



Atopic Keratoconjunctivitis: Pharmacotherapy for the Elderly

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Abstract

Among the different forms of allergic conjunctivitis, atopic keratoconjunctivitis has distinct characteristics, defined by a more common onset in late adolescence or early adulthood, but also affecting the elderly, and with a higher prevalence in male individuals. However, the prevalence of atopic keratoconjunctivitis is scarcely investigated, and the data are often uncertain because other allergic nasal or respiratory disorders occur concomitantly. Mast cells, eosinophils, basophils, and T cells are involved in the pathogenesis of atopic keratoconjunctivitis. Despite its denomination as atopic, negative responses to skin tests or in-vitro immunoglobulin E tests are common. In fact, atopic keratoconjunctivitis can be attributed to a combination of T-helper-1 and T-helper-2 responses, but a higher prominence for T-helper-1 cells was found. The most common symptoms of atopic keratoconjunctivitis are bilateral ocular itching, burning, and tearing with a perennial presentation, although some patients may have seasonal exacerbations in winter or summer. Other symptoms such as photophobia, blurred vision, and mucous chewy discharge, owing to the accumulation of cells and mucin, may occur. The diagnosis of atopic keratoconjunctivitis is mainly clinical, as accepted diagnostic criteria or laboratory tests are not available. The treatment of atopic keratoconjunctivitis is aimed at controlling symptoms, decreasing relapse and exacerbations, and reducing vision loss. Therapeutic options comprise topical ophthalmic drops, including cromones, antihistamines, corticosteroids, and calcineurin inhibitors. Topical ointments are also available for corticosteroids and calcineurin inhibitors. Severe forms may require systemic medications including antihistamines, corticosteroids, and calcineurin inhibitors. Atopic keratoconjunctivitis therapy in the elderly does not differ from the adult population, but the occurrence of multi-morbidities and concomitant drug treatment, which are common in this age group, requires a careful evaluation to determine appropriate and personalized treatment.

Key Points

Treatment of atopic keratoconjunctivitis in the elderly does not differ in a significant manner from the adult population, but a careful evaluation is required when systemic drugs such as oral corticosteroids or antihistamines are prescribed in the elderly because of their well-known side effects.

Second-generation antihistamines are preferred, while first-generation antihistamines should be avoided.

When assessing therapy in the elderly, drug–drug interactions and concomitant diseases should be considered.

1 Introduction

Atopic keratoconjunctivitis (AKC) is an allergic ocular manifestation, reported for the first time in 1952 in association with atopic dermatitis [1]. Allergic conjunctivitis includes seasonal allergic conjunctivitis, perennial allergic conjunctivitis, vernal keratoconjunctivitis, atopic blepharoconjunctivitis, giant papillary conjunctivitis, and AKC. In all these conditions, papillary conjunctivitis is a common feature and (except for giant papillary conjunctivitis) a type I hypersensitivity response [2]. Atopic keratoconjunctivitis is the most severe ocular presentation of an allergy, which may result in vision loss with an end-stage severe dry eye as a result of scarring [3].

Atopic keratoconjunctivitis usually begins in adolescence or at an adult age, with the peak of incidence between 30 and 50 years. However, the onset of symptoms of AKC has been described in people of all ages. There are more male than female individuals affected [1]. With aging, hypersensitivity reactions tend to diminish, while ocular complications such as chronic dry eye, visual loss

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as a result of corneal ulceration and scarring, and cataracts may develop. Furthermore, in the case of topical corticosteroid abuse, further complications including secondary glaucoma and even the risk for retinal detachment after cataract surgery have been reported [4].

There are scant data in the literature regarding the prevalence of AKC in the elderly: in fact, it is not uncommon for older patients to be underrepresented in randomized controlled trials because coexisting diseases and/or concomitant treatments are generally exclusion criteria. Moreover, AKC is usually concomitant with other allergic symptoms from nasal disorders. A survey conducted from 1988 to 1994 in USA evaluated the prevalence of ocular and nasal allergy in the general population, stratified by age groups. According to this analysis, the older age group (> 50 years) showed more frequently isolated ocular symptoms in contrast with the younger population (< 50 years) in whom combined ocular and nasal symptoms were more frequent. The higher frequency of isolated ocular symptoms in the elderly might be caused by age-related eye conditions such as dry eye syndrome [5].

Atopic keratoconjunctivitis is frequently associated with other atopic conditions: the most common being eczema (95%) and asthma (87%) [6], with allergic rhinoconjunctivitis, food hypersensitivity, and urticaria being less common [7]. Severe AKC has a peak incidence at between 30 and 50 years of age, and is seen in 40% of older patients [6], associated with complications such as blepharoconjunctivitis, cataract, corneal disease, and ocular herpes simplex [8–10].

2 Pathogenesis

The major cellular lines involved in the pathogenesis of AKC are mastocytes, eosinophils, basophils, and T lymphocytes [11–14]. A high level of serum total immunoglobulin E is a frequent finding in patients with AKC; however, many patients (45%) show negative responses to skin tests or in-vitro tests to common allergens. When skin or in-vitro tests are positive, sensitization to multiple allergens is more common than monosensitization [15]. Of interest, the model of the conjunctival provocation test, commonly used in allergic rhinitis, proved to be also useful in AKC, showing a typical immunoglobulin E-mediated reaction with a significant change in eye redness and chemosis after 10 min, paralleled by an increase in interferon- γ and interleukin (IL)-10 [16].

Atopic keratoconjunctivitis results from a combination of T-helper-1 and T-helper-2 responses, as shown by the elevated tear levels of interferon- γ , tumor necrosis factor- α , IL-2, IL-4, IL-5, and IL-10 [12–15, 17, 18]. Recently, an emerging role for IL-33 in allergic diseases was highlighted [19]. With regard to AKC, the crucial importance of IL-33

signaling was reported in the regulation of human vascular endothelial cells and the conjunctival epithelium in the giant papillae from patients with AKC, with an in-vitro demonstration of IL-33 contributing to IL-13 messenger RNA induction, ST2 expression, p38MAPK phosphorylation in human mast cells, and the production of pro-allergic cytokine thymic stromal lymphopoietin and chemokines in human corneal epithelial cells [20, 21]. The role of chemokines and their receptors in the pathogenesis of AKC has also been studied. Eotaxin and its receptor CCR3 were found in the tears and mucus of patients with AKC [22] and TARC/CCL17 and its receptors, CXCR4 and CCR4, have been observed to be highly expressed in giant papillae and to be related to levels of IL-4 and IL-13 [23]. In the same study, cultured human conjunctival fibroblasts expressed stromal cell derived factor-1 (CXCL12), which has proangiogenic effects and acts as a costimulatory factor for CD4+ T cells [23]. Similarly, macrophage migration inhibitory factor was found to be elevated in patients with severe AKC and atopic dermatitis [23, 24].

Eosinophils are elevated in the conjunctiva of patients with allergic eye disease [9, 20, 21], but in AKC, eosinophil activation is more relevant than the eosinophil absolute count [9, 10]. Activated eosinophils are able to release gelatinase B, major basic protein, and eosinophil cationic protein, which may lead to the corneal complications of AKC [9, 10]. All these findings suggest that the pathogenesis of AKC is the result of the stimulation of immature and mature leukocytes, which can produce enzymes and proteins that may cause the principal complications of AKC, such as corneal involvement and the formation of the giant papillae.

3 Symptoms and Signs

The most frequent symptoms of AKC are perennial bilateral ocular itching, burning, and tearing; other frequently reported symptoms are blurred vision and photophobia, and a mucous stringy discharge. While some patients report exacerbations in the winter season or in the summer months, others experience flare-ups following exposure to allergens such as dust mites or foods [25]. The clinical expression of signs and symptoms is related to localization in the eyelids, conjunctiva, and cornea.

3.1 Eyelids

Patients with AKC may present with severe eczema of the eyelids and periorbital skin, which is often complicated by chronic blepharitis and staphylococcal infection [6, 26]. When hyperpigmentation is present in association with eczema, this sign is known as “panda eyes” [12].

Dennie–Morgan lines, which are infraorbital linear lid creases secondary to edema and thickening of the lid, may also be seen in AKC. In older patients with severe forms of lid disease, de Hertoghe’s sign could be found: it consists of the absence of the lateral eyebrow and is frequently associated with lateral canthus fissures, caused by intense eye rubbing [10].

3.2 Conjunctiva

Atopic keratoconjunctivitis typically includes chronic inflammation of the conjunctiva, which is always bilateral, characterized by thickening and hyperemia [7, 17, 27]. Papillary hypertrophy affecting the upper and (more frequently) the lower tarsal conjunctiva is evident; cicatrizing conjunctivitis can produce subepithelial fibrosis and symblepharon [7], and the scarring can cause the shrinking of the fornices, especially the inferior fornix [25]. Limbal Horner–Trantas dots, associated with evanescent white cellular infiltrates, although rare, may occur transiently during exacerbations [6, 12, 27–29]. The pre-corneal tear film is reduced in volume and thus the bulbar conjunctiva may show changes similar to those seen in keratoconjunctivitis sicca [25].

3.3 Cornea

Corneal complications can develop during or after repeated exacerbations of blepharoconjunctivitis, and recurrent inflammation can lead to the development of persistent epithelial defects. An early sign of corneal involvement is punctate keratitis. Patients with AKC can also develop corneal ulceration, induced by superimposed microbial infections or recurrent severe herpes simplex keratitis [30], which can be very difficult to manage, especially in patients treated with long-term topical corticosteroids. Keratoconus may also occur in patients with AKC, further exacerbated by chronic eye rubbing in response to irritated eyes; in these patients, keratoconus has been associated with a positive skin prick test to environmental allergens [17]. Multiple episodes of inflammation/infection can cause corneal neovascularization (progressive corneal sclerosis) along with pannus formation affecting the superior third of the cornea, which is usually associated with thinning of the cornea. This phenomenon can produce marked astigmatic changes and severe and permanent visual impairment [25].

3.4 Other Complications

Other complications of AKC include retinal detachment [31], probably caused by degeneration of the vitreous [25], and anterior and posterior subcapsular cataracts, the latter

associated with the use of oral or topical corticosteroids [6, 32].

4 Diagnosis

There are no established diagnostic criteria or laboratory tests for AKC. The ultimate diagnosis is clinical, based on the characteristic signs and symptoms. All patients with suspected AKC, regardless of severity, should be referred to an ophthalmologist and undergo a thorough slit-lamp examination of the cornea, bulbar, and palpebral conjunctiva. Other current methods to assess the ocular surface inflammation status include flow cytometry, conjunctival brush cytology, biopsy, and confocal scanning laser microscopy [33]. With regard to allergy testing to identify the causative allergen(s), it must be considered that a positive test frequently indicates sensitization, which does not necessarily involve a clinical allergy [34].

5 Treatment

The purpose of AKC treatment is to control the symptoms, decrease the recurrence and exacerbations of the disease, and reduce vision loss. The potential for drug interactions increases with age and with the number of drugs prescribed [35]. It is common knowledge that the most important mechanisms involved in drug–drug interactions are pharmacodynamic antagonization or the potentiation and influence on drug metabolism. In older people, reduced renal function, liver impairment, and decreased homeostatic mechanisms play an important role in making these patients more sensitive to the combined postural hypotensive or sedative effects of drugs [36].

Treatment options for AKC include topical medications and systemic drugs. The most commonly used topical medications are ophthalmic drops, such as mast cell stabilizers, antihistamines, corticosteroids, and calcineurin inhibitors, and topical ointments of corticosteroids and calcineurin inhibitors.

5.1 Mast Cell Stabilizers

Cromones have been used as mast cell stabilizers for a long time. However, because of the delayed effect, they may be used only as agents for prevention and not for the treatment of acute symptoms. In addition, the pharmacokinetics of cromones requires frequent daily administration, which may result in low compliance, particularly in elderly patients. If topical medications fail to be effective, systemic medications

can be prescribed; these include antihistamines, corticosteroids, and calcineurin inhibitors [6, 12, 17]. As a general rule, the use of topical treatments might prevent major adverse effects. First-line treatment for AKC is based on topical, mast cell stabilizer ophthalmic drops (cromoglycate and lodoxamide 0.1%), which prevent the release of histamine and other proinflammatory mediators from mast cells in ocular tissues [3]. If a single-acting agent fails, dual-acting agents (olopatadine, ketotifen, azelastine, epinastine, and bepotastine) can be effective; these drugs have both mast cell-stabilizing and H1 receptor-blocking effects [37]. Topical and oral antihistamine use is aimed at the symptomatic relief of pruritus, which is principally mediated by H1 stimulation [6, 12].

5.2 Antihistamines

H1 antihistamines are classified as first and second generation. First-generation H1 receptor antagonists can cross the blood–brain barrier, causing sedation and impaired mental status [38]; their effect on cholinergic or alpha-adrenoreceptors can also cause, particularly in the elderly, urinary symptoms such as urinary hesitancy or retention, constipation, as well as cardiovascular manifestations including arrhythmias, peripheral vasodilatation, and postural hypotension [39]. Furthermore, first-generation H1 receptor antagonists are less specific for the H1 receptor. Considering these findings, first-generation antihistamines should be prescribed with extreme caution in older patients. Second-generation antihistamines are generally not concerned by such adverse effects. Some are metabolized by the cytochrome P450 (CYP) enzyme system in their first pass through the liver, others are excreted unchanged through the kidneys; thus, the former may require a dose reduction in patients with hepatic dysfunction, the latter may instead require a dose reduction in patients with renal dysfunction [40].

Second-generation antihistamines include astemizole, terfenadin, cetirizin, loratadin, ebastine, mizolastin, bepotastin, rupatadine, and bilastine. The more recently introduced are bepotastin and rupatadine (both in the late 1990s) and bilastine (in 2014). Bilastine is a potent and specific second-generation H1 antihistamine that belongs to the piperidine derivatives. It is not metabolized by the hepatic CYP and it is excreted largely unaltered (99.5%) in the urine and feces; it has also limited central nervous system adverse effects owing to its fractional penetration of the blood–brain barrier. The efficacy of bilastine in the treatment of allergic rhinitis has been shown in several large controlled clinical trials [41]. A review of the literature in 2012 highlighted that bilastine 20 mg once daily improved not only nasal but also ocular symptoms of allergic rhinitis and improved quality of life, thus meeting the current Allergic Rhinitis and its

Impact of Asthma-European Academy of Allergology and Clinical Immunology criteria for drugs used in the treatment of allergic rhinitis [42]. Sologuren et al. in 2013 performed a 3-month follow-up aimed at assessing the safety profile of bilastine in patients aged ≥ 65 years, enrolling a total of 151 patients with a mean age of 74.8 ± 6.6 years. The incidence of treatment-emergent adverse events was low, and all serious treatment-emergent adverse events were considered to be unrelated to bilastine; of the related treatment-emergent adverse events, only somnolence was reported by more than one patient. These results were in accordance with the adverse-event incidence reported in previous studies, thus confirming the known safety profile of bilastine 20 mg [43].

Rupatadine is a selective and powerful high-affinity inverse agonist of the H1 receptor, which, unlike other antihistamines, has the ability to interact with the platelet-activating factor, providing also anti-inflammatory effects. Rupatadine has proved to be very effective in the reduction of ocular and nasal symptoms. As it is metabolized mainly by CYP3A4, co-administration of rupatadine with moderate CYP3A4 inhibitors (such as amiodarone, verapamil, and diltiazem) should be carefully evaluated, while concomitant administration with potent CYP3A4 drug inhibitors (such as macrolides and protease inhibitors) should be avoided [44].

Oral bepotastine was found to have, beyond the anti-histamine action, the ability to suppress some allergic inflammatory processes such as eosinophil recruitment and vascular hyperpermeability, and to be well tolerated [45], but currently is preferred for topical use. Several other topical antihistamines are available, as shown in Table 1. They are seldom concerned by side effects; however, there is no clear evidence of efficacy in AKC [3, 12]. The use of cold compresses in combination with ophthalmic antihistamines was recently reported to enhance the effectiveness of traditional pharmacological therapy [46].

5.3 Corticosteroids

For patients who do not respond to 2 or 3 weeks of therapy with a mast cell stabilizer/antihistamine, pulse therapy with topical corticosteroids is considered appropriate [12]. Although corticosteroids are more effective than cromones and antihistamines in controlling AKC, long-term use of topical corticosteroids increases the risk of serious eye infections (e.g., herpes keratitis), cataract formation, ocular hypertension, and glaucoma [12, 16, 47].

Systemic corticosteroids are sometimes used in severe cases of AKC when topical corticosteroids are ineffective or required for a period longer than 6 weeks [3]. Corticosteroid adverse effects concern many organs and systems, and could range from mild (e.g., Cushingoid appearance) to life-threatening events (e.g., severe infections) [48]. Some of these adverse effects may be worse in older

Table 1 Topical medications

Topical mast cell stabilizers	Topical antihistamines	Topical antihistamines/mast cell stabilizers	Topical corticosteroids	Topical calcineurin inhibitors
Cromolyn sodium Lodoxamide	Levocabastine hydrochloride Pheniramine maleate	Olopatadine Alcaftadine Bepotastine Azelastine Epinastine Ketotifen Emedastine	For mild-to moderate symptoms Loteprednol 0.5 or 0.2% ^a Prednisolone acetate 0.12% Fluorometholone 0.10% ^a Hydrocortisone sodium phosphate 3.35 mg/mL Rimexolone 1% ^a For severe symptoms Prednisolone acetate 1%	Tacrolimus 0.03 or 0.1% Cyclosporine 0.05% solution

^aMore satisfactory safety profile

people. Patients receiving prednisolone 5–40 mg/day for at least 1 year can manifest partial loss of explicit memory, and elderly patients may be more susceptible to memory impairment even with less protracted treatment [49]. The risk of developing diabetes mellitus is increased in elderly patients who are newly treated with oral corticosteroid therapy [50]. Other common conditions of old age, such as cataracts [51] and osteoporosis [52] have also been linked to the use of systemic corticosteroids. Moreover, glucocorticoid effects on the central nervous system are well known and vary from depression to delirium, mania, and psychosis. Neuropsychiatric complications are more likely at doses higher than the equivalent of 40 mg of prednisolone per day [53, 54].

Although these effects are usually reversible at the decrease or withdrawal of the drug, the use of systemic corticosteroids should be carefully evaluated in elderly patients with prior cognitive impairment. If corticosteroids are ineffective or adverse effects preclude their use, calcineurin inhibitors can be used [3].

5.4 Calcineurin Inhibitors

When antigen-presenting cells interact with T-cell receptors, calcineurin is activated; activated calcineurin then induces nuclear factor of activated T cells, which up-regulates the expression of IL-2. Cyclosporine A and tacrolimus block the effects of calcineurin, decreasing IL-2 production [12, 46]. Immunosuppressive therapy is indicated to control ocular inflammation when corticosteroids are ineffective, to prevent long-term corticosteroid side effects, and to achieve control in severe forms of AKC at high risk for complications. Cyclosporine A, a cyclic polypeptide of fungal origin, is commercially available as a 0.05% emulsion (Restasis; Allergan, Irvine, CA, USA) [55]. At higher doses (1% or 2%), cyclosporine can cause adverse effects including stinging and irritation [56, 57]. Trial data are limited: in a small

randomized trial, topical cyclosporine (2% four times daily) proved to be more effective than placebo in improving signs and symptoms in patients with AKC and in reducing the need for topical corticosteroids [58].

Tacrolimus, a competitive calcineurin inhibitor and macrolide antibiotic isolated from soil fungus *Streptomyces tsukubaensis*, is available as 0.03% and 0.1% topical ointments (Protopic; Astellas, Toyama, Japan) [46, 59]. Compared with cyclosporine, tacrolimus is a more potent inhibitor of immunoglobulin E-mediated enzyme release and has a more global immunosuppressive effect [46]. In a case series, continuous therapy with topical tacrolimus led to significant improvement in patients with severe AKC. No adverse effect was noted for 2 months to 2 years of continuous therapy [60].

Three small case series found that long-term therapy with oral calcineurin inhibitors (cyclosporine 3–5 mg/kg daily or tacrolimus 0.03–0.08 mg/kg daily) was generally safe and resulted in complete remission in most patients with severe refractory disease [61, 62]. No studies are currently available on the use of these drugs in the elderly population.

5.5 Immunomodulatory Therapy

A recent retrospective analysis of 13 patients affected by severe AKC and presenting with ocular surface disease compared the outcomes of medical intervention with immunomodulatory therapy to that of surgical treatments. Immunomodulatory therapy was exclusively topical in four cases and systemic in one case (oral cyclosporine associated with topical corticosteroids). Patients treated only with medical therapy experienced a decline in visual acuity, while stable-to-improved vision was achieved in the group of patients who underwent a surgical intervention. The authors suggested that immunomodulatory therapy is a valuable tool in the early stages of the disease, but when the ocular surface is compromised surgical intervention may be required. This

means immunomodulatory therapy should be commenced at the early stages of the disease, particularly prior to limbal stem cell deficiency [63].

Disease-modifying anti-rheumatic drugs, such as methotrexate, mycophenolate mophetil, and azathioprine play a well-established role in the treatment of rheumatologic diseases. Disease-modifying anti-rheumatic drugs also play a role in the treatment of ocular inflammation: mycophenolate mophetil has proven to be effective in inducing complete and sustained control of ocular inflammation and to have a valuable corticosteroid-sparing effect [64].

Methotrexate added to an anti-inflammatory regimen has shown a moderate efficacy in disease control and corticosteroid-sparing effect after many months of treatment [65]. Methotrexate is generally well tolerated and carries a small risk of serious side effects. Azathioprine has also demonstrated some efficacy in patients with active ocular inflammation, although the success was modest and after several months of treatment. Side effects, including the well-known gastrointestinal discomfort, are reversible with discontinuation [66].

A study compared the ability to control ocular inflammation and to allow corticosteroid tapering, as well as the incidence of side effects in three groups of patients undergoing immunomodulatory therapy with methotrexate, mycophenolate mophetil, and azathioprine. Mycophenolate mophetil achieved control of ocular inflammation faster than methotrexate, while it was superior to azathioprine regarding the side-effect profile [67].

The effect of antimetabolite drugs on various types of non-infectious ocular inflammations, uveitis, and scleritis above all suggests a possible role for these drugs also in AKC. However, even though antimetabolites have been safely employed for decades in other fields (such as rheumatology), their use can result in systemic side reactions, ranging from gastrointestinal intolerance to hepatotoxicity, cytopenias, bone marrow suppression, and interstitial pneumonia, all of which are reversible by dose reduction or cessation [68]. Table 2 provides the step-up approach for AKC.

5.6 Non-Pharmacological Treatment

Among non-pharmacological treatments, the use of cold compresses in combination with ophthalmic antihistamines to enhance their effectiveness was already mentioned in Sect. 5.2. Another non-pharmacological treatment is based on preservative-free artificial tears that were found to be effective in providing lubrication and diluting inflammatory mediators in the tear film [46].

Table 2 Management of atopic keratoconjunctivitis

Step 1	Step 2	Step 3	Step 4	Step 5
Topical mast cell stabilizer ophthalmic drops (cromoglycate and lodoxamide)	Topical dual-acting agents with both mast cell-stabilizing effects and H1 receptor-blocking effects (olopatadin, ketotifen, azelastine, epinastine, bepotastine)	Topical corticosteroids (loteprednol, fluorometholone, hydrocortisone sodium phosphate, rimexolone, prednisolone acetate)	Topical calcineurin inhibitors (cyclosporine, tacrolimus)	Systemic immunosuppressive agents (prednisone, cyclosporine, tacrolimus); immunomodulatory therapy (methotrexate, mycophenolate, azathioprine)

Topical antihistamine drops and oral antihistamines can be used in conjunction with other treatments in the management of atopic keratoconjunctivitis to relieve pruritus, which is principally mediated by H1 stimulation

6 Conclusion

Atopic keratoconjunctivitis therapy in the elderly does not differ significantly from the application in adult populations, but multi-morbidities and polypharmacy, typical in this age group, require a careful evaluation to assess a correct and personalized treatment. Of all the drugs used for the treatment of AKC, those with the most common and severe adverse effects on the older population are systemic corticosteroids, while first-generation H1 antihistamines usually have mild-to-moderate adverse effects. A study to define the safety and tolerability profile of these treatments in people aged ≥ 65 years, with or without comorbidity, particularly receiving polytherapy, could be of relevant utility.

Compliance with Ethical Standards

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