REVIEW

Topical tacrolimus for allergic eye diseases

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Purpose of review
The spectrum of allergic eye diseases includes a variety of conditions, each characterized by complex immunopathologies.
Antiallergic drugs, such as antihistamines and mast cell stabilizers, are often insufficient without concomitant topical corticosteroid treatment. The chronic course of the more severe allergic eye diseases, such as vernal keratoconjunctivitis (VKC) and atopic keratoconjunctivitis (AKC), limits the treatment with topical corticosteroids to short courses. In addition, topical corticosteroid treatment puts patients at high risk of developing severe ocular complications, particularly during childhood when VKC most frequently occurs. The immunopathology of chronic diseases, such as VKC and AKC, involves predominantly T lymphocytes, and as such, immunomodulators that inhibit T-cell activation seem to be the appropriate treatment for these chronic diseases. In the past years, there is an increased incidence of managing chronic allergic eye diseases with the immunomodulator tacrolimus. The current review presents an update of the recent clinical experience with topical tacrolimus for the management of chronic allergic eye diseases.

Recent findings
Topical tacrolimus significantly improves the symptoms and signs of the various forms of chronic allergic eye disease. Recent studies also demonstrate the efficacy of low concentrations of topical tacrolimus for VKC.
Early medical treatment with topical tacrolimus can also prevent the development of serious ocular complications of VKC, such as shield ulcers or limbal stem cell deficiency.

Summary
Topical tacrolimus has significantly changed the management approaches in severe and chronic allergic eye diseases and has minimized the need for topical corticosteroids.

Keywords
allergic eye diseases, atopic keratoconjunctivitis, immunomodulators, tacrolimus, vernal keratoconjunctivitis

INTRODUCTION

Allergic eye diseases are recurring inflammatory conditions that affect the entire ocular surface [1,2]. The allergic eye disease spectrum includes mild diseases, such as seasonal allergic conjunctivitis (SAC) and perennial allergic conjunctivitis (PAC), both of which are most common, as well as more severe and chronic diseases, such as atopic keratoconjunctivitis (AKC), vernal keratoconjunctivitis (VKC), and giant papillary conjunctivitis (GPC) involving the ocular surface [2,3]. AKC and VKC are the most severe forms of allergic eye disease.

MANAGEMENT OF MILD-TO-MODERATE ALLERGIC EYE DISEASES

The range of treatments for allergic eye diseases has expanded considerably in recent years, providing a wide range of treatments, mostly based on topical application. Management of mild-to-moderate cases includes preservative-free artificial tears, topical antihistamines, topical mast cell stabilizers, and topical dual antihistamine – mast cell stabilizing agents [4,5,6▪,7,8▪].

Topical antihistamines are effective in reducing symptoms and signs of allergic eye diseases. Mast cell stabilizers and the dual actions compounds are effective in reducing tryptase levels and decrease the recruitment of inflammatory cells [9,10]. NSAIDs

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KEY POINTS

- Topical tacrolimus therapy is well tolerated, effective and rendered satisfactory results in treating patients with severe allergic eye diseases.
- Tacrolimus is a useful agent in the treatment of a wide range of severe allergic eye diseases, and specifically for patients with refractory allergic eye diseases. In addition to symptomatic relief, it has the ability to resolve giant papillae in VKC.
- A low concentration of topical tacrolimus was effective in controlling the clinical signs and symptoms of patients with severe refractory VKC.
- Topical tacrolimus is more effective than topical cyclosporine A, and safer than corticosteroids in the management of most of the allergic eye diseases.
- Early medical treatment with topical tacrolimus in severe allergic eye diseases can prevent ocular surface complications.

also provide a beneficial effect on the signs and symptoms of allergic eye diseases [11].

TOPICAL CORTICOSTEROIDS

Visual rehabilitation in eyes with severe and prolonged allergic eye diseases, such as VKC or AKC, is often very challenging. Treatment with topical antihistamines or mast cell stabilizers is often unsatisfactory, and therapy depends on topical corticosteroids [4]. Until recent years, topical corticosteroids provided the mainstay of treatment for severe allergic eye diseases. Topical corticosteroids provide effective therapy for moderate-to-severe forms of allergic eye diseases, and produce dramatic improvement of acute symptoms and signs [12]. However, the use of topical corticosteroids should be strictly limited and carefully monitored since long-term use may result in significant side effects and complications, such as formation of posterior subcapsular cataracts [13], glaucoma [12], and secondary infections, such as bacterial or fungal infections following prolonged steroid exposure [12]. Therefore, topical corticosteroids appear to be more appropriate for short-term courses of treatment [14–16].

IMMUNOMODULATORS

Immunomodulatory agents modify the response of the immune system by either increasing (immunostimulators) or decreasing (immunosuppressives) immune response [17–19]. The immunomodulatory agents have a broad range of biological effects, having applications and use in several fields of medicine among which are allergic eye diseases [17–19]. Immunomodulatory agents have changed the treatment protocols for many diseases where immune functions play a central role.

The immunomodulatory mechanism of action is based primarily on creating immunosuppressive activity by inhibiting T-cell activation. As mentioned, AKC and VKC are the severe forms of allergic eye diseases, which involve predominantly T lymphocytes [20,21]. Immunomodulator agents can effectively inhibit T-cell activation, thereby showing encouraging results in the management of patients with severe allergic eye conditions [4,5,6▪,7,8▪]. The two main topical immunomodulatory agents – cyclosporine A and tacrolimus – have demonstrated efficacy in managing ocular immune-mediated inflammatory diseases [3,22–24]. Although immunomodulators do not demonstrate the rapid effects of topical corticosteroids, they carry fewer risks and are safe for prolonged treatment. Topical ocular preparations of cyclosporine A and tacrolimus have been investigated for severe allergic eye diseases, such as VKC and AKC. Both cyclosporine A and tacrolimus have achieved breakthrough results in treatment for severe allergic eye diseases, and have been proven to be well tlerated with only minor side effects.

The current review will present a coherent picture of the recent investigations of tacrolimus therapy in severe allergic eye diseases, particularly AKC and VKC.

TACROLIMUS

Tacrolimus is a potent immunosuppressive drug that was originally used to prevent allograft rejection of transplanted organs [25]. Tacrolimus is a macrolide antibiotic that has potent immunomodulatory properties, previously known as FK506 (as it binds to FK506-binding proteins in T lymphocytes). Tacrolimus is similar to cyclosporine A in its functional mechanism, but with 50–100 folds higher potency [26–35]. This agent was isolated and produced by fermentation of *Streptomyces tsukubaensis* in 1984 [36]. Tacrolimus has been used and studied in Sjogren's syndrome, bone marrow transplantation, atopic dermatitis, and hepatic and renal transplantation [37–44]. Topical tacrolimus was well tolerated and analysis of long-term studies indicates that it has a good safety profile. Different forms and concentrations of topical tacrolimus have been assessed in the treatment of chronic allergic eye diseases (Tables 1 and 2). Topical tacrolimus is used in two main forms, ointment and suspension. The concentration of topical tacrolimus for treatment of allergic eye diseases is quite diverse, ranging from 0.005% up to 0.1%.

TACOLIMUS MECHANISM OF ACTION

Tacrolimus acts as a powerful immunosuppressant by disrupting the signaling events mediated by the calcium-dependent calcineurin (CaN)–calmodulin (CaM) complex in T lymphocytes [16,45,46]. Tacrolimus is a potent inhibitor of the CaN–CaM complex, a phosphatase, which activates nuclear factor of activated T cells (NFAT). After tacrolimus binds to FK506-binding proteins in the cytoplasm of T lymphocytes, it inhibits the CaN– CaM complex activity [16,45,46].

CaN–Cam complex inhibition prevents dephosphorylation of NFAT and its transfer into the nucleus [16,45,46]. Preventing translocation of NFAT into the nucleus suppresses the formation of various cytokines [16,45,46]. Transcription factors of the NFAT family are essential for antigen-specific T-cell activation and differentiation [47]. NFAT proteins are located in the cytoplasm where they are heavily phosphorylated through synergistic actions of three different families of kinases [47] (Fig. 1).

In T-helper 1 cells, tacrolimus suppresses the production of cytokines, such as interleukin (IL)-2 and interferon-γ [48,49]. In T-helper 2 cells, there is inhibition of secretion of cytokines, such as IL-4 and IL-5 [48,49]. In addition, the immune-suppressive effects of tacrolimus are not limited to T lymphocytes, but may also act on B cells, neutrophils and mast cells [37–43,50,51]. This leads to inhibition of the release of inflammatory cytokines, such as tumour necrosis factor-α and interferon-γ, as NFAT is responsible for regulation of their production [52–54]. NFAT 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. Therefore, blocking NFAT causes an effect on the innate immune response, and further interferes in the allergic inflammatory responses [37–43,50,51]. The systemic responses include reduction of histamine release induced by anti-IgE and leukotriene synthesis in basophils [55]. Recent studies demonstrated the galectin-3 protein as a proinflammatory mediator via the activation of mast cells, macrophages and basophils in allergic eye diseases [56–58]. The antimigratory effect of galectin-3 has been demonstrated in neutrophils and the absence of endogenous galectin-3 in allergic conjunctivitis mice also caused a significant increase cytokines levels in the tear fluid, which was reverted by treatment with tacrolimus [59–62].

CLINICAL STUDIES: LOW-DOSE TOPICAL TACROLIMUS

The efficacy of 0.1% concentration of topical tacrolimus for the treatment of allergic eye diseases has been widely reported in the literature as an alternative treatment for cases refractory to conventional medication, such as topical cyclosporine and topical corticosteroids. However, lower concentrations of topical tacrolimus have become an accepted and common treatment for allergic eye diseases over the past few years (Table 1). Lower concentrations of topical tacrolimus include 0.003, 0.005, 0.01, 0.02 and 0.03% [31,33,65–70].

Studies have shown that, even with low concentrations of topical tacrolimus, the treatment remained effective and controlled the clinical signs and symptoms for patients with severe VKC compared with conventional treatments including topical corticosteroids.

Additionally, low concentrations of topical tacrolimus showed significant improvement in symptoms including photophobia, itching, redness, ocular discomfort, foreign body sensation and discharge [31,33,65–70]. Significant improvement was also observed in clinical signs of conjunctival hyperemia, limbal infiltration, Tranta's dots, conjunctival papillary hypertrophy and superficial punctate keratopathy [31,33,65–70].

A recent prospective and observational study examined pediatric patients over a period of 8 months when treated with topical tacrolimus ointment 0.03% [33]. The study results indicated that topical tacrolimus 0.03% successfully managed VKC in 89% of patients and the patients showed significant improvement in symptoms and signs [33].

The effect of a very low concentration of 0.005% of topical tacrolimus was examined in a long-term study in patients with refractory VKC. The study showed that 0.005% tacrolimus is a well tolerated and effective treatment for steroid-resistant refractory VKC [68].

Several studies have shown that tacrolimus ointment 0.03% is effective, well tolerated, and safe in the treatment of severe atopic eyelid disease [71] in atopic blepharoconjunctivitis, and has led to clinical and cytological improvement of conjunctivitis [70] in VKC and AKC patients [66,67,72].

Several recent studies have reported that a low concentration of tacrolimus treatment has improved symptoms and signs of giant papillae related to VKC and AKC. Kymionis *et al.* reported that treatment with 0.03% tacrolimus ointment applied twice a day resulted in the resolution of severe giant papillae in VKC within 2 weeks [69]. In another study, 0.02% topical tacrolimus ointment resolved giant papillae in AKC and VKC [73].

The ability of tacrolimus to resolve and manage giant papillae caused by 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 treatment in comparison with patients suffering from limbal VKC [74,75].

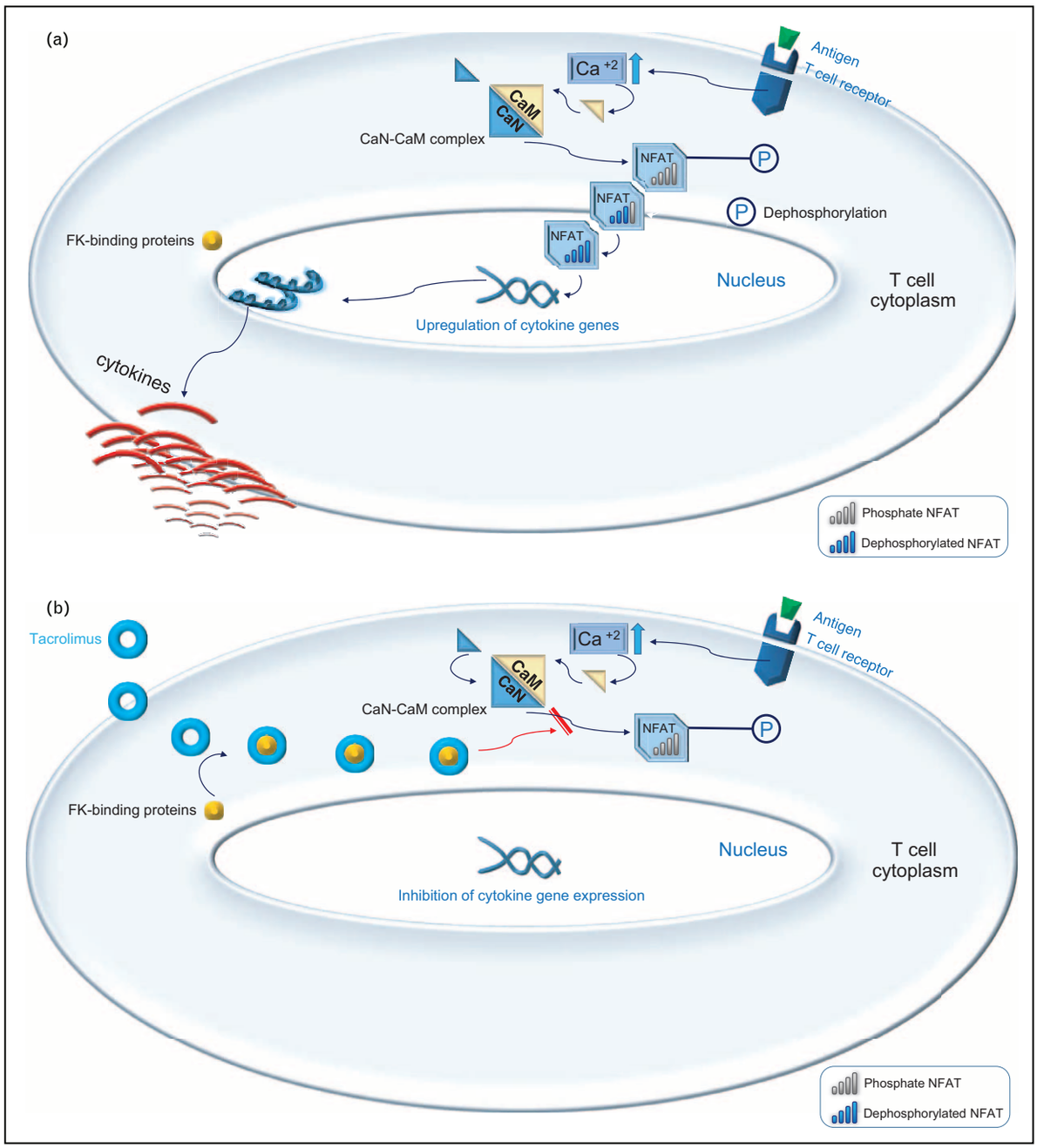

FIGURE 1. (a) Schematic representation of molecular mechanisms of T lymphocyte activation and cytokine release. (b) Mechanism of action of tacrolimus. Tacrolimus blocks T-cell activation by binding to the intracellular protein complex calcineurin – calmodulin, thereby blocking the dephosphorylation of NFAT, which prevents its translocation from the cytoplasm into the nucleus. This inhibits the transcription and production of the major inflammatory cytokines produced in T cells in allergic inflammation. CaM, calmodulin; CaN, calcineurin; NFAT, nuclear factor of activated T cells.

CLINICAL STUDIES: TOPICAL 0.1% TACROLIMUS

The most common concentration of topical tacrolimus for allergic eye disease treatment is 0.1% [16,32,34,35,76▪▪]. Thus, the majority of research in the medical literature relates to clinical studies at this concentration. Cream, solutions, emulsions and gel formulations of tacrolimus ointment are currently available. Studies indicated that propylene glycol, oleyl alcohol, diethyl sebacate and isopropyl myristate were suitable for tacrolimus solvents [16,32,34,35,76▪▪,77]. A cream formulation prepared

Table 1. Clinical studies of low-dose topical tacrolimus in vernal keratoconjunctivitis

Year	Authors	Tacrolimus treatment form and concentrations	Treatment duration	Number of patients	Major conclusions of tacrolimus treatment
2019	Samyukta *et al.* [33]	Ointment 0.03%	4 months	45	89% of patients showed significant improvement
2017	Al-Amri AM *et al.* [31]	Suspension 0.003%	1.5 months	20	Itching, redness, and foreign body sensation reduced by 90% after 6 weeks of treatment
2017	Liendo *et al.* [30]	Ointment 0.03%	13 months	33	60.6% of patients showed significant improvement
2017	Muler *et al.* [29]	Suspension 0.03%	3 months	16	Significantly improved symptoms and signs in all patients
2017	Zanjani *et al.* [28]	Suspension 0.005%	4 months	40	Significantly improved symptoms and signs in all patients Tacrolimus and IFN alpha-2b are equally effective in VKC
2016	Chatterjee and Agrawal [63]	Ointment 0.03%	3 months	30	83% of patients showed significant improvement Safe and effective in steroid-refractory VKC
2016	Shoughy *et al.* [64]	Suspension 0.01%	29 months	62	Significant improvement in symptoms of itching (80%), redness (75%), foreign body sensation (88%), and discharge (84%) Improvement in conjunctival hyperemia (75%), trantas dots (77%), superficial punctate keratopathy (88%) and conjunctival papillary hypertrophy (21%).

IFN, interferon; VKC, vernal keratoconjunctivitis.

by mixture of diethyl sebacate and isopropyl myristate showed high absorption [77].

Utilizing topical tacrolimus at a high concentration with a variable follow-up after treatment has been examined in several studies in the last few years (Table 2). A recent large study from Japan evaluated the efficacy of topical 0.1% tacrolimus ophthalmic suspension for treating chronic allergic eye disease [78]. A total of 1821 patients were included in the analyses and the study results showed that tacrolimus is useful for treating chronic allergic conjunctival disease with and without atopic dermatitis [78]. Another study demonstrated the steroid-sparing effects of 0.1% topical tacrolimus treatment [76▪▪]. This study evaluated 0.1% topical tacrolimus alone or in combination with topical corticosteroids for the treatment of shield ulcers and corneal epitheliopathy. The study examined 791 patients during a 3-month follow-up period with refractory allergic ocular diseases [76▪▪]. The study suggested that topical tacrolimus treatment for shield ulcers and corneal epitheliopathy may be used without the need of topical corticosteroids [76▪▪]. A study of VKC patients who failed to respond to conventional treatment including cyclosporine A, reported effective results with 0.1% tacrolimus treatment without any significant side effects [79]. In a multicenter, randomized, double-masked, placebo-controlled study, 56 patients with severe allergic conjunctivitis were managed with 0.1% tacrolimus. The study concluded that tacrolimus treatment was effective in improving objective clinical signs and subjective symptoms of severe allergic conjunctivitis including giant papillae.

Regarding giant papillae, another study also found that 0.1% tacrolimus ophthalmic suspension was effective in treating severe allergic conjunctivitis, with significant improvement of the giant papillae found after 4 weeks of treatment, and was well tolerated [80]. However, mild irritation with topical instillation was observed in almost half of the patients. A long-term follow-up study evaluated the 0.1% tacrolimus treatment in 11 patients for a period of 48 months. The study found that 0.1% tacrolimus was well tolerated and effective, although all the patients complained of a mild burning sensation [81]. A retrospective study of 30 patients with VKC treated with 0.1% tacrolimus found that the condition of four cases worsened, although infections of the anterior segment were not found [82].

Labcharoenwongs *et al.* examined the efficacy of tacrolimus compared with cyclosporine A treatment in a prospective double-masked randomized comparative study. Twenty-four VKC patients received 0.1% tacrolimus eye ointment twice daily for 2 months, and the others received 2% cyclosporine eye drops for the same duration. The study reported that

Table 2. Clinical studies of topical 0.1% tacrolimus in allergic eye diseases

Year	Authors	Tacrolimus treatment form and concentrations	Disease	Treatment duration	Number of patients	Major conclusions tacrolimus treatment
2019	Benaim *et al.* [34]	Ointment 0.1%	AKC	2 months	18	Palpebral application is effective for AKC The mean OSDI score decreased significantly from 52.3 ± 26.2 to 22.0 ± 27.0.
2019	Yazu H *et al.* [32].	Suspension 0.1%	AKC	2 months	30	Effective for severe AKC refractory to standard conventional treatments Herpes keratitis was observed in three cases during follow-up
2017	Miyazaki D *et al.* [74]	Suspension 0.1%	Allergic ocular diseases	3 months	791	Tacrolimus can be used without topical corticosteroids to treat corneal complications caused by refractory allergic diseases The mean epitheliopathy score at 1 month was reduced to 1.38 with tacrolimus alone, 1.41 with fluorometholone and 1.46 with betamethasone
2016	Barot *et al.* [35]	Ointment 0.1%	AKC and VKC	1 month	36	The mean total score of symptoms was 14.50 at the start of treatment and decreased to 0.56 at last observation The total sign score decreased from 23.00 at baseline to 1.00 at last observation Patients not responding to cyclosporine showed response to tacrolimus

AKC, atopic keratoconjunctivitis; VKC, vernal keratoconjunctivitis.

tacrolimus treatment resulted in improvement of the signs and symptoms of VKC similar to that of cyclosporine treatment. In addition, this study concluded that cyclosporine treatment was associated with burning sensation and pain on application, compared with a transient burning sensation detected in patients with tacrolimus treatment. Objective ocular signs improved more with tacrolimus treatment, even though this was not statistically significant [83].

There is a lack of data regarding the appropriate concentration and duration of topical tacrolimus treatment, as well as side effects in long-term treatment. It should be noted that blood concentrations in the majority of patients using 0.1% topical tacrolimus were below the limit of quantification. 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 [84]. These values were used to set the tacrolimus safety profile [84].

TACROLIMUS POTENTIAL ADVERSE EFFECTS

The side effects of systemic tacrolimus include hypertension, hyperglycemia and renal toxicity [85–87]. Tacrolimus applied as a topical treatment should not induce these systemic side effects, because of its very limited serum concentrations. The major side effect of topical tacrolimus is burning sensation when used either on the skin or in the eye. Several studies evaluated tacrolimus ointment in 0.03 or 0.1% concentrations with vehicle control [64,88–92]. These studies report skin burning in almost half of the patients receiving 12 weeks of treatment with tacrolimus [64,88–92]. The major adverse event apart from burning was itching of the skin, which resolved within the first week of therapy [25,92–94].

In 2006, the US food and drug administration (FDA) and the European medicine agency (EMEA) issued a 'black box' warning on a theoretical risk of lymphoma in patients treated with topical calcineurin inhibitors [95]. Safety concerns were not based on clinical trials but rather on potential molecular mechanisms of action of calcineurin inhibitors, possible risk of systemic absorption and animal studies [96–99].

Despite the FDA warning, postmarketing follow-up, clinical trials in the professional literature and epidemiological studies have failed to establish any association between topical tacrolimus treatment

and lymphoma risk [25,92–94,96–99]. However, the 'black box' warning is still issued on the medication guide brochure that is attached to the ointment preparation, causing confusion and uncertainty among parents to children with VKC who get prescriptions of topical tacrolimus ointment.

CONCLUSION

The molecular mechanisms of action of tacrolimus in T cells involve inhibition of critical signalling pathways that regulate T-cell activation. Tacrolimus inhibits CaN–CaM complex phosphatase activity and as a result inhibits activation of the transcription factor NFAT. This inhibits the production of the major inflammatory cytokines, which play a role in allergic inflammation.

Topical tacrolimus is comparable with topical corticosteroids and causes significantly decreased symptoms and signs in chronic allergic eye diseases and is particularly effective in managing VKC and AKC. Treatment with tacrolimus also has the ability to resolve giant papillae in VKC. Evidence shows that tacrolimus is more effective than cyclosporine A, and is more tolerable. Topical tacrolimus is a useful steroid-sparing agent. In addition, clinical improvement is superior in comparison with steroid therapy, and tacrolimus is also well sustained after the steroids are discontinued.

Low concentrations of topical tacrolimus are also effective in controlling the clinical signs and symptoms in patients with severe refractory VKC.

So far, no scientific evidence demonstrate a causal relationship between tacrolimus treatment and lymphoma risk even though tacrolimus is a calcineurin inhibitor and is used to suppress the immune system.

Additional studies will be required to reveal and determine the optimal tacrolimus concentration and duration of treatment for various allergic eye diseases.

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Conflicts of interest

There are no conflicts of interest.

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- ■■ of outstanding interest

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