Topics in OCULAR ANTIINFLAMMATORIES

A CONTINUING MEDICAL EDUCATION PUBLICATION

ISSUE 10

Prophylaxis for Seasonal Allergic Conjunctivitis

S. LANCE FORSTOT, MD **Timing the administration of medication to prevent mast cell degranulation makes sense for patients with severe seasonal allergic conjunctivitis.**

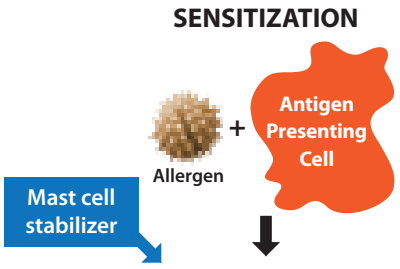

FIGURE 1 Allergic inflammatory cascade and sites of pharmacologic action. See full image inside on page 4.

Each spring, millions of Americans react to the annual explosion of airborne allergens with a predictable hypersensitivity response: seasonal allergic rhinitis and conjunctivitis, popularly known as "hayfever." Approximately 15% to 20% (some estimates suggest 40%) of the US population suffers from some form of acute allergic conjunctivitis—seasonal or perennial—with seasonal allergic conjunctivitis (SAC) being the more common.[1,2]

SAC MORBIDITY

SAC is frequently mild and amenable to self-management; however, many patients, particularly those who present for treatment, experience moderate or severe symptoms—itchy eyes, watery discharge, burning sensation, lid swelling, and discomfort. On a rare occasion, photophobia or blurring of vision may result.[2] Morbidity from SAC can be quite significant for those who are severely affected. Compared with their unaffected peers, SAC patients report diminished quality of life, productivity, social functioning, and perception of overall health.[1,3]

For patients with severe symptoms that cause impairment in work or other aspects of life, prophylaxis with an antiallergic agent is a reasonable option. The rationale for prophylaxis rests upon three pillars: 1) SAC onset is predictable for many patients, being clearly associated with the calendar and observable weather and quantifiable pollen patterns; 2) inflammation associated with SAC occurs in stages, so there is a window of opportunity to interrupt the cascade before major symptoms occur; and 3) agents appropriate for SAC prophylaxis are very safe, and risks associated with their use are small.[4-6]

SEASONALITY

SAC is triggered by airborne plant pollens and molds; and SAC activity correlates with the life cycles of native plants and molds, peaking in spring and fall. Trees, such as mulberry, oak, and juniper, pollinate in late winter to early spring, kicking off "allergy season" for many people. They are generally followed by grasses, such as timothy, bluegrass, and rye, in late spring to summer; and weeds, such as ragweed (the principle culprit), cocklebur, plantain, and sagebrush, in late summer to fall.

TARGET AUDIENCE This educational activity is intended for ophthalmologists and ophthalmologists in residency or fellowship training.

LEARNING OBJECTIVES Upon completion of this activity, participants will be able to:

1. Identify candidates for prophylaxis of seasonal allergic conjunctivitis.
2. Recognize clinical features of ocular GVHD in patients who have undergone bone marrow transplantation.

EDITORS

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Pollen counts are highest in the early morning in rural areas (nearest the plants) and at midday in urban areas after the allergens have traveled on the breeze from their source. Molds, like pollens, are spread by the wind. They thrive on leaf and plant molt, so they reach their apex in late summer.[7]

Shifts in weather influence the presence and density of these aeroallergens. Rain and cold spells reduce overall pollens counts; but damp weather causes some molds to flourish.[7] Heavy winter snowfall and early spring rainfall saturate the ground and contribute to an earlier than usual efflorescence of allergens.[8] In Denver, where I practice, springtime SAC symptoms typically emerge in April and May. But due to record snowfall last winter (the most in 25 years) and an early and long stretch of warm temperatures this spring, I started seeing SAC patients in March.

TRACKING ALLERGENS

Resources abound for helping practitioners and patients navigate allergy season. News outlets and online sites report local pollen and mold counts daily. Online sites—including pollen.com, weather.com, and wunderground.com—provide daily overall pollen count by zip code or city. Pollen.com offers a calendar for keeping up with symptoms and email alerts for high counts. The National Allergy Bureau (NAB) of the American Academy of Allergy, Asthma, and Immunology offers updated allergy counts by region and email reports of the most commonly detected allergens.[9] In addition to overall pollen counts grouped by trees, grasses, and weeds, the NAB, pollen.com, and, in some instances weather.com, designate which specific local allergens (by species) are most active at any given time.

Each year the Asthma and Allergy Foundation of America identifies the "100 most challenging places to live with allergies," based on pollen count, allergy medication consumption, and allergists per capita.[10] Southeastern cities like Louisville, Memphis, and Baton Rouge top the spring 2014 list of "allergy capitals," but large metropolitan areas like New Orleans, New York, and Philadelphia

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STATEMENT OF NEED

The indications for topical ophthalmic antiinflammatory drugs (both steroidal and nonsteroidal) are evolving rapidly, as new agents and new applications emerge. Many of these are novel—eg, the perioperative use of nonsteroidal antiinflammatory drugs (NSAIDs) to prevent cystoid macular edema—and/or fly in the face of older thinking—eg, the use of steroids to calm inflammation and reduce the risk of melting or scarring from infection. Neither of these important applications is on-label.

In addition, new steroidal and nonsteroidal agents continue to come to market, expanding the utility of both classes. Antiinflammatory drugs are now used for: the treatment of ocular surface disease and allergic conjunctivitis; prevention of perioperative pain and inflammation in ocular surgery; infection management; cystoid macular edema prophylaxis following cataract surgery; haze prevention in PRK; and much more.

What has regrettably not followed this expansion of indications, formulations, and new molecular entities are protocols for drug selection and use.[1] These are vital because significant differences in safety, tolerability, and efficacy exist between and within both antiinflammatory drug classes. C-20 ester steroids, for example, have a demonstrated lower risk of intraocular pressure (IOP) elevation than ketone steroids.[2,3] Since a range of steroid formulations and concentrations is available, clinicians need up-to-date information about the indications and optimum uses for each.[3]

Although topical NSAID formulations have been associated with significant adverse events (keratopathy ranging from superficial punctate keratitis to corneal melt), recent work shows these to be uncommon and less severe with newer formulations.[4] Indeed, novel NSAIDs make use of lower concentrations and less frequent dosing, potentially impacting safety profiles and reducing risk from long-term use.[5]

Although both are "antiinflammatory," steroids and NSAIDs act at different points in the inflammatory cascade, and thus offer opportunities for physicians to fine-tune their drug selection. And although they are frequently used together, whether or not the two drug classes can act synergistically is controversial. In the context of recent clinical data, a clear mechanistic understanding of each drug class generally—and of newer formulations specifically—will equip clinicians to make effective, evidence-based prescribing decisions across the many situations that call for ocular inflammation control.

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FACULTY AND DISCLOSURE STATEMENTS

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rank high as well.

It should be remembered that pollen counts are predictions based on very recent (within the last 24 to 48 hours) 24-hour air particle assessments and weather patterns. So, while generally quite reliable, they are not real-time reflections of aeroallergen status.[7]

STAGES OF ALLERGY

A brief review of the stages of type 1 hypersensitivity—the pathophysiologic underpinning of acute mast-cell-mediated allergic conjunctivitis—provides a basis for understanding the mechanisms of antiallergy prophylaxis and treatment. Type 1 hypersensitivity occurs as a stepwise series of immunologic events: sensitization, followed by "early phase," and then "late phase" reactions.

Take, for example, an individual living in Portland, OR, who is allergic to walnut tree pollen. His very first springtime exposure to airborne walnut tree pollen initiates sensitization (which produces no symptoms). During sensitization pollen comes to rest on the conjunctiva or nasal mucosa and is met by resident macrophages and dendritic cells, also appropriately called antigen presenting cells (APCs). APCs break down the pollen particle into peptides that complex with major histocompatibility complex (MHC) class-II molecules on the cell surface. The processed antigen conjoined with MHC molecules triggers T-cell maturation, cytokine production, and the synthesis of IgE by B-cells. This IgE binds to mast cell surface receptors, priming the mast cell for degranulation, should a second exposure occur.[11]

Returning to our example, the allergic individual's second exposure to walnut tree pollen triggers the second phase of the cascade: crosslinking of IgE antibodies on the mast cell surface, altered permeability of the mast cell membrane, an influx of calcium, and an all-at-once release of inflammatory mediators including histamine, serotonin, eosinophil chemotactic factors, and others.[11,12] Within minutes of his second exposure, the individual experiences the early phase effects of histamine, including itching and tearing.

In the late phase, continued activation of mast cell IgE-receptor complexes causes the mast cell membrane to degrade, leading to phospholipid release, more cytokine release, and recruitment of inflammatory cells such as eosinophils and neutrophils.[11] In the conjunctiva, this leads to ongoing inflammation, vasodilation, increased vascular permeability, redness, mucus production, pruritis, and tarsal conjunctiva papillae formation.[12]

ALLERGY PROPHYLAXIS

Since significant symptoms begin with the second and third (ie, early and late) phases of immune activation, prophylaxis is most effectively administered before the first or second exposures to an allergen (Figure 1). (It should be noted that the topical ocular antiallergy medications are indicated for treatment of existing allergy; prophylaxis with these drugs is an off-label use.) Most often, I will start the conversation about SAC prophylaxis with a patient early in the season—perhaps 1 to 2 weeks before anticipated exposures—to try to prevent full-blown SAC. Other times, patients come to the clinic requesting preventive therapy aware that "this is the time of year" they have symptoms. I would estimate that 20% to 25% of SAC patients in my practice use medication prophylactically.

As with all interventions, a targeted approach to prophylaxis is best. Topical ocular medications, including the dual-acting mast cell stabilizer/antihistamine agents (eg, bepotastine, olopatadine, ketotifen) or single-acting H1-receptor blocking antihistamines, are good options for patients whose symptoms are mainly ocular. The dual acting agents prevent symptoms at two junctures: early phase mast cell degranulation (mast cell stabilization role) and blockade of histamine receptors, preventing their activation by histamine that has already been (or is about to be) released. This antihistaminic activity prevents histamine from inducing vasodilation and itching. The dual acting agents are fast acting and can be dosed once or twice a day, which is convenient for patients.[12] They are also well tolerated by patients and carry a low risk for side effects.

SYSTEMIC MEDICATIONS

For patients with significant ocular and nasal allergies, systemic agents—including oral antihistamines, such as the first generation agent diphenhydramine or a second generation agent like loratidine—may be preferred. However, there are downsides to this approach. First, in some patients, systemic antihistamines are less effective than topical agents in relieving ocular symptoms, which make them less than ideal as a preventive agent.[13]

Second, side effects may limit the use of oral antihistamines. First generation agents cause drowsiness, which can impair functioning during the day. Patients taking first gen-

CORE CONCEPTS

- SAC is a very common condition. Although often just a nuisance, SAC can be a source of serious morbidity in some patients.
- Weather patterns and publicized aeroallergen counts make SAC onset relatively predictable for patients who know what they are sensitive to.
- Pollen counts may be high in urban and suburban, as well as rural, areas.
- Allergen seasonality generally proceeds from trees and grasses in the spring to weeds and molds in late summer to fall.
- Allergy pathophysiology is initiated with first contact between a predisposed individual and the allergen to which he reacts; characteristic symptoms begin with the second exposure.
- Topical ocular agents or oral systemic agents administered prophylactically may be of benefit to patients with significant ocular allergies.

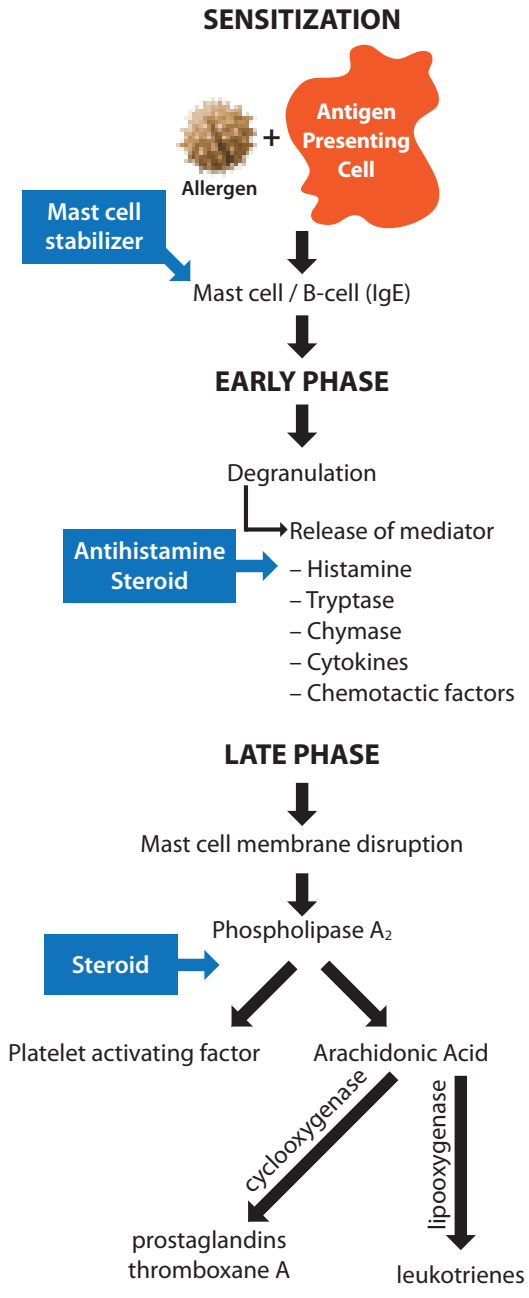

FIGURE 1 Allergic inflammatory cascade and sites of pharmacologic action.

eration antihistamines should be cautioned against driving a car, for example.[12] Furthermore, first and second generation oral antihistamines block muscarinic receptors in lacrimal glands, which has been reported to cause an altered tear film, ocular dryness, and further discomfort.[13]

PROPHYLAXIS FAILURES

When prophylactic medications are properly administered, failure is rare. Patients who do manifest symptoms despite prophylaxis should be switched to an alternative agent for management. If additional antiinflammatory medication is required, topical loteprednol etabonate 0.2% is a mild corticosteroid with a superior side effect profile compared to other corticosteroids, and it is the only topical corticosteroid approved for treatment of ocular allergy.[14] Broad corticosteroid antiinflammatory action (downregulating both early and late phase effects) makes it an attractive option for patients whose symptoms are already underway and/or not controlled by the mast cell stabilizer/antihistamine.

CONCLUSION

SAC can be well controlled by appropriate prophylaxis with topical or systemic antiallergy medications. Patients who experience severe or activity-limiting symptoms may benefit from use of topical antiallergy medication in the weeks or days leading up to allergy season. Because the dual action agents provide very rapid symptom relief, patients with mild allergies may wait until onset of symptoms before starting medication.

S. Lance Forstot, MD, is a founding partner of Corneal Consultants of Colorado and a clinical professor at the University of Colorado Medical School. Dr. Forstot has been a speaker for Alcon, Allergan, and Bausch + Lomb. Medical writer Noelle Lake, MD, assisted in the preparation of this manuscript.

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Ocular Graft-vs-Host Disease

PENNY A. ASBELL, MD, MBA, FACS

Clinical management of patients with ocular graft-vs-host disease is hampered by a lack of proven prophylactic strategies. These are critical because, by the time the disease is recognized, irreversible tissue damage may have already been done. A better understanding of the disease should lead to new approaches to diagnosis, prevention, and treatment.

CORE CONCEPTS

- GVHD is a common complication of allogeneic stem cell transplantation. Ocular GVHD, found in 40% to 60% of patients with these transplants, is typically a chronic inflammatory condition affecting primarily the conjunctiva and lacrimal gland.
- Clinical manifestations of chronic ocular GVHD resemble the ocular effects of autoimmune diseases, with two primary components: dry eye and cicatricial conjunctivitis.
- Treatment goals in ocular GVHD include inflammation reduction, lubrication, tear preservation, and epithelial support.
- Topical corticosteroids are the mainstay of antiinflammatory therapy for ocular GVHD and should be initiated early on.
- Topical cyclosporine can be a safe and effective therapeutic option for ocular GVHD patients. Whether initiating topical cyclosporine eye drops prior to bone marrow transplantation has prophylactic effects is currently under study.

Allogeneic hematopoietic stem cell transplantation is used to treat a variety of malignant and nonmalignant hematologic diseases, usually when chemotherapy fails. For many patients hematopoietic stem cell transplantation is curative, although a substantial portion of patients will develop graft-vs-host disease (GVHD), a major complication that can result in significant morbidity and mortality. GVHD that occurs within 100 days of transplantation is referred to as "acute" and is seen in about 40% of patients receiving an allogeneic hematopoietic stem cell transplant; a chronic form (occurring more than 100 days post-transplantation) is seen in 30% to 70% of transplanted patients.[1,2]

GVHD occurs when transplanted donor T cells recognize the transplant recipient's body as foreign and attack it. In addition to the eye, target organs for attack in GVHD include the skin, oral mucosa, gastrointestinal tract, liver, and lungs. Ocular GVHD is found in 40% to 60% of patients receiving allogeneic hematopoietic stem cell transplantation; and between 60% and 90% of patients with systemic GVHD show ocular effects. When the eyes are affected, it is primarily structures of the ocular surface (cornea, conjunctiva, eyelids, and lacrimal glands) that are damaged.[3]

Ocular GVHD impairs quality of life from dry eye symptoms and, with corneal involvement, can lead to permanent vision loss. In extreme cases, it may threaten patients' psychological health, as, after having gone through the ordeal of stem cell transplantation and surviving a life-threatening illness, they have to face significant chronic pain and poor visual prognosis.

CLINICAL FEATURES

Acute GVHD rarely affects the eye, but when it does, it is often prognostic of mortality.[4] Typical ocular findings in acute GVHD include conjunctival hyperemia, chemosis, pseudomembrane formation, ulceration of the lid margin and the cornea—all signs of active ocular surface inflammation.

Ophthalmologists are more likely to encounter chronic GVHD—indeed, the proportion of patients with chronic systemic GVHD who also have ocular GVHD may be as high as 90%.[1] Ocular chronic GVHD is typically considered a disease of the conjunctiva and lacrimal glands, although its pathogenesis is still poorly understood. Its clinical presentation often mimics the inflammatory ocular surface conditions associated with systemic autoimmune disorders and has two main features: conjunctival inflammation (conjunctivitis) and tear deficiency resulting from fibrotic destruction of the lacrimal gland.

The chronic inflammatory processes on the ocular surface may lead to conjunctival subepithelial fibrosis and corneal epithelial changes such as punctate keratopathy. The latter is frequently accompanied by filament formation and can lead to painful erosions, with secondary infections, ulcerations, and even perforation of the cornea.

Other ocular surface inflammatory conditions, such as limbal keratitis, episcleritis, and scleritis, may also be observed in chronic GVHD but are much less common. A small group (about 13%) of patients have posterior involvement.[5]

DRY EYE

Dry eye (keratoconjunctivitis sicca), typically occurring 6 to 12 months following allogeneic hematopoietic stem cell transplantation, is the most common ocular manifestation of chronic GVHD and a fundamental cause of most of the other serious ocular complications, such as corneal epitheliopathy and infectious or noninfectious ulceration.

Patients presenting with ocular chronic GVHD usually report symptoms that resemble those seen in typical dry eye disease: ocular irritation, redness, itchiness, foreign-body sensation, burning, excessive tearing, light sensitivity, and fluctuating vision. Dry eye is more likely to occur in GVHD patients with skin or mouth involvement; but unlike dry eye disease in patients without GVHD, which is more common in women than men and older rather than younger people, the risk of GVHD-associated dry eye is relatively evenly distributed with respect to sex and age.[3]

The primary pathogenic process of dry eye in chronic GVHD is an increase in stromal fibroblasts and extensive fibrotic tissue destruction of the lacrimal gland.[6] Meibomian gland dysfunction develops in nearly half of chronic GVHD patients and can aggravate ocular surface dryness by increasing tear evaporation.[7] Factors other than GVHD, such as irradiation, chemotherapy, and immunosuppressive therapy, may also contribute.

ASSESSMENT

For patients suspected of chronic ocular GVHD, a comprehensive ophthalmological workup is indicated. This should include visual acuity, intraocular pressure (IOP), Schirmer, and tear film breakup time testing. These tests will both assist in diagnosis and provide a baseline to help assess the patient's response to therapy.

Vital dyes such as lissamine green or fluorescein can be used to stain the conjunctiva and cornea, respectively. Hematologists often use the Schirmer test to evaluate tear production and ocular involvement, considering test scores up to 5 mm in 5 minutes indicative of significant dry eye. Results of the Schirmer test, however, are known to be variable, so variable that its diagnostic value becomes questionable for any measurements higher than 2 to 3 mm. I believe only scores lower than 2- or 3-mm are truly indicative of a dry eye diagnosis.

Recently, Riemens and colleagues found that the profile of inflammatory cytokines in the tear fluid of patients with ocular GVHD showed significantly increased levels of interleukin (IL)-6 and interferon (IFN)-gamma, which most likely represent abnormalities in T cell associated inflammatory responses.[8] The study added to our limited understanding of cytokine involvement in the pathogenic process of ocular GVHD. Since IL-6 is known to promote the differentiation of T-helper 17 (Th-17) cells, which are important regulators of autoimmune responses with characteristic production of IL-17, the increase in tear IL-6 levels suggests a potential role for Th-17 cells in GVHD.

ANTIINFLAMMATORY THERAPY

Topical corticosteroids, because of their potent antilymphocytic and antiinflammatory activity, remain the first line treatment for controlling inflammation and improving dryness symptoms in ocular GVHD. Although certain agents such as loteprednol etabonate are known for their relative safety, corticosteroids in general are associated with increased risks of infection, cataract, and glaucoma. For this reason, pulse therapy rather than long-term treatment is recommended, and patients receiving topical corticosteroid eye drops should be closely monitored for adverse effects. Topical corticosteroids are contraindicated in patients with corneal epithelial defects, stromal thinning, or infiltrates.

Topical cyclosporine, which inhibits T-cell proliferation and production of cytokines, can be helpful for patients refractory to conventional treatment with lubrication and corticosteroid drops. Topical cyclosporine may also increase the goblet cell density of the conjunctiva and decrease epithelial cell turnover. Other agents that have shown a potential to reduce inflammation in ocular GVHD include an IL-1 receptor antagonist, tranilast (an inhibitor of TGF-beta and other cytokines), and tacrolimus (a macrolide antibiotic with T-cell inhibiting activity similar to cyclosporine).

Because of the potential for a broad array of serious side effects, systemic immunosuppression is not recommended for patients with GVHD limited to the eyes. In cases where uncontrolled ocular chronic GVHD is present along with systemic GVHD, systemic immunosuppressive therapy should be considered; close collaboration between ophthalmologist and hematologist is required for optimal outcomes.

TREATING SEVERE DRY EYE

Major goals in the treatment of ocular GVHD include: relieving dry eye symptoms, preservation of the tear film, and maintenance of epithelial integrity. Frequent use of preservative-free artificial tears not only provides lubrication but may also dilute the inflammatory mediators present on the ocular surface. For patients who require extremely frequent artificial tears, thicker formulations such as ointments or gels may be better treatment options than solutions.

Punctal occlusion is used for tear preservation; the number of puncta to be occluded is determined by the Schirmer score and the severity of the patient's dryness symptoms. Autologous serum eye drops have proven a safe and effective treatment for severe dry eye secondary to chronic GVHD. These drops contain components that are found in natural tears and are essential for ocular surface integrity and health. These include epitheliotrophic growth factors, immunoglobulins, nerve growth factors, and vitamins.

Using a sutureless amniotic membrane to cover and protect the ocular surface may be beneficial for patients with superior limbic keratoconjunctivitis and corneal epithelial defects. Scleral contact lenses have been successfully used to relieve symptoms of dry eye in some patients, although many GVHD patients may find it difficult to tolerate any kind of lens because of severe ocular surface dryness.[9]

TREAT IN ADVANCE

Although multiple therapeutic options are available, none of them is fully satisfactory, and ocular GVHD remains challenging to treat. The treatment for ocular chronic GVHD is largely empirical as the pathogenesis of ocular chronic GVHD

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is yet to be fully understood. Usually only symptomatic patients are treated, and by the time treatment is initiated irreversible damage may have been done to lacrimal gland and conjunctival tissues.

At this moment, we lack means to either identify those patients most at-risk for GVHD or to prevent ocular involvement in GVHD. One study has investigated prophylactic use of topical cyclosporine and found that initiation of cyclosporine 1 month before bone marrow transplantation decreases the inflammatory response in the lacrimal glands and resultant dry eye.[10] Larger clinical trials now in progress to evaluate the prophylactic efficacy of cyclosporine eye drops in chronic ocular GVHD may validate the preliminary finding. Prophylaxis and early treatment likely will be the key to improved management of chronic ocular GVHD in the future.

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EXAMINATION QUESTIONS

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Directions: Select the one best answer to each question in the exam (Questions 1–10) and in the evaluation (Questions 11–16) below by circling one letter for each answer. Participants must score at least 80% on the questions and complete the entire Evaluation section on the form below. The University of Florida College of Medicine designates this enduring material for a maximum of 1.0 *AMA PRA Category 1 Credit*™. There is no fee to participate in this activity. You can take the test online at **http://cme.ufl.edu/toai**.

1. Which of the following statements regarding prophylaxis for SAC is most accurate?
   A. All patients with SAC should avail themselves of prophylaxis
   B. Prophylaxis is most effective when it follows mast cell degranulation
   C. Allergy prophylaxis is a logical but off-label use of topical ocular mast cell stabilizer/antihistamines
   D. Prophylaxis with a single-acting antihistamine blocks the antigen sensitization phase

2. Which of the following is NOT true of ocular GVHD?
   A. It is most often a chronic inflammatory condition
   B. It only affects the anterior segment of the eye
   C. The ocular surface effects resemble those of systemic autoimmune diseases
   D. It can result in ocular surface damage

3. The most common ocular manifestation of chronic GVHD is:
   A. Shield ulcer
   B. Epiretinal membrane formation
   C. Dry eye
   D. Scleritis

4. Autologous serum eye drops contain:
   A. Growth factors
   B. Immunoglobulins
   C. Vitamins
   D. All of the above

5. Typically, "pollen counts" are based on measurements of aeroallergens taken:
   A. The same date the year before
   B. Within the last day or two
   C. As continuous "real time" assessments performed minute by minute
   D. Both A and C are correct

6. From spring to fall, the sequence of plant pollen release in the US generally follows which sequence?
   A. Trees, grasses, weeds
   B. Trees, weeds, grasses
   C. Grasses, weeds, trees
   D. None of the above is correct

7. Which of the following topical agents has shown a potential for prophylactic effect in the management of ocular GVHD?
   A. Corticosteroid
   B. Cyclosporine
   C. Tacrolimus
   D. Tranilast

8. Which of the following agents is an appropriate choice for SAC prophylaxis?
   A. A strong topical corticosteroid
   B. An oral corticosteroid
   C. Any drop that contains naphazoline hydrochloride
   D. A topical, dual action mast cell stabilizer/antihistamine

9. Which of the following is an INCORRECT statement about GVHD-associated dry eye?
   A. It may be caused by fibrotic tissue destruction in the lacrimal grand
   B. It is more likely to occur in patients with skin or mouth involvement
   C. It is more common in women than men
   D. It is often accompanied by meibomian gland dysfunction

10. Which of the following does NOT occur during sensitization, the initiating phase of a type 1 hypersensitivity reaction?
    A. Allergen contact with mucosal membrane
    B. Phospholipid release
    C. Allergen processing by antigen presenting cell
    D. B-cell activation

EXAMINATION ANSWER SHEET

This CME activity is jointly sponsored by the University of Florida and Candeo Clinical/Science Communications, LLC, and supported by an unrestricted educational grant from Bausch + Lomb, Inc. Mail to: University of Florida CME Office, PO Box 100233, Gainesville, FL 32610-0233. DIRECTIONS: Select the one best answer for each question in the exam above (Questions 1–10). Participants must score at least 80% on the questions and complete the entire Evaluation (Questions 11–16) to receive CME credit. CME exam expires August 31, 2015.

ANSWERS:

1.	A	B	C	D	**6.**	A	B	C	D
2.	A	B	C	D	**7.**	A	B	C	D
3.	A	B	C	D	**8.**	A	B	C	D
4.	A	B	C	D	**9.**	A	B	C	D
5.	A	B	C	D	**10.**	A	B	C	D

EVALUATION:

1=Poor 2=Fair 3=Satisfactory 4=Good 5=Outstanding

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    Will help me improve patient care: 1 2 3 4 5
    Stimulated my intellectual curiosity: 1 2 3 4 5
    Overall quality of material: 1 2 3 4 5
    Overall met my expectations: 1 2 3 4 5
    Avoided commercial bias/influence: 1 2 3 4 5
13. Will the information presented cause you to make any changes in your practice? Yes No
14. If yes, please describe: _____
15. How committed are you to making these changes? 1 2 3 4 5
16. Are future activities on this topic important to you? Yes No

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