

REVIEW ARTICLE

Vernal keratoconjunctivitis: A severe allergic eye disease with remodeling changes

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Abstract

Vernal keratoconjunctivitis (VKC) is an unusually severe sight-threatening allergic eye disease, occurring mainly in children. Conventional therapy for allergic conjunctivitis is generally not adequate for VKC. Pediatricians and allergists are often not familiar with the severe clinical symptoms and signs of VKC. As untreated VKC can lead to permanent visual loss, pediatric allergists should be aware of the management and therapeutic options for this disease to allow patients to enter clinical remission with the least side effects and sequelae. Children with VKC present with severe ocular symptoms, that is, severe eye itching and irritation, constant tearing, red eye, eye discharge, and photophobia. On examination, giant papillae are frequently observed on the upper tarsal conjunctiva (cobblestoning appearance), with some developing gelatinous infiltrations around the limbus surrounding the cornea (Horner-Trantas dot). Conjunctival injections are mostly severe with thick mucus ropy discharge. Eosinophils are the predominant cells found in the tears and eye discharge. Common therapies include topical antihistamines and dual-acting agents, such as lodoxamide and olopatadine. These are infrequently sufficient and topical corticosteroids are often required for the treatment of flare ups. Ocular surface remodeling leads to severe suffering and complications, such as corneal ulcers/scars. Other complications include side effects from chronic topical steroids use, such as increased intraocular pressure, glaucoma, cataract and infections. Alternative therapies for VKC include immunomodulators, such as cyclosporine A and tacrolimus. Surgery is reserved for those with complications and should be handled by ophthalmologists with special expertise. Newer research on the pathogenesis of VKC is reviewed in this article. Vernal keratoconjunctivitis is a very important allergic eye disease in children. Complications and remodeling changes are unique and can lead to blindness. Understanding of pathogenesis of VKC may lead to better therapy for these unfortunate patients.

Vernal keratoconjunctivitis (VKC) is a bilateral, chronic sight-threatening and severe inflammatory ocular disease mainly occurring in children. In the opening statement of the 2002 review of the subject, Andrea Leonardi elegantly wrote ‘*When you see a child suffering from a severe form of vernal keratoconjunctivitis, you instantly feel the dearth in knowledge of its pathogenesis that prevents you from adequately treating the signs and symptoms that will most likely ruin his childhood*’ (1). Severe and inappropriately treated VKC can lead to severe ocular complications such as glaucoma, corneal scarring, and blindness. Moreover, the disease markedly impairs the child’s quality of life. It interferes with the child’s school performance and ultimately affects his future potential. Over the past 2

decades, progress has been made with regard to knowledge on epidemiology, pathophysiology, and treatment for this once devastating disease. In this review, we aim to present these advances to alert pediatricians and allergists. This may enable them to appropriately work up, diagnose, and treat these patients and to refer them at an appropriate time to prevent unfortunate complications. Recent advances in the treatment and the outlook for future research of VKC are discussed.

Epidemiology

VKC commonly occurs in school-age children. The common age of onset is before 10 years (4–7 years of age) (2). Often,

patients have suffered the affliction for 3–4 years before being properly diagnosed (3). A male preponderance has been observed, especially in patients under 20 years of age, among whom the male:female ratio is 4:1–3:1 (2, 4), whereas the ratio in those older than 20 years of age is 1:1 (2, 4, 5). As intense positive staining for estrogen and progesterone receptors in the epithelium and subepithelium has been shown in tarsal and bulbar conjunctiva of patients with VKC, imbalance of sex hormones has been proposed to play a role in its pathogenesis (6).

Although vernal (spring) implies a seasonal predilection of the disease, its course commonly occurs mostly year round, particularly in the tropics (7). VKC can be found throughout the world and has been reported from almost all continents. As expected, the disease was mostly described around the Mediterranean with most cases reported from Italy (2). Interestingly, a recent epidemiologic survey between 6 countries in the European Union (Italy, France, the Netherlands, Norway, Finland, and Sweden) indicated that VKC can be found both in the northern and in the southern Europe with a higher prevalence in the south than in the north (highest in Italy and lowest in Norway (8)). However, outside of Europe, VKC is often reported from more arid countries such as Cameroon (9), Rwanda (10), Saudi Arabia (11), Israel (12, 13), Pakistan (14), Thailand (7), and India (15). Surprisingly, Japan with a milder climate than most countries in Asia also reported a large number of VKC (16). This indicates that warm weather conditions may not be absolutely necessary for the development of the disease. Most reports have concentrated on referred populations and therefore do not represent a clear disease picture for the general population. It is of note that a population prevalence among African children was found to be as high as 4% (17). Perhaps, the EU study presented the best overall estimate of VKC prevalence which was at a range of 1:30,000–1:80,000 with 20–30% suffering from corneal complications (8). Apparently, these differences in prevalence could be due to the diversity of genetic make ups, environment (climate, socioeconomic status, and living styles), and gene–environment interaction. Unfortunately, efforts to study the genetics and epigenetics on VKC and allergic conjunctivitis lag behind those in other atopic diseases such as asthma and atopic dermatitis.

Commonly, VKC can be divided into three distinct phenotypes, that is, tarsal, limbal, and mixed VKC (3). Limbal VKC has been reported more often from Asia (7) and Africa (10), whereas the tarsal form has been more commonly reported from Europe (4). It is unclear why this difference exists, despite the fact that these two clinical presentations can coexist. The rate of allergic sensitization was reported to be higher in tarsal VKC than in those with the limbal form, indicating that the pathogenesis of the two types of disease could be different (2, 7). As disease severity in patients with limbal VKC is noted to be milder than in those with tarsal and mixed VKC (7), there is some speculation that limbal VKC may be the early stage of VKC, although studies indicating the progress from one type of VKC to the other are still lacking. Atopic sensitization has been found in around 50% of patients (2, 7). The type of allergens sensitized in VKC patients also differs geographically.

In the Mediterranean, most patients are sensitized to seasonal allergens, such as rye grass pollens and *Parietaria* (4), and perhaps render the disease more severe in the spring and autumn, hence supporting the term ‘vernal’. However, in the tropics, house dust mites are the most common allergens causing sensitization, followed by cockroach and grass pollens (7). Bonini et al. (4) also found that 23% of VKC patients had symptoms throughout the years. In addition, almost 16% of patients with seasonal presentation later evolved into the perennial type after a mean duration of 3 years from the disease onset (4).

Thus, allergic sensitization may not be the initial insult that leads to pathology in VKC but rather requires predisposing factors as well as concomitant triggers to the disease development. Whether untreated simple allergic conjunctivitis can evolve into VKC is entirely unknown. Moreover, the early clinical signs of VKC are not known, because there has been no long-term prospective study of this condition. Besides atopy and gender, other risk factors for the development of VKC are not well understood.

Although VKC was frequently observed as a single entity, the proportion of cases with associated atopic conditions have been reported among Italian patients to be as high as 41.5%. Among these conditions, asthma was most commonly encountered, followed by allergic rhinitis and eczema (4). Surprisingly, VKC commonly occurred prior to the development of other atopic conditions in this report. The presence of eczema with eye involvement could lead to consider the diagnosis atopic keratoconjunctivitis (AKC). VKC and AKC are ocular allergic diseases involving both IgE and non-IgE mechanisms which share several common signs and symptoms. The presence of eczema and ocular involvement in the elderly favors the diagnosis of AKC (18).

Symptoms and signs

Patients with VKC usually present at early to late school age (between 5 and 15 years of age) with primarily eye symptoms. The predominant eye symptoms are itching, discharge, tearing, eye irritation, redness of the eyes, and to variable extent, photophobia. As photophobia can be intense, these patients wear baseball caps and eye glasses and typically sit in a darker corner of the waiting area (Fig. 1a,b). In most patients, eye symptoms initially predominate, and thus, they commonly seek help from ophthalmologists. In some, rhinitis and asthma are associated symptoms and render the parents aware of the allergic nature of the problem. Interestingly, in a long-term follow-up of large case series by Bonini et al. (4), development of asthma was noted to occur after eye symptoms.

On examination, conjunctival hyperemia can be observed on the bulbar and tarsal conjunctiva. Thick ropy, mucoid, or frankly purulent discharge is usually noted. In contrast to bacterial conjunctivitis, few VKC patients complain of glued eyes, although they could have difficulties opening their eyes in the morning because of mucous discharge and severe photophobia. With proper eversion of the upper eye lid, the appearance of conjunctival papillae can be observed. The procedure of eye lid eversion is frequently omitted in clinical

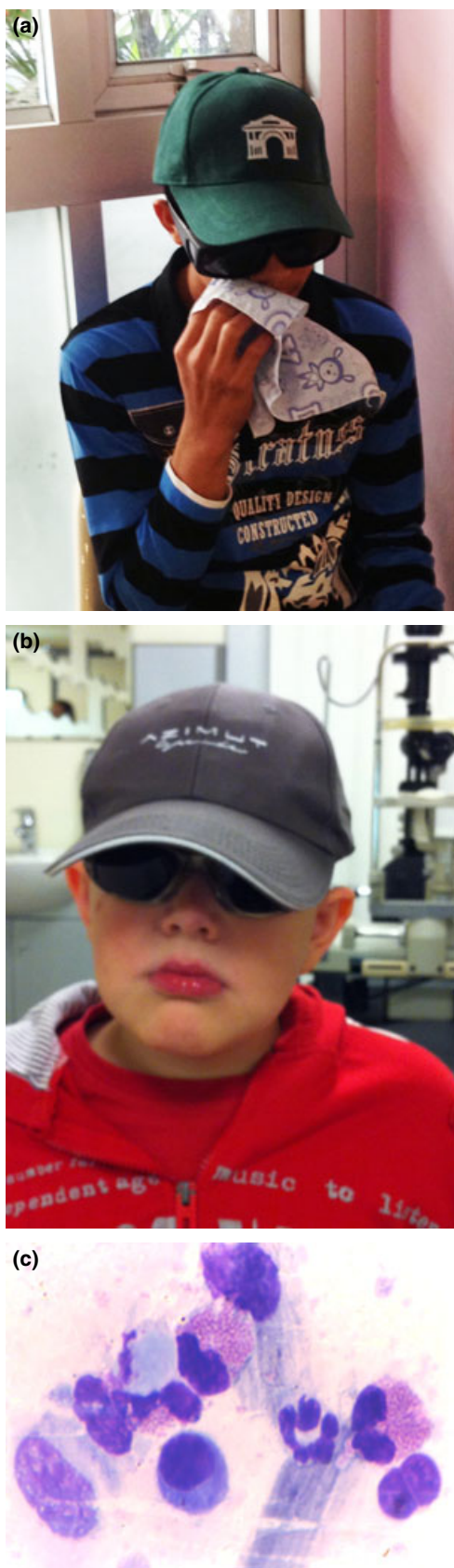


Figure 1 (a & b) Common presentation of VKC in 2 boys from different parts of the world (Thailand – upper panel - a and Italy – lower panel - b). Both wore baseball caps and dark sunglasses. They prefer to sit in the dark corner of the waiting area. Note that the left patient held a handkerchief in his hand to constantly wipe out overflowing tears. (c) Tear cytology from a VKC patient. Several inflammatory cell types can be noted with a predominance of highly activated and degranulating eosinophils (cell-free eosinophilic granules are noted in the foreground). Neutrophils, a plasma cell, and macrophages are also present.

practice because it is tedious (require practice) and uncomfortable to the patient. Pathognomonic papillae are more commonly observed on the upper tarsal conjunctiva than on the lower ones. By definition, papillae are classified as projections from conjunctival surface with diameters more than 0.2 mm. The sizes of papillae vary markedly from less than one to several mms (hence the appearance of the diagnostic ‘giant cobble-stoning conjunctiva’ – Fig. 2a). The surface of papillae can be a smooth solid surface with hyperemia or a ‘melt-down’ ulcerative one. Gelatinous infiltrative substances – the Horner-Trantas dot – can be occasionally observed on the limbus surrounding the cornea (Fig. 2b). These are inflammatory infiltrates consisting primarily of eosinophils. Grading of severity of VKC has been proposed based on the size of the papillae and conjunctival

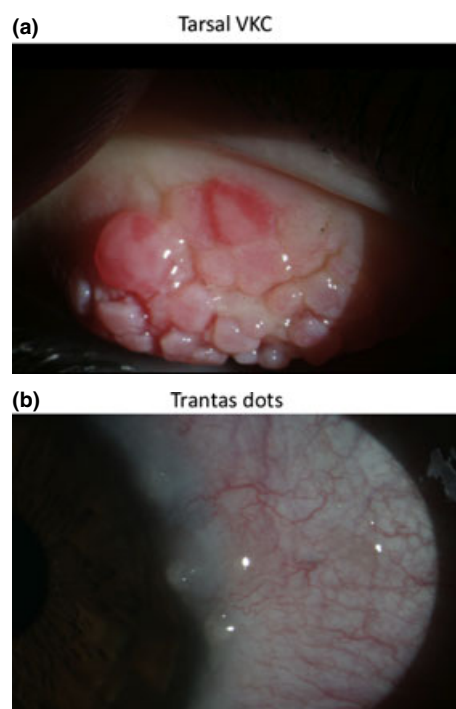


Figure 2 Distinct clinical phenotypes of VKC. Cobblestoning appearance of tarsal VKC resulted from studded giant papilla formation (right – panel a) and gelatinous infiltrations of inflammatory infiltrates around limbus – the Horner-Trantas dot – in limbal VKC (left – panel b).

hyperemia (19). However, in clinical practice, the degree of these two clinical signs may not coincide as proposed. Acquired ptosis, mostly unilateral, is not uncommonly observed in VKC (20, 21). The cause of this ptosis is unknown but could be due to the heavy giant papillae, chronic eye rubbing, or an inflammatory insult to the levator palpebrae superioris muscle and its subsequent dis-insertion (20).

Cornea involvement in VKC

The cornea contributes to most of the eye's optic power. It is a transparent, avascular tissue composed by a non-keratinized stratified squamous epithelium lying on a specialized basal membrane, called Bowman's layer. The corneal stroma consists of regularly arranged collagen fibers with sparsely distributed keratocytes adhering to a monolayer of the endothelium of the anterior chamber. Despite the absence of mast cells and lymphocytes, with only few immature resident dendritic cells, the cornea can be involved in VKC inflammation, taking the form of a superficial punctate keratitis or epithelial macroerosion or ulcers. Punctate epithelial keratitis may coalesce to form an obvious corneal epithelial defect or corneal erosion, leaving Bowman's layer intact. An oval-shaped epithelial defect, known as a 'shield ulcer', usually has its border in the upper half of the visual axis (Fig. 3a). Healed shield ulcers may leave subepithelial ring-like scars. If left untreated, a plaque containing fibrin and mucus is deposited over the epithelial defect (Fig. 3b). Shield ulcers without plaque formation usually undergo rapid re-epithelization, resulting in an excel-

lent visual outcome, whereas plaques delay re-epithelization and may require surgical removal.

Corneal ulceration is reported to occur in 3–11% of VKC patients and may cause permanent reduction in visual acuity. Corneal involvement in VKC has been considered to be a superficial epitheliopathy that can worsen into superficial sterile ulcers associated with a non-specific hypersensitivity, due to changes in corneal sensitivity and epithelial alterations. Corneal confocal microscopy demonstrates that not only the superficial epithelium, but also the anterior stroma and the corneal nerves are involved in the inflammation (22). Corneal nerve abnormalities, including reduction in density and number of the fibers, a higher grade of tortuosity, and inflammatory cell infiltrates, suggests that a distinct corneal neuropathy is involved in VKC. Children with VKC have a high incidence of keratoconus and have more abnormal corneal topography patterns compared with normal eyes (23–25). Central corneal thinning may result from corneal stromal cell apoptosis or could be induced or perpetuated by the activation of matrix degrading enzymes, particularly members of the matrix metalloproteinase (MMP) family and decreased proteinase inhibitors (26).

New insight in the pathophysiology

VKC has been included in the newest classification of ocular surface hypersensitivity disorders as both an IgE- and non-IgE-mediated ocular allergic disease (18). Additionally, not well-defined, non-specific hypersensitivity responses could be implicated in the pathophysiology of the disease. The etiology of VKC may involve a variety of factors, such as genetic predispositions, environmental allergens, and climate changes.

The central role of specific IgE–mast cell activation is supported by evidence, such as the presence of specific IgE in serum and in tears, clinical correlation between allergen exposure and exacerbation of the disease, association with other allergic manifestations, increased number of mast cells in conjunctival tissue, cytologic pattern in tears and tissues (Fig. 1c), and the pattern of mediators in the tears of patients with active disease (1). Nonetheless, it is also well known that not all VKC patients have positive allergy skin tests. Moreover, clinical signs and symptoms among those with and without positive skin tests are indistinguishable.

The increased numbers of CD4⁺ Th2 lymphocytes in the conjunctiva and the increased expression of co-stimulatory molecules and cytokines suggest that T cells play a crucial role in the development of VKC (Fig. 4c). In addition to typical Th2-derived cytokines, Th1-type cytokines, pro-inflammatory cytokines, a variety of chemokines, growth factors, and enzymes are overly expressed in VKC patients (27). Eosinophils and eosinophil-derived major basic protein (MBP) and cationic protein (ECP), neurotoxins, and collagenases, in particular MMP-9, have been shown to damage the corneal epithelium and the basement membrane causing corneal involvement in VKC (28–30). Tear levels of IL-5, eotaxin, and ECP have been shown to correlate with disease severity and corneal damage in VKC (31). In fact, human corneal keratocytes and conjunctival fibroblasts are capable of

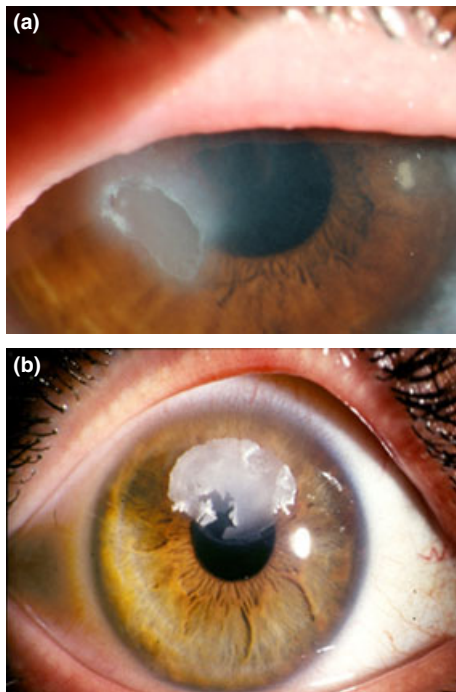


Figure 3 Corneal involvement in VKC. (a) a large corneal ulcer with visible inflammatory debris at the base and margins. (b) a large corneal plaque from a different VKC patient.

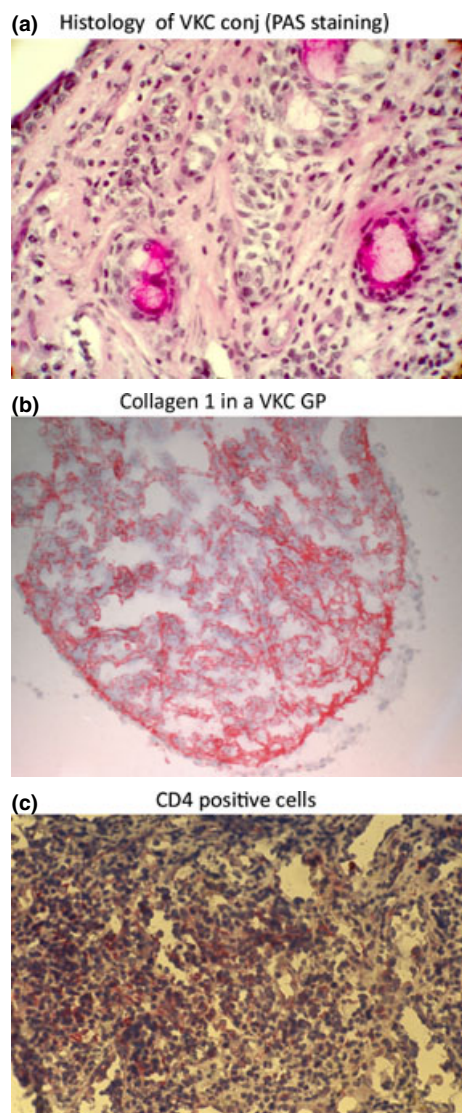


Figure 4 Histopathology of a giant papilla. (a) PAS staining showing epithelial ingrowths some of which produced mucin (glandular hypertrophy), abundant collagen fibers with fibroblasts. Inflammatory cells and neovascularizations can also be appreciated. (b) Anticollagen I immunostaining ($\times 100$) showing collagen – I in a section of a giant papilla. (c) Abundant inflammatory cell infiltrate in VKC with numerous CD4+ cells (anti-CD4 immunostaining, $\times 400$)

producing chemokines after stimulation with IL-4 and TNF- α , suggesting that T-cell-derived factors play important roles in eosinophil recruitment and with consequent corneal ulcer formation in VKC (32). However, a direct activation of allergen-specific T cells within the involved conjunctivae has not been demonstrated.

Tissue remodeling reactions, giant papillae formation, corneal stem cell deficiency, and various degrees of superficial corneal opacification are further consequences of the chronic inflammation typical of VKC (32). Several elements contribute to these remodeling changes, including epithelial changes,

connective tissue deposition, edema, inflammatory cell infiltration, and glandular hypertrophy (Fig. 4a,b). The mechanism of giant papillae formation is mainly epithelial thickening and fibroblast proliferation. Factors that promote fibroblast proliferation include Th2 cytokines (1), growth factors such as TGF- β , bFGF, PDGF, and also histamine (33). These growth factors also increase integrin expression, which in turn promotes cellular infiltration and proliferation in VKC (34). In addition, modified mucin expression has been shown in VKC with corneal ulcers, suggesting that changes in mucus composition and tear film instability reduce ocular surface protection and could facilitate the progression of atopic ocular surface disease (35, 36).

Viral infections and allergy have been shown to link in different ways. In the classic 'hygiene hypothesis', viral infections during the prenatal period or early childhood could prevent development of atopy by stimulating the Th1 response and inhibiting the Th2 immune response (37), whereas acute viral infections such as respiratory syncytial virus (RSV) are well known to exacerbate asthma (38). However, a direct association between infectious agents such as RSV or chlamydial infection and on-going ocular inflammation in VKC has not been substantiated (39). Other infectious agents of interest, such as *Staphylococcus aureus* (40) or human rhinoviruses (41), have not been well studied in the pathogenesis of VKC.

Treatment

Medical treatment

The mainstay of VKC treatment is medical treatment. However, patients should be taught how to avoid non-specific triggers which could aggravate symptoms, such as strong wind, dust, air pollutants, and strong sunlight. The use of sunglasses, visors, and caps should be advised. Despite the fact that sensitization to several specific allergens is observed among these patients (grass and weed pollens, dust mites), a proven role for environmental control measures to these allergens has not been adequately studied in VKC.

Symptoms of eye irritation, burning sensation, and blurring of vision are caused by the presence of inflammatory cytokines and cellular infiltrates on the conjunctival surfaces. Rinsing of the eye with adequate amounts of cool normal saline removes these cellular debris and toxic substances and can bring about significant symptoms relief. Rinsing should be repeated several times a day during the acute exacerbations. Several patients have learnt to use a cold compress to reduce eye irritation. Application of preservative-free artificial tears can also be used. Despite the frequent use of eye rinsing during exacerbations and in maintenance therapy, their efficacy has not evaluated systematically.

The use of topical antihistamines alone has not produced satisfactory results in VKC, despite the fact that histamine is the major mediator in this disease. For instance, topical levocabastine was found to be inferior to lodoxamide in alleviating ocular symptoms/signs such as itching, tearing, and photophobia (42). Newer antihistamines with extended properties such as epinastine and olopatadine are of interest.

Epinastine, besides being an H1 and H2 antagonist, inhibits neutrophil (43) and eosinophil activation (44), as well as decreasing Th2 cytokine production (45). Olopatadine, another potent antihistamine, inhibits anti-IgE-stimulated, conjunctival mast cell up-regulation of ICAM-1 expression on conjunctival epithelial cells *in vitro* (46). Because of their promising roles in allergic eye inflammation, these agents have been increasingly applied in VKC despite the unavailability of clinical data in moderate to severe VKC.

As in treatment for allergic rhinitis and asthma, agents interfering with mediator release have been actively sought as a treatment for VKC. Among these agents (commonly called mast cell stabilizers or dual-acting agents), cromolyn sodium and lodoxamide have been extensively evaluated. Interest in applying cromolyn (DSCG) eye solution for VKC treatment started as early as the late 1970s. Both 2% and 4% DSCG solution were found to be superior to placebo in reducing signs and symptoms of VKC (12, 47–50). However, symptoms in severe VKC often persisted even after prolonged use of DSCG (50). In fact, persistence of symptoms could be observed in up to 42% of eyes treated with DSCG (51). Lodoxamide is a mast cell stabilizing agent which has inhibitory effects on neutrophil and eosinophil migration (52) and down-regulates ICAM-1 expression in cultured conjunctival epithelial cells (53). Its efficacy has been demonstrated in allergic eye diseases (54), as well as in VKC (51, 52, 55). Lodoxamide was found to be more effective than DSCG for the treatment of VKC patients in several comparison trials (55–57) and became a standard therapy for VKC during the early 2000s. Notably, both lodoxamide and DSCG have to be applied four times daily, which could affect patients' compliance. Despite the fact that an excellent response to lodoxamide was reported in a study from Pakistan (94% of VKC patients responded) (14), up to 15% of lodoxamide-treated eyes did not respond to lodoxamide in one trial (51). N-acetyl aspartyl glutamic acid (NAAGA) 6% has been widely used in Europe as topical eye drops in the treatment for VKC (58). NAAGA is known to inhibit leukotriene synthesis, histamine release by mast cells, and complement-derived anaphylatoxin production. Other immunomodulators that have been tried at with varying degree of efficacy in a limited number of studies include mitomycin-C (59), mipragoside (60), and ketorolac (61).

As exacerbations are common in VKC despite a continuing use of mast cell stabilizers as maintenance therapy, patients often need strong topical corticosteroids pulse therapy to bring about disease control (3, 7). Prednisolone, fluorometholone, and dexamethasone are frequently chosen for such purposes (7, 62, 63). Not infrequently, patients resort to use steroids on their own. Together with inadequate monitoring of intraocular pressure, open glaucoma could result, because it has been shown that increased intraocular pressure can develop within 2 weeks of the use of topical steroids (64). Other side effects of topical steroids include infections, cataract, and corneal changes (65, 66). Recently, loteprednol, a 'soft steroid' with less effect on intraocular pressure (65), was found to be as effective as prednisolone (and more effective than fluorometholone) in VKC (67).

As dual-acting agents are infrequently sufficient to control disease activity in moderate to severe VKC, there have been increasing efforts to find immunomodulators that can inhibit T-helper cells, particularly Th2 cells – the key pivotal cells in VKC. Cyclosporine (CsA) and tacrolimus are the agents targeted for this purpose, because they inhibit T-cell activation via calcineurin inhibition and thereby reduce inflammatory cytokine production, including IL-4 and IL-5 (68). Topical CsA has been found to be effective in VKC in several investigations (69, 70). Most studies used CsA 1–2% in various oil bases (such as olive and castor oil) which could potentially cause eye irritation in certain patients (71). CsA dispersed in artificial tear at lower concentrations (1–1.25%) was also reported to be effective in two studies (72, 73). More recently, a report from Japan by Ebihara et al. using CsA at a much lower concentration (0.1%) prepared as an aqueous solution with a novel surfactant, demonstrated an impressive result in treating severe allergic conjunctivitis, including VKC, at even once a day application (16). Most reported trials on CsA in VKC involved a short duration (up to 6 months). Recently, Lambiase et al. (62) reported the results of a 2-year crossover study of CsA vs. ketotifen (1 year each) for prevention of recurrences and as steroid-sparing drugs in moderate VKC patients. Patients in the ketotifen group had 2.4-fold higher rate recurrence and more frequent use of corticosteroids than the CsA group, indicating that the use of these immune-modulating agents in VKC should be a long-term treatment (62). Tacrolimus, another calcineurin inhibitor, in an ointment base (1%), has been used successfully in treating recalcitrant VKC (63, 74–76). Not only the reduction in symptoms was observed within a month of treatment, but reduction in papillary hyperplasia was also observed with prolonged use of this drug

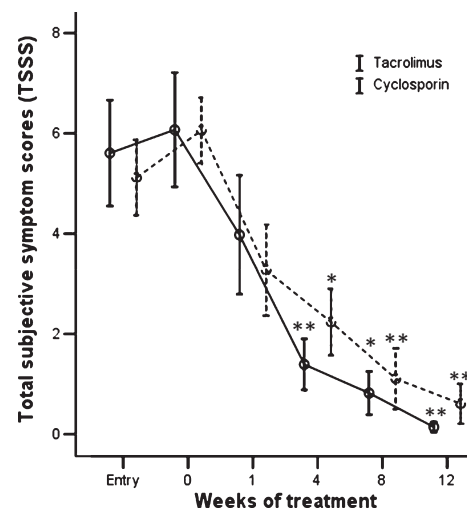


Figure 5 Mean + SE of total subjective symptom scores (TSSS) at various time points of VKC patients randomized to receive 0.1% tacrolimus eye ointment vs. cyclosporine A 2% eye drops. TSSS significantly decreased from baselines at 4th and 8th weeks in both groups (* $p < 0.05$, ** $p < 0.01$). No difference was observed between groups at any time point ($p > 0.05$). From Ref. (73) with a permission from the Asia Pacific Journal of Allergy and Immunology.

(63, 75). A comparative study between 0.1% tacrolimus twice daily and 2% cyclosporine eye drops 4 times daily, however, yielded similar clinical results – Fig. 5 (75). A promising result from a study of the use of a 0.1% suspension of tacrolimus (with polyvinyl alcohol and benzalkonium chloride as dispersant) was reported for treatment of both atopic keratoconjunctivitis and VKC (77).

VKC is often quoted to be a self-limiting disease with improvement observed after puberty. However, there are only a few studies on the long-term prognosis of VKC. In the study by Bonini et al. (4) with a median follow-up period of 47 months, VKC patients had a complete recovery in only 29.8% (n = 22), some improvement in symptoms 35.4% (n = 29), no clinical change 31.7% (n = 26), and worsening symptoms 2.7% (n = 4). Factors related to persistent symptoms were larger papillary size and bulbar type of VKC. Pucci et al. followed patients treated with CsA for 7 years; however, the number of patients was too small to make any firm conclusions (78). Pacharn et al. reported a 3-year experience of tacrolimus ophthalmic ointment in VKC with a remission rate of 40% of the patients (79). Allergen-specific immunotherapy, a promising therapeutic option that could alter the natural history of the allergic diseases such as asthma and allergic rhinitis (80), has not been fully investigated in VKC, although a recent retrospective analysis from Spain showed promising results (81).

Surgical treatment

Rarely, VKC patients require a surgical approach. Surgical removal of corneal plaque is recommended only in persistent cases to alleviate severe symptoms and to allow the corneal re-epithelization. Giant papillae excision with intra-operative 0.02% mitomycin-C followed by CsA topical treatment may be indicated only in cases of mechanical pseudoptosis or the presence of coarse giant papillae and continuous active disease (15, 82, 83).

Cryotherapy of tarsal giant papillae should be avoided because of potential severe post-surgical scarring. Amniotic membrane transplantation (AMT) following keratectomy has been described as a successful treatment in deep ulcers and in cases with corneal stromal thinning (84). However, the presence of membrane remaining under the epithelium may affect postoperative corneal transparency.

Significant limbal stem cell deficiency as a complication of severe and persistent limbal inflammation has been treated with stem cell transplantation (85, 86). These and other more invasive procedures, such as oral mucosal grafting, should be avoided or considered only by ophthalmologists expert in VKC management.

Summary and conclusion

Several questions have been raised and still require answers. These include the followings: a) role of IgE in VKC; Is it possible that only a local (conjunctival) production of IgE occurs and is responsible for this severe inflammation? b) Is it possible that microbes, or TLR-mediated cell activation, or non-specific environmental stimuli act as super-antigens to trigger local IgE production or to mount a Th2-specific immune response on the ocular surface? c) Do we need another class of mechanisms to be included to explain the development of this disease? d) What are other risk factors that lead to VKC and how can it be prevented?

Recent studies of VKC have focused on developing of new pharmacologic treatments, such as various types of immunomodulators. Long-term follow-up studies with immunomodulators are needed to monitor for side effects and to demonstrate the outcome of the treatment. Better understanding of the pathogenesis of the disease has been a challenge for ophthalmologists, allergists, and pediatricians. Such knowledge will lead to new therapeutic options for these patients with unfortunate disease.

References

- Leonardi A. Vernal keratoconjunctivitis: pathogenesis and treatment. *Prog Retin Eye Res* 2002; **21**: 319–39.
- Leonardi A, Busca F, Motterle L, et al. Case series of 406 vernal keratoconjunctivitis patients: a demographic and epidemiological study. *Acta Ophthalmol Scand* 2006; **84**: 406–10.
- De Smedt S, Wildner G, Kestelyn P. Vernal keratoconjunctivitis: an update. *Br J Ophthalmol* 2013; **97**: 9–14.
- Bonini S, Lambiasi A, Marchi S, et al. Vernal keratoconjunctivitis revisited: a case series of 195 patients with long-term followup. *Ophthalmology* 2000; **107**: 1157–63.
- Kansakar I. Profile of vernal keratoconjunctivitis in Nepal: a hospital based study. *Nepal Med Coll J* 2011; **13**: 92–5.
- Bonini S, Lambiasi A, Schiavone M, et al. Estrogen and progesterone receptors in vernal keratoconjunctivitis. *Ophthalmology* 1995; **102**: 1374–9.
- Kosirukvongs P, Vichyanond P, Wongsawad W. Vernal keratoconjunctivitis in Thailand. *Asian Pac J Allergy Immunol* 2003; **21**: 25–30.
- Bremont-Gignac D, Donadieu J, Leonardi A, et al. Prevalence of vernal keratoconjunctivitis: a rare disease? *Br J Ophthalmol* 2008; **92**: 1097–102.
- McMoli TE, Assonganyi T. Limbal vernal keratoconjunctivitis in Yaounde, Cameroon. A clinico-immunology study. *Rev Int Trach Pathol Ocul Trop Subtrop Sante Publique* 1991; **68**: 157–70.
- De Smedt SK, Nkurikiye J, Fonteyne YS, et al. Vernal keratoconjunctivitis in school children in Rwanda: clinical presentation, impact on school attendance, and access to medical care. *Ophthalmology* 2012; **119**: 1766–72.
- Bleik JH, Tabbara KF. Topical cyclosporine in vernal keratoconjunctivitis. *Ophthalmology* 1991; **98**: 1679–84.
- Baryishak YR, Zavaro A, Monselise M, et al. Vernal keratoconjunctivitis in an Israeli group of patients and its treatment with sodium cromoglycate. *Br J Ophthalmol* 1982; **66**: 118–22.
- Neumann E, Gutmann MJ, Blumenkrantz N, Michaelson IC. A review of four hundred cases of vernal conjunctivitis. *Am J Ophthalmol* 1959; **47**: 166–72.
- Das D, Khan M, Gul A, Alam R. Safety and efficacy of lodoxamide in vernal keratoconjunctivitis. *J Pak Med Assoc* 2011; **61**: 239–41.
- Reddy JC, Basu S, Saboo US, et al. Management, clinical outcomes, and complications of shield ulcers in vernal keratoconjunctivitis. *Am J Ophthalmol* 2013; **155**: e1.

16. Ebihara N, Ohashi Y, Uchio E, et al. A large prospective observational study of novel cyclosporine 0.1% aqueous ophthalmic solution in the treatment of severe allergic conjunctivitis. *J Ocul Pharmacol Ther* 2009; **25**: 365–72.
17. Smedt SD, Nkurikiye J, Fonteyne Y, et al. Vernal keratoconjunctivitis in school children in Rwanda and its association with socio-economic status: a population-based survey. *Am J Trop Med Hyg* 2011; **85**: 711–7.
18. Leonardi A, Bogacka E, Fauquet JL, et al. Ocular allergy: recognizing and diagnosing hypersensitivity disorders of the ocular surface. *Allergy* 2012; **67**: 1327–37.
19. Bonini S, Sacchetti M, Mantelli F, Lambiase A. Clinical grading of vernal keratoconjunctivitis. *Curr Opin Allergy Clin Immunol* 2007; **7**: 436–41.
20. Griffin RY, Sarici A, Unal M. Acquired ptosis secondary to vernal conjunctivitis in young adults. *Ophthalm Plast Reconstr Surg* 2006; **22**: 438–40.
21. Keklikci U, Soker SI, Soker Cakmak S, et al. Unilateral vernal keratoconjunctivitis: a case report. *Eur J Ophthalmol* 2007; **17**: 973–5.
22. Leonardi A, Lazzarini D, Bortolotti M, et al. Corneal confocal microscopy in patients with vernal keratoconjunctivitis. *Ophthalmology* 2012; **119**: 509–15.
23. Demirbas NH, Pflugfelder SC. Topographic pattern and apex location of keratoconus on elevation topography maps. *Cornea* 1998; **17**: 476–84.
24. Totan Y, Hepsen IF, Cekic O, et al. Incidence of keratoconus in subjects with vernal keratoconjunctivitis: a videokeratographic study. *Ophthalmology* 2001; **108**: 824–7.
25. Kaya V, Karakaya M, Utine CA, et al. Evaluation of the corneal topographic characteristics of keratoconus with orbscan II in patients with and without atopy. *Cornea* 2007; **26**: 945–8.
26. Smith VA, Matthews FJ, Majid MA, Cook SD. Keratoconus: matrix metalloproteinase-2 activation and TIMP modulation. *Biochim Biophys Acta* 2006; **1762**: 431–9.
27. Leonardi A, Sathe S, Bortolotti M, et al. Cytokines, matrix metalloproteinases, angiogenic and growth factors in tears of normal subjects and vernal keratoconjunctivitis patients. *Allergy* 2009; **64**: 710–7.
28. Leonardi A, Brun P, Abatangelo G, et al. Tear levels and activity of matrix metalloproteinase (MMP)-1 and MMP-9 in vernal keratoconjunctivitis. *Invest Ophthalmol Vis Sci* 2003a; **44**: 3052–8.
29. Messmer EM, May CA, Stefani FH, et al. Toxic eosinophil granule protein deposition in corneal ulcerations and scars associated with atopic keratoconjunctivitis. *Am J Ophthalmol* 2002; **134**: 816–21.
30. Trocme SD, Kephart GM, Allansmith MR, et al. Conjunctival deposition of eosinophil granule major basic protein in vernal keratoconjunctivitis and contact lens-associated giant papillary conjunctivitis. *Am J Ophthalmol* 1989; **108**: 57–63.
31. Leonardi A, Jose PJ, Zhan H, Calder VL. Tear and mucus eotaxin-1 and eotaxin-2 in allergic keratoconjunctivitis. *Ophthalmology* 2003b; **110**: 487–92.
32. Kumagai N, Fukuda K, Fujitsu Y, et al. Role of structural cells of the cornea and conjunctiva in the pathogenesis of vernal keratoconjunctivitis. *Prog Retin Eye Res* 2006; **25**: 165–87.
33. Leonardi A, Radice M, Fregona IA, et al. Histamine effects on conjunctival fibroblasts from patients with vernal conjunctivitis. *Exp Eye Res* 1999; **68**: 739–46.
34. Abu El-Asrar AM, Al-Mansouri S, Tabbara KF, et al. Immunopathogenesis of conjunctival remodelling in vernal keratoconjunctivitis. *Eye (Lond)* 2006; **20**: 71–9.
35. Dogru M, Matsumoto Y, Okada N, et al. Alterations of the ocular surface epithelial MUC16 and goblet cell MUC5AC in patients with atopic keratoconjunctivitis. *Allergy* 2008; **63**: 1324–34.
36. Dogru M, Okada N, Asano-Kato N, et al. Alterations of the ocular surface epithelial mucins 1, 2, 4 and the tear functions in patients with atopic keratoconjunctivitis. *Clin Exp Allergy* 2006; **36**: 1556–65.
37. Thornton CA, Macfarlane TV, Holt PG. The hygiene hypothesis revisited: role of maternal-fetal interactions. *Curr Allergy Asthma Rep* 2010; **10**: 444–52.
38. Stein RT, Sherrill D, Morgan WJ, et al. Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years. *Lancet* 1999; **354**: 541–5.
39. Koulikovska M, van der Ploeg I, Herrmann B, Montan PG. Respiratory syncytial virus and chlamydia are not detectable by PCR in ongoing vernal keratoconjunctivitis. *Ocul Immunol Inflamm* 2001; **9**: 253–7.
40. Heaton T, Mallon D, Venaille T, Holt P. Staphylococcal enterotoxin induced IL-5 stimulation as a cofactor in the pathogenesis of atopic disease: the hygiene hypothesis in reverse? *Allergy* 2003; **58**: 252–6.
41. Caliskan M, Bochkov YA, Kreiner-Moller E, et al. Rhinovirus wheezing illness and genetic risk of childhood-onset asthma. *N Engl J Med* 2013; **368**: 1398–407.
42. Verin P, Allewaert R, Joyaux JC, et al. Comparison of lodoxamide 0.1% ophthalmic solution and levocabastine 0.05% ophthalmic suspension in vernal keratoconjunctivitis. *Eur J Ophthalmol* 2001; **11**: 120–5.
43. Fukuishi N, Kan T, Hirose K, et al. Inhibitory effect of epinastine on superoxide generation by rat neutrophils. *Jpn J Pharmacol* 1995; **68**: 449–52.
44. Kohyama T, Takizawa H, Akiyama N, et al. A novel antiallergic drug epinastine inhibits IL-8 release from human eosinophils. *Biochem Biophys Res Commun* 1997; **230**: 125–8.
45. Kanai K, Asano K, Watanabe S, et al. Epinastine hydrochloride antagonism against interleukin-4-mediated T cell cytokine imbalance in vitro. *Int Arch Allergy Immunol* 2006; **140**: 43–52.
46. Cook EB, Stahl JL, Barney NP, Graziano FM. Olopatadine inhibits anti-immunoglobulin E-stimulated conjunctival mast cell upregulation of ICAM-1 expression on conjunctival epithelial cells. *Ann Allergy Asthma Immunol* 2001; **87**: 424–9.
47. Easty DL, Rice NS, Jones BR. Clinical trial of topical disodium cromoglycate in vernal keratoconjunctivitis. *Clin Allergy* 1972; **2**: 99–107.
48. Tabbara KF, Arafat NT. Cromolyn effects on vernal keratoconjunctivitis in children. *Arch Ophthalmol* 1977; **95**: 2184–6.
49. Foster CS, Duncan J. Randomized clinical trial of topically administered cromolyn sodium for vernal keratoconjunctivitis. *Am J Ophthalmol* 1980; **90**: 175–81.
50. el Hennawi M. A double blind placebo controlled group comparative study of ophthalmic sodium cromoglycate and nedocromil sodium in the treatment of vernal keratoconjunctivitis. *Br J Ophthalmol* 1994; **78**: 365–9.
51. 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**: 23–6.
52. Bonini S, Schiavone M, Magrini L, et al. Efficacy of lodoxamide eye drops on mast cells and eosinophils after allergen challenge in allergic conjunctivitis. *Ophthalmology* 1997; **104**: 849–53.
53. Ciprandi G, Buscaglia S, Catrullo A, et al. Antiallergic activity of topical lodoxamide on in vivo and in vitro models. *Allergy* 1996; **51**: 946–51.
54. Fahy GT, Easty DL, Collum LM, et al. Randomised double-masked trial of lodoxamide and sodium cromoglycate in allergic eye disease. A multicentre study. *Eur J Ophthalmol* 1992; **2**: 144–9.
55. 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**: 632–7.
56. Leonardi AA, Smith LM, Fregona IA, et al. Tear histamine and histaminase during the early (EPR) and late (LPR) phases of the allergic reaction and the effects of lodoxamide. *Eur J Ophthalmol* 1996; **6**: 106–12.
 57. Akman A, Irkeç M, Orhan M. Effects of lodoxamide, disodium cromoglycate and fluorometholone on tear leukotriene levels in vernal keratoconjunctivitis. *Eye (Lond)* 1998; **12**(Pt 2): 291–5.
 58. Leonardi A, Bremond-Gignac D, Bortolotti M, et al. Clinical and biological efficacy of preservative-free NAAGA eye-drops versus levocabastine eye-drops in vernal keratoconjunctivitis patients. *Br J Ophthalmol* 2007; **91**: 1662–6.
 59. 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**: 263–9.
 60. Centofanti M, Schiavone M, Lambiase A, et al. Efficacy of mipragoside ophthalmic gel in vernal keratoconjunctivitis. *Eye (Lond)* 1996; **10**(Pt 4): 422–4.
 61. Sharma A, Gupta R, Ram J, Gupta A. Topical ketorolac 0.5% solution for the treatment of vernal keratoconjunctivitis. *Indian J Ophthalmol* 1997; **45**: 177–80.
 62. Lambiase A, Leonardi A, Sacchetti M, et al. Topical cyclosporine prevents seasonal recurrences of vernal keratoconjunctivitis in a randomized, double-masked, controlled 2-year study. *J Allergy Clin Immunol* 2011; **128**: 896–7 e9.
 63. Vichayanond P, Tantimongkolsuk C, Dumrongkigchaiporn P, et al. Vernal keratoconjunctivitis: result of a novel therapy with 0.1% topical ophthalmic FK-506 ointment. *J Allergy Clin Immunol* 2004; **113**: 355–8.
 64. Kersey JP, Broadway DC. Corticosteroid-induced glaucoma: a review of the literature. *Eye (Lond)* 2006; **20**: 407–16.
 65. Bielory BP, Perez VL, Bielory L. Treatment of seasonal allergic conjunctivitis with ophthalmic corticosteroids: in search of the perfect ocular corticosteroids in the treatment of allergic conjunctivitis. *Curr Opin Allergy Clin Immunol* 2010; **10**: 469–77.
 66. Carnahan MC, Goldstein DA. Ocular complications of topical, peri-ocular, and systemic corticosteroids. *Curr Opin Ophthalmol* 2000; **11**: 478–83.
 67. Oner V, Turku FM, Tas M, et al. Topical loteprednol etabonate 0.5% for treatment of vernal keratoconjunctivitis: efficacy and safety. *Jpn J Ophthalmol* 2012; **56**: 312–8.
 68. Vichayanond P, Kosirukvongs P. Use of cyclosporine A and tacrolimus in treatment of vernal keratoconjunctivitis. *Curr Allergy Asthma Rep* 2013; **13**: 308–14.
 69. Ben Ezra D, Pe'er J, Brodsky M, Cohen E. Cyclosporine eyedrops for the treatment of severe vernal keratoconjunctivitis. *Am J Ophthalmol* 1986; **101**: 278–82.
 70. Secchi AG, Tognon MS, Leonardi A. Topical use of cyclosporine in the treatment of vernal keratoconjunctivitis. *Am J Ophthalmol* 1990; **110**: 641–5.
 71. Pucci N, Novembre E, Cianferoni A, et al. Efficacy and safety of cyclosporine eyedrops in vernal keratoconjunctivitis. *Ann Allergy Asthma Immunol* 2002; **89**: 298–303.
 72. Kilic A, Gurler B. Topical 2% cyclosporine A in preservative-free artificial tears for the treatment of vernal keratoconjunctivitis. *Can J Ophthalmol* 2006; **41**: 693–8.
 73. 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**: 527–32.
 74. Attas-Fox L, Barkana Y, Iskhakov V, et al. Topical tacrolimus 0.03% ointment for intractable allergic conjunctivitis: an open-label pilot study. *Curr Eye Res* 2008; **33**: 545–9.
 75. 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**: 177–84.
 76. Tam PM, Young AL, Cheng LL, Lam PT. Topical tacrolimus 0.03% monotherapy for vernal keratoconjunctivitis—case series. *Br J Ophthalmol* 2010; **94**: 1405–6.
 77. Ohashi Y, Ebihara N, Fujishima H, et al. A randomized, placebo-controlled clinical trial of tacrolimus ophthalmic suspension 0.1% in severe allergic conjunctivitis. *J Ocul Pharmacol Ther* 2010; **26**: 165–74.
 78. Pucci N, Caputo R, Mori F, et al. Long-term safety and efficacy of topical cyclosporine in 156 children with vernal keratoconjunctivitis. *Int J Immunopathol Pharmacol* 2010; **23**: 865–71.
 79. Pacharn P, Visitsunthorn N, Jirapongsananuruk O, Vichayanond P. Vernal keratoconjunctivitis (VKC) treated with 0.1% FK-506 ophthalmic ointment result of three years follow-up. *J Allergy Clin Immunol* 2007; **119**: S153.
 80. Cox L, Nelson H, Lockey R, et al. Allergen immunotherapy: a practice parameter third update. *J Allergy Clin Immunol* 2011; **127**: S1–55.
 81. Lupez-Piedrahita E, Sánchez-Caraballo JM, Ramirez-Girado RH, Cardona-Villa R. Effectiveness of allergen immunotherapy in patients with vernal keratoconjunctivitis. *Rev Alerg Mex* 2013; **60**: 11–6.
 82. Tanaka M, Takano Y, Dogru M, et al. A comparative evaluation of the efficacy of intraoperative mitomycin C use after the excision of cobblestone-like papillae in severe atopic and vernal keratoconjunctivitis. *Cornea* 2004; **23**: 326–9.
 83. Fujishima H, Fukagawa K, Satake Y, et al. Combined medical and surgical treatment of severe vernal keratoconjunctivitis. *Jpn J Ophthalmol* 2000; **44**: 511–5.
 84. Guo P, Kheirkhah A, Zhou WW, et al. Surgical resection and amniotic membrane transplantation for treatment of refractory giant papillae in vernal keratoconjunctivitis. *Cornea* 2013; **32**: 816–20.
 85. Sangwan VS, Jain V, Vemuganti GK, Murthy SI. Vernal keratoconjunctivitis with limbal stem cell deficiency. *Cornea* 2011; **30**: 491–6.
 86. Sangwan VS, Murthy SI, Vemuganti GK, et al. Cultivated corneal epithelial transplantation for severe ocular surface disease in vernal keratoconjunctivitis. *Cornea* 2005; **24**: 426–30.