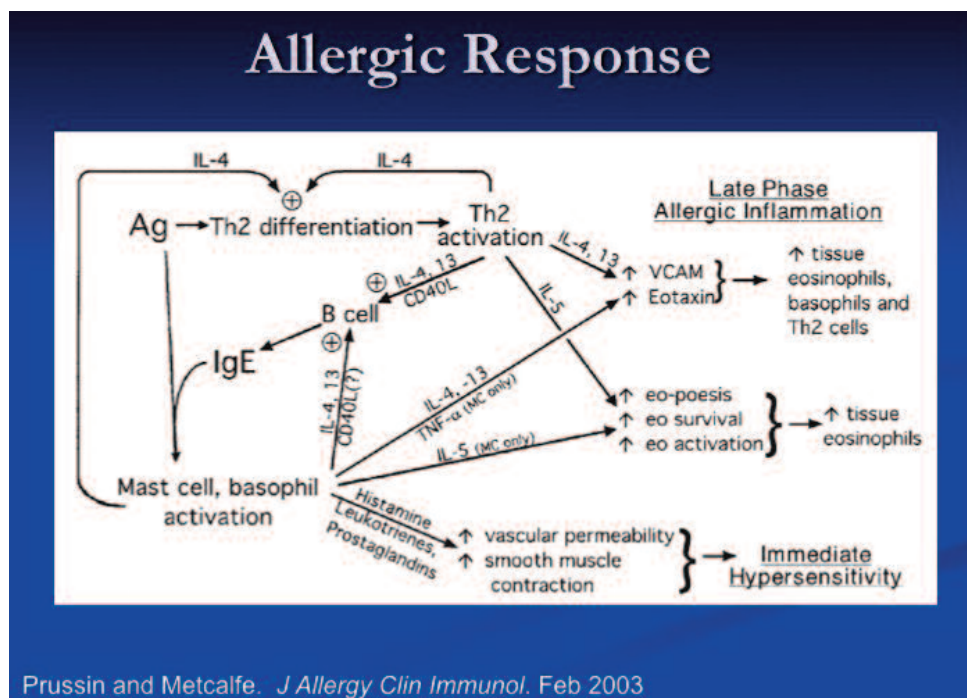
condition and its impact on the lives of their patients.

Dr. Holland, Dr. Lindstrom, and **Stephen S. Lane, M.D.**, clinical professor of ophthalmology, University of Minnesota, were joined by allergist **Warner W. Carr, M.D.**, associate medical director, Southern California Research, Mission Viejo, Calif., for a symposium titled "Dynamics of Ocular Allergies and Impact on Optimizing the Ocular Surface."

Full impact

"It's estimated that anywhere from 7% to 35% of individuals worldwide suffer from dry eye," said Dr. Holland. In the U.S., he said, 55 million Americans suffer from dry eye. Meanwhile, various studies report that between 30 and 40% of Americans has some form of blepharitis.

And now, finally, he said, "There's starting to be more attention paid to al-



Schematic diagram of the complete allergic response

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lergic eye disease and how significant it is." Over 50 million Americans suffer from all types of allergies, with 40% of the total population in the U.S. suffering from ocular allergy symptoms.

The numbers for these three conditions increase with age; a patient's age is about equivalent to that patient's risk of having any one or even all of the three conditions, Dr. Lindstrom has observed in his practice.

The economic impact of these conditions is significant, he said. Sufferers miss work (20%) and productivity decreases (45%). Meanwhile, around \$5.9 billion is spent on treatment for ocular allergy each year—about 10% of the total annual expenditure for eyecare.

In addition, said Dr. Lindstrom, "a significant reduction in quality of life has been measured objectively" in patients with ocular allergies.

Importantly, he added, treatment can significantly improve these quality of life scores.

Multiple dimensions, multiple targets

Approaching the treatment of ocular allergy, an examination of the condition's pathophysiology reveals that the process, said Dr. Carr, involves more than just the eyes.

"We look at allergies as a multi-dimensional disease," he said. "It's not just the eye, it's not just the nose, the skin, the lungs, etc.; it's the whole body."

That is, the allergic response is fundamentally the same throughout the entire human body. "It doesn't matter if it happens in the eye, in the nose, or in the lungs," he said. "It's the same process, just manifesting as a different disease state."

It's quite common, for instance, for allergic conjunctivitis to be associated with allergic rhinitis, the basic difference being little more than where the allergen lands. "Anything that can fall onto the eye, you can breathe in," said Dr. Carr. Inhaled, the same allergen causing allergic conjunctivitis can "cause nasal symptoms; if it goes into the lower airway, you can get lung symptoms."

This aspect of the condition means that clinicians have before them a wide array of potential targets for treatment. These targets depend on what type of allergy the patient is suffering from and what stage the condition is at.

Most patients who consult an ophthalmologist will have either seasonal or perennial allergic conjunctivitis—the difference being basically what allergen is causing the response. Again, this form of

conjunctivitis is simply the manifestation of an allergic response to common inhalant allergens—hence the significant association (about 50%, according to Dr. Carr) with conditions such as allergic rhinitis.

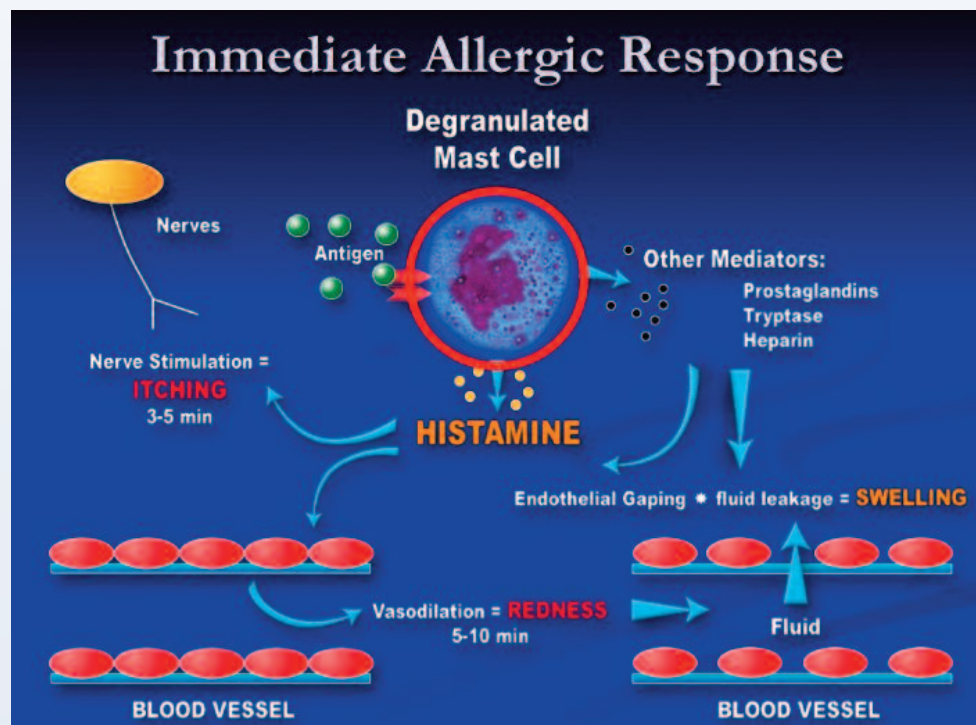
Because of this association, he said, ophthalmologists may want to remember to ask patients about other, non-ocular symptoms. Patients may be consulting for ocular symptoms, but they might also be suffering from nasal, lower respiratory, and/or even skin symptoms. "Think about the allergic disease state," said Dr. Carr.

Seasonal and/or perennial allergic conjunctivitis, he said, is an early, localized, type I reaction; beginning with the sensitization of IgE and mast cells, at presentation, laboratory exams reveal few eosinophils and eosinophil mediators. This is in contrast to more chronic conditions such as vernal or atopic keratoconjunctivitis. "I think of seasonal/perennial allergic conjunctivitis as urticaria of the eye—it's like having a hive in the eye; it's very itchy, swollen, and because it's a mucous membrane, you get watery eye as well as red eye."


Eosinophils, he said, are characteristic of the more severe, chronic conditions on the type I allergic response spectrum: vernal keratoconjunctivitis in children and atopic keratoconjunctivitis in adults. Eosinophilic infiltrates, he said, put the eye at serious risk. "This influx of eosinophils can lead to ulcerations and damage to the surface of the eye. Its mediators such as eosinophilic cationic protein that contribute to chronic damage."

This spectrum of conditions—beginning with seasonal/perennial allergic conjunctivitis and proceeding to vernal atopic keratoconjunctivitis—illustrates clinically the pathophysiologic process that is the inflammatory cascade. The elements of this cascade can then be considered targets for pharmacologic therapy, including histamine, various cytokines, and other mediators, as well as their respective receptors: mast cells, eosinophils, basophils, neutrophils, and other inflammatory cells.

For simplicity, Dr. Carr divides these targets into two groups: preformed mediators such as histamine and proteases, and newly generated lipid mediators



The immediate (early-phase) allergic response



such as leukotrienes in the early phase, inflammatory cells in the late phase.

However, he added, mast cells remain a constant factor throughout the entire range of the spectrum of disease. “Mast cells are the main player in allergic conjunctivitis,” said Dr. Carr. “They provide a variety of different cytokines that elicit this allergic response in the eye.”

The more severe the disease, he said, the more mast cells you will find in the eye, even in conditions that are mediated by eosinophils.

In treating ocular allergies, histamine and leukotrienes are the major targets in the early allergic response, with mast cells remaining an additional, useful target throughout the disease spectrum. Antihistamines and mast cell stabilizers are therefore the mainstay of treatment, said Dr. Carr, although corticosteroids should come into play once you have late-phase, eosinophil-mediated conditions.

Currently available pharmaceutical agents include over-the-counter decongestants—which focus on symptoms without treating their underlying causes—antihistamines, mast cell stabilizers, and, more recently, combinations of antihistamines and mast cell stabilizers, including Bepreve (bepotastine besilate 1.5% ophthalmic solution, ISTA Pharmaceuticals, Irvine, Calif.). This last class of drugs has the advantage of engaging the allergic response on two different levels, at different points in the cascade.

Approaching treatment

Before proceeding with pharmacologic treatment, there are a few things ophthalmologists can suggest patients do to prevent or mitigate the allergic response, said Dr. Lindstrom. He spoke from experience not just treating patients, but being a patient himself, suffering as he does from both acute and seasonal/perennial allergic conjunctivitis.

The most obvious is avoiding known allergens, although desensitization through deliberate, repeated exposure by an allergist is also an option. Dr. Lindstrom encouraged ophthalmologists to work closely with allergists such as Dr. Carr, perhaps themselves initiating the referral for allergen desensitization. In addition to these measures, cold compresses, he said, can be an effective non-

pharmacologic way of providing relief; extending the latter to pharmacologic treatment, he added, using chilled ophthalmic drops can be a soothing way to administer treatment.

These drops, he said, might also be taken prophylactically; at times when patients can anticipate or expect exposure to a known allergen, administering the drops beforehand can prevent or mitigate the response.

As previously noted by Dr. Carr, there are several options currently available for treating ocular allergies; Dr. Lindstrom prefers using combination antihistamine and mast cell stabilizer drugs; it “never made much sense to me” to use just one or the other, he said, “since we have good combination drugs that target the pathophysiology.”

“I see no reason to use just an H1-selective antihistamine, or just a mast cell stabilizer, or make the patient take two drops to achieve that benefit,” said Dr. Lindstrom.

Evaluating drops

Of the currently available formulations of combination therapy, Dr. Lindstrom focused on three: Bepreve; Pataday (olopatadine hydrochloride ophthalmic solution, Alcon, Fort Worth, Texas); and Lastacraft (alcaftadine ophthalmic solution, Allergan, Irvine, Calif.). They’re all good drops, he said, and while a head-to-head trial has yet to be conducted between any of the three formulations, a close look at the available data on each individual agent reveals some useful differences to consider.

Before going into the clinical data, Dr. Lindstrom suggested one extra-clinical factor: healthcare economics. Bepreve, he said, is available in 5 and 10 ml bottles, the equivalent of 30 and 60 days of treatment, respectively; the bottling of Pataday and Lastacraft only provides for treatment up to 30 days. “Sometimes that’s a factor,” he said.

How well do these drops perform clinically? “It turns out that they work quite well, all three of them,” said Dr. Lindstrom. Along with efficacy, safety is of course an important consideration. Bepreve, he said, which is labeled for twice a day administration (Pataday and Lastacraft are labeled for once a day dosing), is safe enough to be given three to

four times a day as needed when allergy symptoms are severe.

A good measure of efficacy, said Dr. Lindstrom, is the percentage of patients who have no ocular itching at 3 minutes following administration after exposure to an allergen.

In a number of trials involving severe response in a controlled laboratory environment, Bepreve eliminated itching by 3 minutes in 68% of patients, comparable to Pataday’s 63%. Dr. Lindstrom could not find similar data for Lastacraft, although he has no reason to believe it would be any less effective. He did note, however, that the latter is “a little less comfortable to use,” a fact that turns people away from the use of non-steroidal anti-inflammatory drugs (NSAIDs) in the eye.

In addition, Bepreve is “the only drop that has some impact on the other secondary findings, like congestion, rhinorrhea, pruritus, even ear itching,” said Dr. Lindstrom. “This drop is good for some of the systemic changes as well as it goes through the tear outflow system.”

In severe cases, however, said Dr. Lindstrom, “don’t forget about steroids.” He prefers loteprednol etabonate 0.2% or 0.5% when severe (Alrex, Bausch & Lomb, Rochester, N.Y.)—a “safe and effective treatment” for cases of seasonal/perennial allergic conjunctivitis that need a steroid. Certainly, IOP rise is a reasonable fear accompanying the use of steroids, but with loteprednol at a reasonable dose, said Dr. Lindstrom, the chance of a pressure spike is “almost zero with a course of therapy of 1 week or less, which is usually enough to gain control of a severe allergic conjunctivitis.”

The “ideal treatment”

What we have today, to reiterate some of the key points presented by Drs. Carr and Lindstrom, are various treatments that “attack this [inflammatory] cascade at different points along the way,” said Dr. Lane. “I think that’s what’s important to understand as you start to formulate how you’re going to be treating these conditions.”

The ideal treatment, said Dr. Lane, would provide “comprehensive coverage of both early- and late-phase inflammatory mediators, with resolution of most of the signs and symptoms, with a rapid

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onset of action, targeted, very site-specific activity, with a very potent formulation that has minimal adverse effects, and comfort to relieve these kinds of problems.”

Unlike Dr. Lindstrom, Dr. Lane suggested a staged approach. “As I come across patients with early and mild signs and symptoms, antihistamines are the mainstay,” he said. All the currently available antihistamine ophthalmic drops provide a very rapid onset of action in a relatively short duration, characteristics that make them “the best agents for pure seasonal/perennial allergic conjunctivitis.”

Meanwhile, treating patients prophylactically, he said, is best done with mast cell stabilizers. He emphasized the

fact that since these drugs inhibit the release of histamine rather than block the mediator’s activity, “they’re probably better at preventing than treating the allergic signs and symptoms ... If patients already have allergic signs and symptoms, it’s too late, and these are going to have a limited capacity to help patients.” Prophylactic therapy with mast cell stabilizers, he said, should therefore be started before onset—“ideally several weeks before,” he said.

However, antihistamines alone, he said, “work only on the early-phase mediators so you miss out on the late-phase mediators,” while mast cell stabilizers “lack the immediate [anti]histamine effect.” Still, it’s for moderate cases that Dr. Lane turns to combination antihista-

mine/mast cell stabilizers—which, he said, are “quite good.” However, no drug is without its limitations. Most of the available formulations combining an antihistamine with a mast cell stabilizer, he said, “are indicated for itching symptoms related to allergic conjunctivitis, and some of the products cannot completely inhibit the redness that’s produced by the inflammation.”

The selection of anti-allergy medication, said Dr. Lane, is therefore “based on a number of considerations: the severity of the disease; the symptoms that the patient presents with; and how long you expect to have to treat the patient to control the signs and symptoms.”

Dr. Lane called Bepreve and all the other recently developed combinations including Pataday and Lastacraft “great additions to our armamentarium,” adding that it’s up to clinicians to try these combinations, to have the opportunity to evaluate each combination in their respective clinics, in their own patients.

For Dr. Lane, the rapid onset of action with Bepreve is most clear. In his clinic, where he has a technician administer the drops in the eyes of patients who come in with symptoms of allergic conjunctivitis, patients experience relief within 3 minutes of administration—as shown in studies and stated earlier by Dr. Lindstrom—clearing up symptoms by the time Dr. Lane sees them.

This is, among other things, a powerful demonstration for his patients of the efficacy of treatment with the combination ophthalmic solution, a formulation that is as safe as it is effective.

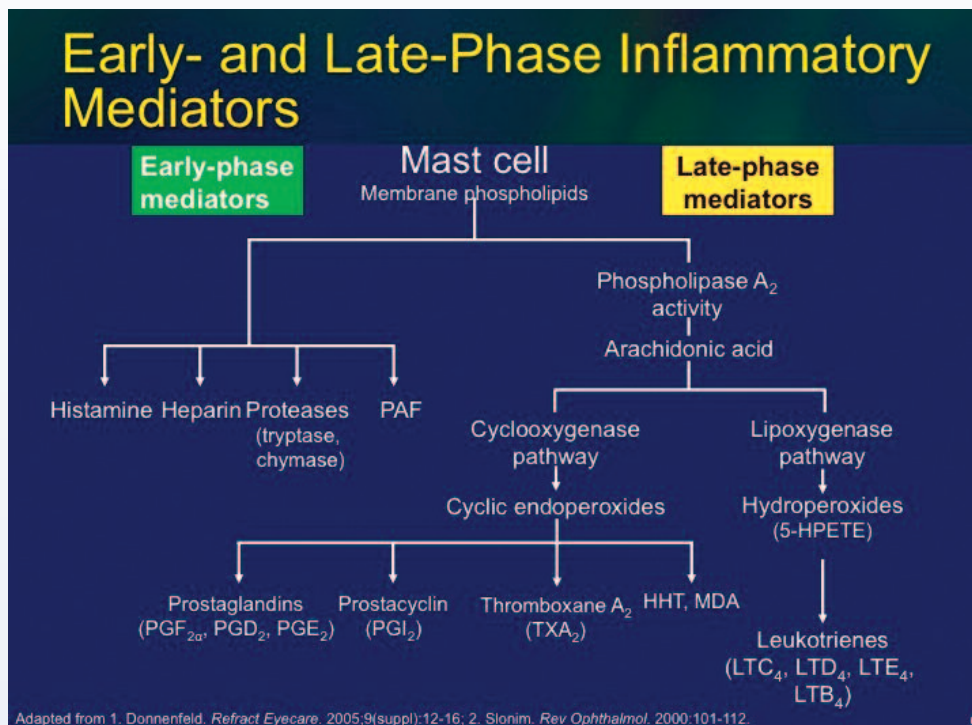
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Early- and late-phase inflammatory mediators

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