Pediatr Drugs
DOI 10.1007/s40272-016-0185-1

REVIEW ARTICLE

# An Update on the Therapeutic Approach to Vernal Keratoconjunctivitis

**Susanna Esposito[1] · Giulia Fior[1] · Alessandro Mori[1] · Silvia Osnaghi[2] · Daniele Ghiglioni[1]**



**Abstract** Vernal keratoconjunctivitis (VKC) is an inflammatory disease of the ocular surface. It commonly occurs in the first decade of life, has a wide geographical distribution, and usually occurs in warm, dry areas. The pathogenesis of VKC seems to have an immune, nervous, and endocrine basis. The most common eye symptoms are itching, discharge, tearing, eye irritation, redness of the eyes, and photophobia. Although VKC generally has a good prognosis, the lack of clarity regarding the origin of the disease makes treatment a challenge for pediatricians and ophthalmologists. The purpose of this review is to discuss the pathogenesis, clinical features, and diagnostic criteria in VKC, with a focus on its therapeutic management. The selection of a therapeutic scheme from the many available options is based on clinical features and the personal preferences of both physicians and patients. Due to the lack of uniform grading of disease severity, there is no worldwide consensus on first-line and second-line therapeutic approaches. The choice of treatment for long-term moderate to severe VKC includes topical cyclosporine or tacrolimus. Further data are needed to define the minimal effective concentration and the safety of these drugs in eye drops and to clarify the diagnosis of VKC in patients who require these drugs. Finally, while promising newly discovered drugs are expected to enter into clinical practice, further studies on their efficacy and safety are required.

**Key Points**

Vernal keratoconjunctivitis (VKC) is a chronic multifactorial disease with acute or sub-acute phases of inflammation of the ocular surface.

VKC is differentiated from ocular allergic diseases in some characteristics based on age at onset, clinical features, and the limited benefits from anti-allergic treatments in these patients.

The pathogenesis of VKC seems to have an immune, endocrine, and genetic basis.

The selection of a therapeutic scheme is based on clinical features and the personal preferences of both physicians and patients.

Moderate to severe clinical conditions may require topical steroid treatment and topical cyclosporine or tacrolimus.

## 1 Introduction

Vernal keratoconjunctivitis (VKC) is a multifactorial disease with acute or sub-acute phases of inflammation of the ocular surface. It is a chronic, seasonally exacerbated disease [1]. It can involve either the tarsal or bulbar conjunctiva, or both. VKC is usually categorized under the

✉ Susanna Esposito
susanna.esposito@unimi.it

[1] Pediatric Highly Intensive Care Unit, Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Via Commenda 9, 20122 Milan, Italy

[2] Oculistic Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

Published online: 26 July 2016

classification of allergic conjunctivitis together with seasonal allergic conjunctivitis (SAC), perennial allergic conjunctivitis (PAC) and atopic keratoconjunctivitis (AKC). However, VKC differs from ocular allergic diseases based on characteristics such as age at onset, clinical features, and limited benefit from antiallergic treatments [2].

VKC commonly occurs in the first decade of life and has a male preponderance [3, 4]. It has a wide geographical distribution, with a prevalence of 5–15 %, and is commonly found in warm, dry areas, including the Mediterranean regions, Central Africa, India, and South America [5]. Despite its name, it occurs year round, not only in the spring, particularly in the tropics [6]. The literature suggests that IgE-dependent (type I) and IgE-independent (type IV) mechanisms are both involved in the immunopathogenesis of VKC. Furthermore, the endocrine and genetic background of the patient probably plays a role in disease progression. However, its exact pathogenesis remains unclear [7]. A few years from the first seasonal attacks, VKC could turn into a perennial disease. Although VKC does not lead to blindness, visual impairment may occur if the cornea is involved [1]. VKC can negatively affects patients' quality of life, affecting school and overall personal development, and treatment with topical corticosteroids and topical immunomodulators or immunosuppressive drugs (i.e., cyclosporine and tacrolimus) is required to control ocular symptoms [5]. The purpose of this review is to discuss the pathogenesis, clinical features, and diagnostic criteria in VKC with a focus on its therapeutic management. PubMed was used to search for all of the studies published over the last 15 years using the key words 'vernal keratoconjunctivitis' and 'pathogenesis' or 'clinical' or 'symptom' or 'sign' or 'diagnosis' or 'therapy' or 'therapeutic'. More than 2500 articles were found, and only those published in English and providing data with implications for therapy were included in the evaluation.

## 2 Pathogenesis

The pathogenesis of VKC seems to have an immune, endocrine, and genetic basis (Table 1).

The clear abundance of T helper 2 ($T_h2$) cytokines [i.e., interleukin (IL)-4 and IL-5] and their receptors together with the lack of $T_h1$ cytokines [i.e., IL-2, interferon (IFN)-γ, and tumor necrosis factor (TNF)-β] in VKC patients' tears and sera highlight the crucial role played by $T_h2$ factors in VKC inflammation [1, 8]. VKC is an IgE-mediated disease, but this is not the only mechanism involved. In fact, 50 % of patients have negative skin tests and show no sensitization in the radioallergosorbent test (RAST). It is likely that an aberration in the $T_h2$ lymphocyte profile is responsible for disease development rather than an exaggerated IgE response to environmental allergens [4].

IL-8 seems to play an important role in VKC pathogenesis. It is produced by various tissues and cells, such as monocytes, macrophages, T lymphocytes, fibroblasts, neutrophils, and eosinophils [9]. It can be found in the conjunctival epithelium and in eosinophils at the site of inflammation. Migrated eosinophils themselves probably produce this chemokine, but further studies are necessary to confirm its origin in VKC.

Moreover, the presence of a significantly higher level of IL-17 in patients with VKC than in healthy controls has been observed, suggesting a possible role of this cytokine in the pathogenesis of VKC [10]. Further studies on larger samples of patients are warranted to confirm these findings in order to identify new possible therapeutic targets.

On the other hand, eosinophils are more abundant in the tears, conjunctiva, and serum of patients with VKC than in those with other ocular allergies. Eosinophils release arginine-rich basic proteins, such as eosinophil cationic protein (ECP) [11]. The tear and serum levels of the eosinophil ECP are higher in VKC patients than in healthy subjects [5]. Furthermore, serum ECP and blood eosinophil counts seem to correlate with the gravity of the giant papillae [12].

Furthermore, serum basal levels of high-mobility group box-1 (HMGB1) and serum soluble receptor for advanced glycation end products (sRAGE) appeared higher in children with VKC when compared with controls while, in patients affected by VKC, no difference was detected between atopic and non-atopic, and between antinuclear antibodies (ANA)-positive and ANA-negative children [13]. In another study, ANA positivity and a familiar history of autoimmune disorders were detected in a high percentage of children with VKC and this association seemed helpful to better understand the association of VKC with systemic autoimmune disorders and atopic condition [14].

Additionally, T lymphocytes (mainly CD4-type cells) and mast cells are increased in the conjunctiva and tears of VKC patients [15–17]. In healthy subjects, the majority of conjunctival mast cells (approximately 80 %) are tryptase- and chymase-positive mast cells (MCTCs), whereas in VKC patients and during allergic inflammation in SAC and AKC, the number of tryptase-positive mast cells (MCTs) increases in the epithelial layer [18]. In VKC patients, the quantity of MCTCs is related to the disease's severity [17].

In VKC patients, conjunctival tissue shows prominent inflammatory cellular infiltration in the epithelium and substantia propria, with evidence of post-inflammatory tissue remodeling [1]. Tissue remodeling is evident, especially in the tarsal conjunctiva.

**Table 1** Pathogenesis of vernal keratoconjunctivitis (VKC)

| Mechanism | Finding |
|---|---|
| Immune-mediated | Abundance of $T_h2$ cytokines (i.e., IL-4 and IL-5) and their receptors |
| | Increase in IL-8 |
| | Increase in IL-17 |
| | Increase in tears, conjunctiva and serum eosinophils |
| | Increase in serum basal levels of high-mobility group box-1 (HMGB1) and serum soluble receptor for advanced glycation end products (sRAGE) |
| | Increase in CD4+ and mast cells in conjunctiva and tears |
| Endocrine | Sexual disparity in disease prevalence |
| | Overexpression of sexual hormone receptors by conjunctival eosinophils |
| | Altered neuroreceptor expression in conjunctival epithelium |
| | Growth factors, neuropeptides and prostaglandins detected in high amounts in serum and tears |
| Genetic basis | Preponderance of limbal VKC in Black population |
| | Different prevalences of the limbal and palpebral VKC forms in various races |

*IL* interleukin

An endocrine role in the development of VKC has been suggested due to the sexual disparity in disease prevalence, the overexpression of sex hormone receptors by conjunctival eosinophils, altered neuroreceptor expression in the conjunctival epithelium in VKC, and high levels of growth factors, neuropeptides, and prostaglandins in the serum and tears of patients with VKC [7].

In addition, the preponderance of limbal VKC in the Black population and the different prevalences of the limbal and palpebral forms of VKC in various races support the role of genetic factors in determining the course of disease [18].

## 3 Clinical Features Suggestive of Vernal Keratoconjunctivitis

Diagnosis is mainly based on symptoms, clinical findings at eye examination, age at onset (3–8 years in 70–80 % of cases), the appearance of symptoms during the spring and their persistence in the summer after the end of allergy season, and the partial efficacy of topical and systemic antihistamine drugs (Table 2).

The most common eye symptoms in VKC are itching, discharge, tearing, eye irritation, redness of the eyes, and photophobia, together with pain and foreign body sensation [1]. Conjunctival hyperemia may be found upon the examination of the bulbar and tarsal conjunctiva. A thick, ropy, mucoid, or frankly purulent discharge is usually present. Conjunctival papillae may be observed under the upper eyelid [19]. Corneal changes include punctate epithelial keratitis, epithelial macro-erosions, shield ulcer, plaque formation, and late corneal vascularization [1]. Acquired ptosis often appears in VKC, probably due to the heavy giant papillae, chronic eye rubbing, or an inflammatory insult and rare subsequent dis-insertion of the elevator palpebrae muscle [20].

A recent diagnostic technique used to non-invasively quantify the morphological characteristics of the conjunctiva and the limbus is confocal microscopy [21]. Very few laboratory tests are useful in confirming the disease. The eosinophils typically found in the conjunctival scrapings of patients support diagnosis, but this test does not have high sensitivity [18]. There may be high variability in IgE levels, and skin tests may not always be positive among VKC cases [4].

Although VKC is frequently observed without other concomitant disease, associated atopic conditions have been reported in the literature. Among Italian patients, an association with asthma, allergic rhinitis, and eczema has been reported in 41.5 % of the cases [4].

Although VKC generally has a good prognosis, 5–15 % of the patients showed a permanent reduction in visual acuity as a result of corneal damage [4]. Patients also complain of frequent conjunctival redness after exposure to nonspecific stimuli, probably due to hyperreactivity when sun, dust, wind, and other general climactic factors or nonspecific stimuli come in contact with the conjunctiva.

## 4 Treatment of Vernal Keratoconjunctivitis

Due to the lack of clarity in pathogenesis, the treatment of VKC has always been a challenge for pediatricians and ophthalmologists. Moreover, despite extensive progress in the field of pharmacotherapy, no single medication is able

**Table 2** Diagnostic criteria in vernal keratoconjunctivitis (VKC)

| Criteria | Finding |
|---|---|
| Age at onset | 3–8 years |
| Symptoms | Itching, discharge, tearing, eye irritation, redness of the eyes and photophobia (caused by corneal involvement), together with pain and foreign body sensation |
| Signs | Conjunctival hyperemia in the bulbar and tarsal conjunctiva; a thick, ropy, mucoid, or frankly purulent discharge; corneal changes, such as punctate epithelial keratitis, epithelial macro-erosions, shield ulcer, plaque formation, and late corneal vascularization; acquired ptosis due to the heavy giant papillae, chronic eye rubbing, or an inflammatory insult |
| Concomitant diseases | Association with asthma, allergic rhinitis, and eczema (>40 % in Italy) |
| Seasonality | Appearance during spring but possible persistence beyond the summer season, all year |
| Response to therapy | Only partial efficacy of topical and systemic antihistamine drugs |

to treat VKC. In addition, the currently available drugs are merely palliative and do not have any influence on the pathogenic pathways, such as the immune auto-perpetuating process of the allergic inflammation of the conjunctiva [22]. Lastly, pharmacological treatment is protracted, and in some cases it should be used throughout the entire year for several years. Patients and parents should be made aware of the long duration of the disease, the efficacy and safety of the different medications, the possible insurgence of complications, and the potential evolution of VKC to inveteracy. Close collaboration between pediatricians and ophthalmologists is recommended to cover all the different aspects of this complicated disease. Table 3 shows the possible therapeutic strategies in VKC.

### 4.1 Non-Pharmacological Strategies

Patient compliance is the first and most important step in VKC management and may also improve the ultimate effects of pharmacological therapy. Patients should be instructed regarding the nature, duration, clinical characteristics, and possible complications of the disease. Moreover, the identification and avoidance of those environmental allergens (i.e., plants, flowers, animals) that could increase ocular symptoms is extremely useful, together with the avoidance of eye exposure to non-specific triggering factors (i.e., excessive exposure to sunlight, wind, and salt water). Sunglasses and any shading measures are helpful and should be used. Rubbing the eye should be strictly avoided because this may lead to mast-cell degranulation and increase the severity of eye symptoms [22]. The use of artificial tears is an important aid in the stabilization of the tear film and in relieving symptoms by removing or at least diluting the concentration of allergens from the ocular surface [22]. Contrarily, eye drops containing herbal extracts, such as chamomile-containing preparations, should not be used because of their effects in cross-reactions with sensitizing allergens [22, 23].

### 4.2 Topical Pharmacologic Treatments

The currently available topical drugs belong to several pharmacological classes: vasoconstrictors, mast-cell stabilizers, antihistamines, non-steroidal anti-inflammatory agents (NSAIDs), corticosteroids, immunomodulators, and immunosuppressive drugs.

#### *4.2.1 Topical Vasoconstrictors and Non-Specific Histamine-Receptor Blocker Combinations*

These formulations contain vasoconstrictors, such as naphazoline or tetrahydrozoline, and anti-histamines, such as pyrilamine or pheniramine. Included in the 'over-the-counter' drug category, they are used as a first-line therapy by many patients and they are effective in reducing common eye symptoms (i.e., redness, itching, stinging sensation), especially in the early stages of the disease. However, literature analysis of these medications shows that their prolonged use may lead to tachyphylaxis and may cause acute or chronic conjunctivitis (with epithelial toxicity) [24], without counting immediate side effects such as burning, a stinging sensation, and rebound hyperemia on installation [22].

#### *4.2.2 Topical Mast-Cell Stabilizers*

As mast-cell degranulation is a central mechanism in the pathogenesis of VKC, the use of molecules with the effects of preventing or at least lessening the degranulation and antagonizing effects of histamine is an interesting approach to VKC therapy. This action on mast cells reduces the amount of cytokines secreted, which leads to less recruitment of inflammation pathways and may prevent chronic transformation to VKC [25].

**Table 3** Possible therapeutic strategies in vernal keratoconjunctivitis (VKC)

| Therapy | Approach |
|---|---|
| Non-pharmacological strategies | Instructions for an adequate compliance |
| | Avoidance of environmental allergens |
| | Avoidance of eye exposure to non-specific triggering factors |
| | Sunglasses and shading measures |
| | Avoidance of eye rubbing |
| | Artificial tears |
| Topical pharmacological treatments | Vasoconstrictors and non-specific histamine-receptor blocker combination |
| | Mast-cell stabilizers |
| | Antihistamines |
| | Corticosteroids |
| | Non-steroidal anti-inflammatory drugs (NSAIDs) |
| | Immunomodulators |
| Systemic treatment in patients with concomitant allergic diseases | Oral antihistamines |
| | Omalizumab |
| | Specific immunotherapy |
| Surgical treatment | Supratarsal injection of corticosteroids |
| | Excision of giant papillae and associated cryotherapy to be considered only for superficial punctate keratitis recalcitrant to medical treatment |
| | Debridement of ulcer base to remove corneal plaque followed by a bandage contact lens for 24–48 h if maximum medical intervention fails |
| New drugs | Lipid conjugates |
| | Chlorogenic acid and its ester derivatives |
| | Glucosamine and its derivatives |
| | Phosphodiesterase inhibitors |
| | Toll-like receptor antagonists |
| | Interfering RNA |

Although it is well tolerated, sodium cromoglicate has limited efficacy because of the latency at which this drug gains full effect, without immediate relief of symptoms [26]. Moreover, sodium cromoglicate has no effect in antagonizing already released histamine [26].

Nedocromile appears to be more potent than sodium cromoglicate and acts on multiple inflammatory cells involved in the allergic response, including eosinophils, neutrophils, macrophages/monocytes, platelets, and mast cells. It reduces chemotaxis and mediator release in these cells [26].

Lodoxamide prevents tryptase release and inhibits eosinophil activation with an effectiveness superior to that of sodium cromoglicate [22, 26, 27].

*N*-Acetyl-aspartyl-glutamic acid (NAAGA) is largely used in Europe because it stabilizes mast cells, inhibits leukotriene synthesis, promotes leukocyte adhesion to the endothelium and complement-derived anaphylotoxin production, and antagonizes TNF-α-induced adhesion molecules. Therefore, it has anti-inflammatory potential [26].

Mast-cell stabilizers are the first-line therapy in patients with seasonal symptoms, and some authors have found that it is worth trying different mast-cell stabilizers in VKC if one fails before abandoning this group of drugs altogether [19]. In cases that fail, mast-cell stabilizer therapy could be enhanced by antihistamines [22].

### *4.2.3 Topical Antihistamines*

This class of drugs acts by antagonizing histamine receptors, which relieves or even prevents symptoms.

Most of these molecules are H1 antagonists, but some agents may act as H2 antagonists and thus modulate cell growth and migration [28].

Topical antihistamines demonstrated a longer duration of action than topical vasoconstrictors, mast-cell stabilizers, and other drops containing NSAIDs and corticosteroids [22].

Levocabastine and emedastine are selective H1 receptor antagonists and have a long-term effect in a manner superior to other antihistamines [29]. This is probably due to the inhibition of cytokine production and the downregulation of surface/adhesion molecules such as ICAM-1; that is, effects that are additional to its anti-H1-receptor action.

In the same group as antihistamines, some drugs (such as olopatadine, ketotifen, epinastine, azelastine, alcaftadine, and bepotastine) have dual actions, as they are both antihistamines and mast-cell stabilizing molecules. Some studies also show that these drugs act to reduce the production of TNF-α, inflammatory mediators, and leukotrienes [30, 31]. All of these medications are well tolerated, and none of them is associated with significant ocular drying effects. They appear useful in patients with mainly seasonal symptoms.

#### *4.2.4 Topical Corticosteroids and Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)*

The treatment of severe VKC using topical corticosteroids should be considered in the acute phase as monotherapy or in addition to other drugs, such as multiple-action antihistamines or artificial tears [27]. Once symptoms are controlled, topical corticosteroids should be suspended, while multiple-action antihistamines should be continued.

The most commonly used molecules are topical dexamethasone and prednisone, but in the last few years loteprednol etabonate, rimexolone, and fluorometholone have become a strongpoint in VKC treatment, along with the supratarsal injection of dexamethasone, triamcinolone or hydrocortisone [22].

Corticosteroids should be avoided as the first-line treatment for VKC. It is well known that the prolonged and uncontrolled use of topical corticosteroids may cause cataracts, ocular hypertension, and glaucoma, and could also increase susceptibility to ocular infections [32–34]. For these reasons, it is ideal to prescribe topical corticosteroids for short-term therapy using drops with low intraocular absorption, such as hydrocortisone, clobetasone, desonide, fluorometholone, loteprednol, difluprednate, and rimexolone.

Topical formulations of ketorolac, diclofenac, and indomethacin may be valid alternatives to topical antihistamines (whenever these are not sufficient in controlling the symptoms) and to topical corticosteroids [35–37]. They have shown itching- and hyperemia-diminishing properties, with a reduction of both serum ICAM-1 and tear tryptase levels. They can be used to reduce the administration of topical corticosteroids. However, their long-term efficacy and safety have not been clearly defined.

#### *4.2.5 Topical Immunomodulators*

Several topical immunomodulatory agents, such as cyclosporine A (CsA), tacrolimus, mycophenolatemofetil (MMF), leflunomid, rapamycin (sirolimus), capoxone, laquinimod, and infliximab, have shown efficacy in the treatment of some ocular immune-mediated diseases, including VKC [38]. The two products for which there is the largest amount of data are CsA and tacrolimus.

CsA is an inhibitor of the calcineurin pathway, and calcineurin is an intracellular protein that binds its receptor, cyclophilin. As a result, the use of CsA reduces the production of cytokines and chemokines in inflammatory cells, such as $T_h2$ cells, which are involved in pathogenesis of VKC [39]. Moreover, it interferes with the recruitment of eosinophils and the degranulation of both basophils and eosinophils [40].

The first use of CsA in VKC treatment dates back to the 1990s. Many studies in the past decade showed the high efficacy of CsA in diminishing VKC symptoms [41–45]. However, the prolonged use of oil formulations containing CsA may induce burning, stinging, and even blepharitis, whereas CsA in an aqueous preparation did not show such effects. The aqueous formulation also has a better tissue distribution than the ointment, which could lower the CsA concentration [41–45]. However, while various CsA formulations with different CsA concentrations (from 0.05 to 2 %) have been evaluated, the minimum effective concentration of CsA remains unknown. De Smelt et al. performed a large prospective, double-masked, clinical trial involving 366 consecutive patients with VKC which were randomized to receive either topical CsA 2 % dissolved in an olive oil vehicle or dexamethasone 0.1 % drops for 4 weeks [46]. Although the majority of participants tolerated the test medications well, the drops that contained CsA were associated with more reported discomfort than the oil placebo and dexamethasone ($p < 0.001$).

Topical CsA is effective rapidly, within 2–15 days of therapy in relation to the state of the disease and the concentration of drug used, but relapses are observed after treatment has ended [47]. In addition, patients who present giant papillae are less responsive. Efficacy studies of responses to topical CsA show an efficacy for a few months in the presence of a good safety profile, suggesting that CsA should be used for long-term treatment and continuously to achieve the most long-lasting benefit and to avoid steroids for as long as possible in patients with persistent VKC [47].

Tacrolimus (formerly known as FK-506), like CsA, is a macrolide antibacterial drug that exerts immunosuppressant effects on T cells. An ophthalmic suspension of tacrolimus for the topical management of VKC has been proven to be effective and free from any adverse effects

after a 4-week trial [47, 48]. Moreover, several recent studies that compared tacrolimus and CsA showed that tacrolimus has a similar efficacy to CsA, with lower adverse effects with tacrolimus than CsA [47–50]. These recent publications highlighted that the high success of tacrolimus and its safety may change the traditional therapeutic approach to VKC.

### 4.3 Systemic Treatment for Patients with Associated Allergic Symptoms

Systemic treatment of VKC (especially in patients with associated allergy) with oral antihistamines is widely used. Oral antihistamines are known to be effective in relieving most VKC symptoms [51, 52]. Second-generation antihistamines are effective in reducing itching, hyperemia, and other ocular symptoms [51, 52]. This group is preferred to its first-generation counterparts because it presents lower sedative and no anticholinergic activities.

Another choice of treatment may be omalizumab, a monoclonal humanized antibody whose target is the IgE receptor-binding domain; this therapeutic strategy is highly effective in patients with associated severe allergic symptoms [47, 51].

If the allergens responsible for the allergic comorbidity are fully known, it is possible to start allergen-specific immunotherapy (SIT) in order to prevent acute symptoms [52]. SIT has an effect on regulatory T cells and is also associated with an increase in IgG4 production, suggesting that SIT could induce a switch in the Ig isotype class. SIT may have a role in VKC patients with mild symptoms and with hypersensitivity towards one or a few allergens [52].

### 4.4 Surgical Treatment

The supratarsal injection of corticosteroids is a treatment option for patients with no response to pharmacological therapies [53]. The excision of giant papillae and variably associated cryotherapy should be avoided because these strategies are merely palliative and should be considered only for superficial punctate keratitis recalcitrant to medical treatment. Debridement of the ulcer base to remove the corneal plaque followed by a bandage contact lens for 24–48 h can be attempted if medical intervention fails [53].

### 4.5 New Drugs

In the last few years, researchers have acquired a great number of patents for newly discovered drugs designed to treat VKC and concomitant allergic symptoms.

A recent invention discloses a method of treating conjunctivitis caused by contact with a pathogen or allergen by administering lipid conjugates [1]. Lipid conjugates have an inhibitory effect on the phospholipase A2 enzyme, which catalyzes the breakdown of phospholipids and starts the eicosanoid (leukotriene B4 and prostaglandin E2) pathway of signaling. Lipid conjugates reduce the production of this group of lipid mediators as well as that of inflammatory mediators such as TNF-α and IL-8.

Chlorogenic acid and its ester derivatives exhibit an anti-inflammatory effect comparable to that of steroidal drugs, although they act on transglutaminase, a protein activated during the inflammation pathway [54]. With its use, researchers found a significant decrease in the degree of conjunctival edema and redness in animals [54]. These compounds can be used in monotherapy or in addition to other anti-inflammatory drugs. They can be formulated in an oral dosage form, into injections for subcutaneous, intravenous or intramuscular routes, or in the form of inhalation sprays, exhibiting a high versatility useful for better patient compliance. Similarly, glucosamine and its derivatives have recently been approved in the treatment of allergic and irritant conjunctivitis as ophthalmic eye drops or ointment [54].

The secondary messenger cyclic adenosine monophosphate (cAMP) plays a central role in the activity of neutrophils, eosinophils and mast cells, and its pathway is regulated by phosphodiesterase (PDE) IV, which hydrolyzes cAMP. Therefore, some studies searched for drugs that increase the intracellular concentration of cAMP and inhibit PDE. New compounds containing 3-anilino-2-cycloalkenon derivatives are claimed to have a PDE IV inhibitory activity and are expected to suppress the activation of the inflammatory cells [55]. Epinastine inhibits the influx of toxic eosinophilic granule protein, enzymes, and mast-cell mediators (such as histamine) into the conjunctiva and prevents long-lasting effects in the treatment of allergic conjunctiva [2]. This compound has an analog activity as a mast-cell stabilizer [2].

Toll-like receptors (TLRs) are expressed on immune system cells, and whenever pathogenic ligands bind to the TLRs, those molecules initiate the production of cytokines and inflammatory mediators that cause inflammation [7]. Additionally, TLRs are hypothesized to modulate $T_h1/T_h2$ lymphocyte equilibrium that leads to allergic diseases [7]. Novel compositions with antagonizing, inhibitory, and down-regulating actions on human TLRs and co-receptors have been studied [7].

Lastly, there is great interest in small interfering RNA, which acts by silencing spleen tyrosine kinase (Syk). Syk is activated by immune receptors, such as FcεRI, which causes the activation of PLCγ and PI3K pathways and results in mast-cell degranulation [5]. Interfering RNA could alleviate Syk-related allergic conditions while avoiding the adverse effects of systemic antihistamines [5]. Although this recently discovered approach could be promising, it is still far from being used clinically.

## 5 Conclusions

The selection of a therapeutic scheme from the many available options in the approach to patients with VKC is based on clinical features and the personal preference of both physicians and patients. Due to the lack of uniform grading of the disease's severity, there is no worldwide consensus on the first-line and second-line therapeutic approaches.

Topical monotherapy with mast-cell stabilizers, with a preference for those with an anti-eosinophil effect (such as NAAGA and lodoxamide), should be started at the onset of symptoms and used continuously throughout the season. Antihistamines or multiple-acting drugs, such as olopatadine and ketotifen, should be added if monotherapy is insufficient to treat symptoms. On the other hand, oral antihistamines could be used together with topical options in patients with allergic comorbidity, which is common. Similarly, if the allergen responsible for the concomitant physiopathology of the allergy is well known, SIT may be considered.

Moderate to severe clinical conditions may require topical steroid treatment, at least for the short-term management of the acute symptoms. The first choice should be the so-called modified corticosteroids (i.e., loteprednol, rimexolone, fluorometholone) in monotherapy or in addition to antihistamines or mast-cell stabilizers. Although their use in VKC treatment has been limited, NSAIDs may be considered for use in a steroid-sparing strategy.

Other choices for the treatment of long-term moderate to severe VKC are represented by topical CsA or tacrolimus. Although results on the use of tacrolimus showed high success in the presence of a positive safety profile, further data are needed to define the minimal effective concentration and long-term safety of these drugs in eye drops and to clarify characteristics of patients who require these molecules.

Before the newly discovered drugs can enter into clinical practice, further studies on their efficacy and safety are required.

**Compliance with Ethical Statements**

**Conflict of interest** SE, GF, AM, SO and DG have no conflicts of interest to declare.

**Funding** This review was supported by a grant from the Italian Ministry of Health (Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Fondo Ricerca Corrente 2016 850/01).

## References

1. Kumar S. Vernal keratoconjunctivitis: a major review. Acta Ophthalmol. 2009;87:133–47.
2. Bonini S, Sacchetti M, Mantelli F, Lambiase A. Clinical grading of vernal keratoconjunctivitis. Clin Immunol. 2007;7:436–41.
3. Leonardi A, Busca F, Motterle L. Case series of 406 vernal keratoconjunctivitis patients: a demographic and epidemiological study. Acta Ophtalmol Scand. 2006;84:406–10.
4. Bonini S, Bonini S, Lambiase A, Marchi S, Pasqualetti P, Zuccaro O, Rama P, Magrini L, Juhas T, Bucci MG. Vernal keratoconjuntivitis revisited. A case series of 195 patients with long-term follow up. Ophtalmology. 2000;107:1157–63.
5. Pattnaik L, Acharya L. A comprehensive review on vernal keratoconjuntivitis with emphasis on proteomics. Life Sci. 2015;128:47–54.
6. Kosrirukvongs P, Vichyanond P, Wongsawad W. Vernal keratoconjunctivitis in Thailand. Asian Pac J Allergy Immunol. 2003;21:25–30.
7. De Smedt S, Wildner G, Kestelyn P. Vernal keratoconjunctivitis: an update. Br J Ophtalmol. 2013;97:9–14.
8. Bonini S, Coassin M, Aronni S, Lambiase A. Vernal keratoconjunctivitis. Eye. 2004;18:345–51.
9. Miyoshi T, Fukagawa K, Shimmura S, Fujishima H, Takano Y, Takamura E, Tsubota K, Saito H, Oguchi Y. Interleukin 8 concentrations in conjunctival epithelium brush cytology samples correlates with neutrophil, eosinophil infiltration, and corneal damage. Cornea. 2001;20:743–7.
10. Zicari AM, Nebbioso M, Zicari A, Mari E, Celani C, Occasi F, Tubili F, Duse M. Serum levels of IL-17 in patients with vernal keratoconjunctivitis: a preliminary report. Eur Rev Med Pharmacol Sci. 2013;17:1242–4.
11. Gomes PJ, Ousler GW, Welch DL, Smith LM, Coderre J, Abelson MB. Exacerbation of signs and symptoms of allergic conjunctivitis by a controlled adverse environment challenge in subjects with a history of dry eye and ocular allergy. Clin Ophthalmol. 2013;7:157–65.
12. Leonardi A, Borghesan F, Faggian D, Depaoli M, Secchi AG, Plebani M. Tear and serum soluble leukocyte. Am J Ophtalmol. 2000;129:151–8.
13. Zicari AM, Zicari A, Nebbioso M, Mari E, Celani C, Lollobrigida V, Cesoni Marcelli A, Occasi F, Duse M. 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;25:57–63.
14. Zicari AM, Nebbioso M, Lollobrigida V, Bardanzellu F, Celani C, Occasi F, Cesoni Marcelli A, Duse M. Vernal keratoconjunctivitis: atopy and autoimmunity. Eur Rev Med Pharmacol Sci. 2013;17:1419–23.
15. Metz DP, Bacon AS, Holgate ST. Phenotypic characterisation of T-cells infiltrating the conjunctiva in chronic allergic eye disease. J Allergy Clin Immunol. 1996;98:686–96.
16. Miyazaki D, Nakamura T, Komatsu N. Roles of chemokines in ocular allergy and possible therapeutic strategies. Cornea. 2004;23(Suppl. 1):S48–54.
17. Tabbara K. Tear tryptase in vernal keratoconjunctivitis. Arch Ophtalmol. 2001;119:338–42.
18. Tuft SJ, Dart JKG, Kemeny M. Limbal vernal keratoconjunctivitis: clinical characteristics and immunoglobilin E expression compared with palpebral vernal. Eye. 1989;3:420–7.
19. Vichyanond P, Pacharn P, Pleyer U, Leonardi A. Vernal keratoconjunctivitis: a severe allergic eye disease with remodeling changes. Pediatr Allergy Immunol. 2014;25:314–22.
20. Griffin RY, Sarici A, Unal L. Acquired ptosis secondary to vernal conjunctivitis in young adults. Ophthalmic Past Reconstr Surg. 2006;22:438–40.
21. Le Q, Hong J, Zhu W, Sun X, Xu J. In vivo laser scanning confocal microscopy of vernal keratoconjunctivitis. Clin Exp Ophtalmol. 2011;39:53–60.

22. Kumar S, Gupta N, Vivian AJ. Modern approach to managing vernal keratoconjunctivitis. Curr Allergy Asthma Rep. 2010;10:155–62.
23. Bielory L. Ocular allergy guidelines: a practical treatment algorithm. Drugs. 2002;62:1611–34.
24. Soparkar CN, Wilhelmus KR, Koch DD, Wallace GW, Jones DB. Acute and chronic conjunctivitis due to over-the-counter ophtalmic decongestants. Arch Ophtalmol. 1997;115:34–8.
25. Church MK, McGill JI. Human ocular mast cells. Curr Opin Allergy Clin Immunol. 2002;2:419–22.
26. Leonardi A. Management of vernal keratoconjunctivitis. Ophthalmol Ther. 2013;2:73–88.
27. Leonardi A, Borghesan F, Avarello A, Plebani M, Secchi AG. Effect of lodoxamide and disodium cromoglicateon tear eosinophil cationic protein in vernal keratoconjunctivitis. Br J Ophthalmol. 1997;81:23–6.
28. Bielory L, Ghafoor S. Histamine receptors and the conjunctiva. Curr Opin Allergy Clin Immunol. 2005;5:437–40.
29. Wiemer 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;115:288–93.
30. Hida WT, Nogueira DC, Schaefer A, Dantas PE, Dantas MC. Comparative study between 0.025 % ketotifen fumarate and 0.1 % olopatadine hydrochloride in the treatment of vernal keratoconjunctivitis. Arq Bras Ophtalmol. 2006;69:851–6.
31. McGill JI. A review of the use of olopatadine in allergic conjunctivitis. Int Ophtalmol. 2004;25:171–9.
32. Carnahan MC, Goldstein DA. Ocular complications of topical, peri-ocular, and systemic corticosteroids. Curr Opin Ophtalmol. 2000;11:478–83.
33. McGhee CN, Dean S, Danesh-Meyer H. Locally administered ocular corticosteroids: benefits and risks. Drug Saf. 2002;25:33–55.
34. Ang M, Ti SE, Loh R, Farzavandi S, Zhang R, Tan D, Chan C. Steroid-induced ocular hypertension in Asian children with severe vernal keratoconjunctivitis. Clin Ophtalmol. 2012;6:1253–8.
35. Sharma A, Gupta R, Ram J, Gupta A. Topical ketorolac 0.5 % solution for the treatment of vernal conjunctivitis. Indian J Ophtalmol. 1997;45:177–80.
36. D'Angelo G, Lambiase A, Cortes M, Sgrulletta R, Pasqualetti R, Lamagna A, Bonini S. Preservative-free diclofenac sodium 0.1% for vernal keratoconjunctivitis. Graefes Arch Clin Exp Ophtalmol. 2003;241:192–5.
37. Gupta S, Khurana AK, Ahluvalia BK, Gipta NC. Topical indomethacin for vernal keratoconjunctivitis. Acta Ophtalmol (Copenh.). 1991;69:95–8.
38. Bertelmann E, Pleyer U. Immunomodulatory therapy in ophthalmology. Is there a place for topical application? Ophthalmologica. 2004;218:359–67.
39. Fukushima A. Roles of T-cells in the development of allergic conjunctival disease. Cornea. 2007;26(Suppl. 1):S36–40.
40. Keklikci U, Dursun B, Cingu AK. Topical cyclosporin A 0.05 % eyedrops in the treatment of vernal keratoconjunctivitis. Randomized placebo-controlled trial. Adv Clin Exp Med. 2014;23:455–61.
41. Pucci N, Novembre E, Cianferoni A, Lombardi E, Bernardini R, Caputo R, Campa L, Vierucci A. Efficacy and safety of cyclosporine eyedrops in vernal keratoconjunctivitis. Ann Allergy Asthma Immunol. 2002;89:298–303.
42. Kilic A, Gurler B. Topical 2 % cyclopsporine A in preservative-free artificial tears for treatmentof vernal keratoconjunctivitis. Can J Opthalmol. 2006;41:693–8.
43. Spadavecchia L, Fanelli P, Tesse R, Brunetti L, Cardinale F, Bellizzi M, Rizzo G, Procoli U, Bellizzi G, Armenio L. Efficacy of 1.25 % and 1 % topical cyclosporine in the treatment of severe vernal keratoconjunctivitis in childhood. Pediatr Allergy Immunol. 2006;17:527–32.
44. Ebihara N, Ohashi Y, Uchio E, Okamoto S, Kumagai N, Shoji J, Takamura E, Nakagawa Y, Nanba K, Fukushima A, Fujishima H. A large prospective observational study of novel cyclosporine 0.1 % aqueous ophtalmic solution in the treatment of severe allergic conjunctivitis. J Ocul Pharmacol Ther. 2009;25:365–72.
45. Wu MM, Yau GS, Lee JW, Wong AL, Tam VT, Yuen CY. Retrospective review on the use of topical cyclosporin a 0.05 % for paediatric allergic conjunctivitis in Hong Kong Chinese. Scient World J. 2014;2014:396987.
46. De Smelt S, Nkurikiye J, Fonteyne Y, Tuft S, De Bacquer D, Gilbert C, Kestelyn P. Topical ciclosporin in the treatment of vernal keratoconjunctivitis in Rwanda, central Africa: a prospective, randomised, double-masked, controlled clinical trial. Br J Ophthalmol. 2012;96:323–8.
47. Vichyanond P, Kosrirukvongs P. Use of cyclosporine A and tacrolimus in treatment of vernal keratoconjunctivitis. Curr Allergy Asthma Rep. 2013;13:308–14.
48. Ohashi Y, Ebihara N, Fujishima H, Fukushima A, Kumagai N, Nakagawa Y, Namba K, Okamoto S, Shoji J, Takamura E, Hayashi K. A randomized, placebo-controlled clinical trial of tacrolimus ophthalmic suspension 0.1 % in severe allergic conjunctivitis. J Ocul Pharmacol Ther. 2010;26:165–174.
49. Labcharoenwongs P, Jirapongsananuruk O, Visitsunthorn N, Kosrirukvongs P, Saengin P, Vichyanond P. A double-asked 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;30:177–184.
50. Pucci N, Caputo R, di Grande L, de Libero C, Mori F, Barni S, di Simone L, Calvani A, Rusconi F, Novembre E. Tacrolimus vs. cyclosporine eyedrops in severe cyclosporine-resistant vernal keratoconjunctivitis: a randomized, comparative, double-blind crossover study. Pediatr Allergy Immunol. 2015;26:256–61.
51. de Klerk TA, Sharma V, Arkwright PD, Biswas S. Severe vernal keratoconjunctivitis successfully treated with subcutaneous omalizumab. J AAPOS. 2013;17:305–6.
52. Vichyanond P, Pacharn P, Pleyer U, Leonardi A. Use of cyclosporine A and tacrolimus in treatment of vernal keratoconjunctivitis. Pediatr Allergy Immunol. 2014;25:314–22.
53. Reddy JC, Basu S, Saboo US, Murthy SI, Vaddavalli PK, Sangwan VS. Management, clinical outcomes, and complications of shield ulcers in vernal keratoconjunctivitis. Am J Ophtalmology. 2013;155:550–559, e1.
54. Sohn J, Kim TI, Yoon YH, Kim JY, Kim SY. Novel transglutaminase inhibitors reverse the inflammation of allergic conjunctivitis. J Clin Invest. 2003;111:121–8.
55. Yanni JM, Sharif NA, Gamache DA, Miller ST, Weimer LK, Spellman JM. 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.