With seasonal allergies expected to start earlier this year, it’s never too soon to make sure you’re up to date with the latest treatment options. By Paul J. Gomes, M.S.

As the final remnants of winter thaw and the new season takes hold, we anticipate the growth and renewal that comes with this time of year. Spring brings a slow but steady increase in outdoor activity, and the inevitable arrival of the first blooms of flowers and trees—followed quickly by the first sneezes and eye rubs of yet another allergy season.

Seasonal and perennial allergies are a significant global health issue affecting approximately 15% of the world’s population; these percentages are even higher in the industrialized countries of Western Europe, Eastern Asia, Australia and North America. In the United States, seasonal and perennial allergies affect 20% of the population, and 70% to 80% of these patients report that their allergies include ocular symptoms. While not life threatening, the symptoms of ocular allergy can have a significant impact on quality of life for those who experience them.

Ocular allergy, or allergic conjunctivitis (AC), is typically cited as one of the most frequent reasons patients seek medical treatment for seasonal allergies. Recent estimates put the annual economic impact of seasonal allergies in the United States at $7 billion, including almost $1 billion in work absenteeism.

While there have been improvements in therapy over the past two decades, there has also been an increase in prevalence of the disease. In addition, most...
of the drugs currently available to treat AC target ocular itching, leaving other signs and symptoms, such as ocular redness and chronic inflammation, untreated or under-treated.

As we prepare for this coming season, let’s take a look at the current treatments for ocular allergies, review the therapeutic developments in years past and describe areas where future efforts could have the most impact.

Changes in Treatment
Specific pharmacological treatments for ocular allergy were non-existent prior to the early 1970s; typically, patients were instructed to use cold compresses and to avoid the offending allergen.4,6 The first topical agents developed to treat AC were adrenergic agonists (such as naphazoline)—these drugs were effective at reducing hyperemia but did little to treat ocular itching.9

A second group of drugs, the mast cell stabilizers, first became available for topical ophthalmic use in the 1980s.10,11 While these drugs showed efficacy in reducing ocular itch, they were relatively short-acting, and were also limited by the nature of their mechanism of action; because they are preventive treatments, they must be taken before the allergen is present to be effective.12

As we discuss below, patients typically used anti-allergics as needed, regardless of label (or practitioner) instructions and so, for the mast cell stabilizers, the arrival of symptoms is too late for drug treatment.

The first topical H1-antihistamines for ocular use (pheniramine and antazoline) came to market in 1990.13,14 These were relatively short-acting medications, but were marketed as topical combinations of antihistamines and adrenergic agonists, creating a formulation that could treat both ocular itch and ocular redness. Some of these formulations are still available today as non-prescription topicals, but they have been replaced in recent years by superior, single-agent antihistamines.

In the last two decades, a number of second-generation H1-antihistamines have been developed to improve upon earlier drugs in terms of duration of action, safety profile and comfort. Important drugs in this group include levocabastine hydrochloride and emedastine difumarate, both of which were available as single-agent topicals.15,17 While still requiring multiple daily dosing, both of these agents are highly effective in reducing ocular itch.

A progression of antihistamines followed, including azelastine hydrochloride, bepotastine besilate, ketotifen fumarate and olopa-
tadine hydrochloride. Each of these compounds is classified as a “dual-action” antihistamine because they exhibit both H1 receptor antagonism and mast cell stabilization effects. In addition to this dual-action effect (or perhaps because of it), these newer drugs all have a longer duration of action than either levocabastine or emedastine. They are indicated for twice-daily dosing to relieve itching due to AC.

Most recently, two agents have been approved for once-daily dosing—a higher concentration formula (0.2%) of olopatadine hydrochloride, (Pataday, Alcon), and the newest ocular antihistamine, alcaftadine (Lastacaft, Allergan). A noteworthy aspect of histamine antagonists is that, unlike the pure mast cell stabilizers, these drugs are effective whenever the patients experience allergic symptoms. This was a significant step forward, and many would say it changed the landscape of ocular allergy therapy. In addition, the high efficacy of these drugs meant that most patients moved from an everyday, “prevention-based” dosing to a more “as-needed” use.

Ironically, it’s possible that antihistamine/mast cell stabilizers could be more effective if used prophylactically; evidence suggests that prevention of acute allergic responses may be one way to minimize the growing trend toward chronic allergies. Daily use of topical antihistamine/mast cell stabilizers during allergy season would be likely to have such an effect.

Treating Poor Responders

Despite this continued improvement in AC therapy, many patients with ocular allergies (some estimates put the number at 30% in the U.S.) show poor response to most currently available therapies. These poor responders to antihistamine therapy appear to fall into two groups: chronic allergies and seasonal allergies.

The first group consists of those with the combination of seasonal and perennial allergies; for these patients, it is always allergy season. The second group includes patients with robust responses to seasonal allergens, so that on days with particularly high pollen levels they present an allergic response that simply overwhelms the ability of any topical antihistamine to suppress.

Both types involve conjunctival recruitment of immune cells in addition to mast cells, and so the goal of any new therapy is to “calm” the conjunctiva, allow the recruited cells time to dissipate and also reduce the inflammatory features of the chronic, late phase response. These patients can be considered chronic ocular allergy sufferers, and they are symptomatically similar to those with more severe allergic conditions such as AKC.

Chronic allergy differs from the more acute forms in that it is primarily mediated by cellular factors, and is dependent upon the activity of immune cells such as basophils and eosinophils that have infiltrated the conjunctiva over the course of prolonged allergen exposure. The increased prevalence of chronic atopic diseases such as AC in recent years, especially in more industrialized countries, is thought to be a result of increased exposure to antigens.
exposure to allergy-exacerbating agents, such as air pollutants and volatile chemicals.

Evidence suggests that these chemicals can prime the immune response to perennial allergens, such as dust mites and molds. As the prevalence of these chronic poor responders increases, current and future anti-allergic drug development must identify therapies to address this unmet need.

Currently, the best available treatments for chronic ocular allergy sufferers are topical steroids, such as prednisolone acetate or loteprednol etabonate. While effective, these drugs are typically used for brief periods (courses of one to two weeks) to minimize the risk of adverse ocular effects such as cataracts or increases in intraocular pressure.

Newer anti-inflammatory compounds are likely candidates for future studies of chronic AC. Beyond trials of compounds with theoretical or demonstrable anti-inflammatory effects, however, it is necessary to establish a clear strategy for identifying and developing the next class of ocular anti-allergics.

Looking Ahead

Researchers at Ora, Inc. have spent the past 30 years developing and refining methods to test new drugs and formulations for ocular allergy. In that time, our conjunctival allergen challenge (CAC) model has become an industry standard, and has been employed for studies used to gain FDA approval for all ocular anti-allergics currently marketed in the U.S. Recently, Japan’s Pharmaceuticals and Medical Devices Agency also adopted the CAC model for allergic drug development. This means that testing of new anti-allergics for both the American and Japanese markets can be conducted simultaneously, and should speed drug development.

The success of clinical models such as the CAC underscores the fundamental importance of study design in the drug development process. The research group at Ora, like others in the ocular therapeutics industry, is focused on how to accurately assess the efficacy of either new chemical entities or repurposed drugs as therapies for chronic ocular allergy. Key to these efforts is the ability to accurately identify the “non-responder” population from the greater population of allergics.

In addition, trials need to employ robust experimental standards that elicit the chronic allergic signs and symptoms, similar to the CAC model for acute allergy. Future therapies will likely employ drugs that interfere with cytokine signaling, or those that can disrupt the intracellular processes that mediate this chronic feedback loop.

Results of pre-clinical studies have focused on a number of factors that define the chronic allergic subject. Prolonged or high levels of allergen exposure lead to infiltration and accumulation of basophils, eosinophils and increased numbers of mast cells. These cells respond to continued presence of allergens by releasing a smorgasbord of cytokines, chemo-attractants, proteases and other signaling molecules. The net effect is continued recruitment of immune and inflammatory cells, breakdown of the ocular surface’s extracellular matrix and destabilization of the protective, barrier function of the conjunctival and corneal epithelium.

Mr. Gomes is vice president of Allergy at Ora, Inc. Ora has provided clinical research services for each product mentioned.


