Topical immunomodulators in the management of allergic eye diseases

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Purpose of review
Allergic eye diseases comprise a spectrum of diseases, with each condition being characterized by a complex immunopathology. The more severe and chronic conditions, such as vernal keratoconjunctivitis and atopic keratoconjunctivitis, involve predominantly mast cells and eosinophils, while also being associated with a preponderance of T cells. Treatment with topical antihistamines or mast cell stabilizers is often unsatisfactory, and therapy depends on topical corticosteroids. Corticosteroids have significant side-effects with long-term use; therefore, they appear to be more appropriate for short-term pulse therapy. Immunomodulatory agents can also be used to inhibit T-cell activation and show encouraging results among patients with severe allergic eye conditions. The present review is an attempt to present a coherent picture of the recent investigations of topical immunomodulatory agents' therapy in severe allergic eye diseases, especially cyclosporine A and tacrolimus, and their mechanisms of action.

Recent findings
Immunomodulatory agents are commonly indicated for the treatment of severe and prolonged allergic conjunctivitis. This article reviews the recent studies of these drugs and the development of immunomodulatory treatments for severe allergic eye diseases.

Summary
Cyclosporine A and tacrolimus are currently available for the treatment of severe allergic conjunctivitis. These agents have led to improved therapeutic results for patients with severe and chronic allergic eye diseases.

Keywords
allergic eye diseases, cyclosporine A, immunomodulators, tacrolimus

INTRODUCTION

Ocular allergy refers to a variety of hypersensitivity disorders that affect the entire ocular surface including the conjunctiva, lids, cornea, lacrimal glands, and tear film, with an estimated prevalence of 20% worldwide and within the United States [1,2]. The external eye is exposed to a host of environmental, cosmetic, and pharmacological antigens. Although individual responses show a wide range of variability, a number of distinctive syndromes have emerged to more precisely define the spectrum of allergic eye disease. The symptoms consist of seasonal allergic conjunctivitis (SAC) and perennial allergic conjunctivitis (PAC), both of which are the most common, as well as atopic keratoconjunctivitis (AKC), vernal keratoconjunctivitis (VKC), contact-lens-associated acute allergic conjunctivitis (AAC), and giant papillary conjunctivitis (GPC) involving the ocular surface [2,3]. The treatment of allergic eye diseases includes mast cell stabilizers, topical antihistamines, NSAIDs, topical ophthalmic corticosteroids, and other topical immunomodulatory ophthalmic agents such as cyclosporine A and tacrolimus [3–6].

TREATMENT OF ALLERGIC EYE DISEASES

Treatment for allergic eye diseases has markedly expanded in recent years, providing a wide range of treatments mostly based on topical application. Eye drops containing antihistamines, mast cell stabilizers, and NSAIDs agents are generally preferred as the first-choice treatment.

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Curr Opin Allergy Clin Immunol 2014, 14:457–463
DOI:10.1097/ACI.0000000000000089

KEY POINTS

- Two immunomodulatory agents cyclosporine A and tacrolimus are well tolerated and effective topical treatment modalities for the management of severe VKC and AKC.
- Tacrolimus is a useful agent in the treatment of a wide range of severe allergic eye diseases and specifically for patients with refractory VKC. In addition to the symptomatic relief, it has the ability to resolve giant papillae in VKC.
- Topical tacrolimus is more effective than topical cyclosporine A and well tolerated than corticosteroids in the management of most of the allergic eye diseases.

Topical antihistamines are effective in reducing the symptoms and signs of allergic eye diseases. Mast cell stabilizers, such as chromoglicate, and the new generation of antiallergy compounds, such as olopatadine, tromethamine, and spaglumic acid, are effective in reducing the tryptase levels and decrease the recruitment of inflammatory cells after allergen challenge [7,8]. NSAIDs agents also produce a beneficial effect on the signs and symptoms of allergic eye diseases [9]. Treatment with topical antihistamines, mast cell stabilizers, and NSAIDs is often unsatisfactory, and current therapy depends on topical corticosteroids, which remain the mainstay of treatment for severe allergic eye conditions. Corticosteroids provide effective therapy for moderate-to-severe forms of allergic eye diseases, and produce dramatic improvement in the diseases' acute symptoms and signs [10]. However, their use should be strictly limited and carefully monitored because long-term use of topical corticosteroids may result in several significant side-effects and complications, such as formation of posterior subcapsular cataracts [11], glaucoma (a 2% incidence of glaucoma has been found in VKC patients [10]), and secondary infections such as bacterial or fungal infections following prolonged steroid exposure [10]. As an alternative to steroids and to avoid steroid-related complications, immunomodulatory agents can also be used to control allergic eye disease. Although immunomodulatory agents do not demonstrate the rapid effect of steroids, they carry fewer risks and are safer for prolonged treatment.

IMMUNOMODULATORY AGENTS AND THEIR MECHANISMS OF ACTION

The immunomodulatory drugs are a novel class of orally available agents and have a broad range of biological effects, with applications and use in several fields of medicine. Their immunomodulatory mechanisms of action are based primarily on creating immunosuppressive activity by inhibiting T-cell activation. This action is possible by the drug binding to the intracellular receptor protein cyclophilin-1, which blocks the dephosphorylation and activation of the main transcription factor of activated T-cells (NF-AT) [12,13]. As a result, a distinct and main proinflammatory cytokine signature is not expressed, including interleukin (IL)-2, IL-4, IL-5, IL-6, IL-8, IL-13, tumor necrosis factor-α, and interferon-γ, as NF-AT is responsible for the regulation of their production [14–16]. NF-AT also interacts with several transcription factors that play a role in immunosuppressive activity, along with the homeostasis of cells involved in the innate immune response, and therefore blocking NF-AT causes an effect on the innate immune response, and further interferes in the allergic process. The systemic responses include reducing the histamine release induced by anti-IgE and leukotriene synthesis in basophils [17]; a reduction in degranulation, cytokine secretion, chemotaxis and longevity in eosinophils, which have been studied in dogs with atopic dermatitis [18,19]; reducing both the number and activity of antigen-presenting cells [20]; reducing histamine release; inhibiting mast cell cytokine production and intercellular adhesion molecule-1 (ICAM-1) in mast cells [21,22]; a reduction in adhesion molecule expression; and the inhibition of the activity of granulocyte-macrophage colony-stimulating factor (GM-CSF) in endothelial cells [23].

IMMUNOMODULATORY AGENTS FOR ALLERGIC EYE DISEASES

Antiallergic drug (antihistamine and mast cell stabilizers) therapy is often insufficient without concomitant steroid use. Although the disease course of the severe allergic eye diseases, such as VKC and AKC is chronic, the use of corticosteroids is limited to short courses. Topical corticosteroids put patients at high risk of developing severe ocular complications, particularly during childhood when VKC most frequently occurs. Immunomodulatory agents are another therapeutic option. The immunopathology of chronic diseases, such as VKC and AKC, involves predominantly T lymphocytes, and therefore the immunomodulatory agents that inhibit T-cell activation seem to be the appropriate treatment for chronic allergic eye diseases. Immunomodulatory treatments that have been used and investigated for severe allergic eye diseases in the form of VKC and AKC are topical ocular preparations of cyclosporine

A and tacrolimus. Both cyclosporine A and tacrolimus are topical immunomodulatory ophthalmic agents which achieve breakthrough results in the treatment of severe allergic eye diseases, and are considered well tolerated with negligible side-effects.

Cyclosporine A

Cyclosporine A is a powerful immunosuppressive and immunomodulatory drug which is used in transplantation medicine and to treat autoimmune diseases. It is a lipophilic molecule and is isolated from the fungus *Beauveria nivea*. It was first used to prevent rejection of transplanted organs and later for the treatment of atopic dermatitis. In ophthalmology, cyclosporine A has been used as an ophthalmic emulsion (0.05% cyclosporine A) and has been a prescription drug in the USA since April 2003 for the treatment of dry eye syndrome [13,14,18,24,25]. In 1986, BenEzra *et al.* [26] first reported on the use and potential efficacy of cyclosporine A for the treatment of VKC. In a pilot study, 11 of 12 VKC patients showed improvement in the first week after starting treatment. However, results at the 2-month follow-up were not promising as only three patients remained free of disease, whereas the rest of the patients showed recurrence of symptoms.

A low concentration of 0.05% cyclosporine A was shown to be effective in patients with VKC and AKC. Ebihara *et al.* [27] evaluated the effectiveness and safety of low-concentration cyclosporine A (0.1%) aqueous ophthalmic solution in 594 patients with VKC and AKC. This study reported that topical 0.1% cyclosporine A is effective for the treatment of severe VKC and AKC, and can be used safely. In addition, a study with lower concentrations of 0.05% cyclosporine A was also performed and showed that 0.05% cyclosporine A was also effective in AKC patients compared with a placebo in a randomized controlled trial. Akpek *et al.* [28] compared 0.05% cyclosporine A to preservative-free artificial tears in 22 patients with severe AKC. The study found that topical cyclosporine A had a beneficial effect in controlling the symptoms and signs without adverse side-effects. Another two studies examined cyclosporine A in lower concentrations to assess the effectiveness. The first study [29] examined 54 patients with severe VKC, and the second study [30] examined 6 patients with severe VKC and 1 patient with severe AKC. Both studies found that topical 0.05% cyclosporine A is well tolerated and an effective treatment in the management of severe VKC and AKC.

However, contradictory results have been found in other studies using lower concentrations of cyclosporine A. This agent was not shown to be of any benefit over a placebo in a randomized placebo-controlled study. In the study by Daniell *et al.* [31], a comparison of 0.05% cyclosporine A to a placebo (vehicle) was studied in 18 patients with AKC and 22 patients with VKC, with no difference between the two treatments.

A prospective, randomized cross-over study [32] was conducted in VKC patients using 0.5% topical cyclosporine A, showing that the drug reduces the symptoms and signs slower than preservative-free 0.5% ketorolac tromethamine.

Moderate-to high concentrations of cyclosporine A were examined in 22 patients with severe VKC in a double-blind, placebo-controlled study. The patients received cyclosporine A in concentrations of 1.00 and 1.25%. The mean objective signs and symptoms were decreased, and the study results suggest that 1% cyclosporine A is probably the minimal effective concentration in treating severe forms of VKC [33].

Several studies evaluated cyclosporine A in relatively higher concentrations, and all of them found that 2% cyclosporine A concentration was very effective for the treatment of severe forms of VKC and AKC. In a small sample size study [34] of 12 patients treated with 2% cyclosporine A, 11 patients showed symptomatic improvement after 1 week of treatment, whereas only 3 patients in the placebo group showed mild symptomatic improvement. In a placebo-controlled, double-masked clinical trial study [35], topical 2% cyclosporine A was found to be well tolerated and effective for a short-term treatment of 20 patients with VKC.

Secchi *et al.* [36] treated 11 patients with VKC with topical cyclosporine in a 2% dilution in castor oil. They showed that both symptoms and signs of the VKC improved significantly. Pucci *et al.* [37,38] conducted two studies in severe VKC patients with cyclosporine A eye drops treatment, either at 1 or 2% concentrations, and found that it resulted in a well tolerated and effective drug for the long-term treatment of VKC. A double-masked study of De Smedt *et al.* [39] reported effective results of 2% cyclosporine A treatment in a prospective, double-masked, clinical trial including 366 VKC patients.

Regarding the side-effects, a high concentration of 2% cyclosporine A does not cause significant side-effects, except for mild and transient burning sensations upon administration, whereas moderate concentrations of 1% and 1.25 still cause mild ocular burning sensation. In lower concentrations of 0.05 and 0.1%, there were no adverse reactions observed [27,28,32,34–36,39].

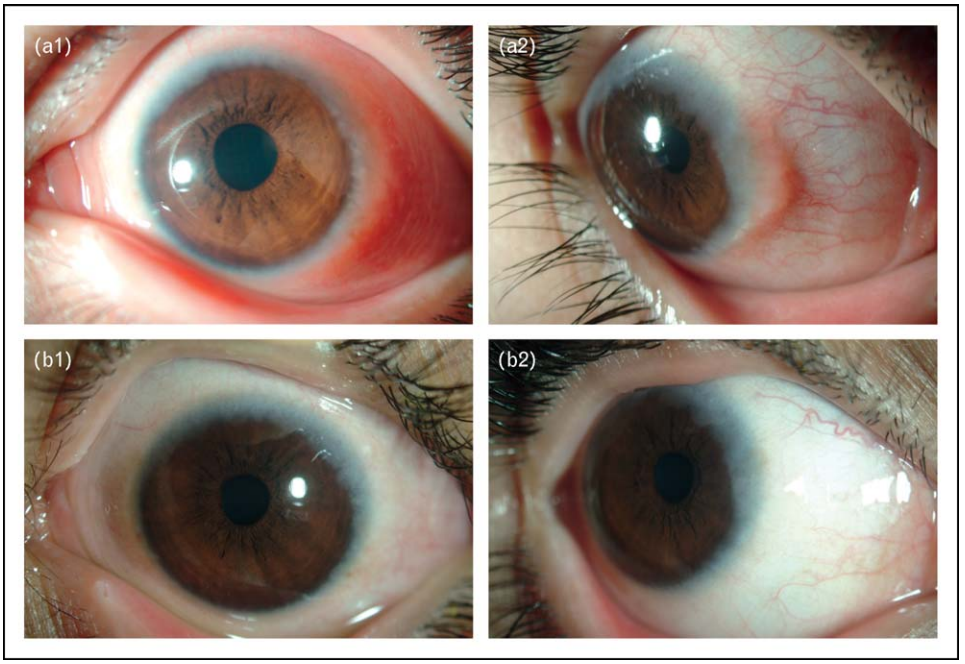

FIGURE 1. External photographs of an 11-year-old girl with severe VKC at baseline (a1 and a2) and after 4 weeks of treatment with topical 0.03% tacrolimus cream (b1 and b2). Note the complete resolution of the limbal hypertrophy following treatment with topical tacrolimus. VKC, vernal keratoconjunctivitis. Reproduced by courtesy of Abraham Solomon, MD, Department of Ophthalmology, Hadassah-Hebrew University Medical Center, Jerusalem, Israel.

Tacrolimus

Tacrolimus is a macrolide immunomodulatory agent (previously known as FK506), which is similar to cyclosporine A in its functional mechanism, but with about 100-fold higher potency [40]. Tacrolimus binds to steroid receptors on the cell surface, inhibiting the release of mediators from mast cells, suppressing T-cell activation, and T-helper-cell-mediated B-cell proliferation. In addition, it also causes a decrease in intracellular adhesion molecules and reduced formation of cytokines, especially interleukin-2 [41–49].

Tacrolimus is produced by the fermentation of *Streptomyces tsukubaensis*. It has been used and studied in Sjogren's syndrome, bone marrow transplant, atopic dermatitis, and hepatic and renal transplantation [41–47,50]. Until now, there have been no commercially available ophthalmic drug formulations for tacrolimus, and only topical tacrolimus dermatologic formulations are used, mainly at concentrations of 0.03–0.1% in managing VKC and AKC.

A very low concentration of tacrolimus was examined in a long-term effect study (6 months of follow-up after the treatment). Concentration of 0.005% tacrolimus treatment has been studied by Kheirkhah *et al.* [51] in 10 patients with refractory VKC. The study showed that 0.005% tacrolimus is a well tolerated and effective treatment for steroid-resistant refractory VKC.

Several studies, as well as the experience of the authors of this review (Fig. 1), have shown that 0.03% tacrolimus ointment with once-daily treatment, is effective, well tolerated, and safe in the treatment of severe atopic eyelid disease [52], and led to clinical and cytological improvement in atopic blepharoconjunctivitis [53] and in VKC and AKC patients [54–56].

Several recent studies have reported that a low concentration of tacrolimus treatment has improved the symptoms and signs of giant papillae related to VKC and AKC. Kymionis *et al.* [57] reported that twice-a-day treatment with 0.03% tacrolimus ointment resulted in the resolution of severe giant papillae due to VKC within 2 weeks. In another study [58], 0.02% topical tacrolimus ointment resolved giant papillae due to AKC and VKC. Ohashi *et al.* [59] also found that a 0.1% tacrolimus ophthalmic suspension is effective in treating severe allergic conjunctivitis, with significant improvement of the giant papillae found after 4 weeks of treatment, and was well tolerated by the patients. The ability of tacrolimus to resolve and manage giant papillae due to VKC and AKC is an advantage over cyclosporine A, as patients suffering from tarsal VKC with giant papillae were found to be less responsive to cyclosporine A treatment compared with patient suffering from limbal VKC [36,37].

Utilizing tacrolimus at a high concentration with a variable follow-up period after treatment was examined in several studies. A phase I trial in 10 VKC patients who failed to respond to conventional VKC treatment, including cyclosporine A, reported effective results with 0.1% tacrolimus treatment without any significant side-effects [60]. In a multicenter, randomized, double-masked, placebo-controlled study, 56 patients with severe allergic conjunctivitis were treated with 0.1% tacrolimus. The study concluded that tacrolimus treatment was found to be effective in improving the objective clinical signs and subjective symptoms of severe allergic conjunctivitis, including giant papillae. Yet, mild irritation upon topical instillation was observed in almost half of the patients. A long-term follow-up study evaluated 0.1% tacrolimus treatment in 11 patients for a period of 48 months. In that study, 0.1% tacrolimus was well tolerated and effective; yet, all of the patients complained of a mild burning sensation [61▪]. A retrospective study [62▪] of 30 patients with VKC treated with 0.1% tacrolimus found that 4 cases worsened in their condition, but infections of the anterior segment were not found. A study which estimated the safety and efficacy of 0.1% tacrolimus ophthalmic solution found that the maximum blood concentration was less than 2 ng/ml. These values were used to set the tacrolimus safety profile, and coupled with its demonstrated efficacy, turned it into an important topical treatment for severe VKC and AKC [63].

Labcharoenwongs *et al.* [64] examined the efficacy of tacrolimus compared to cyclosporine A in a prospective, double-masked, randomized comparative study. Twenty-four VKC patients received 0.1% tacrolimus eye ointment twice-daily for 8 weeks, and the other received 2% cyclosporine A eye drops for the same duration. The study reported that tacrolimus treatment brought about an improvement of the signs and symptoms of VKC similar to that of cyclosporine A treatment. In addition, this study concluded that cyclosporine A treatment was related to a burning sensation and pain on application, compared with a transient burning sensation which was detected in patients with tacrolimus treatment. Objective ocular signs were found to be more improved with tacrolimus treatment, even though this was not statistically significant.

DEVELOPMENT OF NOVEL IMMUNOMODULATORS

The cornea is a multilayered tissue, and the epithelium acts as a barrier to hydrophilic drug transport through intercellular spaces. On the other hand, the stroma, containing aqueous, which allows hydrophilic drugs to easily pass through, acts as a significant barrier for lipophilic drugs. As immunomodulatory drugs have a lipophilic nature and low water solubility, new novel drug delivery strategies are required to enhance the immunomodulators' delivery to the appropriate area, allow effective treatment, and achieve patient compliant therapies. Several drug delivery system strategies such as liposomes, nanoparticles, and nanomicelles have been studied in the delivery of the rapamycin immunomodulator. A formulation of rapamycin was prepared with amphiphilic block co-polymer micelles of poly(ethylene glycol)-b-poly(epsilon-caprolactone) (PEG-PCL). This allowed slowing the release of rapamycin from PEG-PCL micelles with combination of alpha-tocopherol and serum albumin [65]. Other immunomodulatory agents that may inhibit the allergic response are based on the specific DNA sequences (immunostimulatory DNA sequences or C-phosphate-G motifs), which inhibit a Th2 response and stimulate a de-novo Th1 response [66].

The use of topical antibodies against specific mediators in ocular allergy was also investigated. Ono and Abelson [67] reported that neutralization of the chemokine eotaxin 1 using the humanized antieotaxin antibody can inhibit the activation of human conjunctival mast cells.

In addition to exploring a new drug delivery strategy, practical use of advanced bioconjugate chemistry, polymer science, polypharmacology and high-throughput peptide synthesis will enable development of novel immunomodulatory agents in the future.

CONCLUSION

The two main topical immunomodulators currently used to treat allergic eye diseases are cyclosporine A and tacrolimus. Most studies found that topical 2% cyclosporine A was comparable to the topical corticosteroids, and caused significantly decreased symptoms and signs in a variety of allergic eye diseases.

Topical 0.1% tacrolimus is an effective treatment for patients with allergic eye diseases such as VKC and AKC, and treatment with tacrolimus also has the ability to resolve and manage giant papillae due to VKC and AKC. Initial evidence show that tacrolimus is more effective than cyclosporine A and is more tolerable. However, future studies with larger sample sizes will hopefully shed more light on the differences in the safety and efficacy of topical cyclosporine A and tacrolimus agents.

Acknowledgements

N.E. is grateful to the Azrieli Foundation for the award of an Azrieli Fellowship.

The authors would like to thank Michelle Grunin for critical reading of this article.

Conflicts of interest

There are no conflicts of interest.

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- ■■ of outstanding interest

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