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ORIGINAL RESEARCH

Novel Insights in the Management of Vernal Keratoconjunctivitis (VKC): European Expert Consensus Using a Modified Nominal Group Technique

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ABSTRACT

Introduction: Vernal keratoconjunctivitis (VKC) is a rare, severe allergic ocular disease, typically occurring in children and adolescents, that can have a significant impact on quality of life and lead to visual impairment. Long-term treatment may be necessary to tackle chronic inflammation and topical corticosteroid dependency must be minimised due to the risk of complications. There is a need for unified clinical guidance to aid the assessment, diagnosis and management of VKC across Europe. The aim of this expert panel (the EUR-VKC Group) was to provide clear guidance for primary care physicians and general ophthalmologists involved in the diagnosis and management of VKC.

Methods: An expert group of seven European ophthalmologists was convened and a modified nominal group technique used to develop key

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recommendations on VKC management. The recommendations were subject to up to two rounds of voting using a 5-point Likert scale to ascertain consensus and the strength of each recommendation. Consensus was set at a predetermined threshold of ≥ 75.0% of experts selecting 'Strongly agree' or 'Agree'.

Results: A total of 47 recommendations were developed relating to the assessment of key of VKC, guidance on who and when to refer, as well as treatment-escalation pathways, long-term follow-up, and supportive care and education. All recommendations reached consensus after two rounds. The group emphasise how timely diagnosis and treatment initiation that is appropriate to disease severity are crucial to benefit patients with VKC. Patients with signs ('red flags') indicating severe VKC, or persistent mild-to-moderate VKC that is non-responsive following 2–4 weeks of treatment, should be referred to a sub-specialist.

Conclusion: The EUR-VKC Group provides recommendations on the assessment, diagnosis, management, referral and follow-up of patients with VKC. It also provides a framework to facilitate collaboration between primary care physicians, general ophthalmologists and sub-specialists to improve the outcomes for patients with VKC.

PLAIN LANGUAGE SUMMARY

Vernal keratoconjunctivitis (VKC) is a rare, underdiagnosed, chronic allergic eye disease that typically occurs in children and adolescents. If left untreated, VKC can significantly damage the eye, potentially leading to long-term complications, visual impairment and a reduced quality of life for the child and their family and/or caregivers. In the absence of established guidelines, this consensus programme set out to gather expert insights on best practices for assessing and managing VKC across Europe. A group of seven European ophthalmologists engaged in the consensus programme. A total of 47 recommendations were developed relating to the assessment, diagnosis, management, referral and follow-up of patients with VKC. These 47 recommendations underwent two rounds of review and were revised, if necessary, following expert input. Recommendations where ≥ 75.0% of experts agreed were considered as having reached consensus and were included as final recommendations. The experts agreed that VKC can be classified as mild, moderate or severe, and should be managed according to severity in a stepwise manner, with treatment intensity escalating as the disease severity increases. Timely diagnosis and treatment initiation appropriate to the severity of VKC are crucial to prevent sight loss and improve the quality of life of children with VKC. Ongoing treatment may be necessary to tackle the chronic inflammation associated with the disease and, therefore, reliance on steroid eye drops should be reduced to avoid an increased risk of well-known complications. The experts concluded that mild VKC can be assessed and managed in primary care, but patients with severe VKC, or with moderate-to-severe VKC that does not respond to treatment within 2–4 weeks, should be referred to a VKC specialist.

Keywords: Consensus; Europe; Expert panel method; Management; Vernal keratoconjunctivitis; VKC

Key Summary Points

Why carry out this study?

Currently, there are no guidelines or consensus across Europe on the management of patients with vernal keratoconjunctivitis (VKC), a rare ocular disease that mainly affects children and adolescents.

The aim of this European expert panel (the EUR-VKC Group) was to amalgamate expert opinion and the latest evidence to achieve consensus on the management of VKC – to optimise care and improve the quality of life of children with VKC.

What was learned from the study?
The EUR-VKC Group reached consensus on the assessment, diagnosis, management, referral and follow-up of patients with VKC in Europe.
The best-practice recommendations generated can be used by primary care physicians and ophthalmologists to guide the management of VKC in daily clinical practice and improve collaboration throughout the patient journey.
Primary care physicians and ophthalmologists should remain aware of the key signs and symptoms of VKC, as well as key aspects of assessment, diagnosis, management and follow-up of the disease; patients with 'red flags' indicating severe VKC, or with persistent mild-to-moderate VKC that is non-responsive following 2–4 weeks of treatment, should be referred to a sub-specialist ophthalmologist.
Timely diagnosis and stepwise treatment related to disease severity are crucial to prevent sight loss and improve quality of life of children with VKC.
Long-term treatment may be necessary to tackle the chronic inflammation associated with VKC, and dependency on topical corticosteroids must be minimised, due to the risk of long-term complications.
The EUR-VKC Group also highlights key areas for future research to tackle unmet needs in the identification, differential diagnosis and management of VKC.

INTRODUCTION

Vernal keratoconjunctivitis (VKC) is a rare, recurrent, bilateral, chronic inflammatory eye disease with an important allergic component affecting the ocular surface that can cause severe visual complications. VKC mainly affects children before the age of 10 years, and is more common among males than females, although this difference may become less at older ages of onset [1–3]. VKC has a typical seasonal trend (but can be perennial), often worsening with acute exacerbations in spring and summer [1, 2, 4].

VKC is classified into limbal, tarsal and mixed forms based on the presence and location of the papillary reaction and inflammation on the conjunctiva [5, 6]. Limbal VKC most commonly presents with Horner–Trantas dots, which are focal white spots, consisting of degenerated eosinophils and epithelial cell debris, found on top of limbal papillae. The tarsal form is characterised by the presence of giant, cobblestone-like papillae on the tarsal conjunctiva [5]. These papillae can differ in shape and size, but are usually defined as > 1.0 mm in diameter [1].

VKC has an estimated prevalence of 0.7–3.3 cases per 10,000 population, of which 0.3–1.4 cases per 10,000 are estimated to be severe [7, 8]. The pathogenesis of VKC is not fully understood but results from a complex interplay between immune cells, including mast cells and eosinophils, and an immunoglobulin E (IgE)- and T cell-mediated allergic reaction, along with familial history and environmental factors [2, 4, 9–12].

Classical symptoms of VKC include photophobia, itching (with redness), increased tearing, stringy mucus discharge (or secretion), eye discomfort, pain or burning, and even blurred vision. Notable clinical signs include giant, cobblestone-like papillae on the upper tarsal conjunctiva, conjunctival hyperaemia, limbal papillae with or without Horner–Trantas dots, ptosis or pseudoptosis. Other notable signs include shield ulcers, plaques and superficial keratitis (or other corneal involvement), all of which are indicative of more severe disease [1, 2, 13].

Due to limited awareness, diagnosis of VKC can take several months, and during this time treatment may be suboptimal [14, 15]. The inflammatory changes and associated tissue remodelling can lead to long-term complications and severe visual impairment [16], which if left untreated, can impact a patient's vision

and quality of life, interfering with everyday activities of childhood [17, 18]. VKC resolves during puberty in most individuals, but some experience disease progression and permanent corneal damage [16, 17].

Approximately 50% of cases of VKC show allergic sensitisation and, typically, two VKC populations exist: patients with positive allergy test results and a history of allergic manifestations, such as asthma, rhinitis or eczema; and those with negative allergy test results and no personal or familial history of atopy [16, 19]. Various severity grading scales for VKC are used in research and specialist clinical practice, including the Bonini scale, but there is an unmet need for a grading scale that is universally accepted for everyday clinical practice [20–23]. Classifying mild, moderate and severe VKC based on the clinical presentation provides a distinction that can guide management [13]. Mild disease is typically treatment naive, with no sight-threatening signs. Disease is considered to be moderate if symptoms recur despite previous treatment with conventional medications, or if patients are treatment naive with limbitis, larger cobblestone-like papillae on the tarsal conjunctiva, punctate keratopathy or mucus discharge [13]. Severe disease exhibits a lack of response to prior treatments, with repeated flare-ups despite compliance with treatment, the presence of shield ulcers, significant corneal vascularisation and/or disabling symptoms such as frequent photophobia [13].

Treatment should follow a stepwise approach based on disease severity, progression and response to prior lines of treatment [13]. Non-pharmacological and pharmacological therapies are part of the treatment armamentarium for VKC and include topical ocular and non-ocular medications. Conventional topical therapies include antihistamines, mast cell stabilisers and dual-acting agents (i.e. antihistamine + mast cell stabiliser). Other therapies include topical anti-inflammatory agents such as corticosteroids and immunomodulators [e.g. ciclosporin A (CsA)] as well as other allergen-specific or systemic therapies [2, 13, 24]. Surgical interventions to remove corneal plaques and alleviate symptoms may also be considered in patients with severe VKC or recalcitrant disease [2, 24].

Both the presentation and management of VKC may vary across countries, and with few clinical studies and no treatment guidelines, clinical practice is based on experience [13]. Regional recommendations have been previously published [1, 13, 25], but none has focused on the management of VKC across Europe. The aim of this expert panel was to evolve existing recommendations and close the gap between the latest evidence and expert insights to provide clear guidance for primary care physicians and general ophthalmologists to ensure accurate assessment and diagnosis, timely referral and optimal treatment for patients with VKC, and thus ultimately improve outcomes for patients.

METHODS

The information and recommendations provided herein are based on the best available evidence, as interpreted by an expert panel of seven ophthalmologists from six countries in Europe (Denmark, France, Italy, Portugal, Spain, UK), all with specialism and interest in the ocular surface, VKC and paediatric ophthalmology (the EUR-VKC Group). The experts were identified from a variety of clinical and research roles, including authors of high-quality literature pertaining to the subject area, to promote heterogeneity and inclusion of a wide range of knowledge and experience.

The consensus programme was based on a multistep modified nominal group technique (also known as the Expert Panel method) [26, 27], comprising an anonymous topic-generation stage and an iterative refinement process, before formal consensus and validation of key recommendations. This is a recognised approach used to gain consensus between specialists in a particular field where expert opinion is important in shaping judgements, and where the literature may be limited.

The process, which took place between June 2021 and June 2022, was led by Annegret Dahlmann-Noor, with regular input and approval from the rest of the EUR-VKC Group

(see Fig. S1 in the electronic supplementary material). During the topic-generation stage, the lead asked EUR-VKC Group members to independently submit areas of clinical focus and define the scope of the issues or questions that needed to be addressed. These were then ranked, prioritised and categorised into groups, and ratified by the panel of experts. The topics included both contextual issues, relating to the definition and assessment of VKC, and practical issues, relating to different treatments and management strategies in different clinical scenarios.

A partial literature search was performed for each of the proposed topics. The level of evidence was assessed and agreed by the EUR-VKC Group, and only high-quality evidence was considered. The search included non-pharmacological interventions such as surgery, psychological support, lid hygiene and lubricants, as well as the following treatments: antihistamines, mast cell stabilisers, dual-acting agents, non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, calcineurin inhibitors/immunomodulators (CsA and tacrolimus), allergen-specific immunotherapy and biologics. Randomised controlled trials, systematic reviews of observational and interventional studies, high-quality case reports/case series, opinion articles and consensus papers on best practice in VKC were considered, as well as expert insights from the EUR-VKC Group.

Based on the available literature and expert insights, key recommendations were developed by the facilitator (Synergy Vision medical communications agency) and the lead, and presented in a series of EUR-VKC Group meetings. Discussions were led by the facilitator and lead, with the goal of clarifying any issues or recommendations. Secondary review followed an iterative process (offline), where recommendations were reassessed and revised according to group input, in no more than two rounds. While providing unbiased judgement during the initial topic-generation stage and offline review stages, this approach also allowed members the opportunity to listen to their peers' opinions, thus increasing the likelihood of reaching consensus.

Following a final EUR-VKC Group meeting in February 2022, validation of the key recommendations took place with a formal survey – which was completed via an online platform, organised by the facilitator. EUR-VKC Group members were asked to anonymously vote on a series of recommendations about VKC using a 5-point Likert scale based on level of agreement. In each case, the members could select only one option: 'Strongly agree' (associated with a score of 2), 'Agree' (1), 'Neutral' (0), 'Disagree' (–1) or 'Strongly disagree' (–2). Only recommendations on which $\geq$ 75.0% of members agreed (consistent with other consensus programmes and nominal group techniques [26, 27]), as predetermined by the EUR-VKC Group, are included as reaching consensus.

If consensus on a particular topic was not initially reached, members provided input to identify reasons for the lack of agreement. When warranted, the facilitator and lead revised recommendations according to feedback from the group and re-voting then occurred (for a maximum of two votes only).

For each recommendation, the value of the votes was averaged and the strength of the recommendation determined. Recommendations herein are presented with certainty and strength. Recommendations with average scores $\geq$ 1.6 were categorised as 'Very strong' (+ + +); $\geq$ 1.1 to $<$ 1.6 as 'Strong' (+ +); and $\geq$ 0.7 to $<$ 1.1 as 'Moderate' (+).

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors. All members of the EUR-VKC Group (expert panel) are authors of the paper.

RESULTS

Expert Panel Rounds

A total of 47 recommendations were developed relating to the assessment, diagnosis, management, referral and follow-up of patients with VKC. These 47 recommendations underwent two rounds of review and were revised, if necessary, following expert input. In the validation

stage, all seven EUR-VKC Group members completed both rounds of voting in June 2022. Of the 47 recommendations included in the round 1 voting, consensus was reached for 41 (87.2%) and not reached for six (12.8%). These six recommendations were revised and included in round 2 voting, where consensus was subsequently reached. No recommendation did not reach consensus after two rounds of voting.

Staged Assessment of VKC

The EUR-VKC Group agreed on the importance of both primary care physicians and general ophthalmologists assessing the clinical and family history of allergy or atopic conditions (e.g. eczema, asthma, rhinitis), as presence of ocular allergy may require further assessment for differential diagnosis; possible external and environmental triggers/exacerbators of symptoms in patients suspected to have VKC; the impact of the condition on the patient's quality of life; and the duration and seasonality of disease.

The group distinguished common signs and symptoms of VKC of which different specialties should be aware (Fig. 1). Both primary care physicians and ophthalmologists should understand the potential impact of these symptoms on patient quality of life.

If mild symptoms do not abate after 2 weeks of treatment, patients should be referred to an ophthalmologist. Patients with two or more clinical signs and symptoms of moderate VKC should be referred to a specialist ophthalmologist (indicated throughout this manuscript as an ophthalmologist who specialises in cornea, ocular surface or paediatric ophthalmology), and those with corneal involvement or corneal opacity with redness should be referred urgently.

General ophthalmologists should use slit-lamp examination to identify some of the hallmark signs of VKC: giant, cobblestone-like papillae on the upper tarsal conjunctiva, Horner–Trantas dots, stringy mucus discharge (or secretion), conjunctival hyperaemia, ptosis or pseudoptosis, as well as corneal complications (including shield ulcers, plaques,

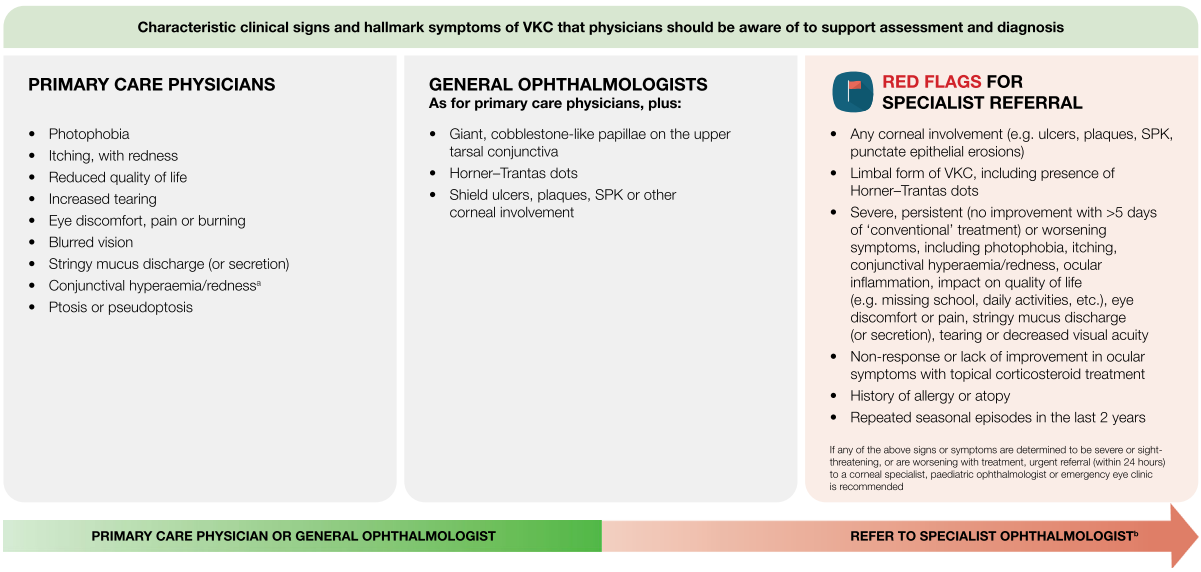

Fig. 1 Clinical signs and hallmark symptoms for the assessment and diagnosis of VKC. [a]If redness or 'watery' eyes are observed in isolation, referral may only be appropriate if there is no improvement in signs and symptoms following 1–2 weeks of conventional treatment (defined as typical first-line pharmacological therapy, including antihistamines, mast cell stabilisers or dual−acting agents). [b]Unless the general ophthalmologist is experienced and competent in the management of VKC. *SPK* superficial punctate keratitis, *VKC* vernal keratoconjunctivitis

superficial punctate keratitis or other corneal involvement). In all patients suspected of having VKC, general ophthalmologists should be consulted to make the diagnosis and assess severity. They should evert the eyelids (if proficient and confident to do so, to avoid distress to the patient) to confirm the diagnosis by assessing the presence and size of cobblestone-like papillae on the upper tarsal conjunctiva.

General ophthalmologists should be aware of the differential diagnosis for VKC, which includes atopic keratoconjunctivitis (AKC), seasonal allergic conjunctivitis (SAC), perennial allergic conjunctivitis (PAC), giant papillary conjunctivitis and blepharokeratoconjunctivitis in some severe cases of ocular surface inflammation. If a diagnosis cannot be confirmed, then the patient should be referred to a specialist ophthalmologist (see Fig. 1 for 'red flags' indicating when urgent specialist referral is required). If available, general ophthalmologists should use fluorescein staining to detect corneal involvement, and any patient with severe corneal involvement (e.g. diffuse punctuate epitheliopathy, macroerosion/large epithelial defects) should be referred to an ophthalmologist specialised in cornea, ocular surface or paediatric ophthalmology, if the general ophthalmology is not experienced in treating VKC.

All patients with clinical signs or symptoms of moderate-to-severe VKC should be referred to a specialist ophthalmologist for further assessment, unless the general ophthalmologist is experienced and competent in the management of VKC.

A full list of recommendations relating to the staged assessment of patients with suspected signs and symptoms of VKC can be found in Table S1 in the electronic supplementary material.

'Red Flags' and Who and When to Refer

VKC can be classified as mild, moderate or severe, and this classification is important to determine next steps for the management of VKC. Mild disease may be managed in primary care with support from an ophthalmologist (if appropriate and depending on the healthcare system) to provide adequate follow-up. Moderate VKC may be managed by a general ophthalmologist until non-urgent referral to a specialist clinic, ideally within 1–2 months. Severe VKC should be managed by a specialist ophthalmologist.

The group agreed that any referral to a specialist should be based on disease severity and/or progression. Figure 1 provides a summary of the 'red flags' indicating urgent referral to a specialist ophthalmologist. If any of the 'red flags' are severe or sight threatening, or are worsening with treatment, then urgent referral (within 24 h) to a corneal specialist, paediatric ophthalmologist or emergency eye clinic is recommended.

A full list of recommendations regarding 'red flags' for urgent referral to a specialist ophthalmologist can be found in Table S2 in the electronic supplementary material.

Stepwise Management Approach Based on Severity and Progression of VKC

The EUR-VKC Group agreed that the patient and family/caregiver should always be provided with supportive care and education, with an emphasis on avoiding triggers or exacerbators and allergens, lid hygiene, and use of cold compresses and ocular lubricants/artificial tears (without preservatives, since these can cause allergies or may damage the corneal surface [28, 29]). As first-line pharmacological therapy, dual-acting agents (e.g. olopatadine, azelastine hydrochloride, epinastine, ketotifen) may be considered rather than monotherapy with antihistamines or mast cell stabilisers (e.g. sodium cromoglycate, nedocromil, lodoxamide), depending on formulary, local recommendations and availability.

Short-pulse topical corticosteroids are effective to tackle inflammation and manage acute exacerbations or when the cornea is involved, and should be considered for patients with moderate-to-severe disease either alone, as an add-on to topical CsA, or as rescue therapy. However, the long-term use of corticosteroids is associated with an increased risk of adverse events including elevated intraocular pressure

(IOP) and glaucoma, formation of cataracts, delayed wound healing and increased susceptibility to infection [2, 30]. Notably, corticosteroid-induced glaucoma is a debilitating disease that may cause irreversible loss of vision and potentially blindness [31, 32]. Because of these risks, topical corticosteroid eye drops should only be used in 'short pulses' (alone or in combination with topical CsA) under the supervision of an ophthalmologist, and repeat cycles avoided, where possible, to prevent dependency. The use of high-frequency or oral corticosteroids (in short pulses) may be appropriate for patients with persistent corneal complications or non-response to prior treatments, but should only be prescribed by a clinician experienced in the use of these medications.

Topical immunomodulators (e.g. CsA) should be considered for patients with moderate-to-severe or persistent VKC, as well as those with corticosteroid dependency, to provide long-term control. If short-pulse corticosteroids are used frequently, for a period of > 3 months, then topical CsA should be considered for long-term control. Topical CsA has shown a marked corticosteroid-sparing effect, potentially allowing control of symptomatology without corticosteroids [33–35]. CsA may not be appropriate for patients with moderate VKC without other signs of progression or risk of recurrences [2, 25, 36].

Oral antihistamines may be used as adjunctive therapy for mild flare-ups or in the case of allergic rhinitis, if required. Advanced systemic treatments (e.g. immunomodulators, biologics) should only be prescribed in appropriate settings (e.g. patients with recalcitrant disease or involving other allergic manifestations) and by clinicians experienced in their use. Allergen-specific immunotherapy is only recommended where there is clearly defined systemic hypersensitivity to an identified allergen. Access to allergen-specific immunotherapy may vary between countries and settings, and referrals should be made accordingly.

The EUR-VKC Group agreed that treatment of VKC should be escalated if there is no improvement in symptoms or if changes in conjunctival papillary or ocular surface clinical signs are observed within 2–4 weeks. In general, if there is no improvement within 2–4 weeks of treatment and symptoms remain persistent, then the patient should be referred to a specialist ophthalmologist. Patients with VKC who may benefit from surgical intervention (e.g. debridement for shield ulcers) should be referred to a corneal specialist or paediatric ophthalmologist, or an emergency eye clinic.

The full list of recommendations regarding the stepwise management of VKC can be found in Fig. 2 and in Table S3 in the electronic supplementary material.

Other Treatments for VKC

The group agreed that before starting treatment with topical corticosteroids, general ophthalmologists should assess patients' IOP for monitoring purposes to avoid potential issues associated with the development of glaucoma. Vasoconstrictors and NSAIDs are not recommended for the treatment of VKC as they do not target the specific inflammatory mechanisms associated with VKC. Vasoconstrictors used to address hyperaemia should be used with caution and only for short periods of time due to adverse events. In addition, products with herbal extracts, such as chamomile-containing eye drops, should be avoided as they may cross-react with allergens (e.g. *Artemisia vulgaris*). Second- and third-generation systemic antihistamines may be preferred over older first-generation antihistamines due to their favourable efficacy/safety profile, pharmacokinetics, and lack of anticholinergic and sedative side effects [1–3, 37].

The complete results for recommendations regarding other treatments for VKC can be found in Table S4 in the electronic supplementary material.

Long-Term Management and Flare-Ups of VKC

The EUR-VKC Group agreed that for patients with seasonal symptoms, follow-up appointments may be scheduled based on the pattern of previously observed exacerbations or arranged via patient-initiated follow-up with primary

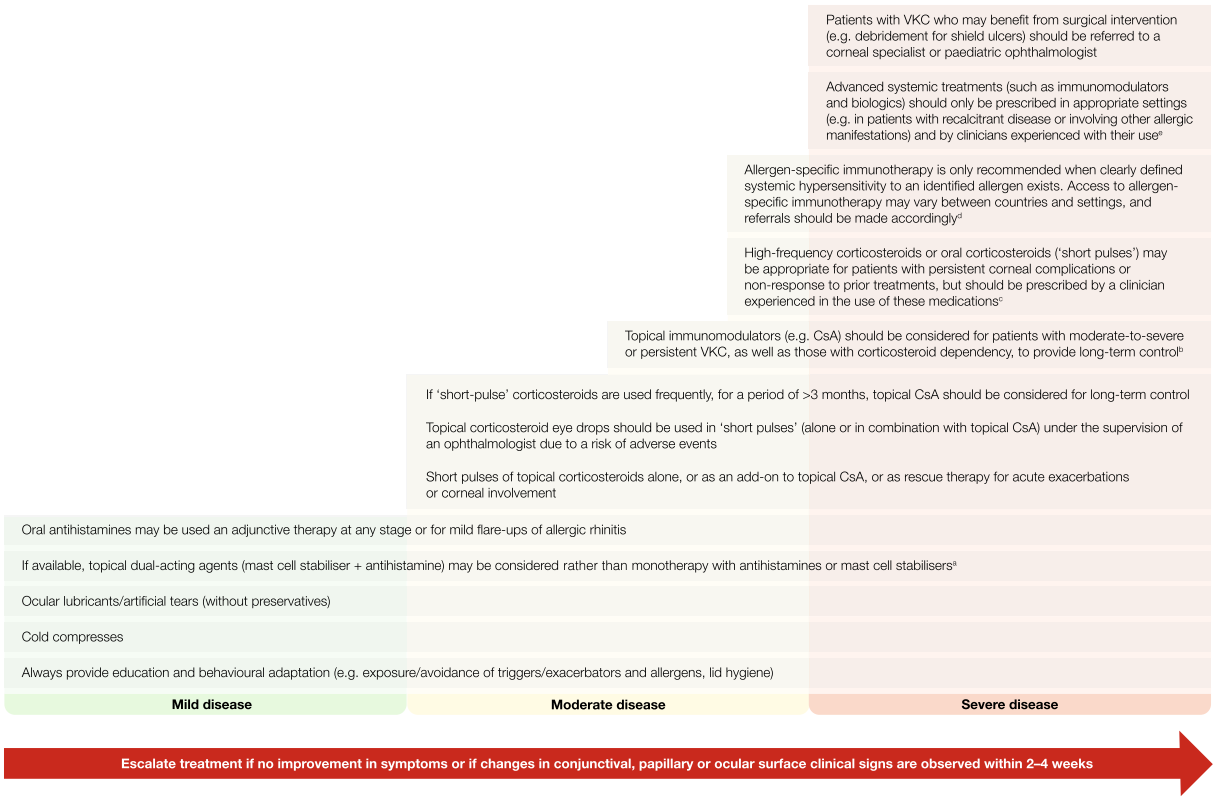

Fig. 2 Stepwise management of mild, moderate and severe VKC. [a]If available and depending on formulary and local recommendations. [b]CsA may not be appropriate for moderate VKC without other signs. [c]Recommendation revised from round 1 (where two out of seven group members did not agree, and the recommendation was 'Weak'): the use of high-frequency corticosteroids or oral corticosteroids ('short pulses') may be appropriate for patients with persistent corneal complications or non-response to prior treatments but should only be prescribed by a corneal specialist or paediatric ophthalmologist. [d]Recommendation revised from round 1 (where two out of seven group members did not agree, and the recommendation was 'Weak'): systemic treatment (e.g. with immunomodulators, such as CsA, biologics or antihistamines) should only be considered in patients recalcitrant or with non-response to prior therapy, or who have other allergic manifestations. [e]Recommendation revised from round 1 (where two out of seven group members did not agree, and the recommendation was 'Weak'): allergen-specific immunotherapy is only recommended when clearly defined systemic hypersensitivity to an identified allergen exists. Patients requiring allergen-specific immunotherapy should be referred to an allergologist or specialist ophthalmologist. *CsA* ciclosporin A, *VKC* vernal keratoconjunctivitis

care. The duration and frequency of follow-up should depend on disease severity and progression, as well as treatment choice. Quality-of-life assessment is an important part of patient follow-up and should be included in the first consultation and then monitored every 6 months, or as most appropriate. Families and caregivers should be made aware that exacerbations can occur even with effective treatment. They should be aware of the need to access an eye clinic immediately if a flare occurs, and of how to access that clinic. If more than one flare-up occurs within 3 months, despite good treatment adherence, therapy should be stepped up and the patient should be referred to a specialist ophthalmologist. The use of topical corticosteroids over an extended period should be avoided but, if prescribed, should be monitored by an ophthalmologist to avoid complications (e.g. elevated IOP). Oral antihistamines can be used as adjunctive treatment for mild flare-ups or in the case of allergic rhinitis. Results from

the VEKTIS study suggest that topical CsA drops used year-round may reduce the risk of exacerbations during the peak allergy season [35], and this should be discussed with the patient and their family and prescribed at the clinician's discretion.

If a patient has been asymptomatic for approximately 12 months, then treatment de-escalation may be considered. Discharge back to primary care may be considered if there is no need for ongoing corticosteroids or topical CsA. If patients with VKC are discharged to primary care, the primary care physician should be made aware of the risk of recurrence and/or flare-ups as well as the steps to take in this situation, including triggers for referral and treatment-escalation pathways.

The full list of recommendations regarding long-term management and flare-ups of VKC can be found in Table S5 in the electronic supplementary material.

Key Information to Communicate with Patients and Caregivers on VKC

The group agreed that caregivers (and patients, if appropriate) should be informed that VKC is a chronic, recurrent condition that usually improves with age, but that excessive rubbing of itchy eyes can make the condition worse (with advice on a 'no-touch zone'). Sunlight, wind, salty water, dust and heat can exacerbate VKC, so the use of sunglasses, hats, visors and swimming goggles may be considered. Furthermore, an air-filtration system in the home may provide relief. Common allergens can exacerbate VKC, and frequently washing the hands, face and hair can reduce exposure to these allergens. Cold compresses and preservative-free artificial tears can provide symptomatic relief.

It is important to reaffirm with patients and caregivers that adherence to treatment is important to ensure treatment success. Caregivers (and patients, if appropriate) should be made aware of the risks associated with the long-term use of corticosteroids and be advised to report any ocular adverse events. It may also be appropriate to educate on how best to manage treatment with topical CsA (e.g. it could be helpful to use preservative-free artificial tears prior to and after instillation or 'cool' the eye drops in the fridge to make administration easier) and advise that the effects will manifest over time and any issues with instillation likely improve with sustained use.

A multidisciplinary team consisting of an ophthalmologist, primary care physician, immunologist, paediatrician, allergologist and/or psychological support may be considered as part of collaborative management of patients with VKC (when appropriate).

Figure 3 summarises key information on VKC for patients and caregivers, while a full list of recommendations can be found in Table S6 in the electronic supplementary material.

DISCUSSION

VKC is a rare, chronic disease requiring prompt management of symptoms to prevent exacerbations, flare-ups and complications [2, 13, 17]. Recent consensus initiatives have provided best-practice guidance on the principles for diagnosis, referral, initial and long-term management, and supportive care, but none has specifically addressed the unmet need for unified clinical guidance for primary care physicians and general ophthalmologists in the European region [1, 4, 13]. At present, clinical judgement and experience guide daily practice in managing patients with VKC [13, 38]. Due to the lack of standardised recommendations and guidelines for diagnosis and management, treatment for VKC varies greatly across countries and regions [1, 4, 13]. This could result in suboptimal management of patients, increasing the risk of prolonged or permanent damage to the cornea and conjunctiva, which may lead to visual impairment [1, 15, 17]. In fact, inadequate counselling and unrealistic expectations, often resulting in the overuse or misuse of corticosteroids can be associated with complications. Over-medication with corticosteroids can cause vision loss, as can under-medication (although uncommon), and persistent inflammation resulting in corneal scarring and stem-cell damage.

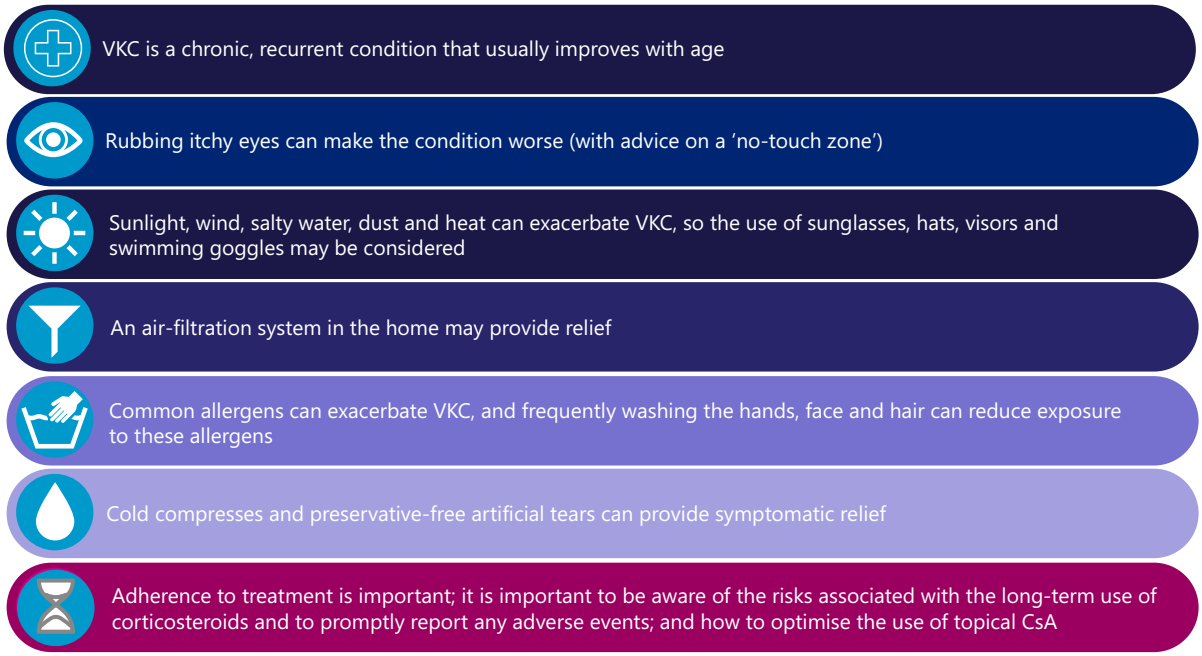

Fig. 3 Summary of the information that physicians should share with patients diagnosed with VKC and their caregivers. *CsA* ciclosporin A, *VKC* vernal keratoconjunctivitis

Using the modified nominal group technique, the EUR-VKC Group of seven European ophthalmologists achieved consensus on best-practice recommendations for the assessment, diagnosis, management and follow-up of VKC in Europe.

Patients with VKC often initially present to primary care or emergency departments [13]. In both scenarios, the decision for referral should depend on disease severity and progression [2]. If any corneal involvement is present, the patient should be referred to a specialist. As VKC is a rare disease, it is anticipated that referral to an ophthalmologist from primary care should not significantly affect waiting lists.

Many studies have found an association between VKC and keratoconus [39–41], with prevalence reported as high as 26.8% among patients with VKC [39]. It may be hypothesised that an increase in protease activity or inflammatory cytokines may be exacerbated during forceful eye rubbing (without clear observation that it is a cause), as seen in patients with allergic conjunctivitis, potentially contributing to the development and progression of keratoconus [40, 41]. However, this remains an unsettled issue because of contradictory results – such as that of a cross-sectional, single-centre study in Italy which found that only approximately 2% of a large series of patients with VKC had keratoconus [42]. The EUR-VKC Group agreed, as other researchers have suggested before, that there still lacks clarity on whether any possible link between ocular allergy (and particularly VKC) and keratoconus is only due to eye rubbing.

No single clinical feature viewed in isolation can accurately differentiate VKC from other ocular allergies such as AKC [1]. For very young children who are unable to communicate their symptoms, photophobia may be the only sign indicating the need for a complete ocular examination. However, VKC is not typically suspected based on one symptom or sign alone [1, 43]. Therefore, a complete ocular examination is required by an ophthalmologist for an accurate diagnosis.

Eversion of the eyelids (to check for giant, cobblestone-like papillae of the upper tarsal conjunctiva) is not mandatory for primary care as it is fairly invasive and may cause distress if not done correctly, but it will likely be needed

to confirm a diagnosis of VKC in most patients [43]. Eversion of the eyelids should be carried out by a competent and confident physician. Ophthalmologists should be able to recognise limbal inflammation and Horner–Trantas dots with or without slit-lamp examination.

Timely initiation and application of a stepwise treatment strategy, that is appropriate for the severity of the disease and inflammatory activity present, is crucial to prevent sight loss and improve the quality of life of children with VKC. Long-term treatment for chronic inflammation may be necessary, and the use of topical corticosteroids should be minimised to avoid complications. There is no consensus on the best approach for the use of anti-inflammatory agents to treat VKC – that is, whether to use topical CsA alone, initiate CsA at the same time as corticosteroids or use corticosteroids then CsA (e.g. such as a bridging approach in dry eye disease). A key question remains as to whether the repeated short-term use of corticosteroids (which are commonly prescribed by both non-specialists and specialists) may impact earlier intervention with more targeted treatments, such as topical CsA, and thus possibly prolong symptoms in the long term.

The EUR-VKC Group suggested that short-pulse corticosteroids are typically positioned before topical CsA in the treatment sequence. However, if corticosteroid pulses are prescribed frequently (e.g. more than three times), or considered for > 3 months, then topical CsA is indicated [35, 43, 44]. VKC may require long-term treatment, and corticosteroids are often used to provide early relief of symptoms [17] but are accompanied with long-term risks, such as increased IOP or steroid-induced glaucoma [31]. Measuring IOP before starting treatment allows the physician to monitor changes over time and identify any potential steroid-induced complications. Some 'soft' corticosteroids (e.g. loteprednol, hydrocortisone) may not completely resolve VKC exacerbations, and long-term treatment can lead to corticosteroid dependency. 'High-potency' topical corticosteroids (e.g. dexamethasone), used as a pulse therapy for 3–5 days without tapering, could be more efficacious in resolving exacerbations and less likely to increase IOP than the longer-term use of 'soft' corticosteroids [2].

The EUR-VKC Group agreed that topical CsA should be considered for long-term control, as CsA is the only immunomodulator indicated and approved in Europe to treat severe VKC (based on the time of the patient's visit and the history of disease) [33–35, 44, 45]. Tacrolimus is an immunomodulator that is approved for the treatment of atopic dermatitis. It has shown some therapeutic effectiveness in VKC, improving ocular objective signs and reducing itching, congestion, tearing and foreign-body sensation [46, 47]. However, tacrolimus is currently only indicated and approved for the treatment of VKC in Japan, and additional data from randomised clinical studies are needed to better understand its potential role in treating VKC in Europe [1, 46].

It may be appropriate to provide a personalised management plan for each child, addressing each medication, the rationale for its use, and the frequency and method of administration. The EUR-VKC Group suggest discharging asymptomatic patients, patients with mild VKC and patients without a need for the ongoing use of corticosteroids or topical CsA to a primary care physician, who can provide fast access to follow-up appointments and, depending on the healthcare setting, discuss whether ongoing treatment can be managed in primary care or general ophthalmology.

All of the currently available treatments for VKC are palliative and do not extinguish the complex immune process that initiates and propagates the ocular inflammation associated with VKC [2]. Further investigation is required into the feasibility of steroid-sparing regimens in the treatment of VKC, as well as other potential options including combinations with mast cell stabilisers, antihistamines, calcineurin inhibitors [4] and/or oral montelukast [48, 49]. Other areas of potential research include individualised treatment to improve outcomes and patient satisfaction [4], understanding the long-term impact on patient outcomes and the cost-effectiveness of treatments. In the future, a national patient association/patient representative(s) or non-VKC specialist physicians, may

be engaged to validate or expand upon the findings of the EUR-VKC Group.

Strengths and Limitations

The modified nominal group technique was chosen rather than the Delphi consensus method due to the small number of contributors in the EUR-VKC Group and the rarity of the disease. The modified nominal group technique facilitates small-group discussions, giving all group members the opportunity to provide input in a timely manner. In the absence of research-based evidence, the technique provided a structured process to support the expert panel in evaluating key aspects of VKC assessment, diagnosis, treatment and follow-up, and in reaching consensus on recommendations for the benefit of primary care physicians and general ophthalmologists.

The EUR-VKC Group members represent a range of nationalities and each brought their unique background and experiences to the panel, thereby strengthening the consensus programme. One potential methodological issue with consensus programmes is the tendency for participants to feel pressure to conform to the group view. This was mitigated by using an anonymous online voting platform while allowing for rapid collection, analysis and dissemination of each round of results.

CONCLUSIONS

VKC is a rare, underdiagnosed, chronic allergic ocular disease that, if left untreated, can cause significant damage to the cornea and conjunctiva, which may lead to long-term complications, visual impairment and a detrimental impact on the quality of life of both the child and their family/caregivers. There is an unmet need for unified clinical guidance on the assessment, diagnosis and management of VKC in Europe. The EUR-VKC Group has provided recommendations on the assessment, diagnosis, management, referral and follow-up of patients with VKC, and should be used as a framework to facilitate further collaboration between primary care physicians, general ophthalmologists and specialists to improve the outcomes for patients with VKC.

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