Prophylaxis and Treatment of Seasonal Allergic Conjunctivitis

RICHARD W. YEE, MD  Treatment of seasonal allergic conjunctivitis can be improved by knowing regional and seasonal allergen patterns, making judicious use of allergen avoidance and preventive therapies, and collaborating with allergists and other specialists.

Allergic eye disease may affect upwards of 30% of the population, with seasonal allergic conjunctivitis (SAC) being the most common form. SAC follows a predictable pattern for most affected patients and, while it is typically transient, can significantly affect quality of life. The clinical picture—red, swollen, itchy eyes—can be complicated by other ocular surface issues, such as dry eye, blepharitis, or even infection; thus careful history and slit-lamp exam are vital for differential diagnosis and optimal management.

SAC is a type I hypersensitivity reaction mediated by immunoglobulin E (IgE). In sensitized individuals, exposure to seasonal allergens (grass or tree pollen, outdoor molds) initiates a rapid cascade of events: allergen particles bind to and crosslink IgE on mast cell surfaces, allowing the release of early-phase inflammatory mediators, namely histamine. Continued IgE activation causes further disruption of mast cell membranes and the generation of other inflammatory mediators (eg, prostaglandins and leukotrienes) that contribute to the late-phase allergic response, in which more inflammatory cells are recruited and eosinophils, basophils, and neutrophils infiltrate the tissue.

Perennial allergic conjunctivitis (PAC), like SAC, is a type I hypersensitivity reaction, often triggered by animal dander, dust mites, and other allergens that are present year-round. More serious allergic eye diseases, such as vernal keratoconjunctivitis (VKC) and atopic keratoconjunctivitis (AKC) constitute type IV (delayed) hypersensitivity reactions, mediated by T cells, and may be chronic or seasonal in nature; VKC and AKC can cause severe papillary hypertrophy and corneal scarring. Correctly differentiating among these diseases helps facilitate optimal treatment.

CONFIRMING SAC

The hallmark signs and symptoms of SAC (rapid onset of itching, tearing, and redness) can also apply in other ocular surface conditions. For example, itching, to varying degrees, is reported by some patients with dry eye disease (DED), blepharitis, or infectious conjunctivitis.

In SAC, itching is typically severe and localized to the eyelids and inner canthal region. At the slit lamp, diffuse conjunctival hyperemia is present, often associated with lid edema and tenderness, but there is usually no corneal involvement. In some cases, depending on the severity of itching, there may be associated physical trauma exacerbating the findings of the eyelids, and even the cornea, in the form of punctate epithelial erosions.

Because the red eye is a diagnostic challenge, it is essential to determine at the slit lamp what type of conjunctival

See INSIDE for:
The Potential Complications of Topical Antiinflammatory Agents
by Victor L. Perez, MD
reaction is evident. A pale, boggy appearance to the bulbar conjunctiva, and small, elevated nodules (papillae) on the palpebral conjunctiva are typical of SAC. Though it can be challenging, it is useful to differentiate papillae from the follicular reaction often seen on the palpebral conjunctiva of patients with viral infections (See box, Papillae vs Follicles).

Medical and family history are key to determining an allergic, and more specifically seasonal, presentation. Ask about prior experience of seasonal or perennial allergy, involving the sinuses, airways, skin, or even digestive tract: this may take the form of asthma, allergic rhinitis, bronchitis, eczema, or food allergies. SAC may be associated with other systemic allergic reactions (eg, rhinitis), or the eyes may be the only or most prominently affected system.

More than one disease mechanism may be at play in any acute red eye presentation. For example, a chronic follicular conjunctivitis and an allergic reaction could be present simultaneously. More severe forms of ocular allergy, such as AKC or VKC, should be suspected where there are significant symptoms, papillary reaction, copiousropy discharge, and corneal involvement, as well as other atopic conditions.

ALLERGEN AWARENESS AND AVOIDANCE

SAC is distinguished from PAC on the basis of its allergen triggers, and most patients, with a little prompting, will be able to identify the time(s) of year when they experience symptoms.

It behooves clinicians to know about the seasonal patterns in their areas and to be attentive to predictions of weather, pollen, and mold levels. Where I practice, in southeast Texas, it is allergy season for much of the year; but we generally know that around February and August, we need to start preparing patients with SAC for the onslaught of pollens to come in March and September.

Beyond what patients are able to piece together by observing the annual timing of their symptoms, specific testing by an allergist can provide more targeted avoidance and even treatment.

TOPICS IN OCULAR ANTIINFLAMMATORIES, ISSUE 22

STATEMENT OF NEED

The control of ocular inflammation is a critical aspect of medical and surgical ophthalmic practice. Despite their side effects, antiinflammatory drugs are used to treat a wide variety of diseases, both inside and outside the eye, from ocular surface disease and allergic conjunctivitis to posterior segment conditions. Use of antiinflammatory agents is also critical in oculary surgery, contributing greatly to patient comfort and positive outcomes.

The ocular antiinflammatory landscape is changing as research reveals more about the role of inflammation in a range of ocular conditions and as new antiinflammatory agents enter the market. Twenty years ago, for example, the idea of using a topical corticosteroid to treat dry eye and/or allergic conjunctivitis was viewed with alarm; today, it is accepted practice.

Although corticosteroids and nonsteroidal antiinflammatory drugs (NSAIDs) have been the mainstays of the ocular antiinflammatory armamentarium, a number of new agents with novel mechanisms of action (and new ocular drug delivery systems) have come to market or are being made ready for market.

As indications expand and change, and as new drugs, formulations, and delivery systems become available, clinicians require up-to-date protocols for drug selection and use. Such protocols are also needed for routine (but nevertheless off-label) uses of corticosteroids and NSAIDs because important differences in efficacy, safety, and tolerability exist between these classes and among formulations within each of these classes.

By putting the latest published evidence into the context of current clinical practice, Topics in Ocular Antiinflammatories equips ophthalmologists to maintain competencies and narrow gaps between their actual and optimal inflammation management practices, across the range of clinical situations in which current and novel ocular antiinflammatories may be used.

REFERENCES


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strategies. I recommend ophthalmologists align themselves with a trusted allergist to refer appropriate patients for skin testing. In addition, some in-office skin tests are becoming available for use in eye care practices. However, allergists may provide a more detailed battery of tests and can help treat associated systemic allergies.

Armed with knowledge from the allergist and tools such as pollen and mold trackers (the American Academy of Allergy, Asthma & Immunology’s National Allergy Bureau is a good resource), patients can begin to prepare themselves for allergy season before it starts.

STRATEGIC SEASONAL PROPHYLAXIS

When thinking about preventive treatment for SAC, the most important thing is to know the local climate and when the seasonal allergy peaks tend to be. Again, in our area, we start thinking about the spring allergy season around Valentine’s Day, in anticipation of peak pollen counts in March; but somewhere like Milwaukee might not hit this peak until May. Knowing these patterns, we can guide patients to initiate SAC prophylaxis with a topical and/or systemic mast cell stabilizer before the allergy season peaks.

This is also when specific knowledge of allergic triggers is particularly useful: in addition to medical prophylaxis strategies, patients can be encouraged to watch pollen or mold counts and take more concerted avoidance measures, such as wearing wraparound sunglasses, washing hair at the end of the day, and administering artificial tears frequently.

I often liken the ocular surface to a car’s windshield, which can become visibly coated with tree pollen in the springtime; and I tell patients to look for ways to keep that windshield clear—either by blocking allergens physically, eg, with a scarf and sunglasses, or even contact lenses, or by diluting them with artificial tears. When using antiallergy medications, patients can be advised to “rinse” their eyes with artificial tears before instilling the active antiallergy agent, especially when coming in from outdoors and feeling acutely symptomatic.

Indeed, in addition to recommending avoidance strategies, a prescription for acute or prophylactic SAC treatment is best accompanied by reminders about nonpharmaceutical therapies. Artificial tears and cold compresses have been shown to improve allergic conjunctivitis symptoms and signs (as compared with no treatment, in a controlled adverse environment study). In this same study, researchers demonstrated that cold compresses measurably enhanced the pharmaceutical effect of the topical antihistamine/mast cell stabilizer epinastine.5

AVAILABLE AGENTS

Topical ophthalmic antihistamines and mast cell stabilizers are among the most common SAC treatments. Most newer topical antihistamines selectively block the H1 histamine receptor, inhibiting the effects of histamine that has already

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been released; while mast-cell stabilizers work earlier in the allergic cascade, to prevent mast cell degranulation. Dual-acting agents (such as epinastine, olopatadine, bepotastine besilate, and alcaftadine) have a relatively rapid onset of effect and are good first-line options for patients who are acutely symptomatic and in the midst of allergy season.¹⁰

Newer dual-acting agents also carry the advantage of less frequent dosing (once or twice daily) than single agents.⁶ The authors of a systematic review published in 2015 noted that in general, topical antihistamines and mast cell stabilizers are safe, well tolerated, and effective in reducing symptoms and signs of SAC and PAC; but heterogeneity of outcome measures and statistical methods made comparison between different agents difficult.⁷

Topical nonsteroidal antiinflammatory drugs (NSAIDs) can be used to treat allergic conjunctivitis and have a demonstrated effect on itching and redness.⁸ NSAIDs inhibit the production of cyclooxygenase (COX) enzymes and the production of prostaglandins, and as such, operate fairly late in the allergic cascade.

Topical corticosteroids, while broadly effective, can usually be reserved for more severe, prolonged allergic conjunctivitis presentations; most cases of SAC can be managed with avoidance/supportive measures and antihistamine/mast cell stabilizers. Oral or intranasal corticosteroids may be appropriate for patients with severe, refractory SAC and involvement of other systems.⁷ Loteprednol etabonate 0.2% (which is indicated for SAC) or fluorometholone 0.1% may be used on a short-term basis to quell an acute flare. Relative to other corticosteroids, these may pose a lower risk of IOP elevation, but a short course and careful monitoring are nonetheless warranted. Loteprednol etabonate has also been studied and used for SAC prophylaxis.¹⁰

Other topical ophthalmic immunomodulatory agents, such as cyclosporine 0.1% or 0.05% and tacrolimus 0.1%, have been investigated for the treatment of allergic conjunctivitis—again, for severe/refractory cases or AKC/VKC patients.⁵⁻⁹ Patients with other autoimmune/inflammatory diseases, managed in conjunction with a rheumatologist or other provider, may be treated with systemic immunosuppressive agents; very rarely, those with severe atopic conditions affecting multiple systems may be treated with apheresis.¹¹

Another preventive approach with the potential to impact SAC is immunotherapy, administered subcutaneously or sublingually, with the goal of desensitizing the immune system to a specific allergen. Again, working with an allergist, patients who are affected by concomitant systemic reactions to a specific allergen may be good candidates for this approach, in conjunction with other therapies.

RISKS
SAC is important to manage, not only because it can be significantly disruptive for patients’ lives, but also because of more serious potential consequences and associations. Severe itching may prompt more eye rubbing, which may exacerbate the progression of corneal ectatic disorders in predisposed patients. Indeed, there is a known association between allergic conjunctivitis and keratoconus; a recent large case-control study found the prevalence of ocular allergy was significantly higher in patients with keratoconus than controls, and allergic conjunctivitis and VKC were significantly associated with keratoconus severity.¹²

Eye rubbing may also cause corneal epithelial trauma and introduce microorganisms onto the ocular surface. The presence of corneal epithelial erosions and mucous discharge in a case of SAC may prompt additional monitoring and treatment with antibiotic drops if secondary bacterial infection is suspected. The use of NSAIDs in patients with corneal defects is often avoided due to concerns about ulceration and melting.¹³

Like any inflammatory ocular surface condition, over the long-term, untreated allergic conjunctivitis could potentially lead to changes of the eyelid margins, scarring of the conjunctiva, and loss of goblet cells.¹⁴

LOOKING AHEAD
Most cases of SAC can be managed successfully using available ophthalmic agents. To the degree that allergen triggers can be known and predicted, prophylaxis strategies can significantly help patients control SAC symptoms and minimize their impact. More severe, multisystem allergies, treated in conjunction with an allergist, immunologist, or rheumatologist, might benefit from recent advances in targeted immunosuppressant drugs.

Ophthalmic agents in development specifically for allergic conjunctivitis include small molecule inhibitors and biologics.¹⁵,¹⁶ A proprietary topical formulation of high-concentration hypochlorous acid is currently being evaluated in a phase 2 study for the treatment of allergic conjunctivitis.¹⁷

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YEE REFERENCES continue on page 7
The Potential Complications of Topical Antiinflammatory Agents

VICTOR L. PEREZ, MD  Topical antiinflammatory agents are associated with side effects of varied severity and frequency of occurrence. Understanding what these side effects are and how they can be minimized is vital for informed decision-making in managing inflammatory ocular surface disorders.

Inflammation is characteristic of a wide variety of ocular surface diseases. These range from blepharitis, dry eye disease (DED), and allergies to more serious entities such as Stevens-Johnsons syndrome, ocular cicatricial pemphigoid, and chemical or thermal burns. Unlike most other body tissues, inflammation of the ocular surface is easily visible. This, and the fact that the eye is directly accessible as the target organ, are perhaps two underlying factors that drive the heavy use of such topical antiinflammatory agents as corticosteroids in eye care.

While topical antiinflammatory agents are important therapeutic tools in managing ocular surface disorders, one major limiting factor in their clinical applications is their potential adverse events. Systemic side effects may be rare with topically applied agents, but local complications are not uncommon, especially when long-term treatment is required. Here, we discuss the side effects associated with ophthalmic antiinflammatory agents and the appropriate preventive strategies.

CURRENT OPTIONS

Currently available ophthalmic antiinflammatory agents fall into three distinct therapeutic groups: corticosteroids, nonsteroidal antiinflammatory drugs (NSAIDs), and T-cell inhibitors. Each has its mode of action and therapeutic roles.

Corticosteroids remain the most effective and also the most commonly used therapies against ocular inflammatory diseases. They act rapidly and broadly as inhibitors of phospholipase A2 and affect gene expression pathways. Nonsteroidal antiinflammatory agents (NSAIDs) are thought to inhibit prostaglandin synthesis by blocking cyclooxygenases (COX) 1 and 2—enzymes downstream to phospholipase A2. They work more effectively as analgesics than as antiinflammatory agents. Topical NSAIDs are known for their use in ameliorating postsurgical pain and discomfort; their role in nonsurgical eye care is relatively limited.

T-cell inhibitors are steroid-sparing immunosuppressants that specifically target T lymphocytes, which are believed to be a perpetrator of inflammatory tissue damage in DED and other chronic ocular surface diseases. The first successful topical T-cell inhibitor was cyclosporine (0.05%), a calcineurin inhibitor approved for use in patients where tear production is presumably suppressed by inflammation associated with DED. Topical cyclosporine is also prescribed as a treatment for contact lens intolerance, vernal or atopic keratoconjunctivitis, limbal stem cell dysfunction, and autoimmune ocular inflammatory disease.

The latest addition to the category of topical T-cell inhibitors, in 2017, is lifitegrast (5.0%), a small molecule integrin antagonist approved for the treatment of the signs and symptoms of DED. Both cyclosporine and lifitegrast are presumed to exert antiinflammatory effects primarily by inhibiting T-cell activation and production of inflammatory cytokines, albeit through different molecular pathways. Lifitegrast may also have the potential to block recruitment of T cells to the ocular surface, another critical step in the cycle of T-cell-mediated inflammation in DED.

THE SIDE EFFECTS

Corticosteroids are efficient antiinflammatory therapies, but with their clinical efficacy comes the risk for serious adverse effects. Theoretically, any form of antiinflammatory therapy that suppresses the local immune response of an already compromised ocular surface could weaken host defense and increase the susceptibility to microbial infection. Of the three antiinflammatory types, topical corticosteroids are the main drug class that has been associated with an increased risk of infections, presumably as a result of their potent and broad actions (Figure 1). Other potential complications of corticosteroids include elevated intraocular pressure (IOP), cataract formation, and delayed wound healing. Topical NSAIDs are less potent than corticosteroids as antiinflammatory therapies, but they also have a less significant side effect profile. The most common side effects of ophthalmic...
NSAIDs are mild and transient and include burning, stinging, and conjunctival hyperemia. Additionally, topical NSAIDs are associated with various forms of corneal toxicity, including superficial punctate keratitis, subepithelial infiltrates, and epithelial defects. One particularly severe complication that has historically been linked to topically applied NSAIDs is corneal melting. Following the spike in corneal melting cases among patients undergoing routine cataract and refractive surgeries in the 1990s, the use of topical NSAIDs declined. Although most of the cases back then involved use of a generic formulation of diclofenac, and subsequent clinical studies suggest that corneal melting likely has a multifactorial etiology and rarely occurs with newer NSAIDs.

By comparison, topical T-cell inhibitors as a drug class are considered safer, with only minor side effects. The most frequently reported adverse effects of topical cyclosporine and lifitegrast are stinging and burning upon instillation. More a matter of tolerability than of safety, such side effects rarely lead to discontinuation of treatment. Of course, lifitegrast has been on the market for far less time than cyclosporine, and it is likely that real-world clinical experience will give new insight into its safety profile. Based on the currently available evidence, lifitegrast, like cyclosporine, is not associated with any serious complications, even in long-term use.

APPLICATIONS IN DED THERAPY

Inflammation has been recognized as a key pathogenic factor in DED and therefore an important disease component to treat. Because DED is chronic in nature and long-term corticosteroid therapy is inclined to produce side effects, topical corticosteroids are most appropriate for short-term “pulse” treatment of acute exacerbations. Marsh and Pflugfelder first demonstrated such use of topical corticosteroids in a small clinical study published in 1999. They showed that 2 weeks of corticosteroid therapy (topical nonpreserved methylprednisolone, dosed three to four times a day) is highly effective in improving signs and symptoms of dry eye associated with Sjögren’s syndrome—a finding consistent with the notion that inflammation is a key pathogenic factor in chronic DED. Among those receiving prolonged therapy, however, the researchers encountered corticosteroid-related complications, including IOP elevation and cataract formation.

The T-cell inhibitors, considered a safer alternative to corticosteroids for the absence of serious side effects in their antiinflammatory actions, have been widely used as a first-line antiinflammatory therapy for the treatment of DED. Symptom-wise, lifitegrast seems to have a more rapid onset of effect than cyclosporine: clinical studies show that patients receiving the treatment have noticed symptom relief in as early as two weeks. It is speculated that underlying the faster relief of symptoms is lifitegrast’s potential to inhibit T-cell recruitment as well as T-cell activation.

The role of topical NSAIDs in the treatment of chronic DED is still an open question. These nonsteroidal agents do not produce severe side effects over extended use as corticosteroids do, but they are not as efficacious either. When they are used, they are used more as analgesics—to address discomfort and pain associated with DED rather than inflammation.

MITIGATING THE RISKS

To get the most therapeutic benefit from antiinflammatory therapies, clinicians need to know not only what the potential side effects are but also how to minimize their impact. As already mentioned, tolerability is in general of greater concern than safety with long-term use of the topical T-cell inhibitors. For patients with chronic DED, a brief course of topical corticosteroid therapy preceding the introduction of cyclosporine treatment has been found to improve the latter’s efficacy while decreasing stinging or burning that often occur upon instillation of cyclosporine eye drop and in severe cases can result in discontinuation of therapy. Since topical NSAIDs are associated with potential deleterious effects on the ocular surface, patients may require closer follow-up during treatment, especially if they already have compromised corneal epithelial integrity.

Although topical corticosteroids are associated with serious ocular side effects, judicious usage can minimize the occurrences. Generally speaking, it is prudent to keep the dose low and the duration of treatment short for all corticosteroid regimens. In addition, patients need to be educated about what to watch for (eg, cataract) and, once therapy starts, to be closely monitored.

In the general population, about one-third of adults are “steroid responders,” who will experience significant increases in IOP with the use of topical corticosteroids. If the patient has a documented history of IOP increase in response to corticosteroid therapy or a family history of glaucoma, the clinician must then weigh in the higher risk for IOP elevation in treatment decisions. Clinicians might consider

CORE CONCEPTS

- Inflammation plays a role in many forms of ocular surface disease.
- Antinflammatory agents from different therapeutic classes have pronounced differences in the potential for side effects. Minimizing the occurrence of side effects is a key aspect of effective antinflammatory therapy.
- Corticosteroids can be safely used in chronic DED as short-term induction therapy prior to initiation of long-term cyclosporine treatment.
- While topical NSAIDs have a better side effect profile than corticosteroids, as antinflammatory agents they have a limited role in the management of ocular surface disorders.
- Topical T-cell inhibitors, including cyclosporine and lifitegrast, are a safe first-line antinflammatory therapy for chronic DED with few side effects. Their long-term use is most often associated with tolerability rather than safety concerns.
agents known to have a lower likelihood of adverse effects, eg, loteprednol etabonate, which has been shown to cause no significant IOP elevation or cataract formation when used as a long-term therapy for DED patients. 22-24 Or maybe it is best to avoid corticosteroids altogether and resort to the nonsteroidal alternatives.

Reduction of side effects is one main focus of the current effort made in developing novel ophthalmic antiinflammatory therapeutics. A nanoparticle formulation of loteprednol etabonate promises to enhance ocular exposure for the corticosteroid by increasing its retention and penetration across the ocular surface. With the new formulation, it may be possible to achieve inflammation control with lower doses and decreased potential for side effects. The successful use of topical T-cell inhibitors like cyclosporine and lifitigast has encouraged exploration of local immunomodulatory agents, such as biologic molecules that antagonize critical proinflammatory cytokines. By acting more selectively, it is hoped that they will deliver effective antiinflammatory action with less side effects.

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YEY REFERENCES continued from page 4
1. How is immunotherapy for SAC administered?
   A. By subconjunctival injection
   B. Sublingually
   C. By subcutaneous injection
   D. Both B and C

2. Which of the following statements is true about topical NSAIDs?
   A. They are more effective in pain relief than in inflammation control
   B. Their most common side effect is corneal melting
   C. They serve as a safer alternative to corticosteroids in DED therapy
   D. They inhibit prostaglandin synthesis

3. Ideally, a discussion and initiation of SAC prophylaxis would take place:
   A. 6 months before season typically peaks
   B. 1 month before season typically peaks
   C. 1 week before season typically peaks
   D. Immediately after seasonal symptoms begin

4. Lifitegrast is:
   A. A calcineurin inhibitor
   B. An integrin antagonist
   C. An analgesic
   D. None of the above is true

5. Which of the following is the most common side effect of topical cyclosporine?
   A. Stinging upon instillation
   B. IOP elevation
   C. Infections
   D. Conjunctival hyperemia

6. Which of the following agents is NOT appropriate for SAC prophylaxis?
   A. Cyclosporine 0.1%
   B. Loteprednol etabonate 0.2%
   C. Bepotastine besilate 1.5%
   D. Epinastine HCL 0.05%

7. Which of the following describes the role of topical corticosteroids in the management of chronic DED?
   A. Repeated pulse therapy for exacerbations
   B. Long-term maintenance antiinflammatory therapy
   C. Induction therapy prior to initiation of cyclosporine treatment
   D. Both a and c

8. Which of the following may have an adjunctive benefit to pharmaceutical treatment of SAC?
   A. Wearing sunglasses
   B. Using cold compresses
   C. Administering artificial tears
   D. All of the above

9. Approximately what percent of the general population will experience a significant elevation in IOP in response to topical corticosteroids?
   A. 10%
   B. 20%
   C. 30%
   D. Greater than 50%

10. Papillae are:
    A. Vascularized nodules
    B. Pathognomonic for SAC
    C. Always found on the inferior tarsal conjunctiva
    D. Generally unilateral