

## R E V I E W

# Vernal keratoconjunctivitis: state of art and update on treatment

*Giulia Brindisi<sup>1#</sup>, Bianca Cinicola<sup>1#</sup>, Caterina Anania<sup>1</sup>, Giovanna De Castro<sup>1</sup>, Marcella Nebbioso<sup>2</sup>, Michele Miraglia del Giudice<sup>3</sup>, Amelia Licari<sup>4,5</sup>, Carlo Caffarelli<sup>6</sup>, Maria De Filippo<sup>4,5</sup>, Fabio Cardinale<sup>7</sup>, Marzia Duse<sup>1§</sup>, Anna Maria Zicari<sup>1§</sup>*

<sup>1</sup>Department of Maternal and Child Health and Urological Sciences, Sapienza University of Rome, Rome, Italy; <sup>2</sup>Department of Sense Organs, Sapienza University, Rome, Italy; <sup>3</sup>Department of Woman, Child and Specialized Surgery, University of Campania “Luigi Vanvitelli”, Naples, Italy; <sup>4</sup>Pediatric Clinic, Fondazione IRCCS Policlinico San Matteo, University of Pavia, Pavia, Italy; <sup>5</sup>Pediatric Unit, Department of Clinical, Surgical, Diagnostic, and Pediatric Sciences, University of Pavia, Pavia, Italy; <sup>6</sup>Pediatric Clinic, Department of Medicine and Surgery, University of Parma, Parma, Italy; <sup>7</sup>Department of Pediatrics, Giovanni XXIII Pediatric Hospital, University of Bari, Bari, Italy

#These authors share first authorship; §These authors share senior authorship

## Abstract

Vernal keratoconjunctivitis (VKC) is a chronic inflammatory disease affecting the ocular conjunctiva and cornea. It is a rare and underestimated pathology, whose missed or delayed diagnosis can lead to the development of serious ocular complications. Moreover, despite VKC symptoms are well known, they can overlap and be mistaken with allergic conjunctivitis. In fact, diagnostic criteria and severity grading are not standardized yet. The pathogenesis of VKC is still controversial and it is difficult to identify a single mechanism underlying the chronic ocular inflammation. Different studies hypothesized both allergies and autoimmune diseases and also oxidative stress contribute significantly to the origin of the disease. However, the unclear pathogenesis and the lack of specific disease biomarkers make treatment a challenge. The standard therapy includes antihistamines, anti-inflammatory and immunosuppressant drugs and novel therapies are currently under investigation. However, considering treatment guidelines and recommendations are not well defined yet, therapy should be personalized on the clinical features of the patient. This paper provides an overview of the VKC and updates on the challenges that need to be addressed in the future to improve the management of the patient with this disease and improve his quality of life. ([www.actabiomedica.it](http://www.actabiomedica.it))

**Key words:** Vernal keratoconjunctivitis, children, therapy, omalizumab, cyclosporine A.

## Introduction

Why an update on Vernal keratoconjunctivitis (VKC)? It is known that the patient affected by VKC has a poor quality of life (QoL). The different challenges characterizing the disease strongly affect QoL and need to be critically analyzed.

1. It is an underestimated disease because it is relatively unknown and is often mistaken for allergic conjunctivitis. Missed or delayed diagnosis can have serious consequences.
2. The pathogenesis is controversial and equivocal, and the resulting therapeutic implications may be uncertain.

3. The diagnostic criteria and a grading of disease severity are not standardized.
4. Treatment guidelines and recommendations are lacking and guiding criteria (biomarkers) for the choice of specific treatment are not identified yet.

**It is an underestimated disease because it is relatively unknown and is often mistaken for allergic conjunctivitis. Missed or delayed diagnosis can have serious consequences.**

VKC is a rare (<1:10 000) chronic ocular disease affecting ocular conjunctiva and cornea, with remitting stages of inflammation in the ocular surface. VKC is more frequent in dry and hot climates (Mediterranean area, Central and South America, Middle East, etc) compared to colder regions, such as Great Britain, Northern Europe, Australia, and North America (1). Usually it occurs in the first decade of life, most frequently between the 6<sup>th</sup> and 7<sup>th</sup> year of life and resolves mainly during puberty, reinforcing the role of hormones in its pathogenesis. Males are affected more frequently than females with a ratio ranging from 2:1 to 4:1 (2).

VKC displays three clinical phenotypes: the tarsal, the limbal and the mixed one, characterized by papillae respectively on the tarsal conjunctiva, on the limbal zone (with the typical Horner-Trantas dots), and on both areas. The disease is bilateral in about the 96.7% of cases; only the tarsal form may be unilateral (3).

VKC is characterized by the symptoms listed in Table 1. Most of them (ocular hyperemia, itching, foreign body sensation and tearing) are completely overlapping those present in allergic conjunctivitis while others are more specific for VKC, such as intense photophobia and ocular pain. Photophobia is one of the

most troublesome symptoms that worsen children's quality of life, limiting their daily activities and requiring the use of sunglasses most of the year (4).

However, these signs are not sufficient to reliably differentiate VKC from allergic conjunctivitis: the disease must be suspected in case of treatment failure with drugs commonly used in allergic conjunctivitis such as topical and/or systemic antihistamines, but the definitive diagnosis can be formulated only if the presence of papillae at the limbus and/or tarsal level is demonstrated. Although VKC is generally a self-limiting disease, if not promptly and adequately treated, may lead to more or less severe complication such as a progressive visual loss, the development of corneal ulcers with serious sequelae up to blindness. Therefore, the disease needs a tight monitoring than allergic conjunctivitis (3).

Complications generally result from a slightly controlled disease. The symptoms are overlapping, (ocular hyperemia, tearing, photophobia and progressive visual loss), but the ocular framework to the slit lamp can be very heterogeneous. The uncontrolled or incorrectly cured inflammation means that the cornea, which is normally avascular, may present blood vessels (corneal neovascularization) or shield ulcers that are generally superficial, painless and located in the upper cornea. Tissue re-epithelialization can be difficult and lead to astigmatism, keratoconus, amblyopia and rarely to corneal perforation (2). Keratoconus is a chronic and progressive disease where the cornea becomes irregular and with a conical shape secondary to corneal thinning, resulting in visual damage often difficult to correct (5).

Pseudogerontoxon is another typical VKC picture; it is a chronic limbal disease secondary to lipid deposition, caused by the development of Horner-Trantas dots with a consequently reduced limbus permeability (6).

Another potentially confounding complication is the punctate keratitis, characterized by multiple punctate epithelial defects at the corneal level, since it can also be secondary to viral or bacterial conjunctivitis, blepharitis, exposure to ultraviolet rays and overuse of contact lenses (2).

Finally, iatrogenic complications should be considered, as ocular hypertension, glaucoma and cataract secondary to prolonged steroid treatment (7).

**Table 1.** The most common VKC symptoms

Itching
Photophobia
Tearing
Sensation of foreign body
Pain, in case of cornea involvement
Burning

### **The pathogenesis is controversial and equivocal and the resulting therapeutic implications may be uncertain.**

The pathogenesis of VKC is still controversial and it is difficult to identify a single mechanism underlying the chronic ocular inflammation. It can therefore be considered a chronic inflammatory disease of the eye, focusing on the concept that VKC is not only a local ocular disease but also a systemic one. Indeed, systemic pro-inflammatory markers such as high mobility group 1 (HMGB1) and its receptor for the advanced glycation end product (sRAGE) were found in children affected by VKC, supporting the evidence of a systemic involvement (8).

Traditionally, inflammation is considered sustained by an IgE-mediated disease, but atopy, skin prick tests (SPTs) positivity and high specific serum IgE levels are found in less than 50% of cases. However, the finding of an eosinophilic inflammation in the ocular conjunctiva supports the hypothesis of a crucial role played by the IgE mediated and the T helper 2 (Th2) response in the pathogenesis of the disease. Exposure to environmental allergens keeps ocular inflammation active as documented by the presence of the eosinophilic cationic protein (ECP), an important marker of inflammation and of histamine, released by mast cell degranulation. However, alongside a Th2 response, several cytokines involved in a Th1 pathway, such as IL-1, IL-4, IL-5, IL-6, IL-8 and IL-13, and transforming growth factor-beta 1 (TGF- $\beta$ 1) have been found in VKC local chronic inflammation (3). Also TNF- $\alpha$  is shown having a pivotal role in this chronic inflammation and its levels are increased in the conjunctival surfaces of VKC. It seems to be involved in an autophagy mechanism, leading to the remodeling of the ocular conjunctiva (9). On the other side, in more than 31% of cases, VKC is associated with a family history of autoimmunity or with the finding of ANA positivity, supporting the hypothesis that at least in some cases autoimmunity may play a role on the pathogenesis of the disease (10-12). Finally, a recent study conducted by Zicari et al, showed that oxidative stress may contribute to the persistence of the ocular and systemic inflammation, in addition to the role of Th1 and Th2 mediators, leading to the development of

disease serious complications (13). In fact, the authors analyzed a cohort of 36 children affected by VKC and found that the naïve patients had high level of Hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>), a derivative of oxidative stress, in both serum and tears. Furthermore, H<sub>2</sub>O<sub>2</sub> level was significantly reduced in patients under cyclosporineA (CsA) therapy, reinforcing also the anti-inflammatory and antioxidant role of CsA. We can conclude that VKC is a chronic inflammatory disease of the eye with important systemic relapses. It can be sustained by both allergies and autoimmune diseases, and also oxidative stress contributes significantly to the pathogenesis of the disease: this new perspective also affects the heterogeneity of therapeutic approaches.

### **The diagnostic criteria and a grading of disease severity are not standardized.**

To date, there is a lack of well-defined and uniform criteria for VKC diagnosis. However, the diagnosis of VKC can be made with three cardinal points: the medical history, the ocular examination and the laboratory investigations. Medical history is useful to guide the diagnostic way: symptoms like intense photophobia, eye itching, tearing and foreign body sensation, that appear in spring and worsen in summer with a resolution in autumn/winter, should raise suspicion of VKC. Other elements of VKC suspicion are no clinical response to antihistamines used in allergic forms or in case of SPTs or specific IgE negativity (2). Laboratory investigations include a serological evaluation with a complete blood count, total IgE serum levels, IgA, IgM, IgG, VES, PCR, anti-nuclear antibodies (ANA) and allergy evaluation with SPTs and specific serum IgEs. To date, the serological evaluation is useful for a proper clinical and therapeutic definition but no kind of cytokine or test can be considered a marker of VKC disease so far. Therefore, diagnosis is clinical and only the instrumental ocular examination with a slit lamp can confirm the VKC diagnosis. The most common ocular findings are reported below (2):

- Scleral and/or tarsal conjunctival hyperemia (in about 86-90% of cases).
- Tarsal papillae in the superior tarsal conjunctiva and only rarely at the lower tarsal level. They are hyper-

emic elements resulting from chronic inflammation, are characterized by a central vascular channel in about 90% of cases and are visible with the eversion of the upper eyelid. Based on the size, they are classified as micro-papillae (<1 mm), macro-papillae (1–3 mm), or giant papillae (>3 mm). The largest ones give the conjunctiva a “cobblestone” aspect

- Horner-Trantas dots, the most typical sign of VKC. They are aggregates of epithelial and eosinophil cells at the peri-corneal level resulting in a gelatinous nodular appearance.

Considering the relevance and usefulness of these signs in discriminating between vernal forms and allergic forms, it is therefore necessary a close collaboration with the ophthalmologists. The follow up must be conducted by both the specialists because all these lesions can evolve into long term dangerous complications (7).

Many studies evaluated the tears composition. Leonardi et al. found not only high levels of IgEs but also other Th2-type cytokines such as IL-4, IL-5 and IL-10 as well as matrix metalloprotease-1 (MMP-1), MMP-2, MMP-3, MMP-9 and MMP-10, multiple proteases and growth factors. These mediators may all play a pivotal role in the pathogenesis of chronic ocular inflammation. However, at the present time, these are still research markers, not standardized nor included in the diagnostic work-up (14-15). Also, it is challenging to carry out eye investigations on tears for the difficulty of their collection and to perform ocular cytological examination using brushing or histological examination of the conjunctiva with a biopsy (16-17).

In addition to diagnostic criteria, for many years attempts have been made to establish severity criteria to better monitor the disease and modulate therapy but, to date, shared national or international guidelines for VKC staging are still lacking (18).

It is worth pointing out that ophthalmologists and pediatricians use different scales. Obviously, ophthalmologists rely on ophthalmological findings more or less integrated with clinical criteria and subjective symptoms: examples are the grading proposed by Leonardi et al (objective symptoms) (19) by Spadavecchia et al (ophthalmological survey and subjective symptoms) (20), by Gokhale (which also introduces the frequency of recurrences) (21), or by Bonini et al

(assessing a mosaic of symptoms and situation) (22), as well as many others (23-25). Instead, pediatricians generally use the grading proposed by Pucci et al, which has the advantage to be extremely simple, as it is based exclusively on subjective symptoms (26).

**Treatment guidelines and recommendations are lacking and guiding criteria (biomarkers) for the choice of a specific treatment are not identified yet.**

Besides standard therapy, there are several useful behavioral precautions such as the use of sunglasses, the reduction of solar exposition and the use of artificial tears. Regarding the pharmacological approach, it is known that both membrane stabilizers and antihistamines by local and systemic routes have very limited efficacy. This is now well understandable considering the role of a Th1-mediated inflammatory pathway alongside a Th2-mediated allergic response and the crosstalk between these two responses. Thus, the failure of these categories of drugs, despite the good efficacy in allergic rhinoconjunctivitis, is considered one of the most suggestive and “easy” criteria that guide the diagnostic suspicion of VKC. However, **topical antihistamines** may be used in mild and moderate forms and are particularly useful in patients with mainly seasonal symptoms (18). Levocabastine and emedastine act as selective H1 receptor antagonists but can also inhibit cytokine production and downregulate surface adhesion molecules. Moreover, other topical antihistamines such as olopatadine, ketotifen, epinastine, azelastine, alcaftadine, and bepotastine, have also the function of mast-cell stabilizers or can be associated in a unique formulation with a mast cell stabilizing molecule like sodium cromoglycate + chlorphenamine (18). As for topical NSAIDs, they are known to provide relief especially on itching in allergic conjunctivitis (27).

However, their long-term efficacy and safety in VKC have not been clearly defined. Moreover, to note, long-time complications of topical NSAIDs are reported on the corneal epithelium with thinning and melting (28,29). so their use warrants further clinical studies.

**Topical steroids** are one of the most effective therapies in controlling signs and symptoms of

VKC. They may be used alone or in association with vasoconstrictors or antibiotics: dexamethasone, prednisone, loteprednol etabonate, rimexolone, and flurometholone are the most used with significantly different therapeutic schemes. As they should be stopped once symptoms are controlled for the risk of ocular complications as cataracts, ocular hypertension, glaucoma, and ocular infections, the short and repeatable 3–5 days cycles seem the best choice. Steroids should be used in the acute phase, but they should be avoided as first-line treatment for VKC. In the most severe cases, the supratarsal injection of dexamethasone, triamcinolone or hydrocortisone can be performed (2,29).

For many years now, the treatment of choice for VKC has consisted in the topical administration of Cyclosporine A (CsA). Cyclosporine A (CsA) is a cyclic polypeptide composed of 11 amino acids with a strong immunosuppressant action, used in VKC as 1% eye drops formulation. It is very effective in reducing inflammation through the inhibition of the T lymphocytes activation and the expression of the class II histocompatibility antigens on the surface of the immunocompetent cells. Thus, blocking the degranulation of mast cells and basophils and the histamine release, the production of IL-2 is substantially reduced. Moreover, it is well documented that CsA can significantly reduce the number of eosinophils in tears, responsible for the formation of giant papillae and shield ulcers. As a result, in addition to relieving the typical symptoms of the disease, CsA is also essential to reduce any future complication such as the development of ulcers and the consequent blindness (20,26). However, CsA, as an immunosuppressant, increases the risk of ocular opportunistic infections, while there is no risk of systemic infection because the systemic absorption is unremarkable (2,30).

Another immunosuppressant, tacrolimus, has been added to CsA in the treatment of VKC. It is a macrolide with immunosuppressive action on T cells. It inhibits the production of IL-2, IL-3, IL-4, IL-5, TNF- $\alpha$ , and IFN- $\gamma$  but it also works on B lymphocytes, neutrophils, and mast cells. Ophthalmic suspension of tacrolimus seems having a similar efficacy to CsA, with lower adverse effects than CsA (18). Indeed, in an open-label 4-week trial on 10 patients resistant to standard therapies, including CsA, Tacrolimus was effective and free

from any adverse effects even after 2 years of follow-up. The most common side effect is ocular burning upon installation, due to the presence of ethyl alcohol in the intravenous vials of tacrolimus used for the galenic preparation of the eye drops. Moreover, as an immunosuppressant, it increases the risk of corneal infections if used for a long time, while no systemic infections are expected because topically instilled tacrolimus is not absorbed into the bloodstream. The use of Tacrolimus is addressed to subjects with poor or no response to therapy with CsA. As an alternative to Tacrolimus, in cases of VKC resistance to CsA treatment, the use of Omalizumab has been attempted with very encouraging results (31). Omalizumab is a recombinant DNA-derived humanized IgG1 $\kappa$  monoclonal antibody that selectively binds to human immunoglobulin E (IgE). It is indicated for severe allergic asthma in patients older than 6 years, for chronic spontaneous urticaria in patients older than 12 years and in adults with chronic rhinosinusitis with nasal polyps.

Since the first attempts with Omalizumab in VKC, its use was then extended to many patients with asthma and symptoms of VKC unresponsive to conventional drugs: an improvement of the ocular symptoms as well as in the need for rescue therapies was observed in all patients already in the first months of therapy (32). However, no clinical trials on biologic drugs specifically for VKC have been carried out in the pediatric population, as dosage and schedule of treatment with omalizumab are currently based on protocols approved for patients with asthma (2,18,32). Finally, many other approaches have been attempted to counteract inflammation; among these, some drugs/molecules that are being studied deserve mention. These therapeutic strategies try to interfere in the different pathways of inflammation avoiding the use of steroids or immunosuppressants. They are largely experimental but may perhaps enter the therapeutic baggage of VKC in the future. The Lipid conjugates inhibit the enzyme phospholipase A2, useful to degrade phospholipids by activating the eicosanoid pathway (leukotriene B4 and prostaglandin E2). Thus, these molecules inhibit the production of the inflammatory mediators TNF- $\alpha$  and IL-8. Their efficacy is still to evaluate (18).

Chlorogenic acid acts on transglutaminase, a protein activated during the inflammation pathway with

an anti-inflammatory effect similar to steroids. These compounds may be used in monotherapy or in addition to other anti-inflammatory drugs (18).

Drugs that increase the intracellular concentration of cAMP and inhibit PDE are intriguing. The secondary messenger cyclic adenosine monophosphate (cAMP) exerts a pivotal role in the activity of neutrophils, eosinophils, and mast cells. Its activity is regulated by phosphodiesterase (PDE) IV that is able to hydrolyze cAMP. By inhibiting PDE, the intracellular concentration of cAMP increases. Recently studies demonstrated that compounds derived from 3-anilino-2-cycloalkene have inhibitory activity of PDE IV and thus ultimately suppress the activation of inflammatory cells (18).

Novel compositions with antagonizing, inhibitory, and down-regulating actions on human TLRs and co-receptors are another field of interest. Toll-like receptors (TLRs) are expressed on several cells of the immune system and the binding of ligands to the TLR induces the production of proinflammatory mediators. TLRs play also a role in modulating the Th1/Th2 balance towards a Th2 profile, leading to the development of allergic diseases. New drugs with down-regulatory and inhibitory effects on human TLRs and co-receptors are being investigated with promising results (18).

Lastly, attention is now focused on a Small interfering RNA, which acts by silencing spleen tyrosine kinase (Syk). Syk seems to be activated by immune receptors, such as FcεRI, that activate the PLCc and PI3K pathways causing mast cell degranulation. Inhibiting this activation may effectively help control inflammation but studies are still very preliminary (18).

## Conclusions

To date there are many therapeutic agents that are still being studied but the mainstay of VKC treatment remains CsA. Although there are no shared official recommendations, there is substantial agreement on the use of cyclosporine as the first-choice therapy. In case of failure, tacrolimus can be used or, if other markers of allergic diathesis (asthma, dermatitis, urticaria) are present, omalizumab can be chosen. Steroids should be used only for the treatment of acute relapses

and avoided as first-line treatment. Other molecules and treatment strategies are in progress, but the precise personalization of therapy is still far, in the absence of precise biomarkers. More studies are warranted in the future to identify a personalized therapy for each patient tailored on the specific cytokine profiles and pattern of inflammation, balanced with both severity of symptoms and disease activity, in order to avoid disease complications and improve patient's quality of life.

**Conflict of interest.** Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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- Correspondence:**  
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Giulia Brindisi,  
Department of Pediatrics, Sapienza University of Rome  
Viale del Policlinico 155, Rome 00161, Italy.  
Phone: 06 49979308  
Email: giulia.brindisi@gmail.com