

Modern Approach to Managing Vernal Keratoconjunctivitis

Sunil Kumar · Nitin Gupta · Anthony J. Vivian

© Springer Science+Business Media, LLC 2010

Abstract Vernal keratoconjunctivitis (VKC), an allergic inflammation of the conjunctiva affecting mainly children and adolescents, is categorized under the rubric of allergic conjunctivitis. Lack of uniform diagnostic and predefined staging criteria has been a bottleneck in formulating fixed guidelines to treat VKC. This lack of consensus among clinicians/researchers regarding diagnostic and grading standards has prevented us from making comparisons between the outcomes of different studies. To treat VKC, selection of a drug from many available options should be based on the duration and frequency of symptoms, grade and inflammation of giant papillae, and severity of corneal involvement. Consideration also should be given to the patient's specific needs. The basic tenet of treatment is optimal control of symptoms with a minimum of toxic side effects resulting from prolonged use of medication.

Keywords Vernal keratoconjunctivitis · Giant papillae · Mast cells stabilizer · Selective antihistamine · Dual-action drugs · Corticosteroids · Cyclosporine

S. Kumar (✉)
Toronto Western Hospital,
5th Floor West Wing, 339 Bathurst Street,
Toronto, Ontario M5T 2S8, Canada
e-mail: sunkaru79@hotmail.com

N. Gupta
West Suffok Hospital NHS Trust,
Hardwick Lane,
Bury St Edmunds IP33 2QZ, UK
e-mail: riniku2000@yahoo.com

A. J. Vivian
Cambridge and Eye Treatment Centre, Cambridge University
Hospitals, Addenbrookes Hospital,
Bury St Edmunds, UK
e-mail: vivianeye@aol.com

Introduction

Vernal keratoconjunctivitis (VKC) is a chronic, bilateral, at times asymmetrical, seasonally exacerbated allergic inflammation of the ocular surface involving tarsal and/or bulbar conjunctiva [1••]. Onset is usually in childhood. It is more common in boys than girls and usually resolves by late-adolescence. In its mildest form, it is an annoying, intermittent conjunctivitis, but in severe cases, it may cause significant, lifelong visual impairment due to involvement of the cornea. The allergic nature of VKC has been accepted for a long time, but more recent studies have convincingly shown that the mechanism of inflammation is much more complex than a mere type 1 hypersensitivity reaction. In addition to mast cells and eosinophils, T-helper type 2 cells and their cytokines, corneal fibroblasts, epithelium, and various growth factors play an important role in the pathogenesis. Elucidating the pathogenic mechanisms has provided new targets of intervention beyond the current mainstay of symptomatic treatments directed against histamine receptors. More selective drugs, such as anti-chemokine receptor antibodies and human monoclonal antibodies targeting eotaxin-1, are under evaluation. The beneficial role of leukotriene receptor antagonists approved for other conditions may provide potential therapeutic options for VKC. Cyclosporine has been effective in the treatment of VKC, but further trials are required to establish the minimum effective concentration.

Diagnosis of VKC

No precise diagnostic and prognostic criteria have been established for VKC. In its early stages, it may mimic seasonal or perennial allergic conjunctivitis, and the only

distinguishing feature in VKC may be the presence of large papillae. Diagnosis is based on typical clinical signs and symptoms; thus, many mild or atypical cases are diagnosed erroneously as seasonal allergic conjunctivitis or episcleritis.

VKC affects mainly children and young adults. Patients present with pruritus, hyperemia, watering, and thick mucus hypersecretion called *ropy discharge*. Presentation is typically bilateral, although minor differences in severity between the two eyes are common. Photophobia, pain, and foreign body sensation suggest involvement of the cornea.

Signs of VKC are confined mostly to the conjunctiva and cornea. Large papillae form on the tarsal surface of the upper lid and on bulbar conjunctiva, predominantly around the limbus. Limbal papillae tend to be confluent and gelatinous. Based on the predominant involvement of tarsal or bulbar conjunctiva, VKC can be divided into palpebral, bulbar, and mixed type. Yellow-white points, known as *Horner-Trantas' dots*, are degenerating eosinophils and epithelial debris and appear transiently on limbal conjunctiva. In atypical cases, perilimbal pigmentation and dirty-looking conjunctiva favor the diagnosis of VKC. Corneal changes include punctate epithelial keratitis, epithelial macroerosions, and shield ulcer. Corneal vascularization is a late manifestation of the condition. The skin of the lid and lid margin are relatively uninvolved, and the conjunctiva of the fornices do not usually show foreshortening or symblepharon formation. Iritis is not reported to occur in VKC.

Management of VKC

The variety of currently available drugs to treat VKC includes antihistamines, mast cell stabilizers, dual-acting agents, corticosteroids, and immunomodulators (Table 1). Our insight into the pathogenesis of VKC has improved, but application of this knowledge to the development of targeted therapeutic agents has been slow. Despite extensive progress in the field of VKC pharmacotherapy, thus far, no single medication is enough to treat the entire multifaceted pathophysiology of VKC. Currently available drugs are merely palliative and do not extinguish the complex immune process initiating and perpetuating the allergic ocular surface inflammation. Thus, recurrence is common when therapy is discontinued.

To address the ambiguity in staging criteria, Bonini et al. [2•] proposed a clinical grading of VKC. In a meta-analysis of randomized clinical trials on topical treatments for VKC, only 10 of 21 were suitable for statistical analysis, and the authors concluded that the currently available topical drugs are effective in treating acute phases of VKC [3•]. However, there is a lack of evidence to support one treatment over another in the management of this disorder. As few comparable randomized controlled trials have been con-

Table 1 List of drugs used to treat vernal keratoconjunctivitis

Vasoconstrictor and nonspecific histamine blocker combination drops
Vasoconstrictors
Naphazoline
Tetrahydrozoline
Nonspecific histamine receptor blockers
Pyrilamine
Pheniramine
Mast cell stabilizers
Sodium cromoglycate
Nedocromil
Lodoxamide
Pemirolast
H1-receptor blockers
Levocabastine
Emedastine
Systemic antihistamines
Dual- or multiple-action drugs
Olopatadine
Ketotifen
Azelastine
Epinastine
NSAIDs
Diclofenac sodium
Ketorolac
Corticosteroids
Topical
Supratarsal injection
Immunomodulators
Cyclosporine
Antimetabolites
Mitomycin-C

ducted, more often than not, the selection of a drug from the many available options is based on the personal experience and preference of the treating physician. More randomized controlled trials assessing the long-term effects of single medication in controlling the disease will be helpful in formulating guidelines to treat VKC.

Patient Education and Preventive Measures

Compliance with medication improves if patients are well-informed. Education of patients and parents about the chronic, recurrent and ultimately resolving nature of VKC is a very important aspect of management. Exposure to nonspecific stimuli causes frequent conjunctival redness among VKC patients. Avoiding provocative triggers such as sun, wind, and saltwater is helpful, but it is not enough to control the symptoms. Contact with commonly known

allergens such as plants, flowers, and animals should be avoided. Use of sunglasses or any shading measures is helpful and should be advised. Applications of preservative-free artificial tears have been shown to be effective in relieving symptoms by direct removal and dilution of allergen from the ocular surface [4]. Rubbing the eye should be avoided, as this leads to mast cell disruption and increases the severity. Cold compresses provide symptomatic relief, especially from ocular pruritus. Frequent hand, face, and hair washing—especially before going to bed—may be helpful [5].

Patient information leaflets including the information listed in Table 2 can help patient compliance.

Pharmacologic Therapy

VKC, a seasonal event initially, evolves into a relentless, perennial disease in most patients with passage of time and burns out around the end of puberty. Twenty-five percent of VKC patients exhibit perennial inflammation of conjunctiva without any remission from the outset.

Judicious use of medication cannot be overemphasized because drug treatment is prolonged and frequent. In some patients, medication needs to be used throughout the year to achieve satisfactory control of symptoms. At times, the complications resulting from prolonged unsupervised medication outweigh the benefit of tight control of symptoms.

Topical Vasoconstrictor and Nonspecific Histamine-receptor Blocker Combinations

Vasoconstrictor and nonspecific antihistamine combination eyedrops have long been available and have withstood the test of time in the management of allergic eye disease. They contain vasoconstrictors such as naphazoline or tetrahydrozoline and antihistamines such as pyrilamine or pheniramine. These drops are safe and effective, at least temporarily. Because of their over-the-counter availability, many patients try these during the early stage of the disease as first-line treatment. By virtue of their vasoconstrictor and nonspecific antihistamine constituents, they relieve itching and reduce redness. Burning or stinging on installation and rebound hyperemia are common side effects with these drugs. They

also exhibit tachyphylaxis (shorter duration of effect with prolonged use).

At present, these nonspecific combination eyedrops have little role to play in the management of VKC, as more efficacious drugs with fewer side effects are available. In cases of longstanding VKC, conjunctival hyperemia may persist even though the patient is asymptomatic. Frequent and prolonged use of topical vasoconstrictors to treat conjunctival hyperemia may lead to acute/chronic conjunctivitis and preservative-induced epithelial toxicity [6].

Mast Cell Stabilizers

Mast cell degranulation is a central event in VKC, and the main therapeutic interventions have been aimed at preventing this degranulation or antagonizing the effects of the histamine released by mast cells. Mediators released by mast cells are responsible for many symptoms and signs associated with VKC. Drug modulation of mast cell activity alleviates the acute symptoms of active disease and reduces the cytokine stimulus for the development of chronic allergic inflammation [7].

The drugs of this group act primarily by stabilizing mast cell membranes and prevent degranulation, probably by blocking calcium channels. The efficacy of sodium cromoglycate (four times daily), lodoxamide (four times daily), nedocromil (twice daily), and pemirolast (four times daily) in the control of symptoms and prevention of exacerbation has been demonstrated by many studies [8–10].

Cromolyn (4%), the prototype mast cell stabilizer, has been prescribed to treat ocular allergy for the past 25 years. Sodium cromoglycate is nontoxic and is excreted unchanged in bile and urine. It can be used for long periods without side effects but takes several days to reach full effect. Relief of symptoms is not immediate, as it does not antagonize already released histamine [11]. Sodium cromoglycate may have a synergistic effect in combination with a corticosteroid in the treatment of VKC [12].

The antiallergic properties of mast cell stabilizers in VKC are not limited to their action on mast cell membrane. Studies have shown that lodoxamide decreases CD4 cells and inflammatory cells, especially eosinophils, in conjunctiva. Nedocromil (2%), in addition to stabilizing mast cells,

Table 2 Information to include in patient information leaflets on VKC to help compliance

1. VKC is a chronic, recurrent condition that usually improves by adulthood.
2. Although your eyes are itchy, try to avoid rubbing them, as this makes the condition worse.
3. The application of cold compresses and the frequent application of preservative-free artificial tears help to provide symptomatic relief.
4. Frequent hand and face washing is important to reduce exposure to allergic factors that make the condition worse.

VKC vernal keratoconjunctivitis

inhibits the chemotaxis, activation, and mediator release from other inflammatory cells.

Lodoxamide was found to control the symptoms and signs of VKC better than cromolyn sodium (4%) and levocabastine [13–15]. Pemirolast, a pyridopyrimidine compound with mast cell-stabilizing properties, is effective in treating allergic conjunctivitis. Nedocromil sodium and lodoxamide were shown to be superior to sodium cromoglycate in the treatment of VKC. A meta-analysis of the efficacy of topical mast cell stabilizers in the treatment of seasonal allergic conjunctivitis found insufficient evidence to recommend one drug over another [16]. We find in clinical practice that it is worth trying different mast cell stabilizers in VKC if one fails before abandoning this group of drugs altogether.

Mast cell stabilizers are the first line of defense in VKC if symptoms are seasonal. In a patient with a history of seasonal symptoms typical of VKC and large papillae, treatment should be started at the onset of the allergic season and used continuously throughout the season. If monotherapy with mast cell stabilizers is not enough to prevent the symptoms, these should be substituted or supplemented with H1-receptor blockers.

Sodium cromoglycate is the drug of choice for children younger than 3 years of age for preventing exacerbation of symptoms of VKC, as most other drugs are not recommended in children younger than 3 years of age.

Systemic Antihistamines

Concurrent allergy of the nose and pharynx is not uncommon in patients with VKC. Oral antihistamines are a good choice when allergy involves the eyes, nose, or pharynx simultaneously, but when allergic complaints are limited to the eyes, focused therapy with topical selective antihistamines is preferable to avoid the systemic effects of oral antihistamines. Topical antihistamines provide faster and superior relief compared with systemic antihistamines and possess longer duration of action than topical vasoconstrictors, pure mast cell stabilizers, NSAIDs, and corticosteroids, the drugs commonly used to treat ocular allergy.

Selective H1-Receptor Blockers

The topical selective H1-receptor blockers, emedastine and levocabastine, are superior to vasoconstrictor/nonspecific antihistamine combination eyedrops in controlling the signs and symptoms of VKC.

Levocabastine (0.05%) is a potent topical antihistamine with rapid and prolonged selective anti-H1-receptor activity. Many studies have shown it to be effective in treating seasonal allergic conjunctivitis compared with placebo. Emedastine

(0.05%) is a relatively selective H1-receptor blocker with no apparent effects on adrenergic, dopaminergic, or serotonin receptors. Emedastine inhibits cytokine production by conjunctival epithelial cells [17]. The anti-inflammatory effect seen with selective H1-receptor blockers is attributed to the blocking of histamine receptors, thus downregulating the expression of intercellular adhesion molecule (ICAM)-1 and limiting chemotaxis of inflammatory cells [18]. The enhanced clinical efficacy of emedastine and levocabastine over first-generation antihistamines may be the result of the inhibitory effects of new-generation antihistamines on the proinflammatory cytokines produced by conjunctival epithelial cells.

H1-receptor blockers as sole agents are effective drugs in treating bulbar or palpebral VKC with minimal or no corneal involvement. If symptoms are not hampering day-to-day activity, patients may require only this intervention to control symptoms. These are quite effective in relieving ocular pruritus and reducing conjunctival hyperemia. H1-receptor blockers can be combined with corticosteroids and play an important role as steroid-sparing agents in the treatment of severe VKC.

Dual-Action Drugs (H1-Receptor Blocker and Mast Cell Stabilizer)

Recently, a new generation of drugs was developed with the dual action of mast cell stabilization and H1-receptor antagonism. Fast H1-receptor-blocking action, along with mast cell stabilization makes them suitable for twice-daily dosing. The action of these drugs is not limited to mast cell stabilization and H1-receptor antagonism. These drugs also exert anti-inflammatory effects through several different mechanisms (hence the new name *multiple-action drugs*).

Olopatadine (0.1%) is a selective H1 antagonist with mast cell-stabilizing properties. In addition to stabilizing mast cells, olopatadine affects the release of tumor necrosis factor- α and various cytokines from conjunctival epithelial cells, thus controlling the allergic inflammation more effectively than the other topical antihistamine formulations [19]. It decreases the mucus discharge in VKC by reducing the goblet cell density in the conjunctiva [20]. Ketotifen (0.025%) is a selective noncompetitive blocker of the H1 receptor. Besides mast cell stabilization and H1-receptor antagonism, it prevents eosinophil accumulation. Ketotifen has been shown to inhibit the release of inflammatory mediators from basophils and eosinophils, chemotaxis, leukotriene activity, and platelet activation, and also to decrease vascular permeability. Epinastine (0.05%) is an H1-receptor antagonist with mast cell-stabilizing and anti-inflammatory activity. Azelastine (0.05%) is a selective H1-receptor antagonist that inhibits histamine

release. It downregulates ICAM expression, reduces eosinophil chemotaxis, and inhibits platelet-activating factors.

Dual-action drugs are a promising alternative to corticosteroids in the treatment of moderate bulbar, palpebral, or mixed-type VKC. These drugs counter the already released histamine by blocking its receptor and prevent the further release of histamine. This dual action takes care of the lack of immediate relief with mast cell stabilizers and lack of sustained relief observed while using H1-receptor blockers. As these drugs, in addition to action on mast cell membranes and histamine receptors, target various other cells and mediators, other drugs of this group should be tried if one fails to bring the desired palliation.

Dual-action drugs should be tried if itching, hyperemia, watering, and mucus discharge persist more and less throughout the day with mild superficial epithelial keratitis. If these are not enough, corticosteroids should be added to dual-action drugs for a few days. Once the symptoms are controlled on this combination regimen, corticosteroids should be tapered, and dual-action drugs should be given for 4 to 6 weeks or longer.

NSAIDs

Topical formulations of ketorolac and diclofenac diminish itching and conjunctival hyperemia associated with allergic conjunctivitis. In a prospective, open study, preservative-free diclofenac (0.1%) eyedrops reduced the symptoms of VKC through the inhibition of prostaglandin production in 40% of patients. Although the conjunctival hyperemia was reduced significantly, the papillary size and corneal lesions remained unchanged [21].

NSAIDs can be tried in a patient with mild symptoms that do not disturb the routine, in whom corneal involvement is mild or absent and giant papillae are not inflamed. NSAIDs, which act by modulating pruritogenic prostaglandin E_2 and I_2 pathways, may be a good alternative if H1-receptor blockers or dual-action drugs are insufficient in controlling the symptoms of VKC. [22].

Corticosteroids

Despite the development of newer drugs in the past decade and safety concerns about the prolonged use of corticosteroids, topical corticosteroids remain the most effective option to control severe VKC. Persistent severe symptoms, thick mucoid discharge with moderate to severe corneal involvement, and inflamed giant papillae necessitate the use of corticosteroids.

The mainstay of treatment has been topical dexamethasone or prednisolone. Recently, however, modified steroids

such as loteprednol etabonate and rimexolone have been developed with a superior safety profile.

Loteprednol is highly effective in the acute and prophylactic treatment of allergic conjunctivitis. In a retrospective study, loteprednol etabonate was shown to be safe and effective when used for 12 months or more for the treatment of seasonal or perennial allergic conjunctivitis [23]. Rimexolone, a derivative of prednisolone, is inactivated quickly in the anterior chamber. Fluorometholone is a weak corticosteroid, but it is effective in controlling the signs and symptoms of VKC. Desonide phosphate has been shown to be as effective as fluorometholone in the treatment of allergic conjunctivitis [24].

Studies have shown that supratarsal injection of dexamethasone sodium succinate, triamcinolone acetonide, and hydrocortisone sodium succinate is effective in the temporary suppression of inflammation associated with VKC [25–27]. The resolution of the limbal form of the disease was more dramatic than the palpebral form [27].

Treatment of severe VKC can be divided into two phases: short-term intensive therapy to treat exacerbation of inflammation and long-term maintenance therapy to maintain the palliation achieved by intensive therapy. In the acute phase, topical steroids can be started alone or in conjunction with dual-action drugs and preservative-free artificial tears. Once symptoms are controlled, topical steroids can be tapered off and treatment with dual-action drugs continued.

Short periods of frequent instillation of steroids (preferably modified steroids with a better side effect profile) followed by maintenance of palliation by dual-action drugs or an H1-receptor blocker is an effective and safe strategy. Depending on symptoms and signs, steroid treatment may have to continue for prolonged periods.

Corticosteroids should be avoided as the first line of defense in the treatment of VKC. Prolonged, unsupervised application of corticosteroids may cause steroid-induced cataracts and glaucoma and increase susceptibility to viral and fungal infections. Modified corticosteroids are preferred over prednisolone or dexamethasone because these have low propensity to cause glaucoma and other steroid-induced side effects. Supratarsal injection of corticosteroids can be used to treat VKC if corneal involvement is severe and refractory to topical treatment [28]. Steroid-antibiotic combination eyedrops should be avoided, as VKC is an allergic inflammation, not an infection.

The patient should not be allowed to use corticosteroid eyedrops unsupervised or be given a prescription for unlimited refills. Patients and their families must understand that the effects of corticosteroids are cumulative and that these should be used in moderation. Although corticosteroids are the most efficacious drugs, steroid-resistant

forms of VKC are not unusual and may necessitate an alternative therapy.

Immunomodulators

Cyclosporine, a fungal metabolite, decreases the signs and symptoms of VKC. BenEzra et al. [29] used topical cyclosporine (2%) in oil solution to treat severe VKC. Cyclosporine is lipophilic, so it must be dissolved in an alcohol–oil base, which causes ocular irritation. Cyclosporine (0.5%–2%) emulsion in olive or castor oil, instilled four times daily, was shown to be effective in treating VKC. More than two decades have passed since the first report of a beneficial effect of topical cyclosporine in VKC; a commercial preparation of cyclosporine in a vehicle better than oil to treat VKC is still awaited.

Clinical improvement in VKC after cyclosporine treatment may result from its immunomodulating effect on components of cell-mediated and humoral immune response [30]. Cyclosporine blocks T-helper type 2 cell proliferation and interleukin-2 production. Furthermore, it inhibits histamine release through a reduction in interleukin-5 production [31, 32]. Accelerated apoptosis induced by cyclosporine in fibroblast cultures obtained from a patient with VKC suggests a potential role for this drug in hyperproliferative conjunctival disorders such as VKC [33].

In double-blind, placebo-controlled trials, cyclosporine (2%) eyedrops were effective and safe in the treatment of severe VKC [34, 35]. In a prospective study of 10 patients with severe VKC, topical cyclosporine (2%) significantly reduced the clinical signs and symptoms. The reduction of CD4 and CD28 cell populations on the conjunctival surface after treatment with cyclosporine can be responsible for clinical improvement in VKC [36]. Cyclosporine (1%) was shown to control the symptoms of VKC, although further controlled trials are needed to find the optimum concentration of cyclosporine needed to treat VKC [37]. As until today, there is no general consensus regarding the minimum effective concentration of cyclosporine, the lesser efficacy of cyclosporine compared with other drugs may be due to a subtherapeutic concentration of cyclosporine [38].

Topical cyclosporine helps in the healing of vernal shield ulcers, but recurrences may occur at lower concentrations and can be treated by increasing the concentration [39]. Off-label use of commercial preparation of cyclosporine (0.05%) eyedrops, recommended for the treatment of dry eye, decreased the symptoms and signs of VKC [40]. Topical corticosteroids and artificial tears have been shown to act synergistically with cyclosporine (0.05%) eyedrops and help in the re-epithelialization of corticosteroid-resistant vernal shield ulcers [41]. Whether this commercially available formulation of cyclosporine is effective in the treatment of VKC needs to be tested in controlled trials.

Currently, cyclosporine is the only promising drug that can be used to replace corticosteroids in the treatment of severe VKC.

Antimetabolites

Mitomycin-C is an inhibitor of fibroblast proliferation. A beneficial role of mitomycin-C is logical in VKC, as proliferation is an important feature. Mitomycin-C (0.01%) eyedrops have been shown to decrease the mucus discharge, conjunctival hyperemia, and limbal edema in VKC refractory to topical steroids and mast cell stabilizers [42, 43].

Mitomycin-C use is compelling in recalcitrant cases of VKC that have failed all other conventional treatment. Unavailability of commercial topical preparations and short duration of studies advocating favorable outcome are major limitations in recommending mitomycin in the treatment of VKC.

Management of Shield Ulcer

Shield ulcer is a corneal manifestation of VKC. At times, treating a shield ulcer is a frustrating exercise despite the judicious use of all available therapeutic options. It requires intensive therapy by frequent instillation of corticosteroids, artificial tears, and cyclosporine. Debridement of ulcer base to remove corneal plaque followed by bandage contact lens for 24 to 48 hours can be tried if maximum medical intervention fails. Surgical or laser-assisted resection of giant papillae can be tried for superficial punctate keratitis recalcitrant to medical treatment.

Conclusions

Due to the current lack of uniform grading, it is not possible to formulate global guidelines to treat VKC. Presentation of VKC may range from mild to moderate seasonal symptoms to perennial smoldering symptoms with frequent exacerbations that affect the productivity of patients profoundly and at times may result in permanent visual impairment. Mast cell stabilizers are the drug of choice if symptoms are purely seasonal and have recurred more than once in the past. Based on past history, initiation of treatment with mast cell stabilizers prior to the onset of the provocative season may be an effective strategy. Currently available drugs, including selective H1-receptor blockers, dual-action drugs, and NSAIDs, can be prescribed to treat seasonal VKC or symptoms due to low-grade inflammation in perennial VKC. Acute exacerbation of symptoms may necessitate the use of more than one drug, and topical corticosteroids are the principal

treatment. When VKC becomes progressive and affects the cornea with a significant risk of visual loss, treatment must be timely, targeted, and aggressive.

Disclosure No potential conflicts of interest relevant to this article were reported.

References

Papers of particular interest, published recently, have been highlighted as:

•• Of major importance

1. •• Kumar S: Vernal keratoconjunctivitis: a major review. *Acta Ophthalmol* 2009, 87:133–147. *This is a comprehensive review.*
2. •• Bonini S, Sacchetti M, Mantelli F, Lambiasi A: Clinical grading of vernal keratoconjunctivitis. *Curr Opin Allergy Clin Immunol* 2007, 7:436–441. *This article introduced a new grading system based on severity of disease; a treatment plan for different grades is also discussed.*
3. •• Mantelli F, Santos MS, Petitti T, et al.: Systematic review and meta-analysis of randomised clinical trials on topical treatments for vernal keratoconjunctivitis. *Br J Ophthalmol* 2007, 91:1656–1661. *This was a meta-analysis of randomized controlled trials on the efficacy of currently available topical drugs for VKC.*
4. Bielory L: Ocular allergy guidelines: a practical treatment algorithm. *Drugs* 2002, 62:1611–1634.
5. Leonardi A: Vernal keratoconjunctivitis: pathogenesis and treatment. *Prog Retin Eye Res* 2002, 21:319–339.
6. Soparkar CNS, Wilhelmus KR, Koch DD, et al.: Acute and chronic conjunctivitis due to over-the-counter ophthalmic decongestants. *Arch Ophthalmol* 1997, 115:34–38.
7. Church MK, McGill JI: Human ocular mast cells. *Curr Opin Allergy Clin Immunol* 2002, 2:419–422.
8. Tabbara KF, Arafat NT: Cromolyn effects on vernal keratoconjunctivitis in children. *Arch Ophthalmol* 1977, 95:2184–2186.
9. Bonini S, Barney NP, Schiavone M, et al.: Effectiveness of nedocromil sodium 2% eye drops on clinical symptoms and tear fluid cytology of patients with vernal conjunctivitis. *Eye* 1992, 6:648–652.
10. Caldwell DR, Verin P, Hartwich-Young R, et al.: Efficacy and safety of lodoxamide 0.1% vs cromolyn sodium 4% in patients with vernal keratoconjunctivitis. *Am J Ophthalmol* 1992, 113:632–637.
11. Sorkin EM, Ward A: Ocular sodium cromoglycate, an overview of its therapeutic efficacy in allergic eye disease. *Drugs* 1986, 31:131–148.
12. Dahan E, Appel R: Vernal conjunctivitis in the black child and its response to therapy. *Br J Ophthalmol* 1983, 67:688–692.
13. Leonardi A, Borghesan F, Avarello A, et al.: Effect of lodoxamide and disodium cromoglycate on tear eosinophil cationic protein in vernal keratoconjunctivitis. *Br J Ophthalmol* 1997, 81:23–26.
14. Avunduk AM, Avunduk MC, Kapicioglu Z, et al.: Mechanisms and comparison of anti-allergic efficacy of topical lodoxamide and cromolyn sodium treatment in vernal keratoconjunctivitis. *Ophthalmology* 2000, 107:1333–1337.
15. Verin P, Allewaert R, Joyaux JC, et al.; Lodoxamide Study Group: Comparison of lodoxamide 0.1% ophthalmic solution and levocabastine 0.05% ophthalmic suspension in vernal keratoconjunctivitis. *Eur J Ophthalmol* 2001, 11:120–125.
16. Owen CG, Shah A, Henshaw K, et al.: Topical treatment for seasonal allergic conjunctivitis: systematic review and meta-analysis of efficacy and effectiveness. *Br J Gen Pract* 2004, 54:451–456.
17. Weimer LK, Gamache DA, Yanni JM: Histamine-stimulated cytokine secretion from human conjunctival epithelial cells: inhibition by the histamine H1 antagonist emedastine. *Int Arch Allergy Immunol* 1998, 115:288–293.
18. Bielory L, Lien KW, Bigelsen S: Efficacy and tolerability of newer antihistamines in the treatment of allergic conjunctivitis. *Drugs* 2005, 65:215–228.
19. McGill JI: A review of the use of olopatadine in allergic conjunctivitis. *Int Ophthalmol* 2004, 25:171–179.
20. Corum I, Yenid B, Bilgin LK, Ilhan R: Efficiency of olopatadine hydrochloride 0.1% in the treatment of vernal keratoconjunctivitis and goblet cell density. *J Ocul Pharmacol Ther* 2005, 21:400–405.
21. D'Angelo G, Lambiasi A, Cortes M, et al.: Preservative-free diclofenac sodium 0.1% for vernal keratoconjunctivitis. *Graefes Arch Clin Exp Ophthalmol* 2003, 241:192–195.
22. Sharma A: Topical ketarolac 0.5% solution for the treatment of vernal keratoconjunctivitis. *Indian J Ophthalmol* 1997, 45:177–180.
23. Ilyas H, Slonim CB, Braswell GR, et al.: Long term efficacy of loteprednol etabonate 0.2% in the treatment of seasonal and perennial allergic conjunctivitis. *Eye Contact Lens* 2004, 30:10–13.
24. Leonardi A, Papa V, Milazzo G, Secchi AG: Efficacy and safety of desonide phosphate for the treatment of allergic conjunctivitis. *Cornea* 2002, 21:476–481.
25. Saini JS, Gupta A, Pandey SK, et al.: Efficacy of supratarsal dexamethasone versus triamcinolone injection in recalcitrant vernal keratoconjunctivitis. *Acta Ophthalmol Scand* 1999, 77:515–518.
26. Singh S, Pal V, Dhull CS: Supratarsal injection of corticosteroids in the treatment of refractory vernal keratoconjunctivitis. *Indian J Ophthalmol* 2002, 50:160–161.
27. Lisaneck M: Supra-tarsal injection of dexamethasone in the treatment of patients with refractory vernal keratoconjunctivitis. *Ethiop Med J* 2003, 41:19–24.
28. Holsclaw DS, Whitcher JP, Wong IG, Margolis TP: Supratarsal injection of corticosteroid in the treatment of refractory vernal keratoconjunctivitis. *Am J Ophthalmol* 1996, 121:243–249.
29. BenEzra D, Pe'er J, Brodsky M, Cohen E: Cyclosporine eye drops for the treatment of severe vernal keratoconjunctivitis. *Am J Ophthalmol* 1986, 101:278–282.
30. Abu El-Asrar AM, Tabbara KF, Geboes K, et al.: An immunohistochemical study of topical cyclosporine in vernal keratoconjunctivitis. *Am J Ophthalmol* 1996, 121:156–161.
31. BenEzra D, Matamoros N, Cohen E: Treatment of severe vernal keratoconjunctivitis with cyclosporine A eye drops. *Transplant Proc* 1988, 20:644–649.
32. Secchi AG, Tognon MS, Leonardi A: Topical use of cyclosporine in the treatment of vernal keratoconjunctivitis. *Am J Ophthalmol* 1990, 110:641–645.
33. Leonardi A, DeFranchis G, Fregona IA, et al.: Effects of cyclosporin A on human conjunctival fibroblasts. *Arch Ophthalmol* 2001, 119:1512–1517.
34. Pucci N, Novembre E, Cianferoni A, et al.: Efficacy and safety of cyclosporine eye drops in vernal keratoconjunctivitis. *Ann Allergy Asthma Immunol* 2002, 89:298–303.
35. Kilic A, Gurler B: Topical 2% cyclosporine A in preservative-free artificial tears for the treatment of vernal keratoconjunctivitis. *Can J Ophthalmol* 2006, 41:693–698.
36. Avunduk AM, Avunduk MC, Erdol H, et al.: Cyclosporine effects on clinical findings and impression cytology specimens in severe vernal keratoconjunctivitis. *Ophthalmologica* 2001, 215:290–293.

37. Spadavecchia L, Fanelli P, Tesse R, et al.: Efficacy of 1.25% and 1% topical cyclosporine in the treatment of severe vernal keratoconjunctivitis in childhood. *Pediatr Allergy Immunol* 2006, 17:527–532.
38. Kosirukvongs P, Luengchaichawange C: Topical cyclosporine 0.5 per cent and preservative-free ketorolac tromethamine 0.5 per cent in vernal keratoconjunctivitis. *J Med Assoc Thai* 2004, 87:190–197.
39. Cetinkaya A, Akova YA, Dursun D, Pelit A: Topical cyclosporine in the management of shield ulcers. *Cornea* 2004, 23:194–200.
40. Ozcan AA, Ersoz TR, Dulger E: Management of severe allergic conjunctivitis with topical cyclosporine 0.05% eye drops. *Cornea* 2007, 26:1035–1038.
41. Kumar S: Combined therapy of vernal shield ulcer: a case report. *Clin Exp Optom* 2008, 91:111–114.
42. Akpek EK, Hasiripi H, Christen WG, Kalayci D: A randomized trial of low-dose, topical mitomycin-C in the treatment of severe vernal keratoconjunctivitis. *Ophthalmology* 2000, 107:263–269.
43. Jain AK, Sukhija J: Low dose mitomycin-C in severe vernal keratoconjunctivitis: a randomized prospective double blind study. *Indian J Ophthalmol* 2006, 54:111–116.