Corneal Diseases in Children: Allergic Diseases

4

Andrea Cruzat and Kathryn Colby

Allergic Conjunctivitis: Seasonal and Perennial

Seasonal allergic conjunctivitis (SAC) and perennial allergic conjunctivitis (PAC) are the most common form of ocular allergies, affecting about 15–20% of the population (Wong et al. 2014). SAC is more prevalent than PAC. The onset of symptoms is seasonally related to specific circulating aeroallergens. The difference between seasonal and perennial allergic conjunctivitis is the specific allergens to which the patient is allergic. SAC is caused by airborne pollens during spring and summer (most commonly ragweed and grass pollen) while PAC is caused by perennial allergens such as animal dander, dust mites, mold, air pollutants, and feathers. Despite this difference, 79% of children with perennial allergic conjunctivitis commonly experience seasonal exacerbations of symptoms (Bielory 2000; Abelson and Granet 2006).

A. Cruzat (✉)
Department of Ophthalmology, Harvard Medical School/Massachusetts Eye and Ear Infirmary, 243 Charles St., Boston, MA 02114, USA
e-mail: andrea_cruzat@meei.harvard.edu

A. Cruzat
Pontificia Universidad Católica de Chile, Santiago, Chile

K. Colby
Department of Ophthalmology and Visual Science, University of Chicago, 5841 S. Maryland Ave, MC2114, Chicago, IL 60637, USA
e-mail: kcolby@bsd.uchicago.edu

Symptoms and Signs

The cardinal symptom of allergic conjunctivitis is ocular pruritus. Watery discharge and milky or pale pink conjunctiva with vascular congestion (mild to moderate hyperemia) that may progress to swelling and conjunctival follicles may also occur. A white exudate may form during the acute state that becomes stringy in the chronic form. Palpebral edema can be mild to moderate, accompanied by venous congestion that gives it a dark appearance known as allergic dark circles. A lower lid crease (the so-called Dennie–Morgan line) may develop. Corneal involvement is rare (Friedlaender 2011). Acute chemosis (an excessive edema of the bulbar conjunctiva) may occasionally occur. In some cases a fine conjunctival follicular reaction or papillary hypertrophy along the tarsal conjunctival surface may also be seen.

Proper diagnosis is usually made clinically based on history and physical examination, with ocular itching the most common and important symptom. Most patients also have history of atopy with symptoms of allergic rhinitis (65–70%) (Takamura et al. 2011). Other frequent co-morbidities are asthma and eczema (Gradman and Wolthers 2006).

Pathogenesis

Seasonal and perennial allergic conjunctivitis are type 1 hypersensitivity reactions. Allergic conjunctivitis is caused by an allergen-induced

K. Colby (ed.), *Corneal Diseases in Children*, Essentials in Ophthalmology,
DOI 10.1007/978-3-319-55298-9_4

inflammatory response in which allergens interact with IgE antibodies bound to the surface of sensitized conjunctival mast cells. Degranulation of mast cells induces enhanced tear levels of histamine, tryptase, prostaglandins, and leukotrienes that induce the symptoms of allergic conjunctivitis. This immediate or *early response* lasts clinically 20–30 min (La Rosa et al. 2013). Mediators released during mast cell degranulation initiate the recruitment of inflammatory cells including neutrophils, basophils, eosinophils, and T lymphocytes in the conjunctival mucosa. This leads to the ocular *late phase reaction* that occurs 4–6 h later and the release of T helper 2 type cytokines (interleukin (IL)-4, IL-5, IL-6 and IL-13) (Leonardi et al. 2007). The presence of specific IgE antibodies to seasonal or perennial allergens can be documented in almost all cases, and this test can be used for a definite diagnosis if in doubt (Bonini 2004). Tear fluid from SAC patients has been found to contain a small amount of eosinophils and histamine but elevated levels of IgE (Bielory 2000). Interestingly, 78% of PAC patients had demonstrated tear-specific IgE for house dust, whereas no SAC patients had measurable levels of IgE specific for house dust in tears (Bielory 2000). Histamine sensitivity has been noted to be different between normal subjects and atopic patients. Atopic patients require lower doses of histamine to cause symptoms than normal subjects (Bielory 2000). Allergic conjunctivitis is characterized histologically by infiltration of the conjunctiva with inflammatory cells, including neutrophils, eosinophils, lymphocytes, and macrophages (Bielory 2000).

Atopic Keratoconjunctivitis (AKC)

AKC is a bilateral chronic inflammatory disorder that involves recurrent episodes of severe inflammation of the conjunctiva and eyelids, which can secondarily affect the cornea. More than 95% of AKC patients also have eczema and 87% have history of asthma (Bielory 2000). AKC typically begins in the late teens and may persist until the fourth or fifth decade of life (Bielory 2000).

Symptoms and Signs

AKC patients tend to be older than children with SAC and present with disabling symptoms most commonly involving the lower tarsal conjunctiva. Symptoms include ocular itching year round, blepharospasm, blurred vision, burning, tearing, photophobia, eye pain, and early-morning mucous discharge. Seasonal exacerbations have been reported to be more marked in the winter or summer months and after exposure to animal dander, dust, and certain foods (Foster and Calonge 1990).

Clinical exam may reveal eyelid eczema with scaling dermatitis with a fine sandpaper-like texture, loss of eyelashes or eyebrows (madarosis), and lateral canthus ulceration. The eczema around the eyes involves the periorbital skin and cheeks. Erythema, dry scales, Dennie–Morgan lines, and allergic shiners (darkness and swelling underneath the eyes) may occur. Secondary staphylococcal blepharitis is common. Corneal findings such as punctate epithelial keratopathy (Fig. 4.1), Horner's points or Trantas dots may also be present. Mild or severe conjunctival injection or chemosis and lower tarsal follicles or papillae may be seen (Abelson and Granet 2006; Bielory and Bielory 2010). The conjunctiva is edematous and may eventually manifest subepithelial fibrosis, fornix shortening, scarring, or symblepharon.

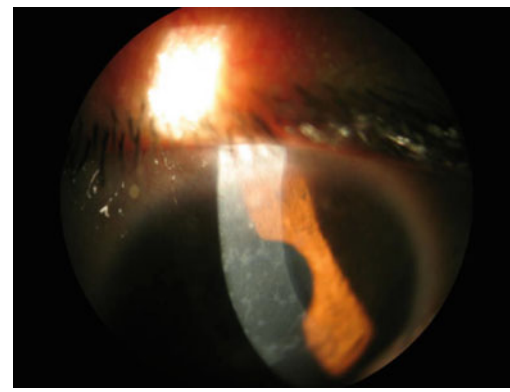

Fig. 4.1 Epithelial keratopathy in atopic keratoconjunctivitis

Complications can be severe and vision-threatening including corneal epithelial defects, keratitis, corneal scarring, and keratoconus. Atopic cataracts that are typically anterior and shield-like, but may be nuclear, cortical and even posterior subcapsular develop in 8–12% of affected patients (Bielory 2000). The use of corticosteroid therapy may also contribute to cataract development. Lichenification of the eyelid skin may cause cicatricial ectropion and lagophthalmos (Abelson and Granet 2006). Eczematous lesions may be found not only on the eyelids but also in any place of the body. Skin lesions are red and elevated in the antecubital or popliteal regions and are itchy. Physical exam findings are similar or overlap between vernal and atopic keratoconjunctivitis; however, VKC usually resolves by age 20 years, whereas AKC can persist throughout life and involves the eyelids (Friedlaender 2011). Approximately 45% of patients with AKC are skin test or allergosorbent test negative to common allergens (La Rosa et al. 2013). Other unusual complications include retinal detachment and a higher incidence of infections with herpes simplex keratitis and staphylococcus (Tuft et al. 1992; Bielory 2000).

AKC is a clinical diagnosis; the history of systemic atopy and the perennial nature aids in distinguishing this from other forms of allergic conjunctivitis. Testing blood levels of histamine and increased total IgE antibodies in serum and lacrimal fluid and positive results of the serum antigen specific IgE antibody can be used as confirmatory tests of suspected disease (Takamura et al. 2011).

Pathogenesis

The pathophysiology of AKC involves both a type 1 hypersensitivity response with a chronic degranulation of mast cells mediated by IgE and a hypersensitivity type 4 response mediated by Th1- and Th2-lymphocyte derived cytokines (La Rosa et al. 2013). The T cell inflammatory response is confirmed by elevated systemic levels of IL-4 and IL-5 in atopic individuals (Jenmalm et al. 2001). The histopathologic findings of AKC include a mixture of mast cell, eosinophil, and lymphocyte infiltration into the conjunctival epithelium with both Th1 and Th2 interactions (Trocme and Sra 2002; Leonardi et al. 2007). Patients with atopic dermatitis and rhinoconjunctivitis commonly have elevated IgE and histamine levels in tears (Trocme and Sra 2002).

Vernal Keratoconjunctivitis (VKC)

Vernal keratoconjunctivitis (VKC) is a rare (1–10.6:10.000) (Kumar 2009) severe usually bilateral—although sometimes asymmetrical or unilateral—seasonal allergic inflammatory disease (Awwad et al. 2006). It is characterized by an inflammation of the ocular surface usually involving the upper tarsal and/or bulbar conjunctiva. VKC is two times more common in boys than girls. Onset is generally before age 10. The disease tends to regress around puberty (Abelson and Granet 2006; Kumar 2009; De Smedt et al. 2013). VKC can develop after puberty; in this case, there is a more equal gender distribution. The initial seasonal attacks in spring and summer may turn into perennial disease after a few years, being not just limited to spring, with episodes of reactivity being quite common in the winter (Kumar 2009).

Although it is a self-limiting disease, patients with VKC may demonstrate periodic exacerbation of inflammatory symptoms with a consequent decline of the quality of life and with a risk of permanent corneal damage that can be vision-threatening. Symptoms often tend to disappear 4–10 years after onset. It occurs more frequently in children who have a history of seasonal allergy, asthma, and eczema. In a study done by Zicari et al. (2013) 46% of VKC patients were found to have a family history positive for immune dysfunction.

Although its prevalence is higher especially in hot and dry climates (Mediterranean areas, Indian subcontinent, Central and West Africa and South America), and is more common in persons of Asian or African origin, VKC has a wide geographical distribution (Kumar 2009).

VKC was first mentioned in the ophthalmic literature as conjunctiva lymphatica more than 150 years ago. Subsequently, most of the notables of ophthalmology during that period (Arlt, Dasmarres, von Graefe, Axenfeld, Trantas, and Herbert) published about this interesting disorder. 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 (Kumar 2009).

Symptoms and Signs

VKC is characterized by intense ocular itching exacerbated by exposure to wind, dust, bright light, hot weather, or sweating. Tearing, mucous discharge, conjunctival hyperemia, photophobia, blepharospasm, eye pain, foreign body sensation, and sometimes ptosis may be seen.

There are two forms of the disease: limbal or palpebral, depending on which portion of the conjunctiva is predominantly affected. Clinical examination may reveal a thin, copious milk-white fibrinous secretion (composed of epithelial cells, eosinophils and Charcot–Leyden crystals). *Palpebral involvement* may include conjunctival hyperemia and edema with papillae (filled with inflammatory cells) on the superior tarsal conjunctiva (Fig. 4.2). Giant papillae are seen as the disease progresses due to fibrous tissue proliferation and can reach 7–8 mm in diameter (so-called "cobblestone" papillae). Fibrin may accumulate on the giant papillae and is known as the Maxwell-Lyons sign. VKC patients can also show Dennie Morgan's line. Persistent forms of VKC are associated with subepithelial fibrosis that appears as a white linear scar running parallel to the lid margin (Arlt's line). *Limbal involvement* includes transient confluent gelatinous limbal papillae and clumps of necrotic eosinophils with dead epithelial cells and neutrophils on the limbus or conjunctiva seen as yellow-white points (Horner's points and Trantas dots) and conjunctival hyperemia with edema (Figs. 4.3 and 4.4) (Kumar 2009). Trantas dots tend to appear when VKC is active, and disappear when symptoms decrease (Friedlaender 2011), while the cobblestones persist even during quiescent phases of the disease. Corneal involvement is associated with more severe disease. Corneal epithelial punctate keratitis (called keratitis epithelialis vernalis of El Tobgy) may evolve to macroerosion, ulcers and plaques, which are all expressions of epithelial toxicity caused by factors released from activated eosinophils (Leonardi et al. 2008). The classic corneal change seen more commonly in patients with superior tarsal involvement, is the development of a noninfectious shield ulcer appearing as an irregular oval corneal plaque with elevated hypertrophic epithelial cells with fibrin and

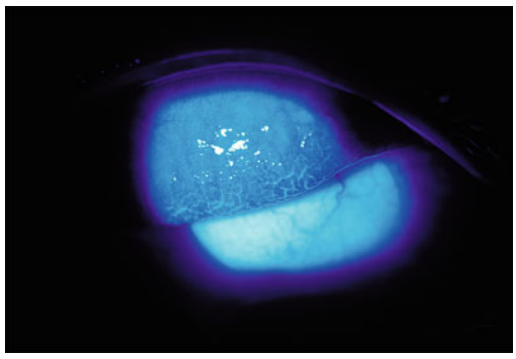

Fig. 4.2 Papillae in upper tarsal conjunctiva in vernal keratoconjunctivitis

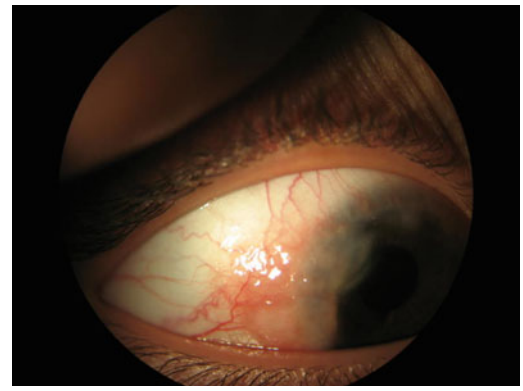

Fig. 4.3 Limbal involvement in vernal keratoconjunctivitis: limbal gelatinous hyperplasia with Horner–Trantas dots

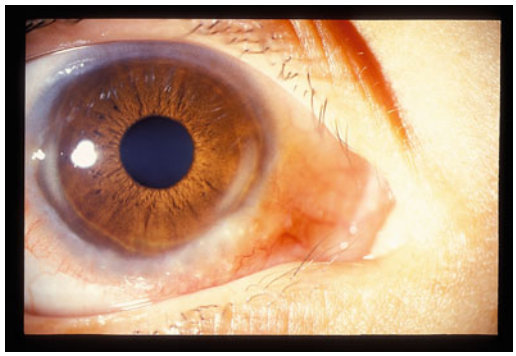

Fig. 4.4 Limbal involvement with limbal hyperplasia, pannus and pseudogerontoxon in vernal keratoconjunctivitis

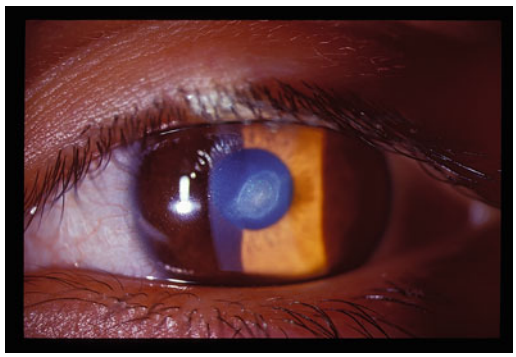

Fig. 4.5 Shield ulcer in vernal keratoconjunctivitis

mucin that stains with fluorescein and contains eosinophils and epithelial cells (Fig. 4.5) (Udell et al. 1981; Abelson and Granet 2006). Superficial corneal neovascularization and sometimes filamentary keratitis may also occur (Zicari et al. 2013).

Although VKC is a bilateral disease, it may affect one eye more than the other.

Ocular complications of VKC include steroid-induced cataract, glaucoma and dry eye, corneal scarring, irregular astigmatism, microbial keratitis, limbal tissue hyperplasia, and keratoconus (Tabbara 1999; Sridhar et al. 2003). Amblyopia seen among VKC may be caused by corneal opacity, irregular astigmatism, and keratoconus (Kumar 2009). A common corneal degenerative change is pseudogerontoxon, in which there is increased lipid deposition in the peripheral portion of the cornea resembling corneal arcus senilis (Fig. 4.4).

No precise diagnostic criteria have been established for this disease. Diagnosis is based on typical and characteristic clinical signs and symptoms; thus many mild or atypical cases may escape diagnosis. The diagnosis is based on the classical symptoms of allergic conjunctivitis (itching, tearing and hyperemia), and on specific ocular signs such as proliferative lesions in the conjunctiva including giant cobblestone papillae on the upper palpebral conjunctiva, limbal proliferation with limbal gelatinous hyperplasia and Horner–Trantas dots (Fig. 4.3) and the corneal findings described above. Even though atopy is common among VKC patients, only 50% of patients with VKC has positive Skin Prick Test and/or elevated allergen-specific antibodies (Pucci et al. 2003; Bonini 2004). Increased total IgE antibodies in serum and lacrimal fluid eosinophils in the conjunctival smear are common findings.

Pathogenesis

Ocular symptoms result from a nonspecific hyperreactivity induced by nonspecific stimuli, such as wind, dust, and sunlight, which is not related to allergen levels in the environment (La Rosa et al. 2013). Immunological data has proved that the pathogenesis of VKC is a type 1 and a type 4 hypersensitivity reaction. Recently, many authors have suggested the existence of a cooperation between the allergic (Th2 mediated) and the inflammatory (Th1 mediated) responses (Leonardi et al. 2006; Zicari et al. 2013). The immunopathogenesis of VKC is multifactorial involving a Th2 mediated mechanism with an overexpression of Th2-derived cytokines, growth factors, mast cells, eosinophils, neutrophils, lymphocytes, and corneal fibroblasts that perpetuate the ocular allergic inflammation (Leonardi et al. 1999; Trocme and Sra 2002; Kumagai et al. 2006). In VKC, antigen presenting cells, such as Langerhan's cells, are associated with co-stimulatory molecules (CD86) that provide an important mechanism for Th2 cell activation (by

interacting with CD28) and further cytokine release (Abu-El-Asrar et al. 2001a).

In the type 1 hypersensitivity reaction, ligands expressed in conjunctival B cells such as CD23, CD21, and CD40 are crucial for the interactions in the production of IgE (Abu-El-Asrar et al. 2001b). The tears of VKC patients contain high levels of IgE, histamine and mast cell mediators, including major basic protein (MBP), eosinophil cationic protein (ECP), Charcot–Leyden crystals, basophils, IgE- and IgG-specific for aeroallergens (e.g., ragweed pollen) and eosinophils (Ballow and Mendelson 1980; Irani et al. 1990; Bielory 2000).

Chemokines such as IL-4 and IL-13 are involved in the formation of giant papillae by inducing the production of extracellular matrix and the proliferation of conjunctival fibroblasts (Leonardi et al. 2007). IL-8 in the extracellular space of the conjunctival epithelium plays an important role in the recruitment of neutrophils and eosinophils and in the pathogenesis of corneal damage in severe allergic diseases (Miyoshi et al. 2001). Degranulated eosinophils and their toxic enzymes such as ECP and MBP have been found in the tears and conjunctiva as well as in the periphery of corneal ulcers, suggesting their etiopathogenic role in many of the problems associated with VKC (Bielory 2000).

The increased conjunctival infiltration with eosinophils, basophils, mast cells, plasma cells, lymphocytes, macrophages, and fibroblasts, when compared to seasonal and perennial allergic conjunctivitis, may contribute to the serious complications seen in VKC (Trocme and Sra 2002). Granules with cytotoxic mediators are secreted by eosinophils releasing major basic protein, eosinophil cationic protein, eosinophil peroxidase, and gelatinase B which damage corneal epithelium and affect wound healing (Trocmé et al. 1993, 1997; Abu-El-Asrar et al. 2001c). Enzymatic degradation of histamine has been shown to be significantly lower in patients with VKC compared with normal patients in both tears and plasma, suggesting that this dysfunction may be a primary factor in the pathophysiology of VKC (Abelson et al. 1995).

Treatment of Allergic Eye Diseases

Treatment of pediatric ocular allergy should be managed by the ophthalmologist in conjunction with the allergist and in a multifactorial approach. Table 4.1 shows a summary of a suggested treatment approach. Avoidance of offending allergens as much as possible in conjunction to allergy medications is the mainstay therapy. For severe cases, topical corticosteroids and immunotherapy may be necessary. It is important to optimize the treatment of children suffering from allergic disease to improve their quality of life and avoid secondary complications.

Primary Interventions

Primary interventions, such as environmental modification and minimizing or avoiding the offending allergens as much as possible, are an important first step for all types of allergic conjunctivitis. For the more common allergens, simple measures including installing high-efficiency air filters and air conditioning, meticulous removal of dust such as vacuum cleaners with special filters, removal of drapes and carpets, protective goggles, sealing bedding, washing linens in hot

Table 4.1 Summary of suggested treatment approach

Mild seasonal allergies
1. Avoidance of allergens and rubbing
2. Preservative-free artificial tears
3. Multimodal allergy medications over the counter, used as needed
Vernal keratoconjunctivitis (*VKC*) *or atopic keratoconjunctivitis* (*AKC*)
1. As above plus
2. Multimodal allergy medications used continuously
3. Cyclosporine 0.05% up to 4 times daily
4. Topical steroids for acute flares
5. Consider immunomodulatory shots
6. Control of dermatitis (AKC)
7. Control of systemic allergy (AKC and VKC)

water, avoidance of pets or keeping pets out of the sleeping areas and washing the child's hair in the evening prior to sleeping, can keep the allergen away from the eyes and the upper respiratory system. Some of these recommendations, especially involving beloved pets, can be difficult to implement. Cold compresses may aid in symptom relief, especially ocular pruritus. Eye lubricants, ideally preservative-free artificial tears, provide a barrier function and help to improve the first-line defense at the level of the conjunctival mucosa, helping to wash out or dilute allergens and inflammatory mediators of the ocular surface. Ointments are commonly used at night and provide moisture to the ocular surface while the child sleeps. Although frequently unsuccessful, discouraging of rubbing the itchy eyes is important.

Secondary Interventions

Topical pharmacological interventions may be required when non-pharmacological strategies do not provide adequate symptom relief. Milder cases can be treated with short-term topical ophthalmic therapy for temporary symptom relief such as decongestants, antihistamine with/without decongestants combination, mast cell stabilizers, a multiple action anti-allergic agent and anti-inflammatory agents.

Topical decongestants have shown to be effective, administered up to four times daily. These medications act as vasoconstrictors, effectively reducing ocular erythema, but have no effect on the allergic inflammatory response. Adverse effects include burning and stinging on instillation, mydriasis and rebound hyperemia with chronic use, and tachyphylaxis (Abelson et al. 1990). Their primary contraindication is in patients with narrow angle glaucoma. Phenylephrine and tetrahydrozoline are sympathomimetic agents that decrease congestion and edema through α-receptor stimulation.

Antihistamines competitively and reversibly block histamine receptors. Topical treatments are preferred over systemic for ocular allergies because of their greater efficacy in relieving itching and redness. However, systemic control of allergy is an important part of the management of ocular allergy. These medications may need to be given up to 4 times per day, and may be irritating to the eye with prolonged use (La Rosa et al. 2013). Combined use of an antihistamine and a vasoconstricting agent is more effective than use of either agent alone. Moderate to severe cases may require longer usage of the above agents and the addition of an oral antihistamine. The combination of H1 receptor blockers with oral antihistamines provides a greater relief than oral antihistamines alone. Newer second-generation oral antihistamines (i.e., terfinadine or loratadine) may be preferred over first-generation antihistamines because they have reduced side effects such as somnolence; however they can induce ocular drying, and worsening allergic symptoms (La Rosa et al. 2013). In addition, ocular challenge testing has shown that use of systemic antihistamines can also result in a several-fold increase in allergen tolerance in both children and adults (Abelson and Granet 2006).

Mast cell stabilizers inhibit the degranulation of mast cells and thus suppress release of inflammatory mediators (e.g., histamine, leukotriene, thromboxane A2). These agents inhibit the early phase reaction of type I allergy and conjunctival local infiltration of inflammatory cells, both of which result in a reduction of the late phase reaction. Mast cell stabilizers do not relieve existing symptoms but they can be used on a prophylactic basis to decrease/prevent degranulation of mast cells, preventing release of histamine and other chemotactic factors. They require a loading period during which they must be applied before the antigen exposure. The exact mechanism of action is not known, but these agents may stabilize cell membranes through increased calcium influx or a reduction in membrane fluidity. Lodoxamine 0.1% has been used continuously for up to 3 months in children aged 2 years and older and pemirolast potassium 0.1% has been used to treat children 2 years and older without serious adverse effects (Abelson and Granet 2006).

Multimodal anti-allergic agents are the drugs of choice for providing immediate symptomatic relief. These multiple action drugs include

olopatadine, ketotifen, azelastine, epinastine, and bepotastine, amongst others. They have multiple pharmacological effects such as histamine receptor antagonist action (H1, H2), stabilization of mast cell degranulation, and suppression of activation and infiltration of eosinophils, generation of leukotrienes and cytokine release. Olopatadine 0.1% is both a mast cell stabilizer and antihistamine with high affinity and selectivity for H1 receptors. In both adults and children as young as 4 years old, it has been shown to be superior to numerous anti-allergic agents (Abelson and Granet 2006). It is one of few agents approved by the US Food and Drug Administration (FDA) for treatment of all signs and symptoms of allergic conjunctivitis. Ketotifen 0.025%, a noncompetitive H1 antagonist and mast cell stabilizer, has proved safe and effective in the treatment of allergic conjunctivitis in children, although several studies have shown to cause mild stinging and shorter long-term duration of action than olopatadine (Abelson and Granet 2006). Azelastine 0.05%, a second-generation H1 receptor antagonist that inhibits histamine release from mast cells, downregulates ICAM-1 expression and prevents activation of inflammatory cells, has been shown to be safe in children aged 2 and older with allergic conjunctivitis (Abelson and Granet 2006).

Nonsteroidal anti-inflammatory drugs (NSAIDs) are generally ineffective in chronic allergic conjunctivitis. Their therapeutic use is related to their ability to block prostaglandin biosynthesis by inhibiting the activity of cyclooxygenase. They can be used as additive drugs in order to reduce hyperemia and pruritus related to prostaglandin D2 and E2, but they do not inhibit histamine (Saari 2010). An adjuvant course of aspirin, can be an effective strategy in treating severe cases of VKC (Abelson and Granet 2006).

Tertiary Interventions

If the previously mentioned approaches are not effective, immunomodulatory medications should be introduced.

Corticosteroids are one of the most potent agents used in the more severe variants of ocular allergy. Corticosteroids possess immunosuppressive and anti-proliferative properties, but their potential ocular adverse effects, such as delayed wound healing, secondary infection, elevated intraocular pressure, and cataracts must be taken into account. Newer topical steroids may have fewer side effects. Topical steroids are used for short courses in patients with inadequate response to secondary interventions and often tapered over several weeks after the acute flare while cell mast stabilizers are continued. Some children with severe disease may need longer courses of topical steroids. Corticosteroids require a loading period typically of 2 weeks before the maximum treatment effect is seen.

"*Steroid-sparing therapy*" calcineurin inhibitors such as cyclosporine or tacrolimus may be used as chronic therapy to reduce dependence on topical steroids.

Cyclosporine, a fungal antimetabolite used as immunomodulator, inhibits various inflammatory mediators and the development of mast cell-mediated allergic conjunctivitis. The use of topical cyclosporine 1% has shown to be effective to control symptoms and local inflammation in severe forms of VKC in childhood when applied at the beginning of the disease and for a long-time period (Tesse et al. 2010). Because cyclosporin A is lipophilic, it must be dissolved in an alcohol–oil base, which may cause ocular irritation (i.e., burning, tearing, erythema, and itching).

Tacrolimus is a macrolide antibiotic that has potent immunomodulatory properties. Tacrolimus acts primarily on T lymphocytes by inhibiting the production of lymphokines, particularly IL-2, as well as IL-3, IL-5, TNF-α, and IFN-γ. Tacrolimus blocks degranulation of mast cells as well as activation of their cytokines. This drug is highly efficient to prevent post-transplant rejection in patients resistant to steroids and cyclosporine. In this regard, tacrolimus is between 10 and 100 times more powerful than the latter (Hooks 1994). It has been effective in the treatment of a variety of other ocular immune-mediated diseases such as corneal graft

rejection, keratitis, scleritis, ocular pemphigoid, and uveitis (Bielory 2000). Regarding the current limited data from literature, ocular application of tacrolimus 0.1%, 0.03% and 0.02% seems effective in treating patients with allergic keratoconjunctivitis; however, ocular irritation may limit its use. Because of the risk of development of herpes keratitis, adequate follow-up is advised (Sánchez Ferreiro and Muñoz Bellido 2013; Westland et al. 2013). At present, tacrolimus cream is available in two approved concentrations (0.1 and 0.3%) by the FDA for skin use in the treatment of atopic dermatitis, but topical ophthalmic drops must be compounded.

Immunotherapy, whether via the subcutaneous route or the intranasal or sublingual route, should be considered in the treatment of persistent severe cases refractory to conventional treatment. Allergen-specific immunotherapy is an effective treatment for patients with allergic rhinoconjunctivitis who have specific IgE antibodies to allergens inducing clinical tolerance to the specific antigen. However, the immune responses to allergen administration are not predictive of the effectiveness of the therapy and the therapy itself can produce systemic reactions depending on the type of allergen administered (La Rosa et al. 2013). The sublingual (oral) immunotherapy is gaining momentum among allergists and it has been shown to control ocular signs and symptoms although less well than nasal symptoms, thus it requires further evaluation for the ocular allergy relief (La Rosa et al. 2011).

Systemic immune suppression is indicated for severe cases of ocular allergy unresponsive to topical treatment where progressive cicatrization is vision-threatening; this therapy should be managed in conjunction with a pediatric rheumatologist.

In the future, newer, more selective drugs like anti-chemokine receptor antibodies, leukotriene receptor antagonists, liposomal delivery systems, anti-IgE therapy and plasmid DNA immunization may become available for treatment of ocular allergy (Abelson and Granet 2006).

Conclusion

Ocular allergy has a wide spectrum of presentation. SAC and PAC, characterized by a type 1 hypersensitivity reaction, are the least severe and easier to manage. VKC and AKC are more serious allergic disorders, characterized by type 1 and 4 hypersensitivity reactions with massive involvement of T cells, macrophages, and eosinophils which may cause severe complications. It is an important ocular disease due to potential sight threatening complications. Thus, it is critical to manage these patients in a multifactorial fashion in conjunction with the pediatrician, allergist, and ophthalmologist. The main objective is to be able to get these children through the disease successfully preventing the complications and possible iatrogenia.

Compliance with Ethical Requirements Kathryn Colby and Andrea Cruzat declare that they have no conflict of interest. No human studies or animal studies were carried out by the authors for this article.

References

Abelson MB, Granet D (2006) Ocular allergy in pediatric practice. Curr Allergy Asthma Rep 6:306–311

Abelson MB, Paradis A, George MA et al (1990) Effects of Vasocon-A in the allergen challenge model of acute allergic conjunctivitis. Arch Ophthalmol 108:520–524

Abelson MB, Leonardi AA, Smith LM et al (1995) Histaminase activity in patients with vernal keratoconjunctivitis. Ophthalmology 102:1958–1963

Abu-El-Asrar AM, Al-Kharashi SA, Al-Mansouri S et al (2001a) Langerhans' cells in vernal keratoconjunctivitis express the costimulatory molecule B7-2 (CD86), but not B7-1 (CD80). Eye (Lond) 15:648–654. doi:10.1038/eye.2001.202

Abu-El-Asrar AM, Fatani RA, Missotten L, Geboes K (2001b) Expression of CD23/CD21 and CD40/CD40 ligand in vernal keratoconjunctivitis. Eye (Lond) 15:217–224. doi:10.1038/eye.2001.65

Abu-El-Asrar AM, Van Aelst I, Al-Mansouri S et al (2001c) Gelatinase B in vernal keratoconjunctivitis. Arch Ophthalmol 119:1505–1511

Awwad ST, Najjar DM, Arlette A, Haddad RS (2006) Vernal keratoconjunctivitis presenting unilaterally. J Pediatr Ophthalmol Strabismus 43:179–180

Ballow M, Mendelson L (1980) Specific immunoglobulin E antibodies in tear secretions of patients with vernal conjunctivitis. J Allergy Clin Immunol 66:112–118

Bielory L (2000) Allergic and immunologic disorders of the eye. Part II: ocular allergy. J Allergy Clin Immunol 106:1019–1032. doi:10.1067/mai.2000.111238

Bielory B, Bielory L (2010) Atopic dermatitis and keratoconjunctivitis. Immunol Allergy Clin N Am 30:323–336. doi:10.1016/j.iac.2010.06.004

Bonini S (2004) Atopic keratoconjunctivitis. Allergy 59 (Suppl 78):71–73. doi:10.1111/j.1398-9995.2004.00570.x

De Smedt S, Wildner G, Kestelyn P (2013) Vernal keratoconjunctivitis: an update. Br J Ophthalmol 97:9–14. doi:10.1136/bjophthalmol-2011-301376

Foster CS, Calonge M (1990) Atopic keratoconjunctivitis

Friedlaender MH (2011) Ocular allergy. Curr Opin Allergy Clin Immunol 11:477–482. doi:10.1097/ACI.0b013e32834a9652

Gradman J, Wolthers OD (2006) Allergic conjunctivitis in children with asthma, rhinitis and eczema in a secondary outpatient clinic. Pediatr Allergy Immunol 17:524–526. doi:10.1111/j.1399-3038.2006.00429.x

Hooks MA (1994) Tacrolimus, a new immunosuppressant—a review of the literature. Ann Pharmacother 28:501–511

Irani AM, Butrus SI, Tabbara KF, Schwartz LB (1990) Human conjunctival mast cells: distribution of MCT and MCTC in vernal conjunctivitis and giant papillary conjunctivitis. J Allergy Clin Immunol 86:34–40

Jenmalm MC, Van Snick J, Cormont F, Salman B (2001) Allergen-induced Th1 and Th2 cytokine secretion in relation to specific allergen sensitization and atopic symptoms in children. Clin Exp Allergy 31:1528–1535

Kumagai N, Fukuda K, Fujitsu Y et al (2006) Role of structural cells of the cornea and conjunctiva in the pathogenesis of vernal keratoconjunctivitis. Prog Retin Eye Res 25:165–187. doi:10.1016/j.preteyeres.2005.09.002

Kumar S (2009) Vernal keratoconjunctivitis: a major review. Acta Ophthalmol 87:133–147. doi:10.1111/j.1755-3768.2008.01347.x

La Rosa M, Lionetti E, Leonardi S et al (2011) Specific immunotherapy in children: the evidence. Int J Immunopathol Pharmacol 24:69–78

La Rosa M, Lionetti E, Reibaldi M et al (2013) Allergic conjunctivitis: a comprehensive review of the literature. Ital J Pediatr 39:18. doi:10.1186/1824-7288-39-18

Leonardi A, DeFranchis G, Zancanaro F et al (1999) Identification of local Th2 and Th0 lymphocytes in vernal conjunctivitis by cytokine flow cytometry. Invest Ophthalmol Vis Sci 40:3036–3040

Leonardi A, Fregona IA, Plebani M et al (2006) Th1- and Th2-type cytokines in chronic ocular allergy. Graefes Arch Clin Exp Ophthalmol 244:1240–1245. doi:10.1007/s00417-006-0285-7

Leonardi A, De Dominicis C, Motterle L (2007) Immunopathogenesis of ocular allergy: a schematic approach to different clinical entities. Curr Opin Allergy Clin Immunol 7:429–435. doi:10.1097/ACI.0b013e3282ef8674

Leonardi A, Motterle L, Bortolotti M (2008) Allergy and the eye. Clin Exp Immunol 153(Suppl 1):17–21. doi:10.1111/j.1365-2249.2008.03716.x

Miyoshi T, Fukagawa K, Shimmura S et al (2001) Interleukin-8 concentrations in conjunctival epithelium brush cytology samples correlate with neutrophil, eosinophil infiltration, and corneal damage. Cornea 20:743–747

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

Saari KM (2010) Updates in the treatment of ocular allergies. J Asthma Allergy: 149. doi:10.2147/JAA.S13705

Sánchez Ferreiro AV, Muñoz Bellido L (2013) Tacrolimus in the treatment of atopic kerato-conjunctivitis. Arch Soc Esp Oftalmol 88:329–330. doi:10.1016/j.oftal.2012.09.023

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

Takamura E, Uchio E, Ebihara N et al (2011) Japanese guideline for allergic conjunctival diseases. Allergol Int 60:191–203. doi:10.2332/allergolint.11-RAI-0335

Tesse R, Spadavecchia L, Fanelli P et al (2010) Treatment of severe vernal keratoconjunctivitis with 1% topical cyclosporine in an Italian cohort of 197 children. Pediatr Allergy Immunol 21:330–335. doi:10.1111/j.1399-3038.2009.00948.x

Trocme SD, Sra KK (2002) Spectrum of ocular allergy. Curr Opin Allergy Clin Immunol 2:423–427

Trocmé SD, Kephart GM, Bourne WM et al (1993) Eosinophil granule major basic protein deposition in corneal ulcers associated with vernal keratoconjunctivitis. Am J Ophthalmol 115:640–643

Trocmé SD, Hallberg CK, Gill KS et al (1997) Effects of eosinophil granule proteins on human corneal epithelial cell viability and morphology. Invest Ophthalmol Vis Sci 38:593–599

Tuft SJ, Ramakrishnan M, Seal DV et al (1992) Role of *Staphylococcus aureus* in chronic allergic conjunctivitis. Ophthalmology 99:180–184

Udell IJ, Gleich GJ, Allansmith MR et al (1981) Eosinophil granule major basic protein and Charcot-Leyden crystal protein in human tears. Am J Ophthalmol 92:824–828

Westland T, de Bruin-Weller MS, Van der Lelij A (2013) Treatment of atopic keratoconjunctivitis in patients with atopic dermatitis: is ocular application of

tacrolimus an option? J Eur Acad Dermatol Venereol 27:1187–1189. doi:10.1111/jdv.12022

Wong AHC, Barg SSN, Leung AKC (2014) Seasonal and perennial allergic conjunctivitis. Recent Pat Inflamm Allergy Drug Discov 8:139–153

Zicari AM, Nebbioso M, Lollobrigida V et al (2013) Vernal keratoconjunctivitis: atopy and autoimmunity. Eur Rev Med Pharmacol Sci 17:1419–1423