
Review Article

Vernal keratoconjunctivitis: a major review

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ABSTRACT.

Vernal keratoconjunctivitis (VKC) is a chronic, bilateral, at times asymmetrical, seasonally exacerbated, allergic inflammation of the ocular surface, involving tarsal and/or bulbar conjunctiva. Though the allergic nature of this entity has been accepted for a long time, the accumulation of a large amount of immunological data has proved that the pathogenesis of VKC is much more complex than a mere type 1 hypersensitivity reaction. In the past several years, many clinical and experimental studies about the cells and mediators involved in initiating and perpetuating the ocular allergic inflammation have shown that T helper type 2 cells and their cytokines, corneal fibroblasts and epithelium along with various growth factors play an important role in the pathogenesis of VKC. Based on this information about the pathogenesis of VKC newer, more selective drugs like anti-chemokine receptor antibodies and leukotriene receptor antagonists are under evaluation. Cyclosporine has been shown to be effective in the treatment of VKC but further randomized control trials are required to establish the minimum effective concentration.

Key words: chemokine – cytokine – eosinophil – immunoglobulin – interleukin – mast cell – T helper cell – vernal keratoconjunctivitis

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Introduction

Vernal keratoconjunctivitis (VKC) is a chronic, bilateral, at times asymmetrical, seasonally exacerbated, allergic inflammation of the ocular surface, involving tarsal and/or bulbar conjunctiva. It is more common in children and young adults having an atopic background. It was first mentioned in the ophthalmic literature as conjunctiva lymphatica more than 150 years ago. Subsequently, most of the doyens of ophthalmology during that period (Arlt, Dasmarrès, von Graefe, Axenfeld, Trantas and Her-

bert) published about this interesting malady (Barney 1997). Different authors, at different times, described it as spring catarrh, phlyctenula pallida, circumcorneal hypertrophy, recurrent vegetative conjunctiva, verrucosa conjunctiva and aestivale conjunctiva, calling attention to the various aspects of this disease. Although the allergic nature of this entity has been accepted for a long time, its exact aetiology and pathogenesis is still unclear. Recently, many clinical and experimental studies about the cells and the mediators involved in initiating and perpetuating ocular allergic inflamma-

tion have broadened our knowledge about the pathophysiology of this disease. The accumulation of a large amount of immunological data has established that the pathogenesis of VKC is much more complex than a mere type 1 hypersensitivity reaction. To the present day, the precise role played by genetic predisposition and environmental factors in the onset, progression and resolution of this self-limiting, but at times incapacitating, childhood entity is an enigma. Despite the universal acceptance of the nomenclature vernal keratoconjunctivitis, occurrence of this disease is not limited to spring, with episodes of reactivity being quite common in the winter. The initial seasonal attacks turn into perennial disease after a few years. The efficiency of school-aged children decreased profoundly because of the chronic and recurrent course. Although this is not usually a blinding disease, visual impairment may occur if the cornea is involved.

Geographical distribution

VKC has a wide geographical distribution. Varying prevalence has been reported in different ethnic groups. Young males in dry and hot climates are primarily affected. It is more common in temperate zones of Mediterranean areas, central and west Africa, the Middle East, Japan, the Indian subcontinent and South America. VKC cases are also seen in Western Europe (including the UK and Sweden), Australia and North America – although the prevalence of

VKC in these countries has probably increased because of migration of susceptible populations. After the recent decline of endemic trachoma, VKC is a leading cause of outpatient ophthalmic morbidity among Palestinians of east Jerusalem, the West Bank and Gaza (O'Shea 2000).

Demography

VKC usually starts before the age of 10 years. The earliest reported age of onset is 5 months (Ukponmwan 2003). It generally resolves after puberty, usually around 4–10 years after onset (Bielory 2000; Leonardi 2002a). The disease is more common among males, with the male to female ratio reported in the literature varying from 4 : 1 to 2 : 1 (Neumann et al. 1959; Beigelman 1965; Bonini et al. 2000). The male preponderance in VKC is conspicuous below 20 years of age but after 20 years, the male and female ratio becomes almost equal (Bielory 2000; Bonini et al. 2000). Positive staining for oestrogen and progesterone receptors in conjunctiva from VKC, predilection for male and resolution after puberty suggest the role of hormonal factors in the development of VKC (Bonini et al. 1995b).

Genetics and family history

So far, no genetic predisposing factor has been identified for VKC but the predominance of VKC in Asia and Africa, along with the persistence of this predilection in migrated African and Asian populations, strengthens the possibility of a genetic predisposition. VKC is more common among individuals of Asian and African origin living in Sweden (Montan et al. 1999). Although no genetic analysis has been performed to confirm a relationship between VKC and a particular genotype, the constant and increased presence of eosinophils in blood, tears and conjunctival scrapings, the expression of a multitude of mediators and cytokines, as well as the predominance of CD4 cells locally suggest that VKC may be a phenotypic model of upregulation of the cytokine gene cluster on chromosome 5q. The cytokine gene cluster, through

its products like Interleukin (IL)-3, -4, -5 and granulocyte/macrophage-colony-stimulating factor (GM-CSF), regulate the prevalence of T helper cell type 2 (Th2), the growth and function of mast cells and eosinophils as well as the production of immunoglobulin (Ig) E in VKC (Bonini et al. 1995a). Family history of allergic disorders such as asthma, rhinitis, eczema, urticaria and multiple atopic diseases was reported in 49% of patients suffering from VKC (Bonini et al. 2000).

Associated conditions

Atopy, defined as the presence of allergen-specific IgE antibodies, is common among VKC patients. One third of VKC patients have multiple atopic diseases (Bonini et al. 2000). Atopy is less common in limbal compared to tarsal VKC (Tuft et al. 1989). Asthma is the most common atopic disease seen among VKC patients.

Fifteen per cent of VKC patients were reported to have keratoconus; 6% of these developed hydrops (Iqbal et al. 2003). A higher incidence of keratoconus and acute hydrops among VKC has been ascribed to excessive eye rubbing (Cameron et al. 1989). Acute hydrops with no history of eye rubbing and no hydrops, despite the history of frequent rubbing in many patients with keratoconus and VKC, suggest that acute hydrops may also be a result of a complex interaction between hereditary and environmental factors directed against the corneal endothelial in a susceptible population (Rehany & Rumelt 1995; Totan et al. 2001). Sex-hormone-related diseases such as gynaecomastia, polycystic ovary syndrome, mammary fibroadenoma, adiposogenital dystrophy and autoimmune diseases were reported by 2% of patients suffering with VKC (Bonini et al. 2000). In a gender- and age-matched study, a positive correlation between eyelash length and severity of VKC has been reported. It is postulated that long lashes may represent the protective mechanism against physical agents that might have an important role in the aetio-pathogenesis of VKC, although the chemical mediator responsible for

lash growth was not identified (Pucci et al. 2005).

Clinical features and diagnosis

In its typical form, VKC presents with pruritus, hyperaemia, photophobia and watering. VKC is bilateral in most (98%) patients, although minor differences in severity between the eyes are common (Bonini et al. 2000). Patients suffering from VKC may have several episodes of active inflammation throughout the year. Initially seasonal disease may become perennial after a few years. In approximately one quarter of VKC patients the disease smolders throughout the year, without any remission, from the onset (Bonini et al. 2000). Pruritus may vary from mild to intense and be exacerbated by exposure to wind, dust, bright light, hot weather or physical exertion associated with sweating. Exaggerated hyper-reactivity to non-specific stimuli such as heat, sun and wind during active and quiescent phases of VKC suggest neural involvement (Bonini et al. 1992a). Interestingly, Tabuchi et al. (2004) reported *Staphylococcus aureus* to be one of the exacerbating factors in VKC.

Thick mucus hyper-secretion with sticky mucous filaments, called 'ropy discharge', is a characteristic of VKC. Transient limbal or conjunctival yellow-white points or deposits, known as Horner-Trantas's dots (Fig. 1) are degenerating eosinophils and epithelial cell debris. In a cohort of Asian patients suffering from VKC, perilimbal conjunctival pigmentation has been reported to be a constant finding. The extent of pigmentation did not correlate with the severity of symptoms and signs of VKC. The pigmentation persisted when the disease was inactive (Rao et al. 2004).

Large (> 1 mm) papillae in VKC occur predominantly at the upper tarsus. Papillae that may attain a size of 7–8 mm are known as cobblestone papillae (Fig. 2). Papillae size correlate positively with the persistence or worsening of symptoms over long-term follow-up (Bonini et al. 2000). These papillae become quite swollen during the active stage but persist even during the quiescent

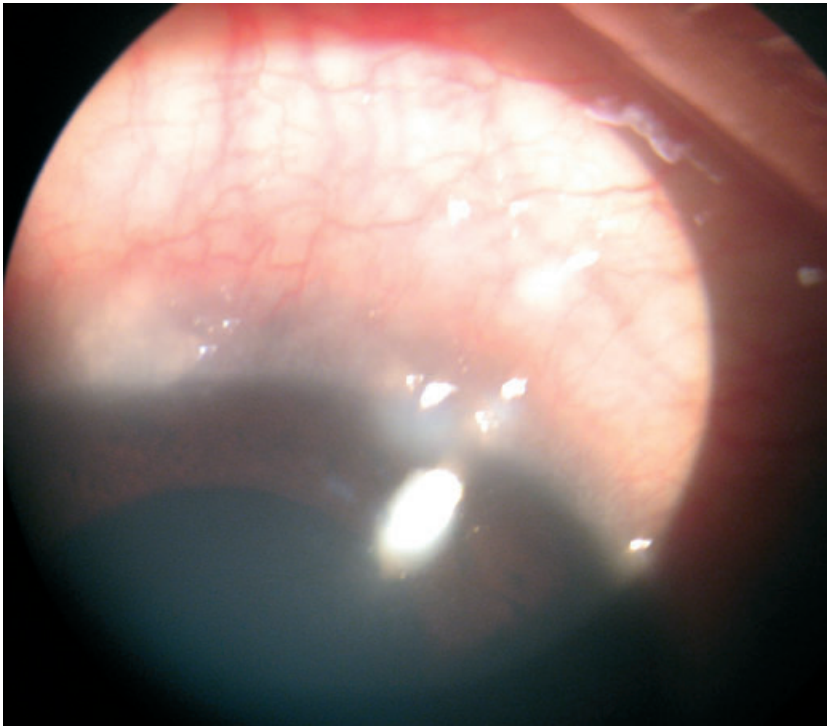


Fig. 1. Horner-Tranta's dots.

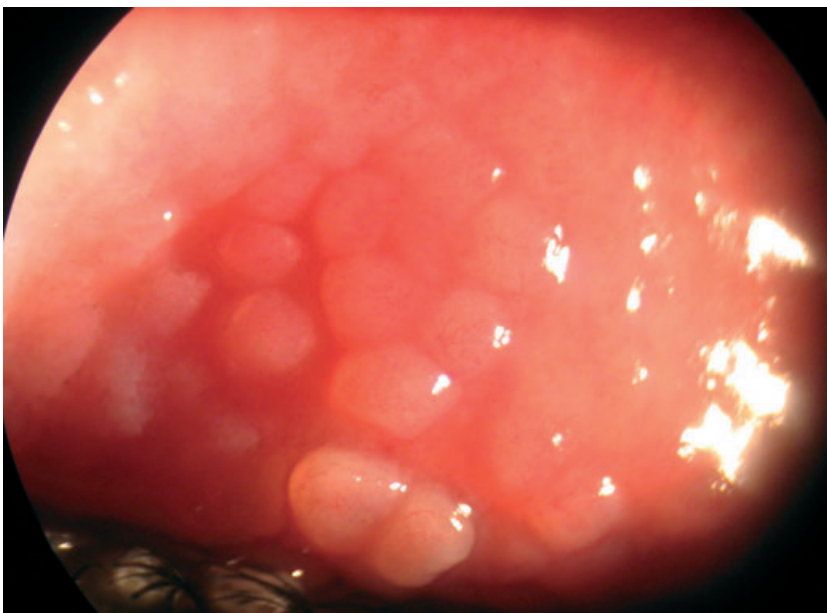


Fig. 2. Cobble stone papillae.

stage. Limbal papillae tend to be gelatinous and confluent (Fig. 3).

Bonini et al. (2000) graded the papillae on the upper tarsal conjunctiva or at the corneoscleral limbus as follows:

- (1) Grade 0: no papillary reaction.
- (2) Grade 1+: few papillae, 0.2 mm widespread over the tarsal conjunctiva or around the limbus.

- (3) Grade 2+: papillae of 0.3–1 mm over the tarsal conjunctiva or at the limbus.

- (4) Grade 3+: papillae of 1–3 mm all over the tarsal conjunctiva or for 360° around the limbus.

- (5) Grade 4+: papillae of more than 3 mm over the tarsal conjunctiva or gelatinous appearance at the limbus covering the peripheral cornea.

Based on the predominant involvement of either tarsal or limbal conjunctiva, VKC can be divided into palpebral, bulbar or mixed type with limbal forms being prevalent in non-White patients (Verin et al. 1999).

Photophobia, pain and foreign body sensation are caused by involvement of the cornea. Corneal changes include punctate epithelial keratitis, epithelial macro-erosions, shield ulcer, plaque formation and late corneal vascularization (Allansmith & Ross 1988; Buckley 1988). Coalescence of punctate epithelial keratitis areas leads to frank corneal epithelial erosion, leaving Bowman's membrane intact. If untreated, a plaque containing fibrin and mucus deposits over the epithelial defect (Rahi et al. 1985). Epithelial healing is then impaired, and new vessel growth is encouraged. The oval-shaped epithelial defects, known as shield ulcers (Fig. 4), usually have their lower border in the upper half of the visual axis. Healed shield ulcers may leave a subepithelial ring-like scar (Fig. 5). Corneal ulcer is reported to occur in 3–11% of patients. Corneal changes cause permanent reduction in visual acuity in 6% of patients suffering from VKC (Neumann et al. 1959; Cameron 1995a; Tabbara 1999). Pseudogerontoxon, which resembles arcus senilis, is a waxing and waning grey-white lipid deposition in the superficial stroma of the peripheral cornea.

Signs of VKC are confined mostly to the conjunctiva and cornea. The skin of the lid and lid margin are relatively uninvolved. The conjunctiva of the fornices does not usually show foreshortening and symblepharon formation. Iritis is not reported to occur in VKC. Ocular complications of VKC have been reported to include steroid-induced cataract and glaucoma, corneal scarring, microbial keratitis and limbal tissue hyperplasia (Sridhar et al. 2003). Amblyopia seen among VKC may be caused by corneal opacity, irregular astigmatism and keratoconus. Dry eye syndrome, reported in patients suffering from VKC, may be caused by unsupervised use of topical corticosteroids (Tabbara 1999).

No precise diagnostic criteria have been established for this disease. Hyperaemia, itching, photophobia, tearing and mucus discharge are

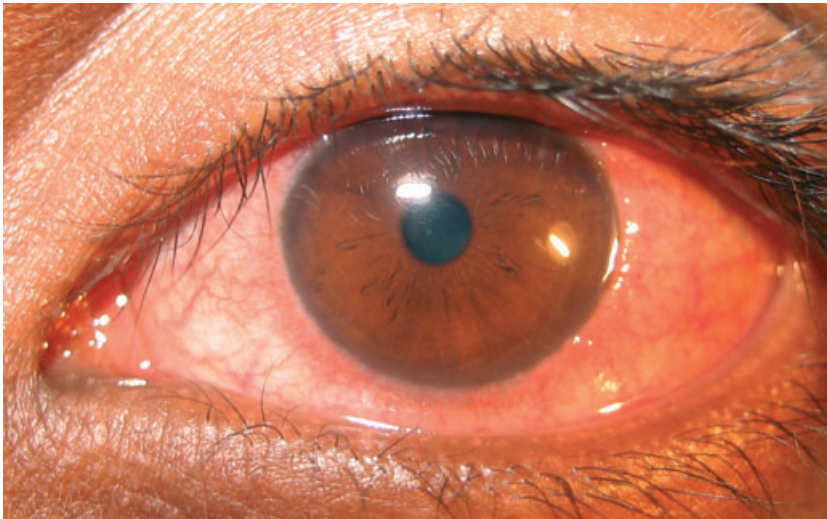


Fig. 3. Limbal papillae.

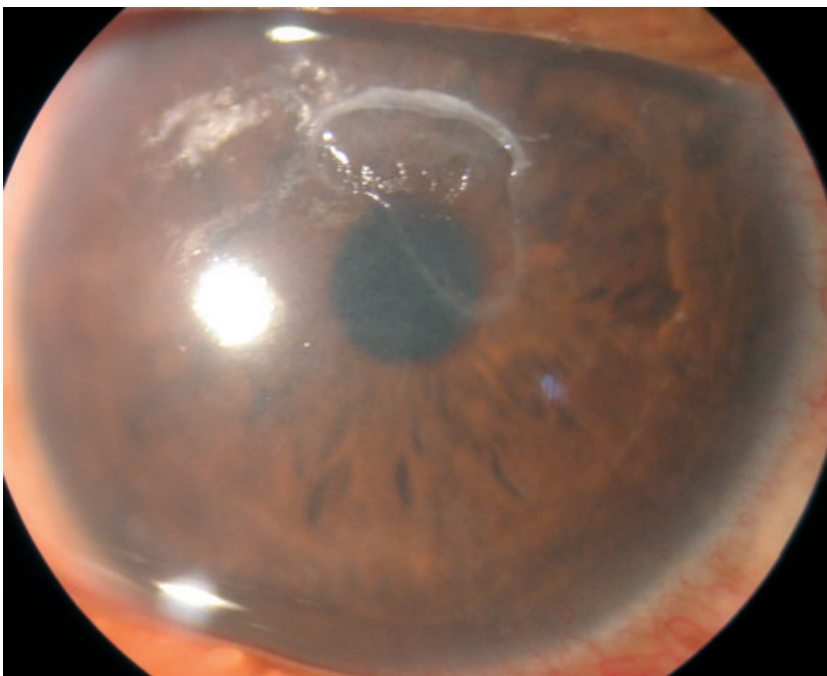


Fig. 4. Shield ulcer.

typical symptoms of VKC. Large papilla on the upper tarsal conjunctiva and corneoscleral junction are hallmarks of VKC. Diagnosis is based on typical clinical signs and symptoms, thus many mild or atypical cases may escape diagnosis. The lack of standardized diagnostic criteria and lack of common language among physicians regarding the severity of VKC renders this disease more difficult to diagnose and treat. Bonini et al. (2007) proposed a clinical grading

according to clinical phases of VKC to help physicians use a common language in the diagnosis and management of VKC and to allow a more homogenous selection of patients for clinical trials. Despite mounting data suggesting the role of both IgE and non-IgE mediated immune responses in the pathogenesis of VKC, no clinical or laboratory test has evolved to support the diagnosis in atypical cases or predict the course of this disease (Bonini et al. 2000).

Pathophysiology

Numerous cytological, immunohistological and molecular biological studies of allergic inflammation have facilitated our understanding of the pathophysiology of VKC. The ability to measure cytokines in tears, along with *in-vitro* analysis of the individual or combined effects of these cytokines on conjunctival mast cells, epithelial cells and fibroblasts has facilitated our understanding of specific processes contributing to the pathogenesis of VKC. The clear abundance of Th2 cytokines, upregulated expression of their receptors and conspicuous paucity of T helper cell type 1 (Th1) cytokines in tear and serum of VKC patients confirm the crucial role played by these factors in the onset and perpetuation of the chronic allergic inflammation observed in VKC. A variety of cells, normally present or infiltrating the ocular surface, are responsible for the profound expression of these cytokines in VKC. The factors stimulating these varied cells to increase their cytokine production are still poorly defined. The immune, nervous and endocrine systems seem to interact with each other in the pathogenesis of VKC (Bonini et al. 2004). Infective factors were thought to contribute to the pathogenesis of VKC but respiratory syncytial virus and chlamydia were not detected in conjunctival biopsies from patients with VKC (Koulikovska et al. 2001). Furthermore, serology for ocular chlamydial disease was also negative (Montan et al. 1999).

Personal or family history of atopy, elevated serum level of total and specific IgE, higher number of mast cells and eosinophils, increased level of mediators and favourable response to anti-allergic therapy – the features of allergic diseases – are also observed in VKC (Allansmith 1982; Bielory & Frohman 1992; Abelson & Schaefer 1993).

Conventionally, VKC was considered primarily a type I hypersensitivity reaction but the IgE-mast-cell-mediated process is not enough to explain the various clinical and histopathological changes associated with VKC (Coombs & Gell 1962; Allansmith 1982; Johansson et al. 2001). Negative response to skin tests or radioallergosorbent test for common allergens in

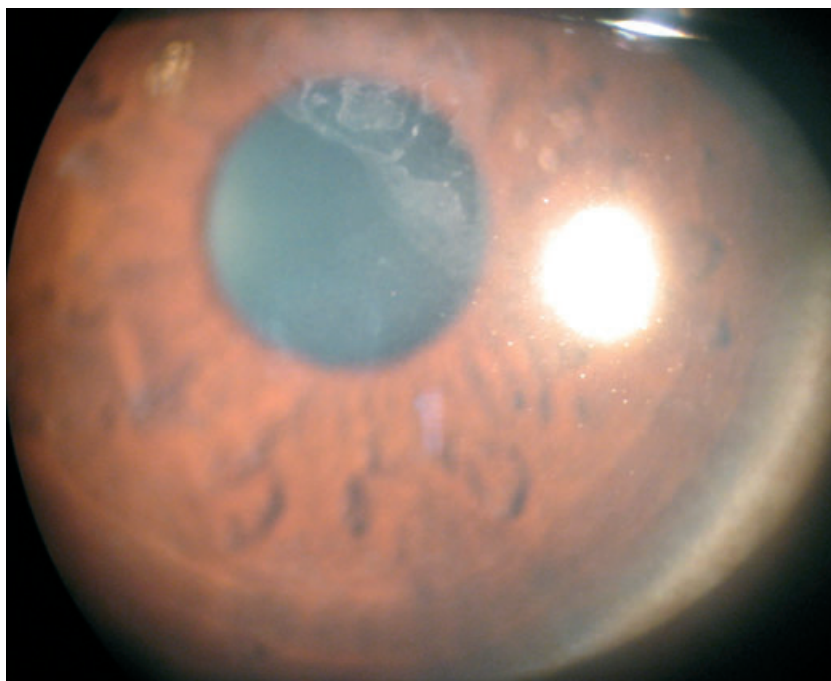


Fig. 5. Ring-shaped corneal opacity after healed shield ulcer.

almost 50% of patients, along with the presence of a multitude of cells and mediators in the conjunctiva, tears and serum of VKC patients, suggest a more complex pathophysiology than a mere type 1 hypersensitivity reaction (Bonini et al. 2000). The prevalence of IgE sensitization was significantly lower in bulbar than in tarsal and mixed VKC. Higher serum eosinophil cationic protein (s-ECP), total serum IgE (s-total IgE) and peripheral blood eosinophil counts have been reported in IgE-sensitized than in non-IgE-sensitized VKC patients (Pucci et al. 2003). Interestingly, Montan et al. (2002) found that the amount of mRNA encoding Th2-type cytokines and inflammatory cell markers in VKC remain the same irrespective of IgE sensitization.

Mediators in VKC

The plethora of mediators and cytokines in VKC compared to controls, seasonal allergic conjunctivitis and giant papillary conjunctivitis provides a new perspective on the complex inflammatory processes occurring on the ocular surface in this chronic disease (Cook 2004).

Cytokines

Cytokines are small secreted proteins that mediate and regulate immunity and inflammation. Unlike hormones,

these are not stored as preformed molecules but must be produced, *de novo*, in response to a stimulus. Different cell types may secrete the same cytokine or a single cytokine may act on several different cell types. Similar functions can be stimulated by different cytokines. ILs are the cytokines that are made by leukocytes and act on other leukocytes.

Activated helper T cells (CD4), mast cells and eosinophils are the main cytokine-producing cell types infiltrating the conjunctiva during chronic allergic eye diseases. Two distinct subtypes of helper T cells produce different cytokines. T cells isolated from conjunctiva of VKC patients and expanded into cell lines showed a Th2-like cytokine profile (Calder et al. 1999).

Th2 cytokines, i.e. IL-4 and -5, were high among VKC patients (Metz et al. 1997; Calder et al. 1999; Leonardi et al. 1999a). Increased expression of mRNA encoding Th2-type ILs was observed in allergic tissue from VKC (Metz et al. 1997; Mori et al. 2002). The serum levels of IL-4 and tear levels of IL-4, 5 were higher in patients with VKC compared to controls. Interestingly, IL-2, interferon (IFN)-gamma and tumour necrosis factor (TNF)- β , the major cytokines secreted by Th1, were not increased in VKC (Leonardi 2002a;

Mori et al. 2002). These findings confirm that VKC has a mainly Th2 profile (Uchio et al. 2000; Fujishima et al. 2002).

Chemokines

Chemokines, a short term for chemo-tactic cytokine (CC), are potent activators and chemoattractants. Chemokines are produced not only by inflammatory cells but also by stimulated epithelial cells, fibroblasts and vascular endothelial cells in the conjunctiva. Chemokines are involved in normal trafficking of leukocytes and recruitment during inflammation but their role is not restricted to cell attraction. These multipotent cytokines localize and enhance inflammation by inducing chemotaxis and cell activation of different types of inflammatory cells present at sites of inflammation. Chemokines bind to transmembrane G-protein coupled receptors (CCRs), which then signal the cells via secondary messengers to alter its behaviour.

Chemokines are grouped into the CXC, CC, C and CX3C subfamilies (Murphy et al. 2000). The CC chemokines – monocyte chemoattractant protein (MCP), regulated upon activation, normal T cells expressed and secreted (RANTES), macrophage inhibitory protein (MIP), thymus and activation-regulated chemokine (TARC) and eotaxin – act on eosinophils, basophils, monocytes and lymphocytes, suggesting their important role in allergic eye diseases (Abu El-Asrar et al. 2000).

High levels of eotaxin were found in mucus from VKC patients. Eotaxin levels correlate significantly with the percentage of eosinophils in tears and may be responsible for the eosinophil recruitment in VKC (Leonardi et al. 2003a). Eotaxin, along with MCP and RANTES, were highly expressed in limbal tissues (primarily by macrophages) and were responsible for the massive eosinophil infiltration in this tissue (Abu El-Asrar et al. 2000).

IL-8 and the CXC chemokine, monokine induced by interferon gamma (Mig), seem to play an important role in the pathogenesis of VKC. The chemokine IL-8 actively secreted by macrophages and epithelial cells in VKC is a chemoattractant as well as an activator of polymorphonuclear cells. It plays a crucial role in

inflammatory cell migration. More polymorphonuclear cells and eosinophils have been correlated with increased IL-8 concentrations (Miyoshi 2001).

Chemokine receptor (CXCR)-3 is greatly upregulated and expressed abundantly on T lymphocytes in the conjunctiva of patients with active VKC. Over-expression of this receptor and chemokine Mig may play an important role in the regulation of lymphocyte recruitment within the conjunctiva of VKC patients (Abu El-Asrar et al. 2001a, 2003).

Histamine

Histamine, an important inflammatory mediator in allergic eye disease, is released by activated mast cells and basophils. Tear concentration of histamine was higher in VKC patients compared to normal volunteers and other inflammatory eye diseases (Abelson et al. 1980). Persistent elevation of histamine levels in VKC tears is probably caused by its reduced inactivation by histaminase and increased production by specific or non-specific activation of mast cells and basophils (Abelson et al. 1995). Patients affected with VKC demonstrate a non-specific conjunctival hyper-reactivity to histamine (Bonini et al. 1992a).

Skin test reactivity to histamine also showed a greater wheal and flare response in VKC patients, further confirming a hypersensitivity to histamine. *In vitro*, histamine has a stimulating effect on conjunctival fibroblasts, increasing the production of procollagen I (Leonardi et al. 1999b). In a study by Weimer et al. (1998), histamine was shown to stimulate the conjunctival epithelial cells H1 receptors to produce cytokines. Thus, histamine not only causes pruritus and hyperaemia but it also seems to participate in allergic inflammation and tissue remodelling by altering the behaviour of the conjunctival epithelium and fibroblasts.

Metalloproteinases

Metalloproteinases (MMPs) are extracellular endopeptidases that selectively degrade components of the extracellular matrix. Inflammatory cells, particularly eosinophils, and structural cells like epithelial cells and conjunctival fibroblasts are the probable cellular source of these enzymes.

Different cytokines act on fibroblasts to up- or downregulate the pro-

duction of collagen and modify the equilibrium between matrix MMP-1 and its inhibitor, tissue inhibitor of MMP (TIMP)-1 (Leonardi et al. 2003b). Tear levels of pro-MMP-1 and pro-MMP-9 were significantly increased in patients with VKC compared to control subjects. MMP-9 activity correlated significantly with corneal involvement and giant papillae formation (Leonardi et al. 2003c).

The increased production and activation of MMPs or imbalance between MMPs and their natural tissue inhibitors (TIMPs) are all probably involved in the pathogenesis of conjunctival inflammation, remodelling and corneal changes in VKC.

Growth factors

Several growth factors, such as epidermal growth factor, fibroblast growth factor and transforming growth factor beta-1 (TGF β -1), were increased in VKC. These factors induce fibroblast growth and procollagen production (Leonardi et al. 1998). Recently, receptors for nerve growth factor were detected in the conjunctiva of patients with active VKC. High plasma levels of nerve growth factor detected in VKC correlate with the number of mast cells in conjunctival tissue, suggesting that neural factors may have a role in the pathogenesis of VKC (Lambiase et al. 1995). Interestingly, substance P – a neuropeptide with well-known activity on immune cells – was detected in tear and plasma of VKC patients (Fujishima et al. 1997; Lambiase et al. 1997).

Cells in VKC

Mast cells, T cells, eosinophils and macrophages are seen in increased numbers among VKC patients.

Mast cells

The mast cells are the key cellular component and play a pivotal role in initiating the inflammatory cascade in allergic eye disease. In histopathology, mast cells are the constant feature of conjunctival tissue from VKC. The greatly increased number of mast cells found in tissue samples from tarsal giant papillae suggests an active role for these cells in the abnormal connective tissue metabolism observed in VKC.

These cells express Fc [epsilon] RI on their cell surface, which enables

them to bind IgE (Church & Levi-Schaffer 1997). The cross-linkage of this IgE by specific allergens results in the release of pro-inflammatory mediators, including histamine, proteases, prostaglandin D2 and leukotriene C4, into the local extracellular environment. These mediators are responsible for causing ocular itching, hyperaemia, lacrimation and chemosis in allergic conjunctivitis (McGill et al. 1998; Church & McGill 2002). Among mast-cell-derived mediators, histamine is a potent and abundant vasoactive agent. Histamine exerts its biological effects by interacting with four G-protein coupled receptors, classified as H1–H4. Vasodilatation, chemosis and itching of eye are caused by histamine interaction with H1 receptors.

Based on their neutral protease content, the mast cells are divided into two subtypes: the mast-cell phenotype containing only tryptase in their granule, known as MC_T, and that containing both tryptase and chymase, called MC_{TC} (Irani et al. 1986). In normal patients, approximately 80% of conjunctival mast cells are of MC_{TC} type. The number of MC_T with a primary role in host defence and allergic diseases were increased in conjunctiva from VKC (Miyazaki et al. 2004).

It has been shown that mast cells in conjunctiva can synthesize IL-4 (Anderson et al. 2001). Mast-cell cytokines are responsible for the initiation of allergic inflammation, resulting in eosinophil infiltration associated with vernal conjunctivitis (Church & Levi-Schaffer 1997). IL-4 plays a key role in allergic inflammation by promoting T cell growth, induction of IgE production from B cells, upregulation of adhesion molecules and regulation of Th2 subset differentiation, which is essential for the allergic reaction. Furthermore, IL-4 is reported to induce eotaxin production in keratocytes, which may promote eosinophil recruitment to corneal ulcer (Fukagawa et al. 2000). Tryptase and chymase, indicators of mast-cell activation, are increased in tears and may serve as sensitive markers for determining the severity of VKC (Tabbara 2001; Ebihara et al. 2004).

Eosinophils

Eosinophils are the constant feature of lacrimal and conjunctival cytology of

VKC. Approximately 50–90% of cells in the tears during the active phase of VKC are eosinophils (Leonardi 2002a). Eosinophils, along with mast cells, are the main effector cells in ocular inflammation in VKC. Numbers of eosinophils are increased significantly in the tears, peripheral circulation and conjunctival tissue from VKC patients. The eosinophil infiltration of the conjunctiva is not affected by the corneal involvement. The presence of degranulated eosinophils as well as ECP and eosinophil major basic protein (MBP) – the toxic enzymes liberated by these cells – in the tears, conjunctiva and periphery of corneal ulcers in VKC patients indicate the significant role played by eosinophils in the aetio-pathogenesis of VKC (Trocme et al. 1989, 1993; Leonardi et al. 1995; Montan & van Hage-Hamsten 1996). Eotaxins are potent chemoattractants, which recruit and activate eosinophils in VKC (Leonardi et al. 2003a). IL-5 induces eosinophil differentiation, recruitment, activation and survival (Takatsu 1992).

Recently, it has been observed that eosinophils can produce cytokines, particularly in allergic disease, although the disease-specific cytokine spectrum of tissue eosinophils is unknown. Activated eosinophils release cytokines, chemokines, leukotrienes and epitheliotoxic proteins such as MBP, ECP, eosinophil peroxidase (EPO) and eosinophil protein X/neurotoxin (EPX) (Tomassini et al. 1994; Leonardi et al. 1995; Leonardi 2002a).

The tear and serum levels of ECP and EPX are higher in VKC patients in comparison to normal subjects (Bonini et al. 1992a; Leonardi et al. 1995; Montan & van Hage-Hamsten 1996). ECP tear levels correlate positively with clinical signs and symptoms and were reduced when treatment with dexamethasone or cyclosporine was instituted (Leonardi et al. 1995). Tear levels of ECP have been used to evaluate the efficacy of drugs in the treatment of VKC (Leonardi et al. 1997). Higher serum ECP levels do not correlate with severity of ocular symptoms, but the total score of giant papillae correlated strongly with serum ECP and peripheral blood eosinophil counts (Leonardi et al. 2000a; Pucci et al. 2003).

Activated eosinophils, with their mediators and adhesion molecules,

play an important role in eliciting ocular surface inflammation and corneal epithelium damage (Trocme et al. 1993; Trocme & Aldave 1994; Bacon et al. 1998). Eosinophil MBP deposition, found in corneal ulcers of VKC patients, suggests the direct deleterious effects of eosinophil proteins on corneal epithelium (Trocme et al. 1993). Gelatinase B is over-expressed by eosinophils in conjunctiva specimen from VKC patients (Abu El-Asrar et al. 2001b). This enzyme may function with other eosinophilic proteins to damage corneal epithelium.

T cells

Numbers of T lymphocytes increase in the conjunctiva of patients with VKC. The activation of these lymphocytes appears to play a vital role in the pathogenesis of chronic allergic inflammation seen in VKC.

T cell clones derived from VKC tissue are mainly of Th2 type (Maggi et al. 1991). Cytokine flow cytometry has shown that 67% of VKC patients have Th2 cells in tears, while Th1 cells are seen in the tears of only 8% (Leonardi et al. 1999a). The predominance of Th2-like cells in tears and conjunctival biopsy suggests a local Th2 response in VKC. Th2 lymphocytes, by virtue of their cytokine profile, are responsible for increased production of IgE, recruitment and activation of mast cells and eosinophils (Umetsu & De Kruffy 1997; Bielory et al. 2002a).

These T cells actively interact with other inflammatory cells, such as macrophages. Co-stimulatory molecule CD86 – critical for successful antigen presentation and the development of Th2 immune response – is prominently expressed by Langerhan's cells in conjunctiva specimen from VKC (Abu El-Asrar 2001c). Thus, antigen-presenting cells provide an important mechanism for Th2 cell activation.

The mechanisms of T cell recruitment within the conjunctiva remain poorly defined, despite mounting evidence suggestive of T cell involvement in VKC. Trafficking of activated T cells into inflammatory sites is a tightly controlled process directed by multiple molecules (Butcher & Picker 1996; Rossi & Zlotnik 2000). Intercellular adhesion molecule-1 (ICAM-1), CC chemokines, macrophage-derived chemokine, E-selectin and human leukocyte antigen DR (HLA-DR),

over-expressed in VKC and acting concomitantly, may be responsible for the recruitment and activation of helper T cells in VKC.

B cells

B lymphocytes expressing the ligands CD23, 21 and 40 in conjunctiva specimen from VKC may be a precursor of IgE producing B cells (Abu El-Asrar et al. 2001d).

Natural killer cells

Lambiase et al. (2007) reported the increased natural killer cells in the conjunctiva of patients with VKC, suggesting a potential role of these cells and innate immunity in VKC.

Epithelial cells

It has been shown that conjunctival epithelial cells not only act as a mechanical barrier, but also participate in the regulation of allergic inflammation through expressing surface antigens such as adhesion/effector molecules (ICAM-1, vascular cell adhesion molecule-1 and HLA-DR) and releasing many cytokines (eotaxin, IL-8, IL-6, RANTES). Histamine, released from the conjunctival mast cells, might stimulate the synthesis of IL-6 and IL-8 by conjunctival epithelial cells and amplify the allergic response (Irce & Bozkurt 2003).

ICAM-1, HLA-DR, IL-3 and GM-CSF are not expressed in normal conjunctival epithelium but these antigens were induced on conjunctival epithelial cells in VKC. RANTES, present in normal conjunctival epithelial cells, was upregulated in VKC. ICAM-1 may allow epithelial cells to recruit, retain and locally concentrate leukocytes. The upregulated epithelial cytokines are known to promote eosinophilic inflammation. Expression of HLA-DR may play an important role in antigen presentation by conjunctival epithelial cells (Hingorani et al. 1998b).

Fibroblast

It has been shown that corneal and conjunctival fibroblasts not only maintain tissue structure but also contribute to the induction and amplification of ocular allergic inflammation as well as tissue remodelling. TGF β -1, IL-1 and Th2 cytokines from allergic inflammatory cells induce vascular endothelial growth factor (VEGF) production in conjunctival fibroblasts,

which may play a crucial role in neovascularization and formation of giant papillae (Asano-Kato et al. 2005).

Corneal fibroblasts express a high-affinity receptor complex for IL-4 and IL-13. Stimulation of corneal fibroblasts with IL-4 or IL-13 induces expression of eotaxin and vascular cell adhesion molecule-1 (VCAM-1), which together mediate eosinophil infiltration into the cornea (Leonardi et al. 2003a; Fukuda 2005). A potent chemoattractant for Th2 cells, thymus-activation-regulated chemokine (TARC), is expressed by corneal fibroblast upon stimulation by IL-4 and IL-13.

In vitro, corneal fibroblasts expressed ICAM-1 and VCAM-1 when activated with IL-4 and TNF- α . Eosinophils can adhere to the activated fibroblasts and induce subsequent fibroblast damage through these adhesion molecules. Eosinophil adhesion to fibroblasts may contribute to the pathogenesis of severe persistent allergic corneal ulcers (Okada et al. 2005).

Fibroblasts can modulate the functions of mast cells and eosinophils through the membrane form of stem cell factor and GM-CSF, respectively. On the other hand, fibroblasts can be affected by inflammatory mediators derived from mast cells and eosinophils, such as TGF β and nerve growth factor and by the Th2 cytokines, IL-4 and IL-13 (Solomon et al. 2003).

Histopathology and immunohistochemistry

Histopathological studies of conjunctival tissue from VKC patients show a prominent inflammatory cellular infiltration in the epithelium and substantia propria and post-inflammatory tissue remodelling. Tissue remodelling is more marked in tarsal than in bulbar conjunctiva.

Tissue inflammation

The histopathology of VKC is characterized by infiltration of the conjunctiva by eosinophils, basophils, mast cells, Th2 cells, monocyte/macrophages, dendritic cells, plasma cells and B lymphocytes, frequently organized as small lymphoid follicles without a germinative centre (Abu El-Asrar et al. 2001d; Leonardi 2002a). The cellular infiltration of

both the stroma and the epithelium was consistent with chronic inflammation, particularly in the biopsy specimens taken from the limbus.

Eosinophils are characteristic constituents of the cellular infiltrate in all stages of the disease. Ultra-thin sections of conjunctiva of patients suffering from VKC showed higher numbers of eosinophils in epithelium and subepithelium of conjunctiva (Hingorani et al. 1998a). In the tarsal conjunctiva, the stromal infiltrate consisted of a diffuse T-lymphocyte reaction with clustering of B-lymphocytes, mast cells, IgE plasma cells and eosinophils. Clustering of B lymphocyte was noted more in patients from tropical areas than in those from temperate zones. In comparison with control subjects, patients with VKC were more likely to show squamous metaplasia of the tarsal conjunctiva (Tuft et al. 1998).

Tissue remodelling

The overgrowth of the conjunctival connective tissue, with the formation of large and sessile papillae on the upper tarsal conjunctiva, is one of the most notable findings in VKC. Conjunctival thickening, subepithelial fibrosis, mucus metaplasia, neovascularization and scarring are typical of chronic VKC. Epithelial changes, connective tissue deposition, oedema, inflammatory cell infiltration and glandular hypertrophy all contribute in the tissue remodelling observed in VKC (Leonardi 2002a).

On morphometric measurements, the thickness of the entire mucosa and basement membrane and superficial epithelial area increase in VKC tissue compared to normal (Leonardi et al. 2000b). On histological examination, the number of goblet cells increased in giant papillae and epithelial in-growth. Epithelial in-growth in stroma is rich in goblet cells and may have a pseudoglandular appearance. Collagen fibres in tissue samples from tarsal giant papilla were thicker and arranged irregularly, with the total amount significantly increased.

A proliferation of capillaries and neovascular formations provide vascular support to the papillae. Various growth factors, e.g. epidermal growth factor fibroblast growth factor, TGF β -1 and many ILs were increased in supernatants of VKC tissue culture

compared to normal subjects (Leonardi 2002a).

Plasminogen activators, in addition to fibrinolysis, also play a role in chemotaxis and collagen degradation. Higher levels of serine protease urokinase, tissue plasminogen activator and tear plasminogen activity in VKC patients suggest that increased expression of fibrinolytic system components and imbalance between plasminogen activators and plasminogen activator inhibitors may contribute to tissue remodelling in VKC (Leonardi et al. 2005).

Treatment

Preventive measures and patient education

Compliance with instructions is better with a well-informed patient and outcome of treatment is gratifying. Education of patients and their parents about the chronic, recurrent and ultimately resolving nature of VKC is a very important aspect of management. Because exposure to non-specific stimuli causes frequent conjunctival redness among VKC patients, avoidance of triggering factors like sun, wind and salt water are helpful but not enough to control the symptoms. Contact with commonly known allergens like plants and flowers should be avoided. Use of sunglasses or any shading measures are helpful and should be advised. Application of cold compresses and use of artificial tears have been shown to be effective in the relief of symptoms by direct removal and dilution of allergen from the ocular surface (Bielory 2002b). Cold compresses provide symptomatic relief, especially from ocular pruritus. Frequent hand, face and hair washing – especially before going to bed –, may be helpful (Leonardi 2002a).

Pharmacological therapy

The variety of currently available drugs to treat VKC include anti-histamines, mast-cell stabilizers, dual acting agents, corticosteroids and immunomodulators but none is enough to treat all aspects of multifaceted pathophysiology of VKC. Most drugs used are merely palliative and do not eliminate the complex immune response initiating and perpetuating the allergic ocular

inflammation, so there is recurrence of disease when the therapy is discontinued. Because there are few randomized control trials, the selection of a drug from the many available options is mostly based on the personal experience and preference of the treating physician. A meta-analysis of randomized control trials will be helpful in formulating the guidelines for the treatment of VKC.

Judicious and scrupulous use of medication cannot be overemphasized because drug treatment is prolonged and frequent. In some patients, medication needs to be used throughout the year for satisfactory control of symptoms.

Vasoconstrictor and non-specific histamines receptor blocker

Vasoconstrictor and non-specific anti-histamine combination eyedrops have long been available and have withstood the test of time. They contain vasoconstrictors like naphazoline or tetrahydrozoline and anti-histamines like pyrilamine or pheniramine. These drops are safe and effective, at least temporarily. Because of their over-the-counter availability, they are tried by many patients during the early stage of the disease as first-line treatment. By virtue of their vasoconstrictor and non-specific anti-histamine constituents, they relieve itching and reduce redness. Burning or stinging on installation and rebound hyperaemia are common side-effects with these drugs.

Mast-cell stabilizers

Mast-cell degranulation is a central event in VKC, so the treatment has been concentrated on preventing the degranulation or antagonizing the effects of the primary mediator (histamine) released by mast cells. Mediators released by mast cells are responsible for many symptoms and signs associated with VKC. Drug modulation of mast-cell activity alleviate the acute symptoms of active disease and also reduce the cytokine stimulus for the development of chronic allergic inflammation (Church & McGill 2002).

The drugs of this group stabilize mast cells and prevent degranulation. The efficacy of sodium cromoglycate (qid), lodoxamide (qid), nedocromil (bid) and pemirolast (qid) in the con-

trol of symptoms and prevention of exacerbation has been shown by many studies (Tabbara & Arafat 1977; Bonini et al. 1992b; Caldwell et al. 1992). These should be used as a first line of defence at the onset of the allergic season and should be used continuously throughout the season.

Cromolyn (4%), the prototype mast-cell stabilizer, has been prescribed by ophthalmologists for the treatment of ocular allergy for the last 25 years. It can be used for long periods without side-effects but takes several days to reach full effect (Sorkin & Ward 1986). Sodium cromoglycate may have a synergistic effect in combination with a corticosteroid for the treatment of VKC (Dahan & Appel 1983).

Lodoxamide 0.1% has been shown to deliver greater and earlier relief in patients with VKC (Fahy G et al. 1988). Lodoxamide was found to control the symptoms and signs of VKC better compared to 4% cromolyn sodium and levocabastine (Leonardi et al. 1997; Avunduk et al. 2000; Verin et al. 2001). Better efficacy of lodoxamide was linked to significantly decreased CD4 cells and inflammatory cells – especially eosinophils in conjunctiva.

Nedocromil (2%), with stabilizing effects on mast cells, also inhibits the chemotaxis, activation and mediator release from other inflammatory cells. Nedocromil sodium and lodoxamide were shown to be superior to sodium cromoglycate in the treatment of VKC but a meta-analysis of the efficacy and effectiveness of topical mast-cell stabilizers in the treatment of seasonal allergic conjunctivitis found insufficient evidence to recommend one drug over another (Verin et al. 1999; Owen et al. 2004). Pemirolast, a pyridopyrimidine compound with mast-cell stabilizing properties, is effective in the treatment of allergic conjunctivitis.

Systemic anti-histamines

Oral anti-histamines are a good choice when allergy involves the eyes, nose or pharynx simultaneously. When allergic complaints are limited to eyes, focused therapy with topical anti-histamines is efficacious and free of untoward effects related to oral anti-histamines. Topical anti-histamines provide faster and superior relief than systemic anti-hista-

mines and possess longer duration of action than topical vasoconstrictors, pure mast-cell stabilizers, non-steroidal anti-inflammatory drugs and corticosteroids, the drugs commonly used in the treatment of ocular allergy.

H1 receptor blocker

Topical selective H1 blocker, emedastine and levocabastine, are better than vasoconstrictor/non-specific anti-histamine combination eyedrops in controlling the signs and symptoms of VKC. Levocabastine (0.05%) is a potent topical anti-histamine with rapid and prolonged selective anti-H1 receptor activity. Many studies have shown it to be effective in treatment of seasonal allergic conjunctivitis when compared to placebo. Emedastine (0.05%) is a relatively selective H1 receptor blocker with no apparent effects on adrenergic, dopaminergic or serotonin receptors. The H1 receptor antagonist emedastine inhibits cytokine production by conjunctival epithelial cells (Weimer et al. 1998).

The enhanced clinical efficacy of emedastine, levocabastine and (recently) olopatadine over first-generation anti-histamines antazoline and pheniramine may be the result of the inhibitory effects of new-generation anti-histamines on the pro-inflammatory cytokines produced by conjunctival epithelial cells. The anti-inflammatory effect seen with pure anti-histamines like levocabastine and emedastine is attributed to the blocking of histamine receptors, thus downregulating the expression of ICAM-1 and limiting chemotaxis of inflammatory cells (Bielory et al. 2005).

H1 receptor blocker and mast-cell stabilizer (dual action drugs)

Recently, a new generation of drugs such as olopatadine, epinastine, ketotifen and azelastine has shown dual activity of mast-cell stability and H1 receptor antagonism. Fast H1 receptor blocking action, along with mast-cell stabilization, makes them suitable for twice-daily dosing. The action of these drugs is not limited to mast-cell stabilization and H1 receptor antagonism: they also exert anti-inflammatory effects through several different mechanisms.

Olopatadine (0.1%) is a selective H1 antagonist with mast-cell-stabilizing properties. Olopatadine, in addi-

tion to stabilizing mast cells, affects the release of TNF- α and various cytokines from conjunctival epithelial cells, thus controlling the allergic inflammation more effectively than the other topical anti-histamine formulations (McGill 2004). It decreases the mucus discharge in VKC by reducing the goblet cell density in the conjunctiva (Corum et al. 2005).

Ketotifen (0.025%) is a selective non-competitive blocker of the H1 receptor. Besides mast-cell stabilization and H1 receptor antagonism, it prevents eosinophil accumulation. Ketotifen has been shown to inhibit the release of inflammatory mediators from basophils and eosinophils, chemotaxis, leukotriene activity and platelet activation, and also to decrease vascular permeability. Epinastine (0.05%) is an H1 receptor antagonist with mast-cell-stabilizing and anti-inflammatory activity. Azelastine (0.05%) is a selective H1 receptor antagonist that inhibits histamine release. It downregulates ICAM expression, reduces eosinophil chemotaxis and inhibits platelet-activating factors.

Non-steroidal anti-inflammatory

Topical formulations of ketorolac and diclofenac have been shown to diminish ocular pruritus and conjunctival hyperaemia associated with allergic conjunctivitis. Prostaglandin E₂ and I₂ has been shown to be pruritogenic. In a prospective, open study, preservative-free diclofenac (0.1%) eyedrops reduced the symptoms of VKC through the inhibition of prostaglandin production in 40% of patients. Although the conjunctival hyperaemia reduced significantly, the papillary size and corneal lesions remained unchanged (D'Angelo et al. 2003).

In a prospective, randomized crossover study, preservative-free ketorolac tromethamine (0.5%) reduced the signs and symptoms of VKC more rapidly than topical cyclosporine (0.5%) (Kosirukvongs & Luengchaichawange 2004). Ketorolac may be a good alternative to topical steroid because it reduces itching by inhibiting the synthesis of prostaglandins (Sharma 1997).

Corticosteroids

Topical corticosteroids are one of the most effective drugs to control the

signs and symptoms of VKC. Because of complications associated with their prolonged use, these should not be prescribed as first-line treatment. Prolonged application of corticosteroids may cause steroid-induced cataract, glaucoma and increase susceptibility to viral and fungal infections. Recently, modified steroids such as loteprednol etabonate and rimexolone were developed. In comparison to other steroids, loteprednol has a superior safety profile, which has been attributed to its 'soft drug' characteristics.

Loteprednol is highly effective in the acute and prophylactic treatment of allergic conjunctivitis. In a retrospective study, loteprednol etabonate was shown to be safe and effective when used for 12 months or more for the treatment of seasonal or perennial allergic conjunctivitis (Ilyas et al. 2004). Rimexolone is a derivative of prednisolone and is inactivated quickly in the anterior chamber.

Fluorometholone is a soft corticosteroid and is effective in controlling the signs and symptoms of VKC. Desonide phosphate has been shown to be as effective as fluorometholone in the treatment of allergic conjunctivitis (Leonardi et al. 2002b).

Supratarsal injection of corticosteroids can be used to treat VKC refractory to conventional treatment (Holsclaw et al. 1996). Supratarsal injection of dexamethasone sodium succinate, triamcinolone acetonide and hydrocortisone sodium succinate is effective in the temporary suppression of inflammation associated with VKC (Saini et al. 1999; Singh et al. 2002; Lisanework 2003). The resolution of the limbal form of the disease was more dramatic than the palpebral form (Lisanework 2003). Although corticosteroids are the most efficacious drugs, steroid-resistant forms of VKC are not unusual and may necessitate an alternative therapy.

Immunomodulators

Cyclosporine, a fungal metabolite, decreases the signs and symptoms of VKC. BenEzra et al. (1986) used cyclosporine 2% eyedrops in oil solution to treat severe VKC almost two decades ago. They reported rapid relief in subjective symptoms in 86% of VKC patients treated by topical cyclosporine. However, symptoms

recurred and required additional therapy after discontinuation of cyclosporine eyedrops in most patients (BenEzra et al. 1988). Cyclosporine is lipophilic so it must be dissolved in an alcohol-oil base, which causes ocular irritation. Cyclosporine (0.5–2%) emulsion in olive or castor oil, instilled four times daily, was shown to be effective in the treatment of VKC. Clinical improvement in VKC after cyclosporine treatment may result from its immunomodulating effect on components of cell-mediated and humoral immune response. (Abu El-Asrar et al. 1996). Cyclosporine blocks Th2 lymphocyte proliferation and IL-2 production. Furthermore, it inhibits histamine release through a reduction in IL-5 production (BenEzra et al. 1988; Secchi et al. 1990). Accelerated apoptosis induced by cyclosporine in fibroblast cultures obtained from a patient with VKC suggests a potential role for this drug in hyperproliferative conjunctival disorders like VKC (Leonardi et al. 2001).

In double-blind, placebo-controlled trials, cyclosporine (2%) eyedrops were effective and safe in the treatment of severe VKC (Pucci et al. 2002; Kilic & Gurler 2006). Most of the therapeutic effect was achieved 2 weeks after commencing the treatment and was maintained during the next 3 months by continuous medication (Pucci et al. 2002). In a prospective study of 10 cases with severe VKC, topical cyclosporine (2%) significantly reduced the clinical signs and symptoms score. The reduction of CD4 and CD28 cell populations on the conjunctival surface can be responsible, at least partly, for clinical improvement in VKC after treatment with cyclosporine (Avunduk et al. 2001). Cyclosporine 1% was shown to control the symptoms of VKC, although further control trials are required to find the optimum concentration of cyclosporine needed to treat VKC (Spadavecchia et al. 2006).

Topical cyclosporine helps in the healing of vernal shield ulcers but recurrences may occur at lower concentrations, which can be treated by increasing the concentration (Cetin-kaya et al. 2004). Off-label use of commercial preparation of cyclosporine (0.05%) eyedrops, recommended for the treatment of dry eye, decreased

the symptoms and signs of VKC (Ozcan et al. 2007). Topical corticosteroids and artificial tears have been shown to act synergistically with cyclosporine 0.05% eyedrops and help in the re-epithelialization of corticosteroid-resistant vernal shield ulcers (Kumar 2008). Whether this commercially available formulation of cyclosporine is effective in the treatment of VKC needs to be tested in controlled trials.

Anti-metabolites

Mitomycin-C is an inhibitor of fibroblast proliferation. Mitomycin-C (0.01%) eyedrops were shown to decrease the mucous discharge, conjunctival hyperaemia and limbal oedema in VKC patients refractory to topical steroids and mast-cell stabilizers (Akpek et al. 2000; Jain & Sukhija 2006).

Future of VKC pharmacological therapy

Despite the development of newer drugs in the last decade, the statement of Professor Lightman – ‘at present however, the current situation for those with severe VKC remains a disturbing dependence upon topical steroids, with all the attendant risks’, emphasizing the need for more selective drugs for better and long-lasting control of VKC – is still appropriate (Hingorani & Lightman 1995). Anti-chemokine receptor antibodies inhibit eosinophil chemotaxis. Inhibition of CC chemokine receptor-3 may be a treatment for corneal ulceration in patients with VKC (Fukagawa et al. 2002). So far, results with topical cyclosporine are very encouraging but because of unavailability of commercial preparations of topical cyclosporine in higher concentrations, its use in VKC is limited. Future developments in the manipulation of eosinophilic products, cytokines and adhesion molecules may also be relevant. High levels of leukotrienes in the tears of patients with VKC and improvements in the signs and symptoms of VKC when given oral montelukast, a leukotriene receptor antagonist, suggest that anti-leukotrienes have therapeutic potential and need further trials (Akman et al. 1998; Lambiasi et al. 2003). Macrobimolecules have been shown to inhibit ocular allergic responses. Anti-flammins, a macrobimolecule, inhibit phospholipase A2.

Topical anti-flammins have been shown to inhibit allergic responses in murine allergic conjunctivitis. Immunostimulatory oligonucleotides (ISS) or CpG motif, another macrobimolecules, inhibits ongoing TH2 response in murine allergic conjunctivitis (Tuo & Chan 2003). Probiotics have been shown to improve allergic inflammation. Furthermore, a report by Iovieno et al. (2008) has shown that *Lactobacillus acidophilus* diluted in saline solution administered as eyedrops improves signs and symptoms in patients with VKC.

Surgical treatment

Surgical excision of giant papillae is recommended if they cause corneal lesions. Excision or cryocoagulation of large papillae helps in the early resolution of corneal epitheliopathy or ulcer, although papillae regrow in most patients. Cryotherapy of giant papillae promotes inflammation and may cause conjunctival scarring. Intraoperative application of 0.02% mitomycin-C (MMC) to the upper palpebral conjunctiva immediately after papillae resection for 2 min reduces the chances of recurrence of papillae significantly. No complications related to MMC use were observed during a follow-up period ranging from 12 to 18 months (Tanaka et al. 2004). Giant papillae can be removed by CO₂ laser. The procedure can be repeated if papillae recur (Belfair et al. 2005).

Debridement of ulcer base, surgical removal of plaque or excimer laser phototherapeutic keratectomy helps in early re-epithelialization of vernal shield ulcer refractory to medical treatment. (Cameron et al. 1995b; Solomon et al. 2004; Ozbek et al. 2006). Amniotic membrane implantation leads to complete re-epithelialization of persistent corneal epithelial defects and vernal plaques recalcitrant to conventional medical treatment (Rouher et al. 2004; Pelegri et al. 2008).

Free autologous conjunctival graft after resection of giant papillae facilitates the re-epithelialization of non-healing shield ulcer (Nishiwaki-Dantas et al. 2000). Cultivated corneal epithelial cells could be transplanted to treat the severe ocular surface diseases associated with VKC. Vision improves significantly after transplant. Corneal

epithelial cell transplants could be beneficial when amniotic membrane transplant is not sufficient to restore the ocular surface (Sangwan et al. 2005).

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References

- Abelson MB & Schaefer K (1993): Conjunctivitis of allergic origin: immunologic mechanisms and current approaches to therapy. *Surv Ophthalmol* **38**: 115–132.
- Abelson MB, Baird RS & Allansmith MR (1980): Tear histamine levels in vernal conjunctivitis and other ocular inflammations. *Ophthalmology* **87**: 812–814.
- Abelson MB, Leonardi A, Smith LM, Fregona IA, George M & Secchi AG (1995): Histaminase activity in patients with vernal keratoconjunctivitis. *Ophthalmology* **102**: 1958–1963.
- Abu El-Asrar AM, Struyf S, Al-Mosallama AA, Missotten L, Van Damme J & Geboes K (2001a): Expression of chemokine receptors in vernal keratoconjunctivitis. *Br J Ophthalmol* **85**: 1357–1361.
- Abu El-Asrar AM (2001b): Gelatinase B in vernal keratoconjunctivitis. *Arch Ophthalmol* **119**: 1505–1511.
- Abu El-Asrar AM (2001c): Langerhans' cells in vernal keratoconjunctivitis express the costimulatory molecule B7-2 (CD86), but not B7-1 (CD80). *Eye* **15**: 648–654.
- Abu El-Asrar AM, Fatani RA, Missotten L & Geboes K (2001d): Expression of CD23/CD21 and CD40/CD40 ligand in vernal keratoconjunctivitis. *Eye* **15**: 217–224.
- Abu El-Asrar AM, Tabbara KF, Geboes K, Missotten L & Desmet V (1996): An immunohistochemical study of topical cyclosporine in vernal keratoconjunctivitis. *Am J Ophthalmol* **121**: 156–161.
- Abu El-Asrar AM, Struyf S, Al-Kharashi SA, Missotten L, Van Damme J & Geboes K (2000): Chemokines in the limbal form of vernal keratoconjunctivitis. *Br J Ophthalmol* **84**: 1360–1366.
- Abu El-Asrar AM, Struyf S, Al-Kharashi SA, Missotten L, Van Damme J & Geboes K (2003): The T-lymphocyte chemoattrac-

- tant Mig is highly expressed in vernal keratoconjunctivitis. *Am J Ophthalmol* **136**: 853–860.
- Akman A, Irkeç M & Orhan M (1998): Effects of lodoxamide, disodium cromoglycate and fluorometholone on tear leukotriene levels in vernal keratoconjunctivitis. *Eye* **12**: 291–295.
- Akpek EK, Hasiripi H, Christen WG & Kalayci D (2000): A randomized trial of low-dose, topical mitomycin-C in the treatment of severe vernal keratoconjunctivitis. *Ophthalmology* **107**: 263–269.
- Allansmith MR (1982): The eye and immunology. St Louis: Mosby 118–124.
- Allansmith MR & Ross RN (1988): Ocular allergy. *Clin Allergy* **18**: 1–136.
- Anderson DF, Zhang S, Bradding P, McGill JI, Holgate ST & Roche WR (2001): The relative contribution of mast cell subsets to conjunctival TH-2 like cytokines. *Invest Ophthalmol Vis Sci* **42**: 995–1001.
- Asano-Kato N, Fukagawa K, Okada N, Kawakita T, Takano Y, Dogru M, Tsubota K & Fujishima H (2005): TGF- β 1, IL-1 β , and Th2 cytokines stimulate vascular endothelial growth factor production from conjunctival fibroblasts. *Exp Eye Res* **80**: 555–560.
- Avunduk AM, Avunduk MC, Kapicioglu Z, Akyol N & Tavli L (2000): Mechanisms and comparison of anti-allergic efficacy of topical lodoxamide and cromolyn sodium treatment in vernal keratoconjunctivitis. *Ophthalmology* **107**: 1333–1337.
- Avunduk AM, Avunduk MC, Erdol H, Kapicioglu Z & Akyol N (2001): Cyclosporine effects on clinical findings and impression cytology specimens in severe vernal keratoconjunctivitis. *Ophthalmology* **215**: 290–293.
- Bacon AS, McGill JI, Anderson DF, Baddeley S, Lightman S & Holgate ST (1998): Adhesion molecules and relationship to leukocyte levels in allergic eye disease. *Invest Ophthalmol Vis Sci* **39**: 322–330.
- Barney NP (1997): Vernal and atopic keratoconjunctivitis. In: Krachmer JH, Mannis MJ & Holland EJ (eds). *Cornea*. St. Louis: Mosby, 811–817.
- Beigelman MN (1965): Vernal conjunctivitis. Los Angeles: University of Southern California Press.
- Belfair N, Monos T, Levy J, Mnitentag H & Lifshitz T (2005): Removal of giant vernal papillae by CO₂ laser. *Can J Ophthalmol* **40**: 472–476.
- BenEzra D, Pe'er J, Brodsky M & Cohen E (1986): Cyclosporine eye drops for the treatment of severe vernal keratoconjunctivitis. *Am J Ophthalmol* **101**: 278–282.
- BenEzra D, Matamoros N & Cohen E (1988): Treatment of severe vernal keratoconjunctivitis with cyclosporine A eye-drops. *Transplant Proc* **20**: 644–649.
- Bielory L (2000): Allergic and immunologic disorder of the eye. Part 2: ocular allergy. *J Allergy Clin Immunol* **106**: 1019–1032.
- Bielory L (2002b): Ocular allergy guidelines: a practical treatment algorithm. *Drugs* **62**: 1611–1634.
- Bielory L & Frohman LP (1992): Allergic and immunologic disorders of the eye. *J Allergy Clin Immunol* **89**: 1–15.
- Bielory L, Bonini S & Bonini S (2002a): Inflammatory mechanism in allergic diseases. In: Zweiman B & Schwartz LB (eds). *Allergic eye disorders*. New York: Marcel Dekker, 311–323.
- Bielory L, Lien KW & Bigelsen S (2005): Efficacy and tolerability of newer antihistamines in the treatment of allergic conjunctivitis. *Drugs* **65**: 215–228.
- Bonini S, Bonini S, Schiavone M, Centofanti M, Allansmith MR & Bucci MG (1992a): Conjunctival hyperresponsiveness to ocular histamine challenge in patients with vernal conjunctivitis. *J Allergy Clin Immunol* **89**: 103–107.
- Bonini S, Barney NP, Schiavone M, Centofanti M, Berruto A, Bonini S & Allansmith MR (1992b): Effectiveness of Nedocromil sodium 2% eyedrops on clinical symptoms and tear fluid cytology of patients with vernal conjunctivitis. *Eye* **6**: 648–652.
- Bonini S, Bonini S, Lambiase A et al. (1995a): Vernal keratoconjunctivitis: a model of 5q cytokine gene cluster disease. *Int Arch Allergy Immunol* **107**: 95–98.
- Bonini S, Lambiase A, Schiavone M, Centofanti M, Palma LA & Bonini S (1995b): Estrogen and progesterone receptors in vernal keratoconjunctivitis. *Ophthalmology* **102**: 1374–1379.
- Bonini S, Bonini S, Lambiase A et al. (2000): Vernal keratoconjunctivitis revisited. A case series of 195 patients with long-term followup. *Ophthalmology* **107**: 1157–1163.
- Bonini S, Coassin M, Aronni S & Lambiase A (2004): Vernal keratoconjunctivitis. *Eye* **18**: 345–351.
- Bonini S, Sacchetti M, Mantelli F & Lambiase A (2007): Clinical grading of vernal keratoconjunctivitis. *Curr Opin Allergy Clin Immunol* **7**: 436–441.
- Buckley RJ (1988): Vernal keratoconjunctivitis. *Int Ophthalmol Clin* **28**: 303–308.
- Butcher EC & Picker LJ (1996): Lymphocyte homing and homeostasis. *Science* **272**: 60–66.
- Calder VL, Jolly G, Hingorani M, Adamson P, Leonardi A, Secchi AG, Buckley RJ & Lightman S (1999): Cytokine production and mRNA expression by conjunctival T-cell lines in chronic allergic eye disease. *Clin Exp Allergy* **29**: 1214–1222.
- Caldwell DR, Verin P, Hartwich-Young R, Meyer SM & Drake MM (1992): Efficacy and safety of Lodoxamide 0.1% vs Cromolyn sodium 4% in patients with vernal keratoconjunctivitis. *Am J Ophthalmol* **113**: 632–637.
- Cameron JA (1995a): Shield ulcers and plaques of the cornea in vernal keratoconjunctivitis. *Ophthalmology* **102**: 985–993.
- Cameron JA, Antonio SR & Badr IA (1995b): Excimer laser phototherapeutic keratectomy for shield ulcer and corneal plaques in vernal keratoconjunctivitis. *J Refract Surg* **11**: 31–35.
- Cameron JA, Al-Rajhi AA & Badr IA (1989): Corneal ectasia in vernal keratoconjunctivitis. *Ophthalmology* **96**: 1615–1623.
- Cetinkaya A, Akova YA, Dursun D & Pelit A (2004): Topical cyclosporine in the management of shield ulcers. *Cornea* **23**: 194–200.
- Church MK & Levi-Schaffer F (1997): The human mast cell. *J Allergy Clin Immunol* **99**: 155–160.
- Church MK & McGill JI (2002): Human ocular mast cells. *Curr Opin Allergy Clin Immunol* **2**: 419–422.
- Cook EB (2004): Tear cytokines in acute and chronic ocular allergic inflammation. *Curr Opin Allergy Clin Immunol* **4**: 441–445.
- Coombs RRA & Gell PGH (1962): The classification of allergic reactions underlying disease. In: Gell PGH & Coombs RRA (eds). *Clinical aspects of immunology*. Oxford: Blackwell Scientific Publications, Chapter 13.
- Corum I, Yeniad B, Bilgin LK & Ilhan R (2005): Efficiency of Olopatadine hydrochloride 0.1% in the treatment of vernal keratoconjunctivitis and goblet cell density. *J Ocul Pharmacol Ther* **21**: 400–405.
- D'Angelo G, Lambiase A, Cortes M, Sgrulletta R, Pasqualetti R, Lamagna A & Bonini S (2003): Preservative-free diclofenac sodium 0.1% for vernal keratoconjunctivitis. *Graefes Arch Clin Exp Ophthalmol* **241**: 192–195.
- Dahan E & Appel R (1983): Vernal conjunctivitis in the black child and its response to therapy. *Br J Ophthalmol* **67**: 688–692.
- Ebihara N, Funaki T, Takai S, Miyazaki M, Fujiki K & Murakami A (2004): Tear chymase in vernal keratoconjunctivitis. *Curr Eye Res* **28**: 417–420.
- Fujishima H, Takeyama M, Takeuchi T, Saito I & Tsubota K (1997): Elevated levels of substance P in tears of patients with allergic conjunctivitis and vernal keratoconjunctivitis. *Clin Exp Allergy* **27**: 372–378.
- Fujishima H, Saito I, Takeuchi T & Tsubota K (2002): Immunological characteristics of patients with vernal keratoconjunctivitis. *Jpn J Ophthalmol* **46**: 244–248.
- Fukagawa K, Nakajima T, Saito H, Tsubota K, Shimmura S, Natori M & Hirai K (2000): IL-4 induces eotaxin production in corneal keratocytes but not in epithelial cells. *Int Arch Allergy Immunol* **121**: 144–150.
- Fukagawa K, Okada N, Fujishima H et al. (2002): CC-chemokine receptor 3: a possible target in treatment of allergy-related corneal ulcer. *Invest Ophthalmol Vis Sci* **43**: 58–62.
- Fukuda K (2005): Role of corneal fibroblasts in the pathogenesis of ocular allergic diseases. *Nippon Ganka Gakkai Zasshi* **109**: 717–726.
- Hingorani M & Lightman S (1995): Therapeutic options in ocular allergic disease. *Drugs* **50**: 208–221.

- Hingorani M, Calder V, Jolly G, Buckley RJ & Lightman SL (1998a): Eosinophil surface antigen expression and cytokine production vary in different ocular allergic diseases. *J Allergy Clin Immunol* **102**: 821–830.
- Hingorani M, Calder VL, Buckley RJ & Lightman SL (1998b): The role of conjunctival epithelial cells in chronic ocular allergic disease. *Exp Eye Res* **67**: 491–500.
- Holsclaw DS, Whitcher JP, Wong IG & Margolis TP (1996): Supratarsal injection of corticosteroid in the treatment of refractory vernal keratoconjunctivitis. *Am J Ophthalmol* **121**: 243–249.
- Ilyas H, Slonim CB, Braswell GR, Favetta JR & Schulman M (2004): Long term efficacy of Loteprednol etabonate 0.2% in the treatment of seasonal and perennial allergic conjunctivitis. *Eye contact lens* **30**: 10–13.
- Iovieno A, Lambiase A, Sacchetti M, Stampachiacchiere B, Micera A & Bonini S (2008): Preliminary evidence of the efficacy of probiotic eye-drops treatment in patients with vernal keratoconjunctivitis. *Graefes Arch Clin Exp Ophthalmol* **246**: 435–441.
- Iqbal A, Jan S, Babar TF & Khan MD (2003): Corneal complications of vernal catarrh. *J Coll Physicians Surg Pak* **13**: 394–397.
- Irani AA, Schechter NM, Craig SS, DeBlois G & Schwartz LB (1986): Two types of human mast cells that have distinct neutral protease compositions. *Proc Natl Acad Sci USA* **83**: 4464–4468.
- Irkec M & Bozkurt B (2003): Epithelial cells in ocular allergy. *Curr Allergy Asthma Rep* **3**: 352–357.
- Jain AK & Sukhija J (2006): Low dose mitomycin-C in severe vernal keratoconjunctivitis: a randomized prospective double blind study. *Indian J Ophthalmol* **54**: 111–116.
- Johansson SGO, Hourihane JO, Bousquet J et al. (2001): A revised nomenclature for allergy: an EAACI position statement from the EAACI nomenclature task force. *Allergy* **56**: 813–824.
- Kilic A & Gurler B (2006): Topical 2% cyclosporine A in preservative-free artificial tears for the treatment of vernal keratoconjunctivitis. *Can J Ophthalmol* **41**: 693–698.
- Kosirukvongs P & Luengchaichawange C (2004): Topical cyclosporine 0.5 per cent and preservative-free ketorolac tromethamine 0.5 per cent in vernal keratoconjunctivitis. *J Med Assoc Thai* **87**: 190–197.
- Koulikovska M, van der Ploeg I, Herrmann B & Montan PG (2001): Respiratory syncytial virus and chlamydia are not detectable by PCR in ongoing vernal keratoconjunctivitis. *Ocul Immunol Inflamm* **9**: 253–257.
- Kumar S (2008): Combined therapy of vernal shield ulcer: a case report. *Clin Exp Optom* **91**: 111–114.
- Lambiase A, Bonini S, Bonini S, Micera A, Magrini L, Bracci-Laudiero L & Aloe L (1995): Increased plasma levels of nerve growth factor in vernal keratoconjunctivitis and relationship to conjunctival mast cells. *Invest Ophthalmol Vis Sci* **36**: 2127–2132.
- Lambiase A, Bonini S, Micera A, Tirassa P, Magrini L, Bonini S & Aloe L (1997): Increased plasma levels of substance P in vernal keratoconjunctivitis. *Invest Ophthalmol Vis Sci* **38**: 2161–2164.
- Lambiase A, Bonini S, Rasi G, Coassin M, Bruscolini A & Bonini S (2003): Montelukast, a leukotriene receptor antagonist, in vernal keratoconjunctivitis associated with asthma. *Arch Ophthalmol* **121**: 615–620.
- Lambiase A, Normando EM, Vitiello L et al. (2007): Natural killer cells in vernal keratoconjunctivitis. *Mol Vis* **13**: 1562–1567.
- Leonardi A (2002a): Vernal keratoconjunctivitis: pathogenesis and treatment. *Prog Retin Eye Res* **21**: 319–339.
- Leonardi A, Papa V, Milazzo G & Secchi AG (2002b): Efficacy and safety of desonide phosphate for the treatment of allergic conjunctivitis. *Cornea* **21**: 476–481.
- Leonardi A, Borghesan F, Faggian D, Secchi A & Plebani M (1995): Eosinophil cationic protein in tears of normal subjects and patients affected by vernal keratoconjunctivitis. *Allergy* **50**: 610–613.
- Leonardi A, Borghesan F, Avarello A, Plebani M & Secchi AG (1997): Effect of lodoxamide and disodium cromoglycate on tear eosinophil cationic protein in vernal keratoconjunctivitis. *Br J Ophthalmol* **81**: 23–26.
- Leonardi A, Borghesan F, DePaoli M, Plebani M & Secchi AG (1998): Procollagens and inflammatory cytokine concentrations in tarsal and limbal vernal keratoconjunctivitis. *Exp Eye Res* **67**: 105–112.
- Leonardi A, De Franchis G, Zancanaro F, Crivellari G, De Paoli M, Plebani M & Secchi AG (1999a): Identification of local Th2 and Th0 lymphocytes in vernal conjunctivitis by cytokine flow cytometry. *Invest Ophthalmol Vis Sci* **40**: 3036–3040.
- Leonardi A, Radice M, Fregona IA, Plebani M, Abatangelo G & Secchi AG (1999b): Histamine effects on conjunctival fibroblast from patients with vernal conjunctivitis. *Exp Eye Res* **68**: 739–746.
- Leonardi A, Borghesan F, Faggian D, Depaoli M, Secchi AG & Plebani M (2000a): Tear and serum soluble leukocyte activation markers in conjunctival allergic disease. *Am J Ophthalmol* **129**: 151–158.
- Leonardi A, Brun P, Tavalato M, Abatangelo G, Plebani M & Secchi AG (2000b): Growth factors and collagen distribution in vernal keratoconjunctivitis. *Invest Ophthalmol Vis Sci* **41**: 4175–4181.
- Leonardi A, DeFranchis G, Fregona IA, Violato D, Plebani M & Secchi AG (2001): Effects of cyclosporin A on human conjunctival fibroblasts. *Arch Ophthalmol* **119**: 1512–1517.
- Leonardi A, Jose PJ, Zhan H & Calder VL (2003a): Tear and mucus eotaxin-1 and eotaxin-2 in allergic keratoconjunctivitis. *Ophthalmology* **110**: 487–492.
- Leonardi A, Cortivo R, Fregona I, Plebani M, Secchi AG & Abatangelo G (2003b): Effects of Th2 cytokines on expression of collagen, MMP-1, and TIMP-1 in conjunctival fibroblasts. *Invest Ophthalmol Vis Sci* **44**: 183–189.
- Leonardi A, Brun P, Abatangelo G, Plebani M & Secchi AG (2003c): Tear levels and activity of matrix metalloproteinase (MMP)-1 and MMP-9 in vernal keratoconjunctivitis. *Invest Ophthalmol Vis Sci* **44**: 3052–3058.
- Leonardi A, Brun P, Sartori MT, Cortivo R, Dedominicis C, Saggiorato G, Abatangelo G & Secchi AG (2005): Urokinase plasminogen activator, uPa receptor, and its inhibitor in vernal keratoconjunctivitis. *Invest Ophthalmol Vis Sci* **46**: 1364–1370.
- Lisanewski M (2003): Supra-tarsal injection of dexamethasone in the treatment of patients with refractory vernal keratoconjunctivitis. *Ethiop Med J* **41**: 19–24.
- Maggi E, Biswas P, DelPrete G et al. (1991): Accumulation of TH-2 like helper T cells in the conjunctiva of patients with vernal conjunctivitis. *J Immunol* **146**: 1169–1174.
- McGill JI (2004): A review of the use of olopatadine in allergic conjunctivitis. *Int Ophthalmol* **25**: 171–179.
- McGill JI, Holgate ST, Church MK, Anderson DF & Bacon A (1998): Allergic eye disease mechanisms. *Br J Ophthalmol* **82**: 1203–1214.
- Metz DP, Hingorani M, Calder VL, Buckley RJ & Lightman S (1997): T-cell cytokines in chronic allergic eye disease. *J Allergy Clin Immunol* **100**: 817–824.
- Miyazaki D, Nakamura T, Komatsu N, Nawata N, Ikeda Y, Inoue Y, Higashi H & Ono SJ (2004): Role of chemokines in ocular allergy and possible therapeutic strategies. *Cornea* **23**: 48–54.
- Miyoshi T (2001): Interleukin-8 concentrations in conjunctival epithelium brush cytology samples correlate with neutrophil, eosinophil infiltration, and corneal damage. *Cornea* **20**: 743–747.
- Montan PG & van Hage-Hamsten M (1996): Eosinophil cationic protein in tears in allergic conjunctivitis. *Br J Ophthalmol* **80**: 556–560.
- Montan PG, Ekstrom K, Hedlin G, van Hage-Hamsten M, Hjert A & Herrmann B (1999): Vernal keratoconjunctivitis in a Stockholm ophthalmic centre – epidemiological, functional, and immunologic investigations. *Acta Ophthalmol Scand* **77**: 559–563.
- Montan PG, Scheynius A & van der Ploeg I (2002): Similar T helper Th2-like cytokine mRNA expression in vernal keratoconjunctivitis regardless of atopic constitution. *Allergy* **57**: 436–441.
- Mori J, Ishizaki M, Senoo T & Obara Y (2002): Cytokine mRNA expression in vernal keratoconjunctivitis. *Nippon Ganka Gakkai Zasshi* **106**: 392–397.
- Murphy PM, Baggiolini M, Charo IF et al. (2000): International Union of Pharmacol-

- ogy. XXII. Nomenclature for chemokine receptors. *Pharmacol Rev* **52**: 145–176.
- Neumann E, Gutmann MJ, Blumenkranz N & Michaelson IC (1959): A review of four hundred cases of vernal conjunctivitis. *Am J Ophthalmol* **47**: 166–172.
- Nishiwaki-Dantas MC, Dantas PE, Pezzutti S & Finzi S (2000): Surgical resection of giant papillae and autologous conjunctival graft in patients with severe vernal keratoconjunctivitis and giant papillae. *Ophthalm Plast Reconstr Surg* **16**: 438–442.
- O'Shea JG (2000): A survey of vernal keratoconjunctivitis and other eosinophil-mediated external eye diseases amongst Palestinians. *Ophthalmic Epidemiol* **7**: 149–157.
- Okada N, Fukagawa K, Takano Y et al. (2005): The implications of the upregulation of ICAM-1/VCAM-1 expression of corneal fibroblasts on the pathogenesis of allergic keratopathy. *Invest Ophthalmol Vis Sci* **46**: 4512–4518.
- Owen CG, Shah A, Henshaw K, Smeeth L & Sheikh A (2004): Topical treatment for seasonal allergic conjunctivitis: systematic review and meta-analysis of efficacy and effectiveness. *Br J Gen Pract* **54**: 451–456.
- Ozbek Z, Burakgazi AZ & Rapuano CJ (2006): Rapid healing of vernal shield ulcer after surgical debridement: a case report. *Cornea* **25**: 472–473.
- Ozcan AA, Ersoz TR & Dulger E (2007): Management of severe allergic conjunctivitis with topical cyclosporine 0.05% eye drops. *Cornea* **26**: 1035–1038.
- Pelegrin L, Gris O, Adan A & Plazas A (2008): Superficial keratectomy and amniotic membrane patch in the treatment of corneal plaque of vernal keratoconjunctivitis. *Eur J Ophthalmol* **18**: 131–133.
- Pucci N, Novembre E, Cianferoni A, Lombardi E, Bernardini R, Caputo R, Campa L & Vierucci A (2002): Efficacy and safety of cyclosporine eyedrops in vernal keratoconjunctivitis. *Ann Allergy Asthma Immunol* **89**: 298–303.
- Pucci N, Novembre E, Lombardi E et al. (2003): Atopy and serum eosinophil cationic protein in 110 white children with vernal keratoconjunctivitis: differences between tarsal and limbal forms. *Clin Exp Allergy* **33**: 325–330.
- Pucci N, Novembre E, Lombardi E et al. (2005): Long eyelashes in a case series of 93 children with vernal keratoconjunctivitis. *Pediatrics* **115**: 86–91.
- Rahi AHS, Buckley R & Grierson I (1985): Pathology of corneal plaque in vernal keratoconjunctivitis. In: O' Connor GR & Chandler JW (eds). *Advances in immunology and immunopathology of eye*. New York: Masson, Chapter 23.
- Rao SK, Meenakshi S, Srinivasan B & Baluswamy S (2004): Perilimbal bulbar conjunctival pigmentation in vernal conjunctivitis: prospective evaluation of a new clinical sign in an Indian population. *Cornea* **23**: 356–359.
- Rehany U & Rumelt S (1995): Corneal hydrops associated with vernal conjunctivitis as a presenting sign of keratoconus in children. *Ophthalmology* **102**: 2046–2049.
- Rossi D & Zlotnik A (2000): The biology of chemokines and their receptors. *Annu Rev Immunol* **18**: 217–242.
- Rouher N, Pilon F, Dalens H, Fauquert JL, Kemeny JL, Rigal D & Chiambaretta F (2004): Implantation of preserved human amniotic membrane for the treatment of shield ulcers and persistent corneal epithelial defects in chronic allergic keratoconjunctivitis. *J Fr Ophthalmol* **27**: 1091–1097.
- Saini JS, Gupta A, Pandey SK, Gupta V & Gupta P (1999): Efficacy of supratarsal dexamethasone versus triamcinolone injection in recalcitrant vernal keratoconjunctivitis. *Acta Ophthalmol Scand* **77**: 515–518.
- Sangwan VS, Murthy SI, Vemuganti GK, Bansal AK, Gangopadhyay N & Rao GN (2005): Cultivated corneal epithelial transplantation for severe ocular surface disease in vernal keratoconjunctivitis. *Cornea* **24**: 426–430.
- Secchi AG, Tognon MS & Leonardi A (1990): Topical use of cyclosporine in the treatment of vernal keratoconjunctivitis. *Am J Ophthalmol* **110**: 641–645.
- Sharma A (1997): Topical ketarolac 0.5% solution for the treatment of vernal keratoconjunctivitis. *Indian J Ophthalmol* **45**: 177–180.
- Singh S, Pal V & Dhull CS (2002): Supratarsal injection of corticosteroids in the treatment of refractory vernal keratoconjunctivitis. *Indian J Ophthalmol* **50**: 160–161.
- Solomon A, Puxeddu I & Levi-Schaffer F (2003): Fibrosis in ocular allergic inflammation: recent concepts in the pathogenesis of ocular allergy. *Curr Opin Allergy Clin Immunol* **3**: 389–393.
- Solomon A, Zamir E, Levartovsky S & Frucht-Pery J (2004): Surgical management of corneal plaques in vernal keratoconjunctivitis: a clinicopathologic study. *Cornea* **23**: 608–612.
- Sorkin EM & Ward A (1986): Ocular sodium cromoglycate, an overview of its therapeutic efficacy in allergic eye disease. *Drugs* **31**: 131–148.
- Spadavecchia L, Fanelli P, Tesse R et al. (2006): Efficacy of 1.25% and 1% topical cyclosporine in the treatment of severe vernal keratoconjunctivitis in childhood. *Pediatr Allergy Immunol* **17**: 527–532.
- Sridhar MS, Gopinathan U & Rao GN (2003): Fungal keratitis associated with vernal keratoconjunctivitis. *Cornea* **22**: 80–81.
- Tabbara KF (1999): Ocular complications of vernal keratoconjunctivitis. *Can J Ophthalmol* **34**: 88–92.
- Tabbara KF (2001): Tear tryptase in vernal keratoconjunctivitis. *Arch Ophthalmol* **119**: 338–342.
- Tabbara KF & Arafat NT (1977): Cromolyn effects on vernal keratoconjunctivitis in children. *Arch Ophthalmol* **95**: 2184–2186.
- Tabuchi K, Inada N, Shoji J, Sawa M & Kato H (2004): The relationship between *Staphylococcus aureus* and atopic keratoconjunctivitis. *Nippon Ganka Gakkai Zasshi* **108**: 397–400.
- Takatsu K (1992): Interleukin-5. *Curr Opin Immunol* **4**: 299–306.
- Tanaka M, Takano Y, Dogru M, Fukagawa K, Asano-Kato N, Tsubota K & Fujishima H (2004): A comparative evaluation of the efficacy of intraoperative mitomycin C use after the excision of cobblestone-like papillae in severe atopic and vernal keratoconjunctivitis. *Cornea* **23**: 326–329.
- Tomassini M, Magrini L, Bonini S, Lambiase A & Bonini S (1994): Increase levels of eosinophil cationic protein and eosinophil derived neurotoxin (protein X) in vernal keratoconjunctivitis. *Ophthalmology* **101**: 1808–1811.
- Totan Y, Hepsen IF, Cekic O, Gunduz A & Aydin E (2001): Incidence of keratoconus in subjects with vernal keratoconjunctivitis: a videokeratographic study. *Ophthalmology* **108**: 824–827.
- Trocme SD & Aldave AJ (1994): The eye and the eosinophil. *Surv Ophthalmol* **39**: 241–252.
- Trocme SD, Kephart GM, Allansmith MR, Borne WM & Gleich GJ (1989): Conjunctival deposition of eosinophil granule major basic protein in vernal keratoconjunctivitis and contact lens-associated giant papillary conjunctivitis. *Am J Ophthalmol* **108**: 57–63.
- Trocme SD, Kephart GM, Bourne WM, Buckley RJ & Gleich GJ (1993): Eosinophil granule major basic protein deposition in corneal ulcers associated with vernal keratoconjunctivitis. *Am J Ophthalmol* **115**: 640–643.
- Tuft SJ, Dart JK & Kemeny M (1989): Limbal vernal keratoconjunctivitis: clinical characteristics and immunoglobulin E expression compared with palpebral vernal. *Eye* **3**: 420–427.
- Tuft SJ, Cree IA, Woods M & Yorston D (1998): Limbal vernal keratoconjunctivitis in the tropics. *Ophthalmology* **105**: 1489–1493.
- Tuo J & Chan CC (2003): Ocular application of macro biomolecules in anti-allergy and anti-inflammation. *Current medicinal chemistry – anti-inflammatory and anti-allergy agents*. Bentham science publishers **3**: 219–227.
- Uchio E, Ono SY, Ikezawa Z & Ohno S (2000): Tear levels of interferon- γ , interleukin (IL) -2, IL-4 and IL-5 in patients with vernal keratoconjunctivitis, atopic keratoconjunctivitis and allergic conjunctivitis. *Clin Exp Allergy* **30**: 103–109.
- Ukponmwan CU (2003): Vernal keratoconjunctivitis in Nigerians: 109 consecutive cases. *Trop Doct* **33**: 242–245.
- Umetsu DT & De Kruffy RH (1997): TH1 and TH2 CD4+ cells in the pathogenesis of allergic diseases. *Proc Soc Exp Biol Med* **215**: 11–20.

Verin PH, Dicker ID & Mortemousque B (1999): Nedocromil sodium eye drops are more effective than sodium cromoglycate eye drops for the long-term management of vernal keratoconjunctivitis. *Clin Exp Allergy* **29**: 529–536.

Verin P, Allewaert R, Joyaux JC, Piozzi E, Koliopoulos J & Bloch-Michel E (2001): Lodoxamide Study Group. Comparison of lodoxamide 0.1% ophthalmic solution and levocabastine 0.05% ophthalmic suspension in vernal keratoconjunctivitis. *Eur J Ophthalmol* **11**: 120–125.

Fahy G, Easty DL, Collum L, Lumbroso P, Ober M, Verin P, Mackie I & Verstappen A (1988): A double mask efficacy and safety evaluation of lodoxamide 0.1% ophthalmic solution versus opticrom 2%. A multicentre study. In: LN Ferraz, De Oliveira (ed.) *Ophthalmology today* Elsevier, 341–342.

Weimer LK, Gamache DA & Yanni JM (1998): Histamine-stimulated cytokine secretion from human conjunctival epithelial cells: inhibition by the histamine H1 antagonist emedastine. *Int Arch Allergy Immunol* **115**: 288–293.

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