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REVIEW

Management of Vernal Keratoconjunctivitis

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ABSTRACT

Vernal keratoconjunctivitis (VKC) is a relatively rare, chronic form of ocular allergy that can potentially cause severe visual complications. Affecting mainly children and young adults, it is an IgE- and T cell-mediated disease, leading to a chronic inflammation in which eosinophil, lymphocyte and structural cell activation are involved. Treatment of VKC requires a multiple approach that includes conservative measures and pharmacologic treatment. Patients and parents should be made aware of the long duration of disease, its chronic evolution and possible complications. Treatment should be based on the duration and frequency of symptoms and the severity of corneal involvement. Mast cell stabilizers and antihistamines have been proven to be effective for the treatment of mild to moderate forms of VKC. In the most severe cases, topical steroids can be used as rescue medication to reduce conjunctival and corneal inflammation. Immunomodulators that have been investigated for VKC treatment include topical ocular preparations of cyclosporine A and tacrolimus. Topical cyclosporine A has been proven to be effective in the long-term treatment of VKC, significantly improving signs and symptoms without significant side effects.

Keywords: Anti-allergic treatment; Cyclosporine A; Grading system; Immunomodulation; Vernal keratoconjunctivitis

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INTRODUCTION

Allergic conjunctivitis is a localized allergic condition frequently associated with rhinitis, but is often observed as the only or prevalent allergic phenomenon. Ocular allergy can involve all of the components of the ocular surface, including the lid and lid margin,

conjunctiva and the lacrimal system. The term allergic conjunctivitis refers to a collection of hypersensitivity disorders that affect the lid and conjunctiva. Various clinical forms are included in the classification of ocular allergy: seasonal/intermittent allergic conjunctivitis (SAC), perennial/persistent allergic conjunctivitis (PAC), vernal keratoconjunctivitis (VKC), atopic keratoconjunctivitis (AKC) and drug-induced dermato-conjunctivitis [1]. Corneal involvement is typically restricted to the two most severe forms of ocular allergy, vernal keratoconjunctivitis (VKC) and atopic keratoconjunctivitis (AKC), which requires particular care in their management.

The current review focuses on the practical management of VKC, a recurrent, bilateral, chronic allergic inflammatory disease of the ocular surface affecting mainly children and young adults and is characterized by incompletely identified pathogenic mechanisms. Several therapeutic measures are required to control signs and symptoms of the disease and avoid potential long-standing or permanent inflammatory sequelae. Although topical anti-allergic and anti-inflammatory eye drops are the mainstay of treatment for VKC, a gold standard treatment has not yet been established for this disease.

VERNAL KERATOCONJUNCTIVITIS

VKC is a severe inflammatory disease that appears in children and adolescents with seasonal recurrence. It is most often seen in boys and tends to resolve at puberty. It is a relatively rare, chronic form of ocular allergy that can cause severe visual complications [2–4]. VKC is more frequent in warmer, arid, windy climates, in the Mediterranean area, central Africa, Japan, India, and South America but is also reported in North America, China, Australia, Great Britain, and Sweden. VKC appears mainly seasonally but can be perennial, chronic or with acute exacerbations. It is an IgE- and T cell-mediated allergic reaction with additional, ill-defined, perhaps nonspecific, hypersensitivity responses. The etiology involves a variety of factors, including environmental allergens, climate, and genetic predisposition. Cytologic, biohumoral, immunohistologic, and molecular biologic studies indicate that VKC is a Th2 lymphocyte-mediated disease. Mast cells and eosinophils and their mediators play major roles in the clinical manifestations. In addition to typical Th2-derived cytokines, Th1-type cytokines, chemokines, growth factors, and enzymes are over-expressed [5]. Increased serum levels of IL-17 and antinuclear antibodies, together with a high association with familial history of autoimmune disorders suggest additional mechanisms involved in the development of VKC [6, 7]. Tissue remodeling reactions, papillae formation of different sizes and shapes, stem cell deficiency, and various degrees of superficial corneal opacification, are further consequences of chronic inflammation [8]. Many elements contribute to this dramatic response, including epithelial changes, connective tissue deposition, edema, inflammatory cell infiltration, and glandular hypertrophy.

Clinical Forms

It is well known that two VKC populations can be defined: (1) those with positive test results, who generally also present with some other allergic manifestation, such as asthma, rhinitis, or eczema and (2) those with negative test

results, and a negative personal and familial history of atopy.

The disease may present in three clinical forms: tarsal, limbal and the mixed form. Large papillae of different shape and size, usually greater than 1 mm in diameter, on the upper tarsal conjunctiva characterize the tarsal form, while Trantas' dots and infiltrates on the limbus are typical of the limbal form. The mixed form is characterized by the presence of both forms in the same eye. VKC sufferers have a characteristic ropey, stringy mucous and/or serous discharge, and corneal complications, such as superficial punctate keratopathy (SPK), and shield ulcers are common. Moderate to intense conjunctival hyperemia, intense itching, photophobia, mild to moderate chemosis, foreign-body sensation, and pain are typical signs and symptoms which may be very intense upon awakening, causing frequently what is called the morning misery. While it is considered a long-term disease with an average duration of 4–8 years, VKC generally subsides before or just after puberty [1, 2, 4]. It can persist or reactivate after puberty, however, a VKC-like disease has been found in young adults without any history of allergic disease in childhood [9]. This new clinical entity is characterized by signs and symptoms similar to the typical VKC. Allergy test results, cytokine production, and quality of life are similar to those in pediatric VKC. It is still unclear if this is a sub-type of VKC with a later onset or a different clinical entity.

Diagnosis

VKC is not difficult to diagnose by clinical examination. Trantas' dots and large cobblestone papillae are indicative of the condition [1, 2]. VKC is differentiated from other ocular allergic conditions, such as SAC, PAC, AKC, ocular rosacea in children, and infectious conjunctivitis, through a comprehensive clinical history and ophthalmic examination. It is important to note that while skin test results may be positive, VKC is not always closely related to allergen exposure, and climate is an equally important factor. Conjunctival scrapings or tear cytology can be useful, revealing increased leukocytes in the conjunctiva, particularly eosinophils [1, 2].

MANAGEMENT OF VKC

Understanding and treating VKC has been a challenge for ophthalmologists, since the pathogenesis is unclear and anti-allergic therapy often unsuccessful. VKC is an IgE- and T cell-mediated disease, leading to a chronic inflammation in which eosinophil, lymphocyte and structural cell activation characterize the conjunctival allergic reaction. Therefore, measures aimed at stabilization of mast cells or histamine receptor antagonists alone are frequently insufficient for controlling conjunctival inflammation and the frequent corneal involvement [1, 2]. Currently available drugs may be merely palliative and do not extinguish the complex immune process that initiates and perpetuates the allergic ocular surface inflammation.

In a meta-analysis of randomized clinical trials evaluating topical treatments for VKC, only 10 of 21 studies were suitable for statistical analysis, and the authors concluded that the currently available topical drugs are effective in treating acute phases of VKC [10]. However, controlling VKC signs and symptoms may be a challenge even for expert ophthalmologists. Because of the chronicity and severity of the disease, avoidance of triggers and life-style planning must be

accompanied by pharmacological treatments: topical ocular and non-ocular pharmacologic treatment, systemic pharmacologic treatments and immunotherapy.

Non-Pharmacologic Management

Patients and parents should be instructed regarding the nature and duration of the disease, clinical characteristics and possible complications. Psychological support may be necessary in severe cases. The first line of VKC management, when possible, is the identification of allergens and avoidance of those environmental factors that may exacerbate the disease. Avoiding exposure to nonspecific triggering factors, such as sun, wind, and salt water, with the use of sunglasses, hats with visors, and swimming goggles should be recommended. Frequent hand, face, and ear washing should also be suggested. Cold compresses may help as natural decongestant. Tear substitutes aid in stabilization of the tear film, act as an eyewash, and dilute the concentration of the allergens and mediators in tears. Eye drops containing herbal extracts, such as chamomile-containing preparations, should be avoided because they may cross-react with sensitizing allergens [11] (Table 1).

Table 1 Patient education and preventive measures to improve the management of vernal keratoconjunctivitis

VKC is a chronic, recurrent condition that usually improves by adulthood
Avoid rubbing itchy eyes, as this makes the condition worse
Avoid provocative nonspecific triggers such as sun, wind, and salt water, that exacerbate the condition, using sunglasses, hats with visors, swimming goggles where necessary
Avoid contact with commonly known allergens
Application of cold compresses and preservative-free artificial tears help to provide symptomatic relief
Hands, face and hair should be washed frequently to reduce exposure to allergens
Plan to take vacations in suitable climates

Topical Ocular Pharmacologic Treatment

Pharmacological treatment should be planned ahead in patients with a history of VKC and started in the early spring or continued all year, depending on the allergen exposure and duration of the symptoms. Currently available topical drugs for allergic conjunctivitis belong to several pharmacologic classes (Table 2): vasoconstrictors, antihistamines, mast cell stabilizers, 'dual-acting' agents (with antihistaminic and mast cell stabilizing properties), non-steroidal anti-inflammatory agents, corticosteroids and immunosuppressive drugs.

Mast Cell Stabilizers

Mast cell stabilizers are the first-line drugs for VKC. Topical mast cell stabilizers are generally safe and have minimal ocular side effects, although there may be some tolerability concerns, since transient burning or stinging may occur upon application. Several studies have demonstrated the efficacy of 2% and 4% sodium cromoglicate (DSCG, cromolyn), nedocromil sodium 2%, lodoxamide tromethamine 0.1%, and spaglumic acid 4% [12–14]. The recommended dosing schedule is 4–6 times daily, with a loading period of at least 7 days and an onset of activity after as much as 2 weeks. DSCG alone has limited effects in the treatment of VKC and is less well tolerated than newer anti-allergic compounds. Nedocromil appears to be more potent than DSCG [15], acting on multiple cells involved in allergic

Table 2 Topical ocular allergy medications for the treatment of vernal keratoconjunctivitis

Class	Drug	Indication	Comments
Vasoconstrictor/ antihistamine combinations	Naphazoline/pheniramine	Rapid onset of action Episodic itching and redness	Short duration of action Tachyphylaxis Mydriasis Ocular irritation Hypersensitivity Hypertension Potential for inappropriate patient use
Antihistamines	Levocabastine Emedastine	Relief of itching Relief of signs and symptoms	Short duration of action Frequently does not provide complete disease control when used alone
Mast cell stabilizers	Sodium cromoglicate Nedocromil Lodoxamide NAAGA Pemirolast	Relief of signs and symptoms	Long-term usage Slow onset of action Prophylactic dosing Frequently does not provide complete disease control when used alone
Antihistamine/mast cell stabilizers (dual-acting)	Alcaftadine Azelastine Bepotastine Epinastine Ketotifen Olopatadine	Relief of itching Relief of signs and symptoms	Bitter taste (azelastine) No reported serious side effects Frequently does not provide complete disease control when used alone
Corticosteroids	Loteprednol Fluormetholone Desonide Rimexolone Dexamethasone Betamethasone	Treatment of allergic inflammation Use in moderate to severe forms	Risk for long-term side effects No mast cell stabilization Potential for inappropriate patient use Requires close monitoring

inflammation, including eosinophils, neutrophils, macrophages, mast cells, monocytes, and platelets.

Lodoxamide has long been available for the treatment of VKC. Its mechanism of action is thought to be similar to that of DSCG, since it was shown to prevent tryptase release [16]. Lodoxamide was shown to be more effective than DSCG for the inhibition of eosinophil activation, evaluated by measuring tear

eosinophil cationic protein ECP before and after therapy [17], suggesting that lodoxamide has an effect on eosinophil activation. Inhibition of eosinophil activation and degranulation is the proposed mechanism for its efficacy against corneal signs such as keratitis and shield ulcers in severe allergic disease [17]. Lodoxamide was shown to be superior to placebo [18] and *N*-acetyl aspartyl glutamic acid (NAAGA) for treatment of VKC [19]. The recommended dosing schedule is four times daily. Lodoxamide may be used continuously for 3 months in children older than 2 years of age.

NAAGA 6% has been widely used in Europe as topical eye drops in the treatment of VKC [20]. NAAGA is known to inhibit leukotriene synthesis, histamine release by mast cells, and complement-derived anaphylatoxin production. This anti-allergic compound was also shown to directly inhibit leukocyte adhesion to endothelial cells induced by proinflammatory stimuli, and abrogates tumor necrosis factor α-induced expression of adhesion molecules on granulocytes and endothelial cells [21]. These pharmacological properties confer a potential anti-inflammatory activity.

Antihistamines

Antihistamines act via histamine receptor (HR) antagonism to block the inflammatory effects of endogenous histamine and prevent or relieve the associated signs and symptoms. Most antihistamines used in the treatment of allergy are H_1 receptor antagonists, although some agents may have affinity for other receptor subtypes [22]. H_2 antagonists have been shown to modulate both cell growth and migration [22]. Ocular drugs with antihistaminic activity may offer therapeutic advantages to patients with allergic conjunctivitis, including VKC, by inhibiting proinflammatory cytokine secretion from conjunctival epithelial cells [23]. The first-generation antihistamines pheniramine and antazoline have a long safety record, but are known for their burn upon instillation, the rapid onset and disappearance of their effects, and their limited potency [24]. These are still available in over-the-counter products, particularly in combination with vasoconstrictors.

The newer antihistamines are still H_1 antagonists, but have a longer duration of action (4–6 h), and are better tolerated than their predecessors. These include levocabastine hydrochloride 0.5% and emedastine difumarate 0.05%.

Levocabastine 0.05% eye drops alone, instilled four times daily for 3 months, was effective, safe, and well tolerated by patients with VKC; however, it was less effective than lodoxamide [25] or NAAGA [20]. Interestingly, in an animal model, levocabastine reduced the clinical aspects of the late-phase reaction and the conjunctival expression of alpha(4)beta(1) integrin by reducing infiltration of eosinophils [26].

Emedastine 0.05% appears to be more potent and selective than levocabastine [27, 28]. Indeed, in direct comparison with levocabastine, emedastine proved significantly more effective in alleviating signs of seasonal allergic conjunctivitis [27, 28]. No specific studies in VKC have been performed.

A meta-analysis of randomized clinical trials in VKC showed a large number of studies (20) evaluated the efficacy of common anti-allergic eye drops (levocabastine, lodoxamide, mipragoside, NAAGA, nedocromil sodium, DCG). Among these, lodoxamide appeared to be the most effective [10].

Topical Antihistamines with Multiple Anti-Inflammatory Activities

New antihistamines that combine mast cell stabilizing properties and histamine receptor antagonism, such as alcaftadine, azelastine, bepotastine, epinastine, ketotifen, and olopatadine, are presently available and show evident benefits in treating all forms of ocular allergy. The advantage offered by these agents is the rapidity of symptomatic relief given by immediate histamine receptor antagonism, which alleviates itching and redness, coupled with the long-term disease-modifying benefit of mast cell stabilization. All of these medications are well tolerated and none are associated with significant ocular drying effects. Although widely used in the treatment of VKC, specific studies in VKC are very few. Olopatadine and ketotifen have shown efficacy in relieving signs and symptoms in patients with VKC. These two drugs may have also anti-inflammatory properties, reducing eosinophil activation and cytokine release. A significant difference in favor of ketotifen-treated patients has being shown in a single-center, simple-masked study comparing these two drugs [29]. However, both drugs were efficient and safe relieving the main symptoms and signs of VKC, including itching, tearing, conjunctival hyperemia, mucous discharge and photophobia. Olopatadine hydrochloride 0.1% was effective for relieving the signs and symptoms of VKC and reducing the number of goblet cells during treatment [30].

Decongestants are a useful adjunctive therapy to mast cell stabilizers and/or antihistamines in mild and moderate forms of VKC, or in adult patients who have demonstrated a notable improvement in symptomatology after adolescence. However, topical decongestants do not reduce the allergic response because they do not antagonize any of the mediators of allergic inflammation. Burning or stinging on instillation is a common side effect. Prolonged use of topical decongestants, as well as the discontinuation of these agents following prolonged use, can lead to rebound hyperemia and conjunctivitis medicamentosa [31]. These events are usually associated with topical first-generation antihistamines such as pheniramine and antazoline that are available as over-the-counter products.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Generally NSAIDS employed in ocular allergy treatment inhibit both cyclooxygenase (COX)-1 and COX-2 enzymes. Ketorolac, diclofenac, and pranoprofen, may also be valid alternatives to steroids, since they have a proven effect on itching, intercellular adhesion molecule-1 expression, and tear tryptase levels [32]. Indomethacin 1% [33], ketorolac 0.5% [34], and diclofenac 0.1% have shown effectiveness in the treatment of VKC [35].

Topical Corticosteroids

Moderate to severe VKC needs repeated topical steroid treatment to downregulate conjunctival inflammation. Persistent severe symptoms, thick mucous discharge with moderate to severe corneal involvement, numerous and inflamed limbal infiltrates and/or giant papillae, indicate a need for corticosteroids. However, corticosteroids should be avoided as the first line of defense in the treatment of VKC. If steroids are used, those with low intraocular absorption, such as hydrocortisone, clobetasone, desonide, fluorometholone, loteprednol, difluprednate and rimexolone, should be used first. Dosages are chosen based on the inflammatory state of the eye, with therapy prescribed in pulses of

3–5 days. Loteprednol etabonate is usually indicated for 7–8 days in the treatment of the acute phase. Prednisolone, dexamethasone, or betamethasone should be used only when the above-mentioned first-choice steroids have proven ineffective. Steroid–antibiotic combination eye drops should be avoided, as VKC is an allergic inflammation, rather than an infection. Corticosteroids should not be recommended for long-term use because of possible ocular adverse effects, including increases in intraocular pressure (IOP), induction or exacerbation of glaucoma, formation of cataracts, delayed wound healing, and increased susceptibility to infection or superinfection. These adverse effects depend, in part, on the structure, dose, duration of treatment and gender disposition [36]. In fact, following daily administration of corticosteroids for 4–6 weeks, approximately one-third of the normal population will be "high or moderate responders" with an increase in IOP of between 6 and 15 mm Hg [36]. Forty-one of 145 (28.3%) patients with severe VKC in a Singapore case series developed a corticosteroid response, of which eight (5.5%) progressed to glaucoma [37]. Six of these patients ($n = 8$ eyes) required trabeculectomy/mitomycin-C. The main risk factor for trabeculectomy was a greater increase in IOP from baseline, which was independent of potential confounders such as type and duration of corticosteroid use [38].

Calcineurin Inhibitors and Other Immunomodulators

Cyclosporine A (CsA) is effective in controlling VKC-associated ocular inflammation by blocking Th2 lymphocyte proliferation and interleukin-2 production. It inhibits histamine release from mast cells and basophils through a reduction in IL-5 production, and may reduce eosinophil recruitment and effects on the conjunctiva and cornea [39]. CsA is lipophilic and thus must be dissolved in an alcohol-oil base [39]. Unavailability of a commercial preparation of topical CsA, technical difficulties in dispensing eye drops and legal restrictions on its topical use in many countries, preclude its widespread use for VKC treatment. The 2% formulation has the longest track record, but lower concentrations (1%, 0.5%, and 0.05%) have been used and shown to be effective. So far, there is no general consensus regarding the minimum effective concentration of CsA. Only the 0.05% formulation is commercially available for the treatment of dry eye.

After long cycles of treatment, CsA has a marked steroid-sparing effect, potentially allowing control of symptomatology without steroids [40]. When necessary, additional topical steroids can be used in short cycles. Systemic absorption of CsA was not detectable by clinical laboratory methods. Burning and irritation are frequent side effects. Treatment can be prescribed seasonally or perennially, reducing doses in the non-active phases of the disease. Adverse events, such as bacterial or viral infections are rare, while IOP changes have not been reported.

CsA 1% or 2% emulsion in castor or olive oil instilled four times daily can be considered for treatment of moderate to severe VKC and can serve as a good alternative to steroids [39, 41]. After 2 weeks, CsA 1% four times daily significantly reduced signs and symptoms and tear levels of ECP in a group of VKC patients [42].

CsA 1% was reported to be the minimum effective concentration in the treatment of shield ulcers, with recurrence observed at lower concentrations [43]. In a randomized,

controlled trial, the effects of CsA 0.05% were similar to placebo [44]. Conversely, in another study, CsA 0.05% decreased the severity of symptoms and clinical signs significantly after 6 months and the need for steroids was reduced, suggesting that CsA at low doses is an effective steroid-sparing agent in VKC [45]. In a clinical prospective and observational study in 594 patients, CsA 0.1% was shown to be effective and safe for the treatment of VKC [46]. A recent systematic review and meta-analysis study suggests that topical CsA is effective and safe for the treatment of VKC, since signs and symptoms significantly improve after treatment, regardless of the CsA dosage [47].

A randomized, controlled two-year crossover study demonstrated the safety and efficacy of CsA 0.05% for long-term prevention of VKC relapses [40]. Patients treated with ketotifen had a risk of recurrences 2.4 times higher than patients treated with CsA. In addition, CsA significantly improved itching, photophobia and conjunctival hyperemia scores in comparison with ketotifen. These data are of great importance for the long-term management of pediatric patients at risk of visual impairment, whether due to steroid abuse or to continued recurrences of acute inflammation [40].

Tacrolimus is a potent drug, similar to CsA in its mode of action, but chemically distinct. A tacrolimus skin ointment is licensed for the treatment of moderate to severe atopic eyelid diseases and may have secondary benefits for AKC [48–50]. Conjunctival application of tacrolimus ointment 0.03% and 0.1% were effective, well tolerated, and safe in the treatment of severe allergic conjunctivitis [49, 51]. In a multicenter, randomized, double-masked, placebo-controlled clinical trial, tacrolimus ophthalmic suspension 0.1% was shown to be effective in treating severe allergic conjunctivitis. Patients were treated twice daily for 4 weeks. Objective signs, subjective symptoms, giant papillae and corneal involvement were significantly improved. The most frequent tacrolimus-related adverse event was ocular irritation [52]. In the same study it is also reported that the dose of tacrolimus was based on the results from a previous dose-ranging study in which tacrolimus ophthalmic suspension 0.01%, 0.03%, and 0.1% were tested. Since 0.1% showed stronger improvement and similar safety profile compared with 0.01% and 0.03%, the 0.1% was considered an optimal dose.

Documentation on the quality, safety and efficacy of the different preparations used in the different clinical reports will be necessary before tacrolimus is granted orphan medication status for VKC.

A prospective double-masked randomized comparative trial comparing the efficacy of 0.1% tacrolimus ophthalmic ointment with CsA 2% showed that both were equally effective in the treatment of VKC [53].

Short-term, low-dose, topical mitomycin-C 0.01% has been considered for treating acute exacerbations in patients with severe VKC refractory to conventional treatment [54]. A significant decrease in signs and symptoms compared with the placebo group was shown at the end of the 2-week treatment period. Unavailability of commercial topical preparations, the short duration of studies, and the lack of data on the safety profile and long-term outcomes are major limitations in recommending mitomycin for the treatment of VKC.

Topical Non-Ocular Pharmacologic Treatment

The efficacy of intranasal corticosteroids in treating allergic nasal symptoms is well

established. Recent data show a promising effect of intranasal corticosteroids on ocular symptoms of allergic rhinoconjunctivitis [55]. At the moment, no studies in VKC have been performed or reported in the literature. The mechanism by which an intranasal corticosteroid reduces ocular allergic symptoms has been under investigation; some effects on both the reflex neural activity and the local inflammation, facilitating nasolacrimal drainage, have been proposed [56]. Meta-analysis studies showed that there is no significant difference in improvement of eye symptoms between intranasal corticosteroids and oral antihistamines [57] including non-sedating antihistamines. Thus, in VKC patients with associated nasal symptoms, nasal corticosteroids may be beneficial.

Systemic Pharmacologic Treatment

Systemic treatment with oral antihistamines or antileukotrienes can reduce the severity of flare-ups and generalized hyper-reactivity. First-generation H_1 receptor antagonists may provide some relief of ocular itching, but are sedating and have anticholinergic effects such as dry mouth, dry eye, blurred vision and urinary retention. Second-generation antihistamines offer the same efficacy as their predecessors, but with a low-sedating profile and lack of anticholinergic activity. These drugs include acrivastine, cetirizine, ebastine, fexofenadine, loratadine and mizolastine. However, even their use has been associated with drying effects, particularly of the ocular surface [58]. Desloratadine and levocetirizine are considered a subsequent evolution of these second-generation agents and are preferred over first-generation antihistamines for the treatment of allergic conjunctivitis [59].

Aspirin 0.5–1 g per day has been shown as a steroid-sparing factor in the treatment of VKC [60]; however, it should be used with caution because of the well-known possible side effects.

In severe cases, systemic treatment with T-lymphocyte signal transduction inhibitors such as CsA or tacrolimus may ameliorate both the dermatologic and ocular manifestations in severe patients who are refractory to conventional treatment [61].

Omalizumab, an anti-IgE recombinant, humanized, non-anaphylactogenic antibody, directed against the receptor-binding domain of IgE, may be used in VKC patients with high levels of total serum IgE [62].

Specific Immunotherapy

Allergen-specific immunotherapy (SIT) is indicated only when a clearly defined systemic hypersensitivity to identified allergens exists. The choice of the allergen to be employed for SIT should be made in accordance with the combination of clinical history and results of skin prick test and specific serum IgE. Since the development of non-invasive formulations with better safety profiles, there is an increasing tendency to prescribe sublingual immunotherapy (SLIT) in young patients. A systematic review and meta-analysis of double-blind, placebo-controlled randomized controlled trials confirmed that SLIT reduces significantly ocular symptom scores in patients with allergic conjunctivitis with or without rhinitis [63]. The SIT treatment in IgE-positive patients with VKC was more effective than topical treatment in improving clinical symptoms and reducing total serum IgE [64].

Surgical Treatment

Supratarsal injection of either a short- or intermediate-acting corticosteroid has been proposed as a therapeutic approach to treating

patients with refractory VKC [65]. Although significant symptomatic and clinical improvements have been reported, persistent increase in IOP occurred in one of 12 VKC patients [65].

Surgical removal of corneal plaques is recommended to alleviate severe symptoms and to allow for corneal re-epithelization. Giant papillae excision with intraoperative 0.02% mitomycin-C followed by CsA topical treatment may be indicated in cases of mechanical pseudoptosis or the presence of coarse giant papillae and continuous active disease [66, 67].

Cryotherapy and/or excision of giant papillae should otherwise be avoided because these measures treat only the complications and not the underlying disease, and may induce unnecessary scarring. Amniotic membrane transplantation (AMT) following keratectomy has been described as a successful treatment for deep ulcers, in cases with slight stromal thinning [68]. The presence of residual membrane under the epithelium may affect postoperative corneal transparency. The treatment algorithm for corneal complication can be based on the Cameron clinical grading of shield ulcers [69]: Grade 1, ulcers received medical therapy alone; Grade 2 and Grade 3 ulcers received either medical therapy alone or medical therapy combined with debridement, AMT, or both. Using this approach, it was shown that Grade 1 ulcers respond well to medical therapy alone; Grade 2 ulcers occasionally may require additional debridement or AMT; Grade 3 ulcers are frequently refractory to medical therapy and require debridement and AMT for rapid re-epithelialization [70] .

Significant limbal stem cell deficiency as a complication of severe and persistent limbal inflammation has been treated with stem cell transplantation [71, 72].

These and other more invasive procedures such as oral mucosal grafting should be avoided or considered only by ophthalmology experts in VKC management.

PRACTICAL MANAGEMENT OF VKC

Treatment of VKC requires a multi-pronged approach that includes conservative measures and the use of drugs, as summarized in Table 3. Close collaboration between ophthalmologists, allergists and pediatricians is recommended. Patients and parents should be made aware of the long duration of disease, its chronic evolution and possible complications.

It is recommended to use a clinical grading system to identify the more severe forms of VKC that are at higher risk of recurrences, corneal ulceration, and worsened final visual outcome [73]. A simple grading system has been proposed to formulate global guidelines for treating VKC (Table 4) [73–75].

The selection of a drug from the many available options is also based on geographical area, personal experience and preference of the treating physician, since there is no standard treatment and a lack of evidence to support choice of drug in the management of VKC.

Topical administration of mast cell stabilizers, with preference for those which have anti-eosinophil effects such as NAAGA and lodoxamide, should be started at the onset of the allergic symptoms and used continuously throughout the season. If monotherapy with mast cell stabilizers is not enough to prevent the symptoms, antihistamines or multiple-acting drugs such as olopatadine and ketotifen, 2–4 times a day should be added and continued for the entire season. Frequent instillations may be inconvenient, however, no significant side effects of these drugs have been reported with

Table 3 Summary of the practical management of VKC

Make an accurate diagnosis
Educate on avoidance of the offending allergens and nonspecific triggers (use sunglasses, hats with visors, and swimming goggles)
Stress the importance of non-pharmacologic treatments (lubricants, lid hygiene, cold compresses)
Two or more topical, complementary drugs must be used in combination (mast cell stabilizers + antihistamines or multiple action components)
Recommend an adequate frequency of instillation of topical drugs (4–6 times per day)
Warn against use and abuse of decongestant/vasoconstrictors
Recommend systemic antihistamines to reduce hyper-reactivity
Use topical corticosteroid formulations as pulsed therapy (3–5 days) to reduce flare-ups
Corticosteroids must be used in case of moderate to severe corneal epitheliopathy and ulcers
Avoid the continuous use and/or abuse of steroids
Avoid corticosteroids as first-line treatment of VKC
Topical CsA can be considered in moderate to severe VKC and can be steroid-sparing
Removal of corneal plaques is the only surgical procedure recommended in cases of corneal complications
Specific immune therapy is indicated only if extra-allergic manifestations are also present, when a specific offending allergen is clearly identified and clinically related to ocular manifestations

Table 4 Clinical grading of vernal keratoconjunctivitis and therapeutical approach

Grade	Clinical findings	Treatment
0 (quiescent)	Absence of symptoms	No treatment
1 (mild)	Presence of symptoms with no corneal involvement	Anti-allergic eye drops daily
2 (moderate)	Presence of symptoms associated with photophobia with no corneal involvement	Combined anti-allergic eye drops daily
3 (severe)	Presence of symptoms associated with photophobia and mild to moderate SPK	Anti-allergic eye drops daily with pulsed low-dose topical steroid
4 (very severe)	Presence of symptoms associated with photophobia and diffuse SPK or corneal ulcer	Pulsed high-dose topical steroid with eventual surgical removal of corneal plaque

SPK superficial punctate keratopathy
Modified from [73, 75]

short- or long-term use. Preservative-free formulations should be recommended.

NSAIDs such as ketorolac, diclofenac and pranoprofen may be considered as steroid-sparing options. However, in clinical practice they have limited use in VKC management. Systemic treatment with oral antihistamines or antileukotrienes can reduce the severity of ocular flare-ups and the nonspecific hyper-reactivity typical of these patients. They

should be started at the onset of symptoms and used continuously throughout the allergic season.

Moderate to severe VKC may require repeated topical steroid treatment to downregulate conjunctival inflammation and reduce cellular infiltrate. "Soft corticosteroids" may be considered preferentially as the first corticosteroid preparations to be used. Dosages are chosen based on the inflammatory state. An instillation frequency of 4 times per day for 5–10 days is recommended. Prednisolone, dexamethasone or betamethasone should be used as a second-line choice, or as first-line treatment in the most severe cases. A "pulsed" treatment of 3–5 days, in addition to the continuous use of mast cell stabilizers and topical antihistamines, is recommended. The use of ointment at night-time may be helpful in children when opening the eyes in the morning is difficult because of photophobia due to the epitheliotoxicity of released mediators while the eyes are closed.

CsA 1% or 2% can be considered for treatment of moderate to severe VKC. It decreases the severity of signs and symptoms and the need for steroids. No significant side effects, except for a burning sensation during administration, have been reported [39]. No randomized studies on dose–effect differences have been published. In clinical practice, one drop of CsA 1% from 2 to 4 times a day, depending on the severity of signs and symptoms, is effective for controlling the disease during seasonal exacerbations. Treatment can be suspended during winter until the first exacerbation of the new season. Adult patients respond better to CsA compared with any other therapeutic regimen [9].

If a patient does not respond to CsA, topical tacrolimus can be considered. Several experiences with tacrolimus have been reported using different preparations and concentrations. It seems to be more effective than CsA, and also effective in patients refractory to CsA. Randomized trials of topical tacrolimus are needed.

Corneal complications should be carefully monitored and anti-inflammatory therapy adjusted; in these cases, steroids should be used, since the pathogenesis of the ulcer is strictly immune-mediated. Corticosteroids are preferred over CsA, since they are more effective in inhibiting the inflammatory component of corneal damage (i.e., eosinophil- and neutrophil-liberated epithelial toxic mediators) [2].

Severe cases that do not respond to any of these topical therapies may require treatment with systemic corticosteroids (prednisone 1 mg/kg per day) for a short period of time.

If a systemic hypersensitivity to identified allergens exists, specific immunotherapy may be considered.

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