

Individualize treatment for vernal keratoconjunctivitis based on clinical features and personal preferences

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Abstract Due to the lack of clarity regarding the pathogenesis of vernal keratoconjunctivitis, the treatment of this condition is challenging. The therapeutic regimen should be selected from among the many options (e.g. oral and/or topical mast-cell stabilizers, antihistamines, corticosteroids, and immunomodulators) based on the clinical features of the disease, personal preferences of the patient and clinical experience of the prescriber. Moderate-to-severe vernal keratoconjunctivitis may require topical corticosteroid treatment during the acute phase, followed by topical ciclosporin or tacrolimus for long-term management.

Vernal keratoconjunctivitis is an inflammatory disease...

Vernal keratoconjunctivitis (VKC) is a chronic, seasonally-exacerbated, multifactorial disease involving acute and sub-acute phases of inflammation of the ocular surface [1]. Usually classified as an allergic conjunctivitis, the disease has a prevalence of 5–15%, is more common in males, and has a wide geographical distribution (most commonly occurs in warm, dry regions, such as the Mediterranean, Central Africa, India and South America) [2–5]. In the tropics, it is particularly likely to be a perennial disease rather than occurring only in the spring [5].

VKC has a generally good prognosis; however, permanent reductions in visual acuity occur in 5–15% of patients [2, 4]. It can also detrimentally impact the health-related quality-of-life of patients, affecting school and overall personal development [5]. This article presents a summary of the pathogenesis, diagnostic criteria and therapeutic management of VKC, as outlined by Esposito et al. [2].

... with an unclear pathogenesis

The immune, nervous and endocrine systems have each been implicated in the pathogenesis of VKC [2].

In the tears and sera of patients with VKC, there is an abundance of T helper 2 (T_h2) cytokines such as interleukin (IL)-4 and IL-5, accompanied by a lack of T_h1 cytokines [1]. While VKC is an immunoglobulin E (IgE)-mediated disease, it is probable that an abnormal T_h2 lymphocyte profile, rather than an exaggerated IgE response to allergens, underlies disease development [2, 4]. VKC is also associated with increased levels of IL-8 and IL-17; further studies on the role of these cytokines in disease pathogenesis are warranted [2].

The conjunctival tissue of patients with VKC shows inflammatory cell invasion [1]. Eosinophils are present at higher levels in the tears, conjunctiva and serum of patients with VKC than in those with other ocular allergies [2]. In addition, serum eosinophil cationic protein and blood eosinophil counts appear to correlate with giant papillae severity [6]. Similarly, T lymphocytes (predominantly CD4-type cells) and mast cells are increased in the tears and conjunctiva of patients with VKC; the quantity of tryptase- and chymase-positive mast cells correlates with disease severity [7]. Increases in serum basal levels of

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high-mobility group box-1 and serum soluble receptor for advanced glycation end products are also seen [8].

An endocrine contribution to the pathogenesis of VKC is suggested by the prevalence of the disease in males, sexual hormone receptor overexpression by conjunctival eosinophils, altered neuroreceptor expression in the conjunctival epithelium of patients with VKC, as well as high levels of growth factors, neuropeptides and prostaglandins in their serum and tears [2, 9].

There may also be a genetic basis to VKC, as the prevalence of its limbal and palpebral forms differ between races [2, 10] and a high proportion of affected children have a family history of autoimmune disorders [11].

Apply diagnostic criteria

VKC is diagnosed mainly on the basis of age at onset (3–8 years in 70–80% of patients), symptoms and signs, seasonality and response to therapy [2]. Common eye symptoms include itching, discharge, tearing, eye irritation, eye redness and photophobia (due to corneal involvement), in combination with pain and foreign body sensation [1]. While symptoms often appear during the spring and persist through the summer, they may also continue throughout the year [2].

Signs of VKC at eye examination include conjunctival hyperaemia in the bulbar and/or tarsal conjunctiva; a thick, ropy, mucoid or purulent discharge; conjunctival papillae under the upper eyelid [12]; corneal changes (e.g. punctate epithelial keratitis, epithelial macro-erosions, shield ulcer, plaque formation and late corneal vascularization) [1]; acquired ptosis due to heavy giant papillae, chronic eye rubbing or an inflammatory insult [13]. Concomitant atopic diseases (e.g. asthma, allergic rhinitis, eczema) may be present [4]. Characteristically, topical and systemic antihistamines show only partial efficacy in treating VKC [2]. VKC can be distinguished from ocular allergic diseases based on characteristics such as age of onset, clinical features and the limited benefit of anti-allergic treatments [3].

Confocal microscopy is used to quantify the morphological characteristics of the conjunctiva and limbus in a non-invasive manner [14]. Most laboratory tests are of little use in confirming VKC [2]; eosinophils in conjunctival scrapings support the diagnosis but are not invariably present and skin tests in patients with vernal conjunctivitis are not always positive (50% test negative) [4].

Foster patient compliance...

The treatment of VKC is challenging, due to the pathogenesis of the disease being insufficiently elucidated [2]. Currently, no single medication is available to treat VKC,

and the available options are merely palliative and do not address the pathogenic pathways of the disease [2]. Furthermore, pharmacological treatment is protracted and may be required to be consistently used over several years [2]. The first and most crucial step in the management of VKC, therefore, involves promoting patient compliance through educating patients and their parents regarding the long duration of the disease, the efficacy and safety of different medications, the potential complications of VKC and non-pharmacological management strategies [2] (Fig. 1).

... and collaboratively select a treatment regimen

Many pharmacological options are available to treat VKC, including vasoconstrictors, mast-cell stabilizers, antihistamines, NSAIDs, corticosteroids, immunomodulators and immunosuppressive drugs (Table 1). With a lack of universal grading of VKC severity, worldwide consensus on first-line and second-line treatment is also absent [2]. Prescribers are advised to select a therapeutic scheme based on the clinical features of the disease, taking into account their clinical experience and the preferences of the patient [2].

Topical vasoconstrictors and non-specific histamine-receptor blocker combinations contain vasoconstrictors (e.g. naphazoline, tetrahydrozoline) and antihistamines (e.g. pyrilamine, pheniramine); patients often use these 'over-the-counter' drugs as first-line therapy [2]. Topical mast-cell stabilizers are first-line therapy in patients with seasonal symptoms [2] (Fig. 1). Mast-cell stabilizers reduce or prevent mast-cell degranulation, in turn reducing cytokine secretion and the recruitment of inflammation pathways [2, 15]. Through this route, they may act to prevent chronic VKC [2, 15]. Topical antihistamines are active for a longer duration than topical vasoconstrictors, mast-cell stabilizers and other eye drops containing corticosteroids and NSAIDs [16]. They relieve or prevent the symptoms of VKC through antagonizing histamine receptors [usually H₁ (e.g. levocabastine, emedastine), although some antihistamines antagonize H₂ receptors and consequently modulate the growth and migration of cells] [17, 18].

Topical corticosteroids may be required to treat VKC in the acute phase (Fig. 1); those most commonly used are dexamethasone and prednisone, although loteprednol etabonate, rimexolone and fluorometholone have emerged as options in recent years [16]. Topical NSAIDs may be valid alternatives to antihistamines and be used to reduce the use of topical corticosteroids (Table 1).

A number of topical immunomodulators [e.g. ciclosporin, tacrolimus, mycophenolate mofetil, leflunomide] have been successful in treating ocular immune-mediated

Patient care guidelines

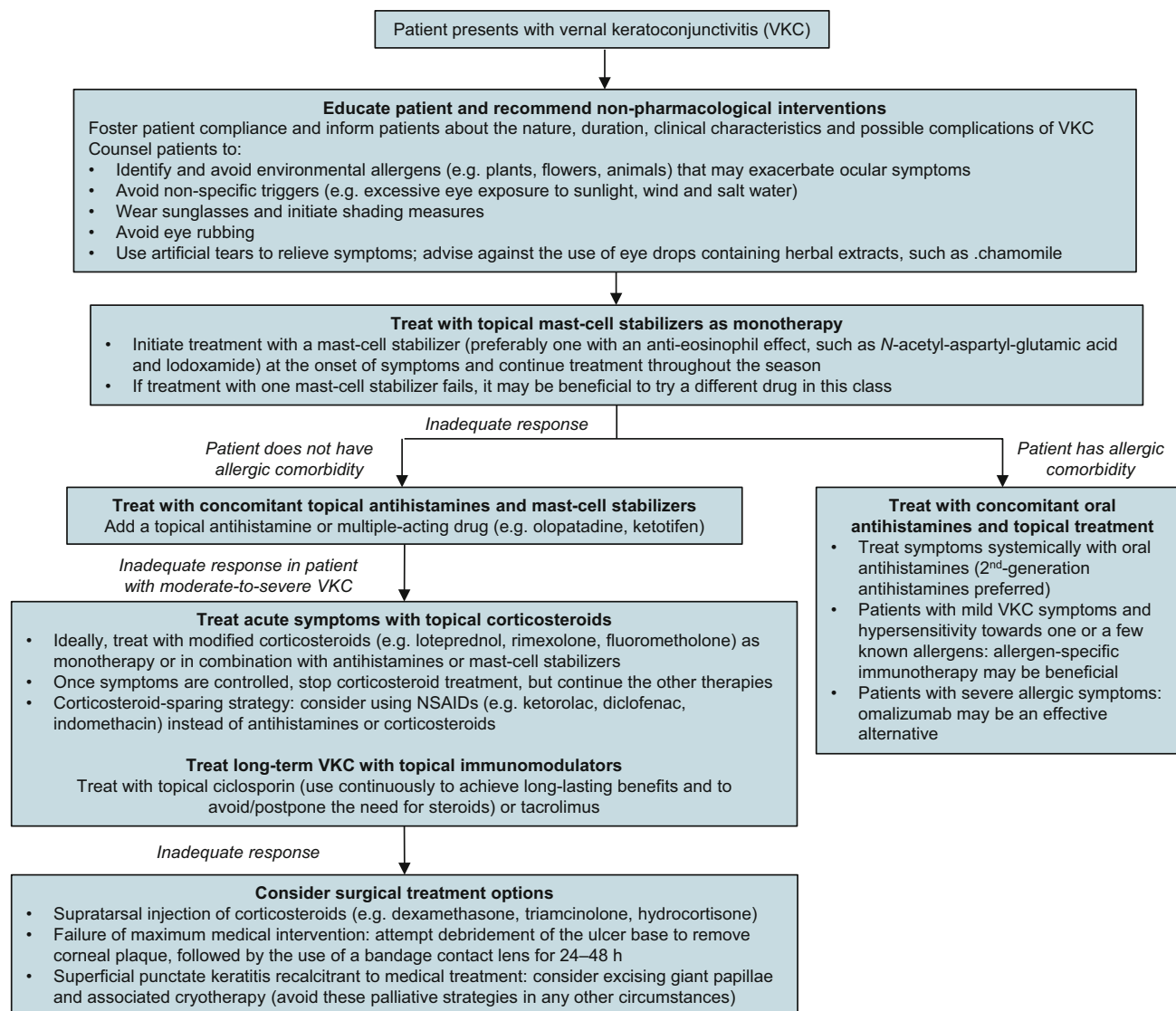


Fig. 1 Approach to the management of vernal keratoconjunctivitis, as suggested by Esposito et al. [2]

diseases [19] (Table 1). Ciclosporin inhibits the calcineurin pathway, reducing cytokine and chemokine production in inflammatory cells that play a role in VKC [20, 21]. Ciclosporin also disrupts eosinophil recruitment and the degranulation of eosinophils and basophils [20, 21]. Another macrolide antibacterial drug with immunosuppressant effects on T cells is tacrolimus, which has performed well in recent studies [31–33] and may alter the traditional treatment of VKC [2]. Further data are needed to determine the minimal effective concentration of ciclosporin and tacrolimus, their long-term safety when administered as eye drops and the clinical characteristics of patients in whom they should be used [2].

VKC may also be treated systemically (Table 1), particularly in patients with concomitant allergies (Fig. 1). Oral antihistamines are commonly used [12, 34]; other options in patients with concomitant allergic symptoms include omalizumab (a monoclonal humanized anti-IgE antibody) and allergen-specific immunotherapy (affects regulatory T cells and increases IgG4 production, which possibly indicates a drug-induced switch in Ig isotope class [12]) [2]. Supratarsal corticosteroid injections and surgery are options in patients who do not respond to pharmacological treatment (Fig 1).

Although further studies are needed, a number of new drugs appear to hold promise for the treatment of VKC and concomitant allergic symptoms (Table 1).

Table 1 Pharmacological options for treating vernal keratoconjunctivitis, as reviewed by Esposito et al. [2]

Treatment	Efficacy and adverse effects
Topical drugs	
Vasoconstrictors + non-specific histamine-receptor blockers [16, 22]	Effectively ↓ common eye symptoms, particularly in the early stages of VKC Immediate adverse effects on instillation: burning, stinging sensation and rebound hyperaemia Prolonged use may result in tachyphylaxis and acute or chronic conjunctivitis with epithelial toxicity
Mast-cell stabilizers [23]	Sodium cromoglycate: well-tolerated, but has limited efficacy and offers no immediate relief from symptoms, as it does not antagonize histamine that has already been released Nedocromil: may be more potent than sodium cromoglycate; ↓ chemotaxis and mediator release in multiple inflammatory cells (e.g. eosinophils, neutrophils, macrophages/monocytes, platelets, mast cells) Lodoxamide: induces ↑ eosinophil inhibition than sodium cromoglycate; prevents tryptase release N-Acetyl-aspartyl-glutamic acid: anti-inflammatory potential (e.g. stabilizes mast cells, inhibits leukotriene synthesis, promotes leukocyte adhesion to the endothelium and complement-derived anaphylotoxin production, antagonizes TNF- α -induced adhesion molecules); widely used in Europe
Antihistamines [17, 24, 25]	Levocabastine and emedastine: selective histamine H ₁ antagonists with better long-term effects than other antihistamines, which is perhaps due to actions additional to their antagonism of H ₁ receptors (e.g. inhibition of cytokine production and down regulation of surface/adhesion molecules, such as ICAM-1) Olopatadine, ketotifen, epinastine: act as both an antihistamine and a mast-cell stabilizer; ↓ production of TNF- α , inflammatory mediators and leukotrienes; are useful in treating VKC that is mostly seasonal; well-tolerated with no significant ocular drying effects
Corticosteroids [16, 26, 27]	Prolonged and uncontrolled use can cause cataracts, ocular hypertension, glaucoma and ↑ susceptibility to ocular infections; use drops with low intraocular absorption (e.g. desonide, hydrocortisone, clobetasone)
NSAIDs [28–30]	↓ itching and hyperaemia, as well as both serum ICAM-1 and tear tryptase levels; long-term efficacy and safety not yet determined
Immunomodulators [19, 31–33]	Ciclosporin (aqueous solution): provides rapid (within 2–15 days) and long-lasting efficacy, depending on disease state and drug concentration; good safety profile; relapses occur with discontinuation Oil formulations of ciclosporin: may cause burning, stinging and blepharitis with prolonged use Tacrolimus (ophthalmic suspension): efficacious in a 4-week trial, with no adverse effects; recent studies suggest tacrolimus has similar efficacy to ciclosporin, but is better tolerated
Systemic treatments for patients with concomitant allergic diseases	
Oral antihistamines [12, 34]	Effective in relieving most symptoms; 2nd-generation antihistamines are preferred over 1st-generation antihistamines, as they are associated with ↓ sedation and lack anticholinergic activity
Omalizumab [31, 34]	Highly effective therapeutic strategy in patients with concomitant severe allergies
Allergen-specific immunotherapy [12]	Allergens underlying the allergic comorbidity must be fully known; may be useful in patients with mild VKC symptoms and hypersensitivity towards one or a few specific allergens
Promising new drugs or developments	
Lipid conjugates	↓ the production of phospholipase A ₂ -initiated lipid mediators, TNF- α and interleukin-8; may be useful in treating conjunctivitis caused by pathogen or allergen contact [1, 2]
Chlorogenic acid and its ester derivatives	Act on transglutaminase to produce anti-inflammatory effects similar to those of corticosteroids; significantly ↓ conjunctival oedema and redness in animal models [2, 35]; are highly versatile with regard to dosage form and route
Glucosamine	Ointment and eye drops have been approved to treat allergic and irritant conjunctivitis [2, 35]
Phosphodiesterase inhibitors	Inhibit phosphodiesterase IV, which suppresses inflammatory cell activity [2, 36]
Epinastine	Acts as a mast-cell stabilizer; protects the conjunctiva through inhibiting the influx of toxic eosinophilic granule protein, enzymes and mast-cell mediators [2, 3]
Toll-like receptor inhibitors	Prevent the production of cytokines and inflammatory mediators [2, 9]
Small interfering RNA	Potential in spleen tyrosine kinase-related allergic conditions; avoids histamine-related adverse effects [2, 5]

ICAM-1 intercellular adhesion molecule 1, TNF tumour necrosis factor, VKC vernal keratoconjunctivitis, ↑ increase(s/d), ↓ decrease(s/d)

Take home messages

- A growing number of options are available to treat VKC
- Uniform grading of disease severity and global consensus on treatment strategies are not available
- Prescribers should collaborate with patients to individualize the therapeutic regimen

- Moderate to severe cases of VKC may require treatment with topical corticosteroids and, although further data are needed, topical ciclosporin or tacrolimus
- Further studies are required on promising new drugs before these can be used in clinical practice.

Compliance with ethical standards

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References

- Kumar S. Vernal conjunctivitis: a major review. *Acta Ophthalmol.* 2009;87(2):133–47.
- Esposito S, Fior G, Mori A, et al. An update on the therapeutic approach to vernal keratoconjunctivitis. *Paediatr Drugs.* 2016;18(5):347–55.
- Bonini S, Sacchetti M, Mantelli F, et al. Clinical grading of vernal keratoconjunctivitis. *Curr Opin Allergy Clin Immunol.* 2007;7(5):436–41.
- Bonini S, Bonini S, Lambiase A, et al. Vernal keratoconjunctivitis revisited: a case series of 195 patients with long-term followup. *Ophthalmology.* 2000;107(6):1157–63.
- Pattnaik L, Acharya L. A comprehensive review on vernal keratoconjunctivitis with emphasis on proteomics. *Life Sci.* 2015;128:47–54.
- Leonardi A, Borghesan F, Faggian D, et al. Tear and serum soluble leukocyte activation markers in conjunctival allergic diseases. *Am J Ophthalmol.* 2000;129(2):151–8.
- Tabbara KF. Tear tryptase in vernal keratoconjunctivitis. *Arch Ophthalmol.* 2001;119(3):338–42.
- Zicari AM, Zicari A, Nebbioso M, et al. High-mobility group box-1 (HMGB-1) and serum soluble receptor for advanced glycation end products (sRAGE) in children affected by vernal keratoconjunctivitis. *Pediatr Allergy Immunol.* 2014;25(1):57–63.
- De Smedt S, Wildner G, Kestelyn P. Vernal keratoconjunctivitis: an update. *Br J Ophthalmol.* 2013;97(1):9–14.
- Tuft SJ, Dart JK, Kemeny M. Limbal vernal keratoconjunctivitis: clinical considerations and immunoglobulin E expression compared with palpebral vernal. *Eye (Lond).* 1989;3(Pt 4):420–7.
- Zicari AM, Nebbioso M, Lollobrigida V, et al. Vernal keratoconjunctivitis: atopy and autoimmunity. *Eur Rev Med Pharmacol Sci.* 2013;17(10):1419–23.
- Vichayanond P, Pacharn P, Pleyer U, et al. Vernal keratoconjunctivitis: a severe allergic eye disease with remodeling changes. *Pediatr Allergy Immunol.* 2014;25(4):314–22.
- Griffin RY, Sarici A, Unal L. Acquired ptosis secondary to vernal conjunctivitis in young adults. *Ophthalm Plast Reconstr Surg.* 2006;22(6):438–40.
- Le Q, Hong J, Zhu W, et al. In vivo laser scanning confocal microscopy of vernal keratoconjunctivitis. *Clin Exp Ophthalmol.* 2011;39(1):53–60.
- Church MK, McGill JI. Human ocular mast cells. *Curr Opin Allergy Clin Immunol.* 2002;2(5):419–22.
- Kumar S, Gupta N, Vivian AJ. Modern approach to managing vernal keratoconjunctivitis. *Curr Allergy Asthma Rep.* 2010;10(3):155–62.
- 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(4):288–93.
- Bielory L, Ghafoor S. Histamine receptors and the conjunctiva. *Curr Opin Allergy Clin Immunol.* 2005;5(5):437–40.
- Bertelmann E, Pleyer U. Immunomodulatory therapy in ophthalmology: is there a place for topical application? *Ophthalmologica.* 2004;218(6):359–67.
- Fukushima A. Roles of T-cells in the development of allergic conjunctival diseases. *Cornea.* 2007;26(9):S36–40.
- Keklikci U, Dursun B, Cingu AK. Topical cyclosporine A 0.05% eyedrops in the treatment of vernal keratoconjunctivitis: randomized placebo-controlled trial. *Adv. Clin Exp Med.* 2014;23(3):455–61.
- Soparkar CN, Wilhelmus KR, Koch DD. Acute and chronic conjunctivitis due to over-the-counter ophthalmic decongestants. *Arch Ophthalmol.* 1997;115(1):34–8.
- Leonardi A. Management of vernal keratoconjunctivitis. *Ophthalmol Ther.* 2013;2(2):73–88.
- McGill JI. A review of the use of olopatadine in allergic conjunctivitis. *Int Ophthalmol.* 2004;25(3):171–9.
- Hida WT, Nogueira DC, Schaefer A, et al. Comparative study between 0.025% ketotifen fumarate and 0.1% olopatadine hydrochloride in the treatment of vernal keratoconjunctivitis [in Portuguese]. *Arq Bras Oftalmol.* 2006;69(6):851–6.
- Carnahan MC, Goldstein DA. Ocular complications of topical, peri-ocular, and systemic corticosteroids. *Curr Opin Ophthalmol.* 2000;11(6):478–83.
- McGhee CNJ, Dean S, Danesh-Meyer H. Locally administered ocular corticosteroids: benefits and risks. *Drug Saf.* 2002;25(1):33–55.
- Sharma A, Gupta R, Ram J, et al. Topical ketorolac 0.5% solution for the treatment of vernal keratoconjunctivitis. *Indian J Ophthalmol.* 1997;45(3):177–80.
- D'Angelo G, Lambiase A, Cortes M, et al. Preservative-free diclofenac sodium 0.1% for vernal keratoconjunctivitis. *Graefes's Arch Clin Exp Ophthalmol.* 2003;241(3):192–5.
- Gupta S, Khurana AK, Ahluwalia BK, et al. Topical indomethacin for vernal keratoconjunctivitis. *Acta Ophthalmol (Copenh).* 1991;69(1):95–8.
- Vichayanond P, Kosirukvongs P. Use of cyclosporine A and tacrolimus in treatment of vernal keratoconjunctivitis. *Curr Allergy Asthma Rep.* 2013;13(3):308–14.
- Labcharoenwongs P, Jirapongsananuruk O, Visitsunthorn N, et al. A double-masked comparison of 0.1% tacrolimus ointment and 2% cyclosporine eye drops in the treatment of vernal keratoconjunctivitis in children. *Asian Pac J Allergy Immunol.* 2012;30(3):177–84.
- Pucci N, Caputo R, di Grande L, et al. Tacrolimus vs. cyclosporine eyedrops in severe cyclosporine-resistant vernal keratoconjunctivitis: a randomized, comparative, double-blind, crossover study. *Pediatr Allergy Immunol.* 2015;26(3):256–61.
- de Klerk TA, Sharma V, Arkwright PD, et al. Severe vernal keratoconjunctivitis successfully treated with subcutaneous omalizumab. *J AAPOS.* 2013;17(3):305–6.
- Sohn J, Kim T-I, Yoon Y-H, et al. Novel transglutaminase inhibitors reverse the inflammation of allergic conjunctivitis. *J Clin Invest.* 2003;111(1):121–8.
- Yanni JM, Sharif NA, Gamache DA, et al. A current appreciation of sites for pharmacological intervention in allergic conjunctivitis: effects of new topical ocular drugs. *Acta Ophthalmol Scand Suppl.* 1999;228:33–7.