Topics in OCULAR ANTIINFLAMMATORIES

A CONTINUING MEDICAL EDUCATION PUBLICATION

ISSUE 18

Managing Inflammation in Patients with Serious Allergic Conditions of the Ocular Surface

JAY S. PEPOSE, MD, PhD

The two most serious allergic conditions of the ocular surface are vernal keratoconjunctivitis (VKC) and atopic keratoconjunctivitis (AKC) due to their tissue remodelling and sight-threatening potential. Although both conditions may be managed using mast cell-stabilizing, antihistamine, or corticosteroid agents—with varying degrees of success depending upon disease severity—new agents capable of modifying the allergic response in a more targeted manner are needed.

Allergic conditions of the ocular service include several clinically diverse conditions with different forms of pathogenesis, hypersensitivity mechanisms, and diagnostic criteria, although an individual allergic condition of the ocular surface is characterized by a single or dominant presentation of a local, allergic sensitization.[1] Ocular allergies are a common problem, with approximately 15% to 20% of the global population being affected by some form of allergic disease. Of those affected, it is estimated that 40% to 60% have ocular symptoms, which may progress to have a negative impact on patient quality of life.[2-4]

Ocular allergy encompasses the two acute disorders of seasonal allergic conjunctivitis (SAC) and perennial allergic conjunctivitis (PAC), as well as the more serious chronic conditions of vernal keratoconjunctivitis (VKC) and atopic keratoconjunctivitis (AKC). All of these conditions are characterized by early acute phase inflammation of the ocular surface resulting in itching, tearing, conjunctival and lid edema-redness and photophobia. In some individuals, this may progress to the late phase responses of eosinophilia and neutrophilia. Chronic disease, which can develop in some patients, is associated with tissue remodeling of the ocular surface and, in severe cases, sustained damage.[5] Ocular allergy is often associated with other allergic conditions, and thus optimal management may require the involvement of both an ophthalmologist and an allergist.

DIAGNOSING SERIOUS OCULAR ALLERGY

An accurate medical history and a clinical examination are fundamental to determining if the patient has acute or chronic allergic conjunctivitis. VKC is a condition most commonly observed in hot, dry environments such as West Africa, parts of India, and Mexico.[6] In the US, it mostly occurs during the warmer months of spring and summer in children and young adults. Typically observed more frequently in males than females (at a ration of 3:1), VKC usually resolves at puberty. The reasons for this variance in incidence with age and geographical region remain unclear. Symptoms include intense itching, tearing, and photophobia but may progress to mucous

See INSIDE for:
Inflammation Control in Corticosteroid Responders
by Ronald M. Caronia, MD, FACS

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. Recognize the signs and symptoms of AKC and VKC and the underlying mechanisms involved in the inflammatory response.
2. Know the current management practices for the treatment of AKC and VKC.
3. Understand the risk of steroid response for different patient groups and types of medication.
4. Outline postsurgical management strategy to control IOP and inflammation.

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discharge and, in some instances, reactive ptosis and blepharospasm. The tarsal form of VKC commonly involves the upper tarsus with the development of cobblestone papillae.[1] Through excessive rubbing against the upper lid, these papillae may result in the development of shield ulcers and plaques on the cornea. The limbal form of VKC is seen in subtropical countries and characteristically has transient, multiple conjunctival yellow-grey infiltrates with overlaying white deposits (Horner-Trantas dots) and papillae at the limbus.[1]

AKC occurs equally between the sexes. Onset occurs in young adults and continues through to the fifth decade of life, with a peak incidence between the ages of 30 to 50 years. This chronic condition, which can develop at any time of the year, is characterized by persistent inflammation involving the eyelids, the conjunctiva, and sometimes the cornea. The lower tarsus is often involved with patients showing cicatrization (this may be so severe as to be associated with entropion or ectropion) and persistent epithelial defects that have vision-threatening potential. Other features may include madarosis or trichiasis, keratoconus and/or subcapsular cataract, and peripheral neovascularization. Patients often present with atopic dermatitis and/or asthma.[6] Interestingly, AKC is a risk factor for developing herpes simplex keratitis, which typically presents unilaterally while in patients with AKC often presents bilaterally.

INFLAMMATORY MECHANISMS

The mechanisms underlying severe ocular allergy are complex and involve the upregulation of multiple pro-inflammatory mediators that cause breakdown of the corneal epithelial cell barrier. In the case of VKC, IgE-mediated mechanisms are involved in approximately 50% of patients.[7] Increased numbers of CD4+ Th2 cells, costimulatory molecules, and multiple chemokines and cytokines all act synergistically to enhance ocular surface production of IgE,[8] leading to corneal impact and tissue remodelling.[9,10] Potent T-cell-mediated responses are also observed for VKC in association with a massive infiltration

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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 very wide range of conditions throughout the eye, from ocular surface disease and allergic conjunctivitis to posterior segment conditions. Use of antiinflammatory agents is also critical in ocular 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.[1,2] 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 anti-inflammatory 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.[3,4]

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.[5,6]

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.

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of macrophages, neutrophils, and eosinophils, the latter of which plays an important role in producing eosinophilic-derived factors (notably eosinophil cationic protein) that are cytotoxic to the corneal epithelium.[1] The involvement of matrix metalloproteinases MMP-1 and MMP-9 also contributes to the enzymatic degradation of the corneal basement membrane and stroma. In many patients, non-IgE-mediated activation pathways are present, confirming the complexity of this condition.[6]

AKC is associated with alterations of the mucous component of the tear film and leads to mucous discharge, epithelial disease, dry eye signs/symptoms, and reduced tear film stability.[11] It is thought that mechanisms linked to the activation of innate immunity receptors play a key role in the chronic inflammatory response that occurs.[12] In the case of AKC, specific allergen(s) are likely involved, and an accurate medical history and allergy testing is advised to identify allergen(s) to which the patient is sensitized. Both a genetic predisposition to atopy and environmental allergens/irritants may be implicated.[6] Although 45% of patients do not have any specific sensitization, high serum IgE levels and polysensitization are often found.[13] In addition, it is believed that Th1- and Th2-lymphocyte-mediated mechanisms may be involved in AKC.[14,15]

MANAGING OCULAR INFLAMMATION

Management of ocular allergy typically includes allergen avoidance, an air-conditioned environment, pharmacological treatment, immunotherapy, and patient education. The use of artificial tears may enhance the function of the ocular surface barrier, and cold compresses often give relief from symptoms.[1]

With AKC, treatment options include topical ophthalmic drops (mast cell stabilizers, antihistamines, corticosteroids, calcineurin inhibitors), topical ointments (ophthalmic corticosteroids, calcineurin inhibitors), and systemic medications (antihistamines, corticosteroids, calcineurin inhibitors).[16] Topical mast cell stabilizer ophthalmic drops (cromoglycate and lodoxamide 0.1%) are effective as first-line treatments due to their ability to block histamine release from mast cells and are primarily used as maintenance therapy in chronic disease. The use of agents that have both mast cell-stabilizing effects and H1 receptor-blocking effects can be effective, particularly in cases where single-acting agents fail.[16]

Topical corticosteroids are usually required to control severe signs and symptoms of AKC.[17] The use of topical cyclosporine 2% has been observed to effectively reduce the amount of topical corticosteroid needed to treat severe AKC,[18-20] while topical cyclosporine A 0.05% may be effective in alleviating signs and symptoms in cases that are refractory to topical steroid treatment.[21] Supratarsal injection of a corticosteroid may also be considered in sight-threatening cases of AKC.[22] In cases where systemic disease accompanies the presentation of AKC, treatment of the disease with systemic medications may be very helpful. AKC is a complex condition and the choice of therapy needs to be individualized for each patient.

Patients with mild VKC disease may be managed with allergen avoidance and use of lubricants, antihistamines, and mast cell stabilizers. For those with more serious disease, the use of repeat short-term therapy with topical corticosteroids is advised, if needed. Maintenance treatment can include a topical cyclosporine (1%) or a tacrolimus ointment (0.03%).[6,23] Patients should be informed of the potential complications of corticosteroid therapy with the aim being to minimize corticosteroid use. Systemic immunosuppression is rarely needed for the management of VKC. For cases in which there is eyelid involvement, pimecrolimus cream 1% or topical tacrolimus ointment may be applied.[24,25] Tacrolimus ointment 0.03% may be used for children aged 2 years to 15 years and either 0.03% or 0.1% for patients aged 16 years and older.[26]

Patients with blinding disease may require the continuous use of potent steroids in addition to the above-stated therapies, although use should be judicious to avoid further epithelial degradation and complications such as infection, cataract, and glaucoma.[23] Either cyclosporine drops 2% or tacrolimus ointment (0.03%, or 0.01% available in Japan) can be used as adjuncts. These patients may also need supratarsal steroids and debridement of any shield ulcers, and some patients may require systemic steroids to treat highly refractory inflammation.[23]

CORE CONCEPTS

- The two most serious allergic conditions of the ocular surface are AKC and VKC.
- When chronic, these diseases can result in ocular surface tissue remodeling and threaten sight.
- First treatment choice should include topical antihistamines, mast cell stabilizers, or double-action medications.
- When the cornea is involved, topical corticosteroids should be used as short, pulsed therapy.

FUTURE THERAPIES

Lifitegrast ophthalmic solution 5%, which is currently indicated in the US for the treatment of dry eye,[27] is under investigation for the treatment of allergic conjunctivitis (NCT00882687). This product is a novel, small molecule, integrin antagonist that blocks the binding of intercellular adhesion molecule 1 (ICAM-1) to lymphocyte function-associated antigen 1 (LFA-1). In addition, mapracorat is under investigation for the prevention of allergic conjunctivitis (NCT01289431). This new type of antiinflammatory is a selective glucocorticoid receptor agonist designed with similar antiinflammatory and immunosuppressive effects as the glucocorticoids but with a decreased potential of the steroid side effects.[28]

Certainly, new investigational products that target specific immunomodulation of the T-cell-mediated response or have targeted vasoconstriction and anti-histamine effects would be valuable additions to the therapies currently available to treat serious ocular allergy.

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Inflammation Control in Corticosteroid Responders

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Corticosteroids are highly effective at controlling inflammation after cataract removal or glaucoma surgery. However, the risk of elevated intraocular pressure and steroid-induced glaucoma requires balancing the benefits with the potential complications.

CORE CONCEPTS

- Diagnosis or family history of glaucoma are the strongest risk factors for high-level steroid response.
- Possible mechanisms may involve changes to cytoplasm, inhibition of phagocytosis, prostaglandins, or mutations in MYOC.
- Different corticosteroids have different propensities to elicit a response.
- Inflammation should be treated quickly with steroids and then tapered as soon as possible.
- Treatment strategies should take into account patient history, and the level of IOP elevation, including health of the optic nerve.

Increases in intraocular pressure (IOP) due to topical corticosteroids have been reported in approximately one third of the general population, with 5% of the population exhibiting high-level responses.[1,2] Elevated IOP carries the risk of damage to the optic nerve and, although IOP will usually return to normal after withdrawal of steroids, secondary glaucoma ensues in up to 4% of patients.[3]

The criteria for a high-level steroid response are an IOP of greater than 31 mm Hg[1] or an increase of more than 16 mm Hg above baseline[4] following topical steroid application. In practice, the health of the patient's optic nerve should be considered when deciding how to treat a steroid response. A patient with a healthy optic nerve will be able to tolerate an elevated IOP for a short time while inflammation is being controlled; whereas for a patient who has optic nerve damage, even a relatively small increase may require prompt intervention.[3]

RISK FACTORS FOR STEROID RESPONSES

More than 90% of patients diagnosed with primary open-angle glaucoma (POAG) will exhibit a high-level steroid response.[1,2] Patients with a first-degree relative with POAG are also at increased risk,[2] with 19% of patients whose parents were diagnosed with POAG reported to be high-level responders.[1]

Other risk factors include diabetes, (62.5% of responders[5]) connective tissue disease such as rheumatoid arthritis (35% of responders, including 15% of high-level responders, who were notably all male[6]) and myopia (21.9% of patients with axial length greater than 29 mm were steroid responders[7]). There is conflicting evidence regarding the relationship between age and steroid response, with evidence that children under 10 and older adults are at greater risk;[2] and another study showing an inverse relationship between age and steroid response.[7]

Risk factors for persistent IOP elevation include a family history of POAG and steroid use for more than 4 years.[8] One can speculate that patients with elevated IOP that does not resolve after withdrawal of steroids had previously undiagnosed POAG exacerbated by steroid treatment.

MECHANISMS OF STEROID RESPONSE

The mechanism underlying the steroid response has not yet been completely elucidated. Several possible mechanisms have been proposed (Figure 1) and some or all of these mechanisms may be involved. One possibility is that corticosteroids reduce aqueous outflow through the trabecular meshwork (TM) by increasing the deposition or decreasing the degradation of the extracellular matrix.[9] Excess glycosaminoglycan accumulates in the TM of steroid responders and in cultured cells exposed to dexamethasone.[9] Dexamethasone also affects the structure of F-actin and causes contraction of TM cells, reducing the intercellular space available for aqueous flow. TM cells are phagocytic and remove debris from the TM. Dexamethasone inhibits phagocytosis by TM cells, which could result in reduced clearing of debris and increased IOP as the trabecular outflow channels become blocked.[2,8]

Genetic factors including myocilin (MYOC) have been implicated in the steroid response. MYOC is expressed in TM cells, and mutations causing defective MYOC secretion lead to decreased trabecular outflow.[2] Overexpression of glaucoma-causing mutants of human MYOC induces raised IOP in mice[10] and MYOC is strongly upregulated after dexamethasone exposure.[11] Mutations affecting expression and secretion of the product of the mucin-encoding gene HCG22 were identified as potentially pathogenic in steroid-induced elevations in IOP,[12] and an additional 14 genes induced by dexamethasone in human TM cells have been identified in genomic regions associated with glaucoma.[13]

Another potential mechanism of the steroid response is inhibition of prostaglandin activity. Prostaglandins are part of the inflammatory cascade, and prostaglandin analogues are effective in reducing IOP.[9] Prostaglandin production is inhibited by dexamethasone in cultured human TM cells,[14] so it is possible that reduced prostaglandin production in the TM of steroid responders could contribute to elevated IOP.

PROPENSITY FOR STEROID RESPONSE WITH DIFFERENT DRUGS

Both the type of corticosteroid and the duration of usage

influence the risk of a steroid response in the patient. Difluprednate and 1% prednisolone acetate are both highly effective in reducing inflammation.[15] Clinical experience suggests that difluprednate is the steroid that is most likely to elicit a response, and IOPs of 40 mm Hg to 50 mm Hg can occur by day 4 or 5 after surgery. IOP increases of up to 17.8 mm Hg above baseline in 5% of patients have been reported, with 60% of responses occurring on day 1 after surgery.[16] Steroid responses can also be induced by prednisolone acetate but usually to a lesser degree than with difluprednate.[8,9,15] Methylprednisolone, which is used in the treatment of inflammatory dry eye disease, can cause increased IOP and requires careful monitoring when used for more than two weeks.[17]

Steroid responses are less common with loteprednol etabonate, which is rapidly metabolized following glucocorticoid receptor activation.[18] A meta-analysis comparing IOP elevation due to loteprednol etabonate and prednisolone acetate revealed a significantly smaller incidence of clinically significant IOP elevation in patients treated with loteprednol etabonate (3.4% versus 11.3%; $P < 0.001$).[19]

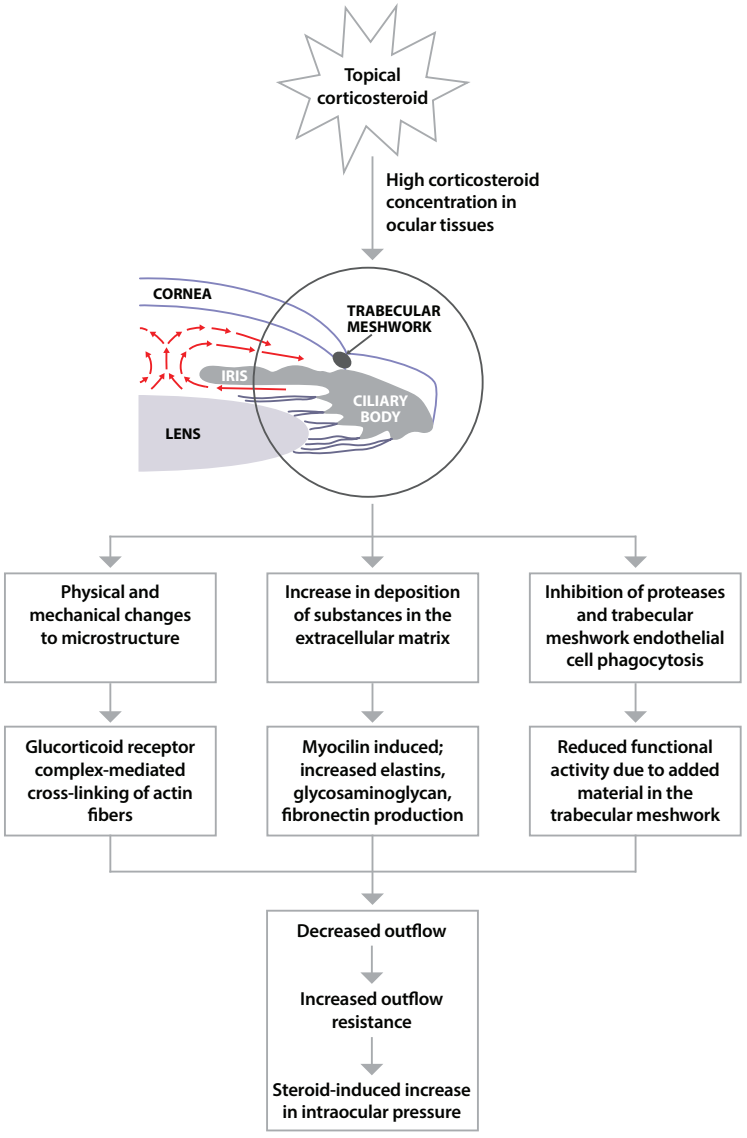

FIGURE 1 Proposed mechanisms underpinning the steroid response.

BALANCING IOP AND INFLAMMATION

For most patients, including suspected steroid responders, the recommended strategy is to treat inflammation aggressively and taper the steroids as soon as possible. Postoperative inflammation after cataract surgery or many minimally invasive glaucoma surgery (MIGS) procedures is usually limited and can be controlled quickly. After conventional glaucoma surgery, difluprednate can be used QID or 1% prednisolone acetate every 2 hours to effectively control inflammation, based on clinical experience. For MIGS and cataract procedures, difluprednate can be used BID or 1% prednisolone acetate QID.

In many cases, the patient can either be tapered off steroid drops and treated with NSAIDs or moved to milder steroids before elevated IOP becomes a concern. Conventional glaucoma surgeries are inherently more inflammatory and steroid drops are necessary for longer periods to suppress inflammation and minimize scarring, which can jeopardize the long-term success of the surgery. With patients who need topical steroids for an extended period and for whom a steroid response is likely, beta-blockers, carbonic anhydrase inhibitors, or an alpha agonist such as brimonidine are effective for controlling IOP.[2] Prostaglandin analogs and miotics may be effective in situations where further reductions in IOP are needed, but are not recommended as first-line treatments because of their inflammatory properties, and should be avoided in uveitic patients.[2,20]

It is important to ascertain whether IOP is elevated because of a steroid response or continued inflammation. A good approach is to continue with steroid treatment and control the elevated IOP medically with topical and/or systemic carbonic anhydrase inhibitors. Systemic steroids can also be used, especially short term to control inflammation in a pulse style treatment. Lower dose prednisolone acetate or alternative corticosteroids such as loteprednol etabonate are other options that potentially allow control of both inflammation and IOP. Once the inflammation is controlled, inflammatory etiology of elevated IOP will be eliminated. At this time, steroids can be tapered.

POSTOPERATIVE MONITORING

The frequency of postoperative monitoring depends on the patient's optic nerve health and IOP. As a general guideline, for a patient with an IOP of 20 mm Hg to 30 mm Hg and a healthy optic nerve, especially if it is confirmed by optical coherence tomography (OCT), monitoring on day 1, week 1, and week 3 is probably acceptable. For patients with higher IOP (30 mm Hg to 50 mm Hg), and preexisting optic nerve damage, follow-up visits after 1 or 2 days are recommended. An extended consultation might be necessary to treat and monitor

IOP. The timing of the follow-up visit should be decided upon based on the examination results.

Steroid medications can also be delivered via intraocular injections or slow-release implants. These approaches are effective in controlling inflammation, are convenient for the patient, and remove any issues with patient compliance.[21] Treatment of steroid responses, however, can be more challenging because of the difficulty in removing residual steroid. Implant removal may be effective,[2] but when steroids have been injected into the eye, treatment could require anterior chamber washout to remove residual steroid.

One possible approach to treating sustained elevated IOP is selective laser trabeculoplasty (SLT). The effectiveness of SLT has been tested in patients with elevated IOP following subtenon and intravitreal steroid injections, resulting in a greater than 50% reduction in IOP after 9 months.[22] On rare occasions incisional surgery might be required to control persistent IOP elevation that is refractory to other approaches.

Treatment with biologic agents and antimetabolites, in collaboration with a uveitis specialist or a rheumatologist, are other options for managing inflammation that can't be controlled by steroids or to allow steroids to be tapered when a steroid response is developing. Methotrexate, which inhibits rapidly dividing cells, and mycophenolate, which selectively targets B and T lymphocytes, are well established agents for controlling ocular inflammation.[23] B cells can also be targeted with the monoclonal antibody rituximab and TNFα, an inflammatory cytokine, can be targeted by a soluble receptor (etanercept) or monoclonal antibody (infliximab, adalimumab).[23]

OTHER CAUSES OF ELEVATED IOP

Alternative causes of postsurgical elevated IOP should be investigated in addition to steroid responses. Viscoelastic agents are known to decrease outflow facility, and insufficient removal at the end of surgery can cause elevated IOP in the early postoperative period.[24] Trabecular precipitates, cellular debris, and inflammation of the TM can also decrease trabecular outflow.[25] Elevated IOP after cataract surgery is more likely in patients who also have glaucoma, perhaps because their TM is already compromised and cannot tolerate the additional insult from cataract surgery. The elevated IOP may not be secondary to steroid use, but to already compromised TM. Aqueous misdirection syndrome occurs most commonly after surgery for angle-closure glaucoma but can also occur after routine cataract surgery; it presents as a shallow anterior chamber with raised IOP.[26]

Elevated IOP following conventional glaucoma surgery and MIGS can have the same etiology as for cataract surgery. An additional cause of elevated IOP after trabeculectomy is overtightening of the flap sutures, which restricts outflow.[27] All glaucoma procedures can have short term fluctuations in IOP, in addition to early and late failure to control IOP.

CONCLUSION

Perhaps the most important aspect of treating potential steroid responders is to be aware of the risk of a steroid response occurring. Considering the patient's history will prepare you to effectively control a response should it occur. NSAIDS and cyclosporine are useful for treating inflammation; using them in combination might be considered as an alternative to steroid treatment. However, these drugs are less effective than steroids and, in most cases, changes in dose or type of steroid will result in lower IOP. Monitor the patient after surgery and treat the problem accordingly. This will prevent the sequelae of a steroid response which can lead to a major, debilitating condition for the patient.

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1. Which of the following antiinflammatory therapies is recommended to treat vernal keratoconjunctivitis (moderate disease)?
   A. Topical timolol
   B. NSAID
   C. Topical lubricant
   D. Short-term therapy with topical corticosteroids

2. The underlying pathogenesis of vernal keratoconjunctivitis may include:
   A. Ig-E-mediated mechanisms
   B. Infiltration of macrophages, neutrophils and eosinophils
   C. Eosinophil cationic protein and MMP-9
   D. All of the above

3. Which one of the following statements is NOT correct about atopic keratoconjunctivitis?
   A. It develops during spring and is self-limiting
   B. It occurs equally between the sexes
   C. Patients often have dermatitis and may have asthma
   D. Ectropion or entropion may be observed

4. Rapid steroid responses have been reported most frequently with:
   A. Loteprednol etabonate
   B. 1% prednisolone acetate
   C. Difluprednate
   D. 0.1% prednisolone acetate

5. Possible mechanisms for the steroid response include:
   A. Increased glycoasaminoglycans and reduced phagocytosis
   B. Decreased glycosaminoglycans and reduced phagocytosis
   C. Increased intercellular space
   D. Excess prostaglandin activity

6. Which one of the following statements is NOT correct about vernal keratoconjunctivitis?
   A. It occurs in children and young adults
   B. It affects more females than males
   C. It is more common in hot, dry environments and with upper tarsus involvement
   D. Typical symptoms include intense itching, tearing, and photophobia

7. Which one of the following pathological changes may be found on the ocular surface of patients with vernal keratoconjunctivitis?
   A. Reduced mucin production
   B. Disrupted barrier function of the intact corneal epithelium
   C. Shield ulcer on the cornea
   D. All of the above

8. A high-level steroid response has been reported in what proportion of POAG patients?
   A. 62%
   B. 21.5%
   C. more than 90%
   D. 35%

9. Other potential risk factors for high-level steroid response include:
   A. Myopia
   B. Diabetes
   C. Family history of glaucoma
   D. All of the above

10. What are the criteria for a high-level steroid response?
    A. IOP greater than 31 mm Hg
    B. IOP rise of more than 31 mm Hg above baseline
    C. IOP rise of more than 16 mm Hg above baseline
    D. A or C

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