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By Gregory A. Caldwell, OD

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A once-rare pathogen may be more prevalent than initially believed in cases of fungal keratitis, reports new research published online in Cornea. Researchers identified 47 of 1,542 culture-proven cases of keratomycosis as being caused by Exserohilum, which is generally associated with paranasal sinus, skin and subcutaneous infections.

“To our knowledge, this is the largest case series so far on keratitis caused by Exserohilum,” the researchers say. Patients in hot and humid areas appear to be most at risk, and further research is necessary to identify the best treatment protocols.

Moisture chamber spectacles (MCS) may be useful to treat dry eye, suggests a study in the February 2016 issue of Optometry & Vision Science. Researchers in China randomized 30 patients with dry eye into a group instructed to wear MCS for 30 minutes and a second group instructed to instil a drop of sterile non-preserved 0.9% sodium chloride solution. Results indicated improvements in ocular comfort, tear meniscus height (TMH) and noninvasive tear film break-up time (NIBUT) in the former.

“The present study is the first to show that the use of MCS had a significant positive effect on TMH and NIBUT, demonstrating that tear film stability was improved after MCS wear,” the researchers say. “MCS may be a safe and promising alternative treatment for dry eye, especially for patients who work in adverse environmental conditions.”

Bausch + Lomb has announced the release of new Ultra lenses for Presbyopia. The multifocal lenses are specifically designed to combine the company’s three-zone progressive design in the Biotrue OneDay for Presbyopia, daily disposable lenses with its MoistureSeal lens technology.

Blanchard Contact Lenses has announced its list of cities and dates for the 2016 Beyond the Limbus Scleral Lens Workshop tour. A component of the company’s educational division for the sixth year running, the workshops are designed to provide scleral lens training for eye care practitioners. The list is available at blanchardlab.com/blanchard-u/events-education/.

In this investigation, researchers at Seoul National University Hospital in Korea divided NOD.B10.H2b-infected mice into four subgroups characterized by administration of one of four treatments for a period of seven days. The NOD.B10. H2b strain manifests clinical signs in mice similar to that of Sjögren’s syndrome in humans.

Treatments included recombinant TSG-6 (i.e., 1µg in a 10µL phosphate buffered solution) QID, Restasis (0.05% cyclosporine ophthalmic emulsion, Allergan) BID, Pred Forte (1% prednisolone) QID, and phosphate buffered solution. All remained below that of the NOD.B10.H2b infected mice receiving the TSG-6, Restasis and Pred Forte treatments was markedly increased in comparison with that of the NOD.B10.H2b mice receiving phosphate buffered solution. All remained below that of the control group, however.

Researchers also noted levels of proinflammatory cytokines TNF and INF were reduced following treatment with the three aforementioned applications.

With respect to corneal staining, both the NOD.B10.H2b mice receiving TSG-6 and those receiving Restasis had decreased levels, while those receiving Pred Forte did not. “Together, data demonstrated that topical administration of 0.1% TSG-6 was as effective in improving signs of DED as 0.05% cyclosporine or 1% prednisolone ophthalmic solution,” the researchers say. “In addition, both TSG-6 and cyclosporine significantly reduced punctate corneal epithelial staining, but prednisolone did not.” These results suggest TSG-6 could be considered as a future dry eye treatment on par with cyclosporine; further study, however, on the effects of TSG-6 on dry eye parameters like tear film stability and tear osmolarity are necessary, as is investigation into mass production.

Application of topical tumor necrosis factor (TNF)-stimulated gene protein-6 (TSG-6) may be a suitable alternative to cyclosporine use in patients with inflammation-mediated dry eye, suggests a study published online in the journal Cornea. Previous research on the protein produced by mesenchymal stem/stromal cells within the body has indicated therapeutic effects in animal models of the heart, cornea, brain and other organs; however, further research and widespread clinical application remains limited due to production issues and variations in chemical stability.

In Korea, the Biotrue OneDay for Presbyopia daily disposable lenses with its MoistureSeal lens technology, with corticosteroid use, make these lenses promising treatments for ocular inflammation-mediated dry eye.

Researchers say. “MCS may be a promising new dry eye therapy for dry eye patients who experience ocular inflammation.”

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Scleral Lens Treatment for Keratoconic Dry Eye

Short-term scleral contact lens wear may be beneficial for patients with keratoconus who also suffer from dry eye, reports a study in the February 2016 *Optometry & Vision Science.* The rigid lenses are currently indicated for use in patients with severe corneal irregularities, including keratoconus, and have also been slated as a means to manage dry eye due to their ability to improve ocular surface integrity. To date, however, no study has investigated the effects of scleral lens wear on the ocular surface physiology of patients with keratoconus.

In an effort to remedy this discrepancy, researchers at the Complutense University of Madrid in Spain conducted an experimental pilot study involving 26 patients with keratoconus ranging from age 25 to 51. Patients were separated into those with an intrastromal corneal ring, and those without; each was fit with an intrastromal corneal ring, and those without; each was fit with a 16.5mm scleral lens design that provided clearance thickness between 300µm and 400µm.

The research team administered the Ocular Surface Disease Index (OSDI) questionnaire and measured tear osmolarity, Schirmer score, tear break-up time, matrix metalloproteinase-9 (MMP-9) concentration and Ap4A concentration before and after eight hours of lens wear. No significant changes were identified during the Schirmer test and tear break-up time following lens wear. OSDI scores and osmolarity were lower and MMP-9 concentration was higher, however, in both groups following lens wear. Lastly, Ap4A concentration was lower following lens wear in the keratoconus group, but not the corneal ring group. These results, the researchers say, demonstrate that “symptomatology, osmolarity and Ap4A concentration decrease after short-term scleral lens wear in KC patients, but MMP-9 concentration rises significantly.”

The researchers note that the lenses used in the study were manufactured using a high Dk material and 0.3mm of central thickness. “There is no evidence of the influence of the physical properties and scleral lens design over the ocular surface physiology,” they say. “In the future, however, it might be interesting to evaluate the differences between different scleral lens designs, taking into account the central thickness, overall diameter and adaption period.”

“In conclusion, short-term scleral lens wear improves the symptomatology and some signs of dry eye, such as osmolarity and Ap4A concentration, in keratoconus patients. However, there is an increase of MMP-9 concentration, probably because of tear film stagnation and the use of preserved saline for filling the lenses.”

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There exists a fascinating observation in technology circles known as Moore’s Law, which states that the number of transistors in a computer chip doubles every two years. In that same vein, the law also indicates that the size of computer chip circuitry like processors, sensors and memory storage is also cut in half every two years. Moore’s Law has held true since its original formulation in 1965, and Intel predicts that 10nm computer chips will arrive within the next few years. Such an advancement could have profound implications for integrating biosensors into contact lenses, allowing for revolutionary applications like monitoring the levels of glucose in a diabetic patient.

**Comprised of a number of different components, the tear film has enormous potential to provide us with valuable medical information about the health and wellbeing of the patient. A contact lens used as a biosensor could easily capture data on the various proteins, enzymes, lipids and salts within the tear film and translate it to practitioners in real time.**

Prototype biosensor lenses have already been used to investigate glucose levels and monitor intraocular pressure.2,4

**POTENTIAL SETBACKS**

Measuring tear glucose levels using diagnostic devices is not a new concept. Reports of this technique being used date back at least two decades, and biosensor patents are a dime a dozen. Yet, some obstacles remain in the path of bringing such a device to market. The first is the problem of technology: glucose-monitoring contact lens devices are not yet refined enough for marketable use. In fact, the only contact lens device currently on the market is used to assess intraocular pressures. The second hurdle that must be overcome is more practical—supply and demand for such a device. Aside from considerations like manufacturing costs, there are a handful of medical conditions that would actually benefit from—or even require—continuous monitoring. Developing devices that require FDA approval for marketing is an expensive initiative. Accordingly, potential sponsors or manufacturers may be reluctant to commit the funding needed to bring such a product to market.2

Despite these issues, however, it’s no surprise that contact lens biosensors are still viewed with excitement. Several different types have been considered, including colorimetric fluorescent sensors and electrochemical contact lenses sensors.2 Another question remains, however: what impact will alternative wireless continuous monitors (for measuring other body fluids as well) have on the future development of lens sensors? Alternative devices are already available for patients using an insulin pump or other attachment devices worn on the arm or abdomen.2,3 Other concerns relate to the variability of tear compositions and lag time for biomarkers to appear in tears compared with blood serum levels and the lag in recording time.2,3

I remain optimistic that as this technology evolves, contact lenses will eventually be used beyond their current indication for glaucoma and diabetes. Time will tell if we truly reach the “Holy Grail” or whether alternative devices will overtake the quest for the best contact lens biosensor in the diagnostic sector. For now, we’ll continue to watch as the story unfolds and prototypes advance.4

**“THE HUMAN TEAR FILM HAS ENORMOUS POTENTIAL TO PROVIDE US WITH VALUABLE MEDICAL INFORMATION.”**

**DATA ON DEMAND** could revolutionize the care of patients with diabetes or glaucoma.

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Scratching the Itch
Ocular allergies can complicate contact lens fittings. Here’s how to manage them.

Congratulations, you have ocular allergies. Most eye care professionals have never uttered this statement offhand to their patients, but for those with ocular allergy sufferers who may be interested in wearing contact lenses, it’s an important point to consider. Proactively identifying contact lens candidates who may experience allergy-related discomfort gives us the opportunity to turn a possible negative into a positive before it becomes a larger issue.

Treating current lens wearers’ ocular allergies will also allow those who are experiencing limited wearing success to more comfortably enjoy the benefits of contact lens wear. Some of these patients may have been told by other eye care professionals that nothing can be done to ease their symptoms and may have resorted to dropping out of contact lens wear during allergy season to avoid discomfort. So, if you are able to offer the possibility of comfortable contact lens wear during allergy season, you may very easily earn yourself a lifelong patient. But, how do you achieve this? Here are some tips to help you manage this unique group of patients.

1. Ask the right questions at the right time. Many practitioners employ technical staff to discuss symptoms with the patient at the beginning of the exam and help administer medication as needed. While patients who present with an ocular infection typically report continual symptoms during the period of infection, patients with ocular allergies may only experience symptoms during certain times of the year—which may not be during the time of their exam. These patients often neglect to mention their allergies when discussing their eye history for the simple reason that it slips their mind, so tailor your symptom questionnaire to catch them even during the offseason. By asking the right questions, you may be surprised how many allergy sufferers go undiagnosed and untreated in your practice.

Even if the patient indicates no allergy-related discomfort (i.e., their contact lenses become more difficult to wear during certain times of the year, or while in their work environment), make sure to ask follow-up questions during the anterior ocular exam. Peek around the slit lamp and ask, “Do your eyes ever burn, itch or water, or do your eyelids ever swell or turn red?” Look closely for mild eyelid and conjunctival edema and/or redness (Figure 1).

Evert the upper and lower eyelids to reveal the presence of papillae or other complicating factors. These can often be seen more easily when visualized with the use of fluorescein. You can also follow up with, “Do you ever experience intermittent blur with your contact lenses during certain times of the year?” These factors, while not directly related to contact lens comfort, can also be indicative of possible allergies that may eventually lead to lens issues.

Fig. 1. Inferior palpebral conjunctival papillae and redness due to ocular allergies.
2. **Address the issue and treat the underlying condition.**

Patients are often surprised to hear that their allergies are responsible for their issues with contact lens wear, especially if the reaction is mild. Once informed of their diagnosis, however, they are now aware and looking for solutions. Take the appointment a step further by informing them that there are still possible contact lens options.

Daily disposables are one suitable option for patients who suffer from ocular allergies. Because surface allergens do not build up on these daily replacement lenses, patients’ clinical reactions are limited. Additionally, there are no compliance issues that could further aggravate a patient’s allergic reaction because a clean lens is placed on the eye each day. If your patients have not heard about these lenses already, this is an ideal time to educate them.

3. **Individualize the approach.**

In some cases, the patient’s contact lens fitting and allergic treatment regimen may collide. This is because the presence of ocular allergies may decrease lens awareness or reduce vision during the fitting, complicating the process. Also, if the patient is using topical steroids throughout the day, lens wear would be contraindicated.

This is the time to customize a treatment plan according to the patient’s particular needs. Take a step back and explain to them how their allergic condition may need specific medical attention (and not just an OTC product) and what steps would be required to clear it. For example, they may need to remove their lenses for a period of time, treat the allergic state and then consider other lens options. Be sure to stress that the treatment will help them with symptoms.

**CASE IN POINT**

A 26-year-old female patient presented complaining of frequent itching and burning. She reported using OTC Visine-A Allergy Relief Drops (Johnson & Johnson) to no relief. She is an IT consultant who has never worn contact lenses because she was informed in the past she could not wear them. During her examination, it was evident ocular allergies were the cause of her issues. Her inferior palpebral conjunctiva was red, inflamed and chemotic in both eyes (Figure 2).

The patient was treated with a topical ocular steroid for two weeks, then moved to a daily antihistamine/mast-cell stabilizer for maintenance. After finishing the steroid eye drops, she was successfully fit into hydrogel daily disposable lenses. This made a huge difference in her ocular irritation, even compared to no contact lenses. She had less allergic symptoms throughout the day, and she enjoyed the convenience her new daily contact lenses provided.

Above all, the challenge with current contact lens wearers and allergy sufferers is identifying allergies as the underlying cause of symptoms. Many eye care professionals look to place the “blame” on their patient’s current contact lenses. Instead, consider identifying and treating any underlying conditions prior to a successful contact lens fit.

T

hough El Niño tempered this year’s winter weather in parts of the country, the promise of spring is still an inviting one. For many patients, spring means warmer temperature and more daylight—and more time spent outdoors. As such, spring can also mean an exacerbation of the itchy, red and watery eyes commonly associated with seasonal allergic conjunctivitis. While “allergy season” is often attributed to the increased presence of airborne pollen in the spring, many symptomatic patients continue to present into summer and autumn, depending on local climate and temperature.

Allergic conjunctivitis may not be the only culprit responsible for seasonal discomfort, however: recent research still indicates a clear seasonal pattern with respect to presentations of dry eye, as the condition was most common in the winter and spring and least common in the summer.1 The pattern was ascribed to low humidity in the winter and seasonal allergens in the spring; as such, the findings suggest allergy may not be the only factor in seasonal eye disease.

When an affected patient presents to the clinic, clinicians must ask: Is it allergy or dry eye—or both? Reviewing the epidemiology, clinical examination and treatment of both allergic conjunctivitis and dry eye can further our understanding of these coexisting conditions and help clarify a diagnosis. Additionally, recognizing how each can present clinically and identifying which patients are most likely to be affected can help guide providers in tailoring the treatment regimen to the individual patient.

DEFINING THE CONDITION

The International Dry Eye Workshop (DEWS) classified dry eye as a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance and tear film instability that may cause damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface.2 Similarly, the committee identified allergic conjunctivitis as an extrinsic cause of dry eye. In their model, conjunctival and corneal irregularities (e.g., punctate keratitis and shield ulcers) can destabilize the tear film and contribute to dry eye.2,3 In chronic disease, meibomian gland dysfunction further contributes to dry eye by interfering with the lipid layer of the tears.

These definitions suggest that the two conditions share elements of the underlying disease process and reinforce that inflammation is a key component of both. For example, a past study of allergic conjunctivitis reported that patients with itchy eyes were more than twice as likely to experience dry eye as patients with non-itchy eyes.4 As such, significant symptoms of itching in conjunction with dry eye may also suggest coexisting atopic disease. Patients with allergic conjunctivitis who exhibit disruptions in tear film integrity, symptoms of burning or both may also be suffering from coexisting dry eye disease.

PATTERNS OF PREVALENCE

Although it’s difficult to isolate the affected populations for conditions as common and multifactorial as allergy and dry eye, some epidemiologic patterns have been documented in the literature.

• Allergic Conjunctivitis.

Conventional wisdom holds that approximately 15% to 20% of the United States population suffers from ocular allergy.5 However, 40% of the participants in the third National Health and Nutrition Examination Survey reported symptoms of ocular allergy at least once during the previous year.6 Older allergy suffers (those above age 50) were more likely to report isolated ocular symptoms, while younger suffers were more likely to report nasal and ocular symptoms. This observation is consistent with the present understanding that dry eye tends to increase with age while

ABOUT THE AUTHOR

Dr. Wagner is a professor of clinical optometry at Ohio State University, where she also serves as the director of extern programs. She is a diplomate in the Cornea, Contact Lenses and Refractive Technologies Section of the American Academy of Optometry and a member of the American Optometric Contact Lens Educators, the American Optometric Association and the Association for Research in Vision in Ophthalmology.

If one presents hand-in-hand with the other, use these tips to differentiate and resolve.

By Heidi Wagner, OD, MPH

DOUBLE TROUBLE:

When Allergy and Dry Eye Coexist

10 REVIEW OF CORNEA & CONTACT LENSES | MARCH 2016
Symptoms related to atopy tend to decrease with age. It’s also noteworthy that seasonal and perennial allergic conjunctivitis is often present in both genders from childhood through middle age, while vernal keratoconjunctivitis is more likely to present in young males under the age of 18 years. Allergic conjunctivitis is often associated with nasal symptoms and history of prior allergic events.

Dry Eye. This condition has been reported in 5% to 30% of the population. Variations in these estimates may be the result of differing diagnostic criteria across studies. Importantly, low estimates may reflect patients with moderate to severe disease while high rates may also include patients with more mild forms of the condition. Large studies of dry eye, including the Women’s Health Study and the Physician’s Health Study, estimate that nearly five million Americans age 50 or older suffer from moderate to severe dry eye, with approximately twice as many women as men presenting with the condition.

In addition to female gender and older age, other reported risk factors for dry eye include LASIK and refractive excimer laser surgery, connective tissue disease, antihistamine use, radiation therapy, hematopoietic stem cell transplantation, vitamin A deficiency, hepatitis C infection and androgen deficiency.

IDENTIFYING THE CULPRIT

Symptoms of allergic conjunctivitis include tearing, itching, burning, foreign body sensation and dryness. The clinical exam should begin with a thorough case history, followed by a careful physical evaluation. A personal or family history of atopic disease is common and may occur in isolation or with nasal symptoms. Signs of allergic conjunctivitis include conjunctival hyperemia and chemosis, papillae, lid edema and watery discharge.

While pollen is a trigger of seasonal allergic conjunctivitis, other environmental irritants such as pet dander and mold can also exacerbate symptoms. The presence of large papillae at the upper tarsal conjunctiva or limbus is a hallmark of the vernal form of the disease.

If itching is considered the hallmark symptom of allergy, then burning and foreign body sensation are preeminent symptoms of dry eye. Clinical observations typically include severity and frequency of ocular discomfort, visual symptoms like fluctuating vision, conjunctival and corneal staining, conjunctival injection and disruptions in tear film quantity, quality or both. Common measures of health and tear film integrity include tear break-up time, tear meniscus, Schirmer’s or phenol red thread test and rose bengal or lissamine green. Less commonly available measures include tear osmolarity and impression cytology.

Examination typically includes lids and lashes due to their direct influence on the tear film. Recently, this examination includes surveillance for Demodex due to the association of these mites with meibomian gland dysfunction. While Demodex is difficult to view during a standard biomicroscopic exam, clinicians should be aware that cylindrical dandruff at the base of the lash and peculiar skin debris are associated with the condition.

Point-of-care tests like matrix metalloproteinase 9 (MMP-9), while non-specific, can be used to...
DOUBLE TROUBLE: WHEN ALLERGY AND DRY EYE COEXIST

support a diagnosis and to identify patients who would benefit from anti-inflammatory therapy.\(^\text{12}\) Similarly, tear osmolarity testing can be used for both initial diagnosis and for monitoring the treatment response of patients with dry eye.

The two traditional classifications of dry eye—aqueous tear-deficient and evaporative dry eye (intrinsic and extrinsic)—are based upon etiology.\(^\text{13}\) However, recent work suggests that as dry eye progresses, hybrid forms of the condition can develop.\(^\text{14}\) Identification may require the practitioner to prescribe additional treatment modalities to address the spectrum of disease. Thus, advanced aqueous-deficient dry eye includes meibomian gland dysfunction and vice-versa. Furthermore, there has been a shift in emphasis from the aqueous-deficient model of dry eye to a lipid-deficient evaporative dry eye model that is associated with meibomian gland dysfunction. As a result, current treatments emphasize the strategies typically recommended for evaporative dry eye.

TREATING THE DISEASE

Clinicians and patients are fortunate to have a multitude of treatment options that range from simple lifestyle adjustments and home remedies to over-the-counter or prescription medications:

- **Allergic Conjunctivitis.** Avoidance of the allergen, cool compresses and preservative-free lubricants may suffice for some patients. When these non-pharmacological treatments are inadequate, topical antihistamines, mast-cell stabilizers and nonsteroidal anti-inflammatory agents make up the mainstay of treatment for allergic conjunctivitis due to their efficacy and safety profile. Short-term judicious use of steroids for patients with severe allergic conjunctivitis is commonly advocated when other treatments are inadequate. Newer corticosteroids provide significant relief with fewer side effects (e.g., ocular hypertension, cataract and infection), but still require supervision by an eye care provider.

Contact lens wear may require modification depending on its association with symptoms of allergic conjunctivitis. Lens wear may even need to be discontinued temporarily. Reducing lens wearing time, increasing lens replacement frequency (in particular, advocating single-use lenses during allergy episodes) and prescribing a preservative-free lens care regimen are management options for mild to moderate presentations of allergic conjunctivitis.

- **Dry Eye.** Often, signs and symptoms of dry eye do not correlate. This requires the clinician to take a holistic approach in assessing disease severity and initiating treatment. Treatment regimens can then be modified based upon the patient’s initial response. Preservative-free artificial tears, gels and ointments are the mainstay of dry eye treatments. In addition to tear supplements, management often includes modification of the environment (e.g., adjustments to humidity and temperature) and treatment of any complications like punctate keratopathy, filamentary keratitis or vision problems.

Cyclosporin A has traditionally been indicated to suppress inflammation in the aqueous-deficient form of dry eye. In contrast, evaporative dry is managed using therapies that target meibomian gland dysfunction such as gland expression and heat application. Eyelid scrubs and mechanical devices like LipiFlow (TearScience) can also help manage evaporative dry eye. Treatment may also include topical or oral antibiotics with anti-inflammatory properties. As with allergic conjunctivitis, topical corticosteroids may also be used for short-term therapy to increase overall treatment efficacy.

Adjunctive therapy may include nutritional support (i.e., ingestion of fish oil and omega-3 fatty acids to reduce inflammation) and patient education regarding avoidance of preservatives and other environmental irritants. Tea tree oil treatments and lid scrubs have been advocated to eradicate *Demodex* and ocular inflammation associated with this condition.\(^\text{15}\) While mild dry eye may benefit from the previously described modifications in contact lens wear, scleral lenses have been used successfully as a treatment option to ameliorate the signs and symptoms of moderate to severe dry eye.\(^\text{16}\)

NEW OPTIONS

Additionally, there are a number of emerging treatments for both dry eye and allergic conjunctivitis. These build on existing treatment regimens and our understanding of the immunopathophysiology for both diseases. With the recognition that dry eye and allergic conjunctivitis coexist, pharmaceutical management can target both diseases.\(^\text{15,17}\) Future treatments will likely target ocular surface inflammation with fewer side effects than with traditional glucocorticoids.\(^\text{18}\)

It is important to differentiate between these two overlapping conditions, considering both have significant health indications. They are commonly encountered in clinical practice and have the potential to impair quality of life and incur significant health care costs from professional services, therapies and pharmacological treatments.\(^\text{1,6,9,19-21}\)

Recognition of the coexistence of dry eye and allergic conjunctivitis allows the eye care provider to treat the presenting problem more
Dry eye and allergic conjunctivitis can mean “double trouble.” When the eye is dry, allergies tend to address each in the best way possible. 

The ocular surface is part of a complex network of mucous membranes spread throughout the body. While membranes exhibit similar essential characteristics, each has its own unique attributes as well. For example, the mucous membrane of the nose and throat produces significant quantities of mucus to help enable the capture of airborne pathogens. Cilia then move the contaminated mucus upward, where it is expelled through the nose and mouth. The eye is no exception to this, possessing a specialized epithelium that maintains and protects the ocular surface. However, because of the tremendous sensory advantage the eye's external structures give an individual, the conjunctival and corneal epithelium is also exposed to an almost constant environmental assault—more so than any other mucous membrane. Environmental toxins, ambient humidity and allergens in the environment are some of the assailants that must be defended against. This article discusses their effects and methods of patient management.1,2

HUMIDITY
Low ambient humidity can have a significant effect on the tear film evaporation and evaporative dry eye. Geographical considerations for humidity vary not only with local weather patterns and with altitude. Humidity levels vary both with local weather patterns and altitude: as such, patients located in different areas of the vast and varied geographic makeup that comprises the United States may be affected differently. For example, as altitude increases, air pressure decreases, reducing the amount of water vapor the air can hold. Temperature has the inverse relationship, with air of a higher temperature able to contain more water than that of a colder temperature.

The importance of ambient humidity is often overlooked in patients with dry eye symptoms for one reason: it’s a local environmental factor that remains relatively consistent from day to day. Thus, it often fails to even register as an external influence. However, a factor that is easily augmented in both the home and work environments with commercially available humidifiers, which come in two basic varieties: heated and cool-mist. Heated humidifiers produce warm steam and are highly effective at quickly modulating indoor humidity. Cool-mist humidifiers, in contrast, use ultrasonic pulses to create water vapor. While not as effective as heated humidifiers, they are less likely to raise the temperature of the room or cause water to condensate on the walls.

ENVIRONMENTAL TOXINS
Chemical or irritative conjunctivitis may develop in response to significant irritation brought on by environmental toxins. These include smoke, chlorine in swimming pools, air pollution and volatile organic compounds.4,5 Effective treatments include limiting exposure to the offending chemical, if possible, increasing local ventilation and washing remaining toxins away from the ocular surface. In extreme cases this may require lavage, but generally frequent use of nonpreserved artificial tears is sufficient and will not only help clear the toxin, but also help soothe the ocular surface.

ALLERGENS
Most common environmental irritants are not toxic in and of themselves; rather, the human body’s inappropriate inflammatory response to them, known as allergy, is what results in discomfort. The word antigen is derived from the word antibody and the Greek suffix -gen, meaning “that which induces production” of something (in this case, antibodies).

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Antigens are not limited to triggering allergic reactions; rather, they encompass anything the immune system reacts to. This can be virtually anything in the environment that is not essential for life.

The subcategory of infectious antigens is comprised of proteins and molecules produced by various microorganisms, while allergic antigens are innocuous substances that pose no threat to the health of the individual, yet elicit an inappropriate immune response. For example, pollen responsible for the mating and fertilization of different plants are not harmful if inhaled, but can be responsible for triggering an allergic response. Other common environmental allergens include mold, pet dander and dust mite feces.6

When considering the pathophysiology of allergy and allergic eye disease, it is crucial to understand some fundamental key concepts. First and foremost is the recognition that, at the cellular level, allergic responses are essentially initiated the same way no matter where they occur in the body. From an immunology standpoint, key players in the allergic response to environmental allergens include T-cells and the action of mast-cell degranulation that produces the symptomatology we are familiar with.

To adequately counteract any potential threats and protect the body, the human immune system must be prepared to halt anything it perceives as threatening, even though it may not know what it might encounter. A newborn infant’s immune system is considered the most naive in that it has not encountered much prior to exiting the womb. After birth, however, it is immediately subjected to an onslaught of antigens. Each initial encounter may trigger the development of an immune response, known as T-cell priming and sensitization. If the response is to an antigen that poses no threat to the individual, it is then, by definition, allergic. It can take 10 to 14 days to set the stage for an initial allergic response.7

During subsequent encounters, when the T-cell encounters the allergen, it communicates with B-cells to mass-produce IgE subtype antibodies—Y-shaped proteins that tightly bind to the antigens they are indicated for upon an encounter. Once created, these antibodies are released from the B-cells into the bloodstream, where they locate mast cells that reside in superficial layers in the skin and mucosa. These mast cells include a receptor on their surface that binds to the antibodies and are packed with granules that contain many factors. When an allergen encounters the tethered IgE antibodies, it triggers degranulation, spilling inflammatory factors like histamines into the surrounding tissue.

The release of histamine is responsible for much of the signs and symptoms we observe in allergic eye disease. Upon binding to receptors on nearby blood vessels, they elicit vasodilation and increased the permeability of the nearby vasculature. Vasodilation is responsible for the hyperemic appearance of the conjunctiva characteristic of ocular allergies; this increase in permeability of blood vessels also allows leakage of serum components into the surrounding tissues, causing chemosis. Histamine release also induces significant pruritis, or the moderate to intense itching most commonly associated with allergic conjunctivitis.

**MILD TO MODERATE OCULAR ALLERGY**

Simple allergic conjunctivitis can be divided into two primary subtypes: seasonal allergic conjunctivitis (SAC) and perennial allergic conjunctivitis (PAC). Together, SAC and PAC account for 95% of allergic conjunctivitis presentations in the United States.8 While this distinction may suggest they are two different clinical entities, the terms are in fact more descriptive of the timing of onset and types of allergens involved.

Though spring is predominantly thought of as allergy season, different pollens are produced at different times of the year depending upon the plant variety and geographic weather patterns such as average temperature and prevailing winds. As such, certain offending allergens may in fact peak in the summer, fall, winter or even during multiple seasons throughout the year.

Perennial allergic conjunctivitis, in contrast, does not follow seasonal patterns because it involves allergens that do not fluctuate throughout the year; these include mold spores, pet dander and dust mite feces.

Common clinical findings associated with these conditions include chemosis of the bulbar conjunctiva, hyperemia of the bulbar and palpebral conjunctivae and the formation of small papillae on the

**Fig. 1. Hyperemia and papillary response of the conjunctiva in seasonal allergic conjunctivitis.**
upper and lower tarsal conjunctiva (Figure 1). Many patients also report moderate to intense itch and watery or mucoid discharge.

To differentiate between the mucoid discharge in allergic conjunctivitis and the mucopurulent discharge of bacterial conjunctivitis, ask the patient to describe the color and intensity of discharge upon waking. Discharge from bacterial conjunctivitis tends to be yellowish or greenish in color, and lids are often matted shut upon waking, while in the case of allergic conjunctivitis, discharge is typically grey or white in color. Discharge from allergic conjunctivitis can also matte the eyelids shut, though this is not as common as in bacterial conjunctivitis. To differentiate between allergic conjunctivitis and viral conjunctivitis—which presents similarly—note the presence of pruritis.

Laterality in allergic eye disease is approached by many clinicians as absolute. There is a misconception that symptoms must be bilateral and symmetric because the response is to a factor that is ubiquitous in the environment, and therefore would cause similar reactions in both eyes. While true overall, there are two scenarios that may lead to a unilateral or asymmetric presentation. The first is that the patient is allergic to something that is not airborne, but rather is transferred to the ocular surface via a vector like the patient’s hand. The second is individuals with an allergy to dust mite feces who regularly sleep on their side.

Treatment for SAC and PAC is often confined to palliative measures like cold compresses and nonpreserved artificial tears. For patients who require pharmaceutical intervention, however, a non-drowsy oral antihistamine should be used. Allergy sufferers can often achieve relief from multiple allergic conditions. In the case of a patient with significant ocular symptoms who also presents with severe dry eye, try treating with a multimodal antiallergy drop such as ketotifen, olopatadine or alcaftadine.

MODERATE TO SEVERE ALLERGIES

The two more severe ocular allergic conditions are atopic keratoconjunctivitis (AKC) and vernal keratoconjunctivitis (VKC). These are chronic allergic inflammatory conditions with acute exacerbations that have severe visual consequences because of the potential for corneal involvement. In addition to findings of simple allergic conjunctivitis, AKC and VKC sufferers often report more discomfort and photophobia. These symptoms can have a profound impact on quality of life.

Many of the clinical findings associated with AKC and VKC are characteristic of both conditions. Patients typically develop large papillae on the tarsal conjunctiva of the upper lid (Figure 2). Additionally, gelatinous lesions referred to as Horner points or Trantas dots form on the limbus, and a filamentary keratitis is sometimes present. Pseudomembranes can materialize in the lower and upper fornix and should be removed to prevent eventual formation of symblepharon. If left untreated, the corneal epithelium will begin to decompensate, with the potential for shield ulcers that leave the patient open to a higher risk of infection and eventual corneal scarring. Scarring of the upper palpebral conjunctiva from chronic inflammation can lead to shortening of the fornix and corneal scarring secondary to trichiasis.

Distinguishing AKC from VKC relies on a few key clinical features. VKC typically affects preadolescent to early-adolescent males and may become exacerbated in certain seasons over others. Papillae on the upper tarsal conjunctiva are large, giving the appearance of cobblestones on exam. AKC, by contrast, has a late adolescence to early adulthood onset and generally does not show a gender predilection. Additionally, though the conjunctival papillary response can be pronounced, it is
generally less so than with VKC. Most AKC patients have an associated atopic dermatitis (eczema) on or around the lids, though this is not always the case. One unique feature of AKC is the development of a “polar bear rug” cataract, or an anterior subcapsular cataract with a characteristic appearance that earns its nickname (Figure 3).

Acute episodes of VKC and AKC are typically treated with topical steroids such as loteprednol or prednisolone drops. Due to the multitude of negative side effects, however, long-term steroid use should be avoided. New research suggests that immune modulators like cyclosporin A and tacrolimus may actually be better options for long-term management; however, these treatment options are still experimental and considered off-label.14–16

The environment poses a constant threat to the ocular surface. The key to minimizing its effects is avoidance of the causative environmental agents and using supportive and therapeutic measures when avoidance is not practical or, as is often the case, not possible. 1


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Eye disorders are widely prevalent, with an estimated 3.5 million Americans age 40 years or older exhibiting some form of impaired vision. Though some of these are rare inherited conditions, more common issues make up a large segment of the group. Allergic conjunctivitis affects approximately 40% of the population yearly, including an increase in incidence over the last decade. Meanwhile, anterior ocular inflammatory diseases (AOID) like ocular allergy, dry eye and tear film dysfunction can present as comorbidities in patients with bacterial or viral infections. Clinicians are actively aware of the mechanisms that cause symptoms, yet many of these cases remain hard to treat.

Currently, a significant amount of research exists with regards to decreasing ocular inflammation from ocular allergies, infections and dry eye. Multi-drug therapies target the mediators responsible for clinical signs and symptoms, while mast-cell stabilizers combined with antihistamines enhance treatment effects throughout the body. The purpose of this article is to discuss the spectrum of receptors responsible for maintaining the homeostatic environment by modulating the innate and adaptive immune system.8

PASSING GO
When an initial allergen penetrates through the physical barriers of the body, antigen-presenting cells (APC) grab it and migrate to the nearest lymph node, where they bind to the T-helper cells present there. The bound B-cell then awaits a cytokine signal from the Th2 cell in the form of interleukin IL-4. This signal triggers the formation of IgE-antibodies specific to the allergen within the B-cell that flow throughout the body, binding to mast cells that prompt a release of histamine and leukotrienes in response. Th2 helper cells also release cytokines, activating both basophils and eosinophils, which produce mediators to assist with the release of histamines and leukotrienes. This further amplifies the body’s allergic response; histamine release in particular accounts for many of the symptoms attributed to allergic conjunctivitis.

Following primary exposure, the allergens present in the body bind to the IgE on mast cells, triggering a release of mediators and IL-4, which causes the B-cells to produce more IgE antibodies in a positive feedback loop.9 Understanding this allergen pathway allows clinicians to target specific cells and mediators to control symptoms.

Allergic conjunctivitis constitutes a range of allergic inflammatory disorders that affect the anterior surface of the eye—namely, acute, seasonal and perennial conjunctivitis, and chronic allergic forms like atopic keratoconjunctivitis, vernal conjunctivitis and giant papillary conjunctivitis.1-3,6,7 Stored mediators like histamine and de novo chemicals (including derivatives of the arachadonic acid cascade comprising of leukotrienes and prostaglandins) initiate the acute phase reaction, while the late phase response is initiated by cytokines that facilitate the infiltration of eosinophils.10 The late phase is also the basis for chronic allergic disorders, with remodeling that involves stimulation, activation and localization of lymphocytes.

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Dr. Leonard Bielory is an allergist-immunologist in New Jersey who is affiliated with multiple hospitals in the area, including Robert Wood Johnson University Hospital and St. Barnabas Medical Center.
within the follicles and papillae of the conjunctival surface. Acute presentations of allergic conjunctivitis can be controlled with different topical ocular agents, while more severe forms may require a multidisciplinary approach in partnership with an ophthalmologist.3,10

COMPARING THE EARLY AND LATE RESPONSES

An examination of the tear fluid content of an affected patient typically reveals the presence of a “soup” containing various preformed and de novo mediators like IgE antibody, histamine, leukotrienes and tryptase.10 Preformed mediators like histamine, tryptase and bradykinin immediately disperse following exposure to an allergen, while release of de novo mediators like leukotrienes and prostaglandins peaks at roughly eight to 24 hours following exposure. Cytokine release helps mediate both early- and late-phase responses to the allergen; these are direct contributors to the signs and symptoms of AOID. Early responses to allergen exposure typically present as pruritus and conjunctival erythema, which results from the release of histamine.3,7,10 Due to the direct relationship between early symptoms and histamine, early-phase reactants tend to respond best to antihistamine therapy for symptom relief.10

The allergic late phase, in contrast, is a delayed response without sustained exposure to the allergen. This phase involves a greater inflammatory response than the early phase, and is not primarily the result of histamine; this characteristic in fact contributes to the ineffectiveness of antihistamine therapy in patients with chronic allergic diseases.3,10 Unlike the immediacy of the early phase, the late phase can occur months after the initial allergen exposure and is marked by the recruitment of immune cells (i.e. dendrocytes, basophils, and eosinophils) to the site of the allergic response. Symptoms of late phase allergic responses include edema, pruritus, erythema, excessive tearing and lid and conjunctival edema. If corneal involvement is present, photophobia may also develop.

Dual action H1 subtype antihistamines in conjunction with mast cell stabilization are much more effective in combating symptoms of late-phase allergic reactions; however, the best available therapy for late phase symptoms may be steroids like loteprednol. Due to their ineffectiveness in the early phase and ocular side effects, however, steroids should not be considered as first-line therapy.1,2,7,10

Fig. 1. Treatment path of ocular allergy.

Source: Leonard Bielory, MD. Reproduced with permission of the author.
Antihistamines act as antagonists to histamine receptors, inhibiting the release of acute-phase allergic reactants. Many antihistamines differ in their ability to treat specific AOID symptoms due to their varying affinities for each subtype of histamine receptor. Symptomatic relief is directly correlated with a clinician’s ability to find the antihistamine that targets the right receptor, and, since mast cells are responsible for the late-phase allergen response, the role of antihistamines and their relative potency are extremely valuable to patient care. Comparing the binding affinity of each antihistamine to each of the four subtypes of histamine receptors can help a clinician choose a more targeted therapy plan for the patient.

The ability to bind with histamine receptors is based on the rate the drug binds to receptors, the duration of binding and the maintenance of the drug-receptor complex. These factors combine to enable the drug’s ability to antagonize the activation of histamine receptor to achieve symptomatic control and minimize side effects.

Commonly, antihistamines work by binding to the active site of receptors, leading to the inactivation of histamine. Inhibition of histamine receptors is achieved when enough of the drug is present to prevent activation of the receptor. Drugs that have poor binding affinities require higher concentrations to achieve the same inhibition, compared to drugs with a higher binding affinity. As such, a drug’s affinity for a targeted histamine receptor can be used to predict how potent its antihistamine effects will be.

Drug vs. histamine binding at the receptor is a competitive process, as both the drug and histamine bind to and release from the receptor. As such, the compound that spends the most time bound to the receptor will cause the receptor to be stimulated or inhibited. Efficacy of antihistamines can be greatly enhanced by rapid equilibrium and onset of action, or by slow dissociation rates from the receptor. Note, however, antihistamines carry an anticholinergic effect that can cause ocular drying. This side effect is the result of muscarinic receptor inhibition. In some cases, however, it can be used for the treatment of insomnia or excessive allergic rhinorrhea. Thus, it is important to understand binding affinities for muscarinic receptors of current antihistamines to prevent adverse side effects without affecting the efficacy of the treatment provided.

### Histamine Receptor Subtypes

Histamine is considered both an autacoid and a neurotransmitter; nearly all organs and a wide range of biological functions are affected by it. These effects are mediated through the distribution of four types of G-coupled proteins. Histamine binds to receptors throughout the body based on location of the necessary receptors and the physiological response that triggered its release. All histamine receptors exhibit constitutive activity, however, and are able to function without bound histamine. Research has also indicated that H₁ and H₂ receptors are more widely expressed than H₃ and H₄ receptors.

<table>
<thead>
<tr>
<th>Table 1. Histamine Receptor Subtypes</th>
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<tr>
<td><strong>Immunomodulatory effects</strong></td>
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<tr>
<td><strong>Itching</strong></td>
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<tr>
<td><strong>Swelling</strong></td>
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<tr>
<td><strong>Erythema</strong></td>
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<tr>
<td><strong>Vascular permeability</strong></td>
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<td><strong>Pain</strong></td>
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<tr>
<td><strong>Vasodilation</strong></td>
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<tr>
<td><strong>Nasal congestion</strong></td>
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Histamine receptors are triggered via a second messenger system associated with G-coupled proteins. All histamine receptors are heptahelical transmembrane molecules that transduce extracellular signals by way of G proteins to intracellular second messenger systems. These include Ca²⁺, cGMP in H₁.
cAMP in H₂, Ca²⁺ and MAP kinase for H₁ and H₂ receptors. Different cell types and their physiological locations give histamine its ability to trigger varying effects based on its target receptor.⁷-¹⁰

With respect to the four subtypes described in Table 1, H₁ receptors are predominately located in the bronchi, heart, central nervous system (CNS) and arterial and intestinal smooth muscle.⁷,⁸ The sedative effect of H₁ antagonism seen in first generation oral antihistamines, (i.e., diphenhydramine) is the result of their ability to cross the blood-brain barrier, while the appearance of histamine receptors in smooth muscle contributes to the cardiac side effects present in some oral antihistamines.⁷-¹⁰ H₁ stimulation is associated with inflammation, prostaglandin production, headache, hypotension, tachycardia, and bronchoconstriction. H₁ is the only histamine responsible for pain, and is also the subtype most contributory to itching. Research has indicated H₁ antagonism prevents cytokine release and ocular itching associated with allergic conjunctivitis, and also increases vascular permeability.⁷,⁹,¹⁰

H₂ receptors are located in the parietal cells of the gastric mucosa, CNS, uterus and the heart. Drugs like cimetidine and famotidine inhibit this receptor’s role in gastric acid secretion. H₂ receptors cause increased vascular permeability, flushing and relaxation of bronchial smooth muscle relaxation. H₂ receptors also have a vasodilatory effect and have been shown to prevent stimulated vasodilation with prior administration of H₂ antagonists.⁷,¹⁰ H₂ receptors are present in neurons throughout the CNS and peripheral nervous systems, as well as in the heart and bronchioles. H₃ receptors are located pre-synaptically, and their stimulation enhances modulation of the blood-brain barrier while inhibiting release of histamine and other neurotransmitters. H₃ receptors are responsible for bronchial relaxation, inhibition of sympathetic neurotransmission, decrease in gastric vascular permeability, and it is generally well tolerated for up to eight hours or more.

### HISTAMINES ON THE MARKET

**Olopatadine** is a selective H₁ receptor antagonist and cell-stabilizing agent. The 0.1% formulation is unique in that it is also approved for use in allergic conjunctivitis. Most other H₁ blockers are only approved for ocular itching. In previous studies, Olopatadine was found to be superior to ketotifen when it came to the alleviation of ocular itching. Pataday (olopatadine, Alcon) is an increased concentration formulation for once-daily dosing. Allergic rhinitis can now also be treated with a once-a-day olopatadine intranasal formulation.¹²,⁶,⁷,¹⁰

Azelastine is a selective H₁ receptor antagonist that also exhibits H₂ blocking properties. Azelastine also blocks the release of histamine from mast cells, and formation of leukotrienes. It has a relatively low pH of 5.0–6.5, making its major side effect mild ocular irritation on administration. It is relatively long acting, being efficacious for up to eight hours when used twice daily and is available in an intranasal formulation as well.¹²,⁶,⁷,¹⁰

Epinastine is an antihistamine with a high affinity for H₁ receptor and H₂ receptor antagonism, with mast cell-stabilizing properties as well. Originally approved for rhinitis, with ocular administration it has shown significant improvement of itching, swelling and tearing compared with the placebo. It is recommended twice daily with duration of eight hours or longer. Side effects include burning and infection, and it is generally well tolerated for up to eight hours after instillation.

Bepotastine is an H₁ receptor selective antagonist with mast cell-stabilizing and eosinophil modulating properties. It is approved as an ophthalmic solution for the treatment of itching associated with allergic conjunctivitis. It was effective in controlling ocular itching and tearing, but shows little effect on conjunctival redness. Bepotastine has been shown to have rapid onset and can give symptomatic relief in as soon as three minutes after administration and last for up to eight hours with a statistically significant number of patients achieving complete relief. Bepotastine besilate 1.0% was able to inhibit vascular permeability due to histamine blockade substantially better than olopatadine 0.1%. In addition to ketotifen, bepotastine has shown an ability to inhibit eosinophil infiltration into the conjunctiva.¹²,⁵,⁶

Alcaftadine is a tricyclic piperidine aldehyde approved for the treatment of itching associated with allergic conjunctivitis. It is administered once daily and demonstrates substantial relief of symptoms at both the 15-minute and 16-hour mark after administration. Both oral and ophthalmic formulations show very similar pharmacokinetic activity. Cytosolic enzymes via aldehyde oxidation metabolize alcaftadine to its acid metabolite. It is believed that cytochrome p450 enzymes play a minor role in the metabolism of the drug.²⁶ Alcaftadine exhibits antagonistic activity on H₁ and H₂ subtype receptors, as well as low affinity for the H₃ subtype. Furthermore, alcaftadine prevents the recruitment of eosinophils and inhibits mast cell degranulation. Treatment with alcaftadine has shown less eosinophil infiltration into the conjunctiva compared to olopatadine and the placebo in murine models. In direct comparison with other ocular allergy agents, alcaftadine has shown to provide similar relief to current marketable agents.¹⁴,¹⁷

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**Table 1**

<table>
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acid production and control of vasoactive mediators. These effects are kept in mind when targeting $H_3$ receptors to control insomnia, obesity, inflammatory diseases, schizophrenia and certain disease states mediated by neurotransmitter release.1-10

$H_3$ receptor antagonism has been shown to aggravate pruritic symptoms, which appears to contradict the normal histamine-induced pruritus pathway. It was found to increase the incidence of scratching behavior in mice; further research indicated intradermal injections of an $H_3$ receptor antagonist (lodophenpropit or clobenpropit) triggered a significant increase in scratching behavior in both mast cell-deficient and wild type mice. $H_3$ antagonism-induced pruritus appears to be mediated by substance P, a known pruritus-causing agent. Some speculation has occurred that clobenpropit induced a pruritic response through $H_1$ subtype antagonism in combination with $H_4$ subtype agonist.6,7,9,10

As such, $H_3$ blockade may provide relief of nasal congestion symptoms. Research supports the opinion that $H_3$ receptors are involved with sympathetic transmission, and that combined $H_1$ and $H_3$ antagonism can provide treatment for allergic rhinitis symptoms. This is useful in patients that continue to be symptomatic when only using an antihistamine as a treatment regimen. Combination $H_3$ antagonism (chlorpheniramine) and $H_1$ antagonism (clobenpropit or thioperamide) revealed significant decongestive effects, while evading hypertension. Further research into combining $H_1$ receptor antagonist (fexofenadine) with a novel $H_3$ antagonist found statistically significant relief of subjective symptoms like rhinorrhea, itching and sneezing compared with the placebo.3,4,7

The $H_4$ receptor is directly related to pruritus as well. It is expressed on hematopoietic cells and plays a crucial role in the function of mast cells, eosinophils, monocytes, dendritic cells and T-cells. Studies have identified that the chemotactic response of mast cells, eosinophils, dendritic cells, monocytes and natural killer cells to histamine is through the $H_4$ subtype receptor.10 These receptors are involved in autoimmune reactions, allergies and, specifically, symptoms of pruritus. The immunomodulating effects of the $H_4$ subtype receptor are currently under investigation for its uses in anti-allergy therapy. $H_4$ receptor antagonism is also being investigated for treating immune-related diseases like asthma. $H_3$ receptor antagonism alone has been shown to be ineffective in the treatment of asthma, but in combination with $H_1$ receptor blockade may provide symptomatic relief.2,3,6,7,8,10

$H_4$ subtype antagonism has been studied in a long-term experimental murine model of pruritus associated with a chemical-induced contact dermatitis induced by repeated challenge with 2,4,6-trinitrochlorobenzene [TNCB].19 $H_4$ antagonist [JNJ7777120] was administered and shown to reduce pruritus and resolve skin lesions in a dose-dependent manner. Compared to when managing $H_1$ receptor antagonism with fexofenadine, however, relief was not seen in both inflammation and pruritus.7 It was also demonstrated that $H_4$ receptor agonists elicited a scratching response that can be ameliorated by pretreating with a selective $H_4$ receptor antagonist, and that when $H_1$ and $H_4$ subtype receptors are both antagonized, scratching behavior was nearly completely relieved. Pruritic symptoms were also brought under control with $H_1$ antagonism in $H_4$ subtype receptor knockout mice.5,6,7,10

Murine models have hypothesized the concept of synergistic control of symptoms relating to allergic disease states. Studies have shown in murine models with induced pruritus, there is statistically increased symptomatic control when $H_1$ and $H_4$ receptor antagonists were used concretely. It was also noted that any pruritus in the $H_4$ knockout mice was resolved with administration of diphenhydramine.7

THE TIES THAT BIND

Literature comparing the binding affinities of 19-marketed anti-histamines has indicated differences in receptor affinity and drug potency—namely, a larger binding affinity value [i.e., $Ki$] correlates with a weaker binding affinity of the drug for the receptor. If the binding affinity of the drug to the receptor is weak, a larger dose of the drug will be needed to achieve the same inhibition as a drug with a lower $Ki$.

Table 2. Binding Affinity [Ki] Comparison

<table>
<thead>
<tr>
<th></th>
<th>$H_1$ Receptor [nM]</th>
<th>$H_2$ Receptor [nM]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olopatadine</td>
<td>35.0nM</td>
<td>1,000,000nM</td>
</tr>
<tr>
<td>Azelastine</td>
<td>6.8nM</td>
<td>4,200nM</td>
</tr>
<tr>
<td>Ketotifen</td>
<td>1.3nM</td>
<td>1,000nM</td>
</tr>
<tr>
<td>Epinastine</td>
<td>9.8nM</td>
<td>4,030nM</td>
</tr>
</tbody>
</table>
Relative potency can also be determined using these Ki values. Antihistamines marketed for muscarinic receptor inhibition were compared for potency and possible trends in anti-cholinergic side effects; these studies of binding affinities were separate studies and were not in direct comparison, but some trends become apparent.\(^6,7,10\)

The binding affinity for histamine to the H\(_4\) receptor is 1,80,000nM. Thioperamide has the lowest affinity for H\(_4\) receptor with a Ki of 2,80,000nM. Pyrilamine had a Ki value of 0.8nM, giving it the highest affinity for the H1 receptor of all the agents compared. The first-generation drug diphenhydramine is also a very potent binder, with a Ki of 12.5nM, while potency was variable with regards to the second-generation compounds. Desloratidine (Ki 4nM) and cetirizine (Ki 6.3nM) showed the highest affinity, while loratadine (Ki 35nM) and fexofenadine (Ki 83nM) had much lower binding affinities. Topical ophthalmic formulations have very high potency, with olopatadine (35nM) having the lowest affinity and ketotifen with olopatadine (35nM) having the greatest affinity. Topical ophthalmic formulations have very high potency, with olopatadine (35nM) having the lowest affinity and ketotifen with olopatadine (35nM) having the highest affinity.\(^7,10\)

H\(_4\) receptors have much weaker binding affinities compared to those of the H\(_1\) receptor. The binding affinities for H\(_2\) subtypes are two to four orders of magnitude weaker than those for the H\(_1\) receptor. Ranitidine showed the greatest affinity for the H\(_2\) receptor with a Ki of 187nM. Olopatadine [Ki 1,00,000nM] had the weakest binding affinity to the H2 receptor whereas diphenhydramine, azelastine, epinastine and ketotifen showed binding affinities in the range of cimetidine [Ki >10,000nM]. Using histamine’s affinity to H\(_2\) subtype receptors, we can model the drug’s ability to compete and produce the desired antihistamine effect. Histamine’s affinity to H\(_2\) subtype receptors is 18,350nM, but it can be inferred that drugs such as emedastine (Ki 49,067nM) and olopatadine would need much higher concentrations to overcome competition with histamine for the H\(_2\) receptor.\(^1,2,7,10\) H\(_3\) and H\(_4\) subtypes have more similarities between the two than the H\(_2\) and H\(_1\) subtypes. The highest affinity for H\(_3\) was thioperamide (Ki 79,400nM) and olopatadine (Ki 79,400nM) exhibited the lowest affinity for the H\(_3\) receptor.\(^7\)

Available data on H\(_4\) receptor affinities is limited. Only five antihistamines were compared: thioperamide [Ki 27nM] had the greatest affinity while cimetidine and ranitidine [Ki >10,000nM] exhibited relatively low affinity for the H\(_4\) subtype receptor. More in-depth research into H\(_4\) receptors and their function must be conducted to determine the suitability of using H\(_4\) subtype agonists or antagonists for treatment of conditions as it relates to allergic and inflammatory disease processes.\(^7,10\)

Due to the ability of some antihistamines to exert an effect on muscarinic receptors, antihistamines that offer the least amount of anticholinergic activity while maintaining high antihistamine potency would be ideal. Drugs such as desloratidine have shown the greatest effect on muscarinic receptors.\(^1,2,7,10\) Ketotifen is a strong H\(_1\) antagonist and mast cell stabilizer with leukotriene inhibition. It is the only topical ophthalmic agent available without a prescription in the United States. If administered twice daily, it has been found to be effective in the prevention of itching, redness and general symptoms of allergic conjunctivitis compared to the placebo. Emedastine difumarate was compared to ketotifen fumarate; both showed marked improvement in the incidence of itching compared with the placebo.\(^1,2,4,7,10\)

The ever-increasing incidence of AOIDs suggests clinicians must continue to develop new, innovative treatments to alleviate patient symptoms. Of the four known types of histamine receptors, each has varied effects dependent on location and physiological signal. Additionally, each exhibits its own specific response to acute inflammation; thus, understanding each receptor’s unique and localized actions is key for targeting treatment. Persistent research relating to the affinity of antihistamines and the ability to target subtypes may also open the door for new allergic disease management techniques; as such, these may be the next step in managing AOIDs.\(^7\)

MANAGING THE OCULAR

By Gregory A. Caldwell, OD

While a seemingly simple ailment, ocular allergy is, in fact, multifaceted, encompassing multiple diagnostic categories differentiated by a complex cascade of inflammatory mediators, cytokines and other chemicals. As such, while grouping these disparate conditions into a single diagnostic category called “allergic conjunctivitis” can ease treatment selection, doing so can also result in therapeutic failure. Instead, approaching ocular allergy as a spectrum of different diseases—each with its own initiating factors, presentations and methods of management—can help clinicians select more appropriately targeted therapies to enhance the likelihood of resolution.

The human allergic response is classically considered an overreaction of the body’s immune system to foreign substances perceived as a threat to ocular health (i.e., allergens). Said substances are not necessarily pathogenic, but rather perceived as so. In effect, an allergic reaction is a result of a beneficial immune response that has gone awry.

Allergies can be subdivided into four categories based on the cascade of events that comprise each reaction and the time it takes for them to occur. Of the four, Type I and Type IV are considered true ocular allergy. Immediate hypersensitivity reactions, or Type I ocular allergies, include seasonal allergic conjunctivitis (SAC), perennial allergic conjunctivitis (PAC), vernal keratoconjunctivitis and atopic keratoconjunctivitis. Delayed hypersensitivity reactions, or Type IV ocular allergies, include contact dermatitis.

A Type I allergic reaction begins with a sensitization phase in which the patient is exposed to the offending antigen. Additional re-exposure results in an early-phase response and subsequent late-phase response. The early response is the degranulation of the mast cell, which has preformed mediators—the most common being histamine. Most patients in this phase exhibit the hallmark symptom of itching in conjunction with mild conjunctival hyperemia, chemosis and a conjunctival papillary response. At times, a stringy white mucus or concurrent rhinitis is also present. Antihistamines and mast-cell stabilizers, or better yet agents that combine both properties, are the best treatment methods for the early phase.

The ensuing late-phase allergic response involves white blood cell (i.e., eosinophil and basophil) infiltration that results in cell-mediated cytotoxicity or tissue damage and edema. The late-phase reaction typically commences between four and six hours after sustained mast cell degranulation. T-lymphocyte activation and infiltration of the conjunctival mucosa by eosinophils, neutrophils, monocytes and basophils are hallmarks of the late phase. If intervention is initiated while the allergic reaction is predominately in the early phase, control can be achieved using anti-allergy products that have antihistamine and mast cell stabilizing effects. Once Type I allergies have progressed to the late phase, however, more potent anti-inflammatory agents in the form of topical corticosteroids or non-steroidal anti-inflammatory agents (NSAIDs) may be necessary to mitigate the inflammatory/immune response.

UNDERSTANDING THE PRESENTATION
Determining whether patients with seasonal or perennial allergic conjunctivitis are in the early or late phase can be completed using details from their patient history and results from a clinical exam. When performing the exam, note type, severity and duration

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COMPLEX ALLERGIC REACTION

of signs and symptoms: patients in the early phase present with itching and chemosis, while those in the late phase exhibit evidence of eosinophil and basophil infiltration and accumulation in the ocular tissues.

In the case of vernal keratoconjunctivitis (VKC), which is seen primarily in children, the allergic reaction moves rapidly from the early to late phase. In this instance, the accumulation of eosinophils and basophils in the limbal area of the bulbar conjunctiva are known as Horner’s points or Trantas’ dots, and are a classic example of cell-mediated cytotoxicity or tissue damage.

Treatments for allergic conjunctivitis consist of reducing or eliminating the antigen when possible and prescribing pharmaceuticals to prevent or decrease the immune response; however, non-pharmaceutical interventions can also be beneficial as a first line of defense. Examples for managing both Type I early and late phases and Type IV hypersensitivities include:

• **Allergen/antigen avoidance.** Using air conditioners and HEPA filters can prevent pollen from infiltrating indoor areas. Instructing patients to avoid outdoor activities during high pollen periods is also beneficial, though not always possible. Patients can track tree, grass and weed pollen counts and mold spore counts one of numerous smartphone apps; this may assist patients in reducing antigenic exposure.

• **Artificial tears.** Though these can flush away antigens from the ocular surface, sporadic use makes this option only marginally effective, especially in more severe cases. Excessive lacrimation in allergic conjunctivitis is an example of the body’s attempt to emulate this action.

• **Cold compresses.** Applying chilled temperatures triggers vasoconstriction and limits the eosinophilic response. Cold compresses may also have a psychological benefit, in that patients have something to occupy their hands with rather than scratching, which increases mast cell degranulation, eosinophil release and subsequently, severity of itching.

• **Washing hair before going to bed.** Hair—particularly longer strands—acts as a filter to trap airborne allergens throughout the day. These allergens transfer to the pillow when the patient lies down and then into the eyes overnight. Rinsing hair before bed reduces and even eliminates this problem.

THE TYPE I ALLERGIC RESPONSE

Pharmacologic options for managing Type I acute phase allergic responses include:

• **Prescription topical antihistamine/mast-cell stabilizers.** These agents employ multiple mechanisms of action to bring relief; antihistamine competes for and reversibly blocks histamine receptors in the conjunctiva and eyelids, while the mast-cell stabilization properties inhibit mast-cell degranulation. Most patients prefer to use antihistamine/mast-cell stabilizers instead of other options because of the rapid onset of relief they provide. Examples include Patanol (olopatadine hydrochloride 0.1%, Alcon), Pataday (olopatadine hydrochloride 0.2%, Alcon), Pazeo (olopatadine hydrochloride 0.7%, Alcon), Lastacaft (alcaftadine ophthalmic solution 0.25%, Allergan), Bepreve (bepotastine besilate 1.5%, Bausch + Lomb), Optivar (azelastine hydrochloride 0.05%, Meda Pharmaceuticals) and Elestat (epinastine hydrochloride 0.05%, Allergan).
Over-the-counter (OTC) topical antihistamine/mast-cell stabilizers. Often more cost-effective than their prescription counterparts, OTC topical antihistamine/mast-cell stabilizers are also less effective due to their lower affinity for histamine receptors and inhibited mast-cell stabilization effects. However, they still maintain a place in many treatment regimens. Examples include Zaditor (ketotifen fumarate 0.025%, Alcon), Claritin Eye (ketotifen fumarate 0.025%, Bayer) and Alaway (ketotifen fumarate 0.035%, Bausch + Lomb).

Topical mast-cell stabilizers/cromones. When a patient cannot tolerate antihistamines due to allergy or severe dry eye, agents like Crolom (cromolyn sodium 4%, Bausch + Lomb), Alomide (lodoxamide tromethamine 0.1%, Alcon), and Alocril (nedocromil sodium 2%, Allergan) make suitable alternatives. Alamast (pemirolast potassium 0.1%, Vistakon) is another option, but is no longer available on the market. Note, these drugs’ mechanism of action is slow in comparison, and relief is delayed, compared to the aforementioned options. They are much less effective than dual-action medications due to their limited action.

Topical antihistamines. Emadine (emedastine difumarate 0.05%, Alcon) is a single-agent antihistamine. It provides rapid relief like mast-cell stabilizers, but is limited in efficacy due to its single mechanism of action.

Topical NSAIDs. These may help with itching in the Type I acute allergic phase when other medications are not effective.Topical NSAIDs have analgesic and anti-inflammatory activity; this is why they are indicated for ocular pain and postoperative inflammation in patients who have undergone cataract extraction or corneal refractive surgery. In this case, the analgesic benefit would help manage the itch (pain). Examples like Acular LS (ketorolac tromethamine 0.4%, Allergan), Xibrom (bromfenac 0.09%, Mylan), Voltaren (diclofenac 0.1%, Novartis) or Nevanac (nepafenac 0.1%, Alcon) could be used when needed.

Therapeutic options for managing a Type 1 late-phase allergic response include:

Topical steroids. Corticosteroids inhibit the inflammatory process by stabilizing vascular membranes to decrease capillary dilation and permeability, which restricts eosinophils, basophils and macrophages from invading tissues. Corticosteroids function primarily by obstructing the arachidonic acid pathway via inhibition of phospholipase A2 to stop formation of the inflammatory mediators prostaglandin, thromboxane and leukotriene. Note: extended use can lead to elevated intraocular pressure in susceptible individuals.
An additional side effect of cataract formation is also especially prevalent with use of acetate or phosphate topical steroids; these include Pred Forte (prednisolone acetate suspension 1%, Allergan), Pred Mild (prednisolone acetate suspension 0.12%, Allergan), Durezol (diluprednate emulsion 0.05%, Alcon) and FML (flurometholone suspension 0.1%, Allergan).

These higher-risk steroids are used in certain cases, such as when drug formularies may limit or dictate a treatment regimen. The release of newer generation site-specific or ester-based steroids like loteprednol etabonate have helped decrease many ocular complications associated with topical steroids; examples include Alrex (loteprednol etabonate suspension 0.2%, Bausch + Lomb), Lotemax (loteprednol etabonate suspension 0.5%, Bausch + Lomb) and Lotemax gel (loteprednol etabonate gel 0.5%, Bausch + Lomb).

Still, monitoring for the above signs is key for protecting a patient from further adverse effects.

- **Topical immunosuppressants.** Cyclosporine offers potent immunosuppressive properties, reflecting its ability to block transcription of cytokine genes in activated T-cells. This makes cyclosporin A a highly potent inhibitor of T-cell activation and, as such, a potential alternative for patients unable to tolerate topical steroids, such as those with glaucoma. Cyclosporin A may also be used in conjunction with topical steroids, however.

Restasis (cyclosporine ophthalmic emulsion 0.05%, Allergan) is one option for treatment of the late phase response. A second, not-yet-FDA-approved drug, lifitegrast (Shire)—being studied for the treatment of dry eye—may also have an off-label use in the late-phase allergic reaction due to its ability to inhibit T-cell migration and activation.2

- **Oral NSAIDs.** These are a good alternative when steroids are contraindicated; for example, in patients allergic to corticosteroids or those with glaucoma. As already mentioned, topical NSAIDs have analgesic and anti-inflammatory activity. The anti-inflammatory benefit is key in the late-phase as a means to relieve inflammation.

**THE TYPE IV ALLERGIC RESPONSE**

Type IV ocular allergies typically present as contact dermatitis on the upper and lower eyelids. The patient usually presents with itching, burning and red and scaly eyelids, often quickly following exposure to a noxious substance. When contact dermatitis is persistent, the eyelids typically thicken. As such, more aggressive treatments supersede the supportive therapies mentioned above.

Therapeutic options for managing Type IV allergic response include:

- **Topical steroids.** The most appropriate treatment vehicle in mild to moderate contact dermatitis is cream or ointment. Examples include the ointment forms of Lotemax or FML, as well as OTC hydrocortisone 1% cream. Because limited options exist for topical corticosteroid ointments, it may be necessary to employ alternate preparations such as combination antibiotic/steroid ointments like Maxitrol (neomycin and polymyxin B sulfates and dexamethasone, Alcon) and Tobradex (tobramycin 0.3% and dexamethasone 0.05%, Alcon). Be aware, however, that some of these combination ointments may have antigenic properties themselves.

- **Oral steroids.** Severe contact dermatitis is most often responsive to a short course of oral corticosteroids. Oral prednisolone can be given, but methylprednisolone may work best to treat this ocular allergy. The latter is available as a six-day Medrol 4mg dose-pack.

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**DOSE NOTES**

- Pazeo, Pataday and Lastacaft are the only once-a-day prescription topical antihistamine/mast-cell stabilizers available.
- Pazeo and Lastacaft are indicated in patients two years of age and older.
- All topical antihistamine/mast-cell stabilizers fall in the historic pregnancy category C, except for Lastacaft, which is in the historic pregnancy category B.
- Single-agent mast-cell stabilizers and single-agent antihistamines all fall in the historic pregnancy category B.
- Lotemax gel does not require shaking, contains 70% less preservatives than its suspension and contains two moisturizers—propylene glycol and glycercin.10
- Topical NSAIDs inhibit cyclooxygenase, which blocks a segment of the arachidonic acid pathway. Thus, taking a topical antihistamine/mast-cell stabilizer in conjunction with topical NSAIDs would provide the most symptom relief.
- If cyclosporine is used as an alternative, it will need to be combined with a topical antihistamine/mast-cell stabilizer to relieve symptoms.
The treatment of Type I and Type IV hypersensitivities has long been based on the known abilities of antihistamines, mast-cell stabilizers/cromones, NSAIDs, immunosuppressants, and corticosteroids. However, none of these drugs completely eliminate the clinical features of these allergic reactions; furthermore, current estimates suggest that at least 20% of the overall population suffers from some form of allergic conjunctivitis, many who do not seek treatment at all. Identifying these patients in need is an opportunity to improve lives as well as our practices. The second step is to apply knowledge of how each individual drug works in combination with insights into the pathophysiological mechanisms of ocular allergy to refine your therapeutic strategy and increase success of resolution. So, get out there and prepare for allergy season!

1. The Type I allergic reaction begins with which of the following?
a. Early-phase response.
b. Late-phase response.
c. Sensitization phase.
d. Inflammatory phase.

2. How many categories of allergies are there?
a. 2.
b. 3.
c. 6.
d. 4.

3. What is the most common type of preformed mediator involved in the allergic response?
a. Histamine.
b. Neutral protease.
c. Proteoglycan.
d. TNF-alpha.

4. How many hours after mast cell degranulation does the allergic late-phase reaction commence?
a. 1 to 3.
b. 4 to 6.
c. 8 to 10.
d. 12 to 14.

5. What is the primary purpose of antihistamine?
a. To block antihistamine receptors in the conjunctiva and eyelids.
b. To inhibit mast-cell degranulation.
c. To relieve conjunctival hyperemia.
d. To prevent rhinitis.

6. Why are OTC topical antihistamine/mast-cell stabilizers considered less effective than their prescription counterparts?
a. Longer shelf life.
b. Lower affinity for histamine receptors.
c. Better mast-cell stabilization effects.
d. Contraindication for VKC.

7. What side effect(s) may accompany topical steroid use in treating allergies?
a. Inflammation.
b. Elevated intraocular pressure.
c. Cataract formation.
d. A and C.

8. What combination of drugs is most likely to provide the most symptomatic relief of ocular allergies?
a. Topical NSAIDs and topical antihistamine/mast-cell stabilizers.
b. Topical steroids and topical NSAIDs.
c. Topical immunomodulators and topical antihistamines.
d. Topical antihistamine/mast-cell stabilizers and topical NSAIDs.

9. What is the key hallmark sign of Type IV allergies?
a. Chemosis.
b. Contact dermatitis.
c. Giant papillary conjunctivitis.
d. Cataract formation.

10. Current estimates suggest what percentage of the overall population suffers from allergic conjunctivitis?
a. 10%.
b. 20%.
c. 30%.
d. 60%.
Springtime for Sclerals

Even Adolf Fick himself, who created the first scleral contact lens in 1888, would be surprised by the longevity of his creation. Composed of blown glass, Fick’s lenses and those that followed enjoyed relatively limited popularity due to difficulties with manufacturing and poor oxygen transmission. Materials improvements weren’t enough to keep the design from being eclipsed by corneal-fitted lenses, first gas permeables and then hydrogels.

However, the intractable symptoms experienced by patients with ocular surface disease and their persistent inability to comfortably wear contact lenses—coupled with developments in computer-aided design—has led these specialty lenses to regain popularity in more recent years. Sclerals are most commonly indicated for correction of irregular astigmatism in corneal conditions like keratoconus, or following surgical procedures like penetrating keratoplasty.

**FITTING THE LENS**

The appropriate fit for a scleral contact lens is comprised of complete vault of the cornea, clearance of the limbus and alignment with the sclera, with little to no blanching of the conjunctival blood vessels. Vault, or corneal clearance, is defined as the space between the back surface of the scleral lens and the front surface of the cornea. Practitioners can use diagnostic lenses when trial fitting a patient; additionally, they can employ optical section slit beam or anterior segment optical coherence tomography (OCT) to assist.

With the former, corneal clearance is determined via comparison of the known center thickness of the contact lens with the thickness of the post-lens tear fluid reservoir. Instilling fluorescein into the lens chamber may make assessment easier.

OCT, by contrast, employs a cross-sectional view of the cornea and scleral lens to generate a clear measurement of central vault. This minimizes the amount of subjective influence on vault assessment to provide a more precise measurement. OCT-guided fitting is especially useful for troubleshooting cases in which a patient may be experiencing discomfort, but the underlying cause is not evident during a slit lamp examination. For example, if a patient is complaining of rebound redness and soreness following a day of lens wear, but no conjunctival blanching is observed, the lens may be fitting tighter than expected; this can be determined using OCT to assess the degree of lens settling.

Scleral contact lenses can be differentiated based on the overall diameter or location of lens bearing on the eye. Most recently, sclerals have been divided into two groups: corneo-scleral and full scleral. A corneo-scleral GP lens (12.5mm to 15.0mm in diameter) shares bearing on the cornea and the sclera. This is in contrast to a full scleral in which the entire lens bearing is on the sclera. The full scleral group can be further divided into mini-scleral (15.0mm to 18.0mm in diameter) and large scleral (18.0mm to 25.0mm in diameter). In comparison to corneal GP lenses, scleral lenses have minimal tear exchange, a thick tear layer and increased lens thickness. It is important to use materials with Dk values of 100 or more to increase oxygen transmissibility.

Scleral lenses settle into the conjunctiva over a period of time, resulting in a reduction of corneal clearance by 100µm to 150µm. It is necessary to take this into account when evaluating the lens on the eye to ensure there is enough corneal clearance for the patient. In a study evaluating changes in over-refraction after settling, there was no significant change in over-refraction. Therefore, visual acuity is not affected following lens settling.

Though the amount of corneal vault prescribed varies, a minimum...
of 100µm to 400µm of sagittal depth post-settling is recommended to avoid complications such as apical touch of contact lens on cornea, hypoxia and corneal edema. Some larger diameter scleral lenses may even require up to 500µm of clearance for a proper fit. For patients with ocular surface disease in particular, a greater sagittal depth is typically best. Larger diameter scleral lenses also allow for more hydration of the complete ocular surface.10

Practitioners should remain aware that the aforementioned rule may not always be the case. A study that attempted to establish an average central corneal vault at which dry eye patients were successful in scleral lenses did find the average vault for successful patients was 380µm, with a standard deviation of 110µm. However, the range of successful vaults in the study led researchers to conclude that precision in central vault was not important in scleral contact lenses for a successful fit over a compromised ocular surface. They also determined there was no correlation between vault and corneal curvature or vault and visual acuity. Patients with as low as 220µm and up to 600µm of central vault were able to achieve a visual acuity of 20/20.8 Ultimately, it is up to practitioners to determine what is best for each patient.

MANAGING OSD

Many practitioners have begun to use scleral lenses to manage different ocular surface diseases—including keratoconjunctivitis sicca, graft-vs.-host disease, cicatricizing conjunctivitis, neurotrophic keratopathy, exposure keratopathy and limbal stem cell deficiency—in place of extensive artificial tear, topical cyclosporine, punctal occlusion or topical corticosteroid use.14 Scleral lens therapy may also bypass the need for more aggressive surgical interventions like tarsorrhaphy, conjunctival flap or amniotic membrane grafting.6

Patients suffering from ocular surface disease who may be good candidates for scleral lens wear often display symptoms related to ocular pain, visual disturbance and tear film instability.7 The continued hydration and protection provided by these lenses both improves visual acuity and provides lasting comfort. A retrospective study in which 212 subjects were fit with scleral lenses to evaluate the success of long-term therapy found that goals of better visual acuity, comfort, ocular surface protection and resolution of keratopathy were achieved in all but two subjects. Researchers noted the participants had attempted an average of 3.2 other forms of intervention prior to scleral lens wear; they concluded that commercially available scleral lenses are suitable for the management of moderate to severe ocular surface disease.8

TIPS FOR ALLERGIES

Ocular allergies affect up to 30% of the general population and have been shown to result in tear film instability.11 In patients suffering from allergies, scleral lenses can pose more of a problem as the allergens remain in the lens reservoir for prolonged periods of time due to minimal tear exchange underneath the lens. Though little has been published on this topic, from personal experience scleral lens wear with allergies requires more maintenance to avoid bulbar injection and itchy, irritated eyes. A common issue with allergies is the development of a biofilm on the front and back surface of the contact lens. This not only affects the quality of vision but can also lead to lens discomfort. Usually, patients remove their lenses, clean the front and back surface to remove any biofilm or debris buildup and replenish the lens with non-preserved saline multiple times throughout the day.

Use of a prescription strength antihistamine and mast-cell stabilizer

(Continued on page 33)
A Firm Foundation
New mucin-enhancing drug could support tear film stability from the ground up.

Dry eye treatment recently received a publicity boost when Allergan announced a licensing agreement with Mimetogen Pharmaceuticals to develop and commercialize MIM-D3 in November 2015. MIM-D3 is an ophthalmic solution of tavilermide that is currently in Phase III trials for treatment of ocular surface disease.

This stable, cyclic peptide that mimics part of the structure of nerve growth factor (NGF) and is mechanistically classified as a partial TrkA receptor agonist. Like the recent column on lifitegrast (Nov. 2015), discussion of this drug marks another encounter with a novel mechanism that warrants an examination.

**MIM-D3 appears to be an exciting drug that may provide us with a new mechanism to establish a normal, healthy ocular surface.**

NGF belongs to the neurotrophin family and is an essential protein in the differentiation and survival of neurons. Signaling of NGF is mediated by the activation of a tyrosine kinase receptor (TrkA) and p75 neurotrophin receptor (p75NTR). When NGF binds to TrkA, numerous pathways are activated including the phospholipase C-1 cascade.

NGF increases goblet cell density. Therefore, interest in MIM-D3 as a novel mimicker of NGF is attractive. Using a rat model of dry eye, MIM-D3 showed a significant improvement in corneal staining.

A Phase II study randomized 150 dry eye patients to one of three groups: tavilermide 1%, tavilermide 5% or placebo. Study participants used the medication twice a day for 28 days, while a controlled adverse environment (CAE) was incorporated to exacerbate and standardize dry eye presentations. Primary outcomes included one objective (i.e., fluorescein corneal staining) and one subjective (i.e., diary worst symptom score over 28 days) measure. Patients rated symptoms of burning, dryness, grittiness and stinging on a scale of zero to five.

No serious ocular adverse events occurred in any treatment group, but the primary endpoints were not met. There was, however, an improvement in corneal staining. Additionally, in a subset of participants with higher symptom scores at the time of randomization, there was a significant treatment effect noted in both treatment groups.

Recently, a Phase III trial enrolling 403 dry eye patients to receive MIM-D3 1% or placebo concluded. The patients used the study medication twice a day.
for 56 days and were stratified into patients with cataracts and those with a normal crystalline lens. There was significantly less fluorescein corneal staining in the treatment groups after 56 days, and improvements in symptoms were also noted. A dramatic difference in treatment response was noted in the cataract group compared with those with no lenticular opacities. Patients with cataracts had significant improvement in staining and the ocular surface disease index questionnaire (OSDI). Those with normal lenses had improvement in the ocular discomfort symptom scores compared with the placebo.5,6

A decrease in conjunctival goblet cell density along with a corresponding reduction in the secretion of ocular surface mucins may be noted in patients with dry eye. Although therapies rarely target this specific mechanism or these deficiencies, MIM-D3 appears to be an exciting drug in the pipeline that may provide us with a new mechanism to establish a normal, healthy ocular surface.

THE GP EXPERTS: SPRINGTIME FOR SCLERALS

(Continued from page 31)

combination drop is recommended prior to the application of scleral lenses. The use of non-preserved artificial tears several times throughout the day may be necessary. Adding a few drops of a non-preserved artificial tear with higher viscosity into the lens reservoir may help slow tear exchange.

Giant papillary conjunctivitis (GPC) may occur with scleral lens wear due to mechanical irritation of the lid with potential lens surface debris buildup. GPC can also cause excessive debris issues on the surface of the lens and affect wettability. In patients with allergies, it is best to use a peroxide care system for overnight cleaning. Peroxide systems are neutral and safe to the eye and provide adequate disinfection. Special large cases made specifically for scleral lenses are available for those requiring peroxide cleaning.10

There are numerous scleral lens products available already, with continued improvements in design and function being made daily. Scleral lenses now provide practitioners with a tool to better manage patients who suffer from ocular surface disease and help them regain clear and comfortable vision.11

4. Ousler G, Meervik K, High CAE Responders show greater improvement in signs and symptoms of dry eye after treatment with MIM-D3. IOVS 2015;54; E-Abstract 4543.
6. Meervik K, Brazzell K, Ousler GW, Cumberledge G. Improvements in signs and symptoms of dry eye with MIM-D3 1% ophthalmic solution compared to placebo in different patient populations. IOVS 2015;56; E-Abstract 4460.
Are You Allergic to Change?

While getting past certain barriers to practice-building can take some effort, long-term benefits are worth it.

It feels like I’ve been discussing the addition of dry eye and allergy services to eye care practices for a while now. So, when I began this month’s column, I asked myself what other strategies I could possibly share with practitioners that I hadn’t already covered. After taking a step back to think for a moment, I realized the question should be: Why haven’t more adopted these ideas already? More to the point—why are practitioners so resistant? After all, with the prevalence of dry eye and ocular manifestations of allergy so high, it’s almost a given that these issues should be part of every primary eye care practice. So, why don’t more of us include them?

The answer, of course, is typical: change, and our resistance to it. More specifically, the uncomfortable confrontation of the inevitable fear that happens before a new action or policy is added. However, facing this emotion head-on is key to serving our patients—and ultimately, our practices and ourselves—better, so we must consider it.

OBSTACLES TO OVERCOME

Here are four reasons why many doctors are likely hesitant to include more dry eye and allergy care into their practice:

• Getting sucked into the dry eye “treatment fad of the month” vortex and forgoing individuality. My teenage daughter has joked with me for years, “But Dad, all the cool kids are doing it!” In this case, “it” refers to a common adolescent behavior that I can’t relate to but that my daughter wishes to partake in. Some eye care practitioners feel the same with dry eye and allergy and are happy to offer the same range of treatments to their patients as everyone else. Others, however, may feel doing so is effectively forfeiting their sense of autonomy and control over their practice to become “just another eye care practitioner.”

My advice is to get past this concern and realize that your patients will not see it this way. Going with the flow with dry eye and allergy actually provides nothing but patient benefits—after all, with these being common enough problems, not providing them will, in fact, likely drive patients away. To alleviate some of the shock, try adding certain treatments before others and asking for feedback from patients.

• We’re more comfortable with the devil we know. Few of us can honestly say our practices are perfect, but at least we’re familiar with our imperfections and their effects on our day-to-day operation. However, no one can say for certain what offering a higher or different standard of care might do. Not knowing what’s around the corner can be extremely unnerving and potentially cause practice-building paralysis.

My advice: acknowledge and accept these fears. It’s true that you don’t know what awaits you if you make changes to your practice. However, keep in mind that you also have no idea what the future will bring. What if forgoing those changes in fact leads to a worse outcome? In this case, the best option is to institute careful planning and education prior to any decisions to mitigate disastrous results and stack the odds in your favor. Plan to be successful, and you will be.

• My staff will hate me for this. On the contrary, it’s likely that nearly all—if not all—of your staff members are anxious to learn more and assist patients in a better capacity. Most staff members are excited to break away from routine activities to learn and execute something new. My advice is simply to avoid springing everything on them at once. Share with them some of the changes, let them digest and process the information and then provide them with more.

• What if I can’t do this? Fear of clinical failure is a common reason many practitioners avoid change. This is even more the case with the legal ramifications that can come with clinical missteps. However, if we never took any risks in an attempt to design a better solution, refractions would still be performed with trial frames, and penlights would still be used for contact lens exams. It’s likely you have already learned new clinical skills repeatedly in the past and thought nothing of it. Why would now be any different? And as always, help can be found along the way in the form of literature and colleagues. So take a deep breath, and a step forward.
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