

Systemic Tacrolimus in the Treatment of Severe Atopic Keratoconjunctivitis

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Purpose: Severe atopic keratoconjunctivitis (AKC) forms part of the spectrum of allergic eye disease and is often refractory to conventional topical treatment. Topical cyclosporin A and tacrolimus have been shown to reduce immunologic activation, symptoms, and signs of patients suffering from AKC, but there are no reports on safety and efficacy of systemic tacrolimus for this condition.

Methods: We report on a retrospective study of 3 patients with severe AKC, where the disease did not respond to conventional therapy, and they were therefore treated with low-dose systemic tacrolimus for at least 1 year as an adjunct to their existing treatment.

Results: There was a good clinical response in all patients to low-dose systemic tacrolimus, with a low incidence of side effects and no relapse of symptoms after discontinuation of treatment.

Conclusion: Low-dose systemic tacrolimus is a safe and effective treatment of some patients with severe AKC, which is refractory to conventional treatment. Such patients need careful monitoring for side effects, and the long-term benefits need to be assessed as part of a clinical trial.

Key Words: atopic keratoconjunctivitis, allergy, tacrolimus, cyclosporin A

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There is a spectrum of allergic eye disease that ranges from the relatively mild seasonal allergic conjunctivitis (SAC) to the more severe and potentially sight-threatening atopic keratoconjunctivitis (AKC). Although there is minimal immunologic activation in SAC, a persistent state of mast cell, eosinophil, and lymphocyte activation has been noted in AKC, with increased corneal pathology, follicular development, and conjunctival fibrosis.¹

Most patients with SAC and mild AKC can be adequately managed with topical antihistamines, mast cell stabilizers, or steroid treatment. However, there is a small proportion of patients with severe AKC, where such topical

treatment is not effective and second-line topical or systemic immunosuppressant treatment is required.

Steroids have been used for many years to control inflammatory responses; however, they are associated with many local and systemic side effects. Second-line immunosuppressants, such as cyclosporin A (CsA) or tacrolimus, have been used to control inflammation in the field of transplantation medicine and systemic autoimmune diseases.

Tacrolimus is a potent immunosuppressive agent, and in the United Kingdom, it is currently licensed in ointment form for treating moderate to severe atopic eczema and in the oral/systemic form for primary immunosuppression in liver and kidney allograft recipients. The drug suppresses T-cell activation and T helper cell–dependent B-cell proliferation, as well as the formation of cytokines, and it also inhibits expression of the interleukin-2 receptor. However, tacrolimus also has several well-characterized side effects, such as pancytopenia, hyperglycemia, hyperkalemia, tremor, headache, insomnia, hypertension, dyspnea, pleural effusion, diarrhea, nausea and vomiting, pruritus, muscle cramps, nephropathy, and arthralgia (British National Formulary 2005). Because most of these are reversible and respond to dose reduction or cessation of treatment, it is imperative that patients are monitored regularly.

The use of topical CsA has been shown to have beneficial effects in humans with AKC by inducing a reduction in the number and activation of T cells and T-cell cytokine expression with minimal effects on type 1 hypersensitivity responses.² Tacrolimus is more effective than CsA and has fewer side effects. Furthermore, systemic but not topical tacrolimus has been shown to have beneficial effects in an animal model of allergic conjunctivitis.³ In humans, topical tacrolimus has also been shown to be effective on the skin of patients with atopic blepharitis⁴ and in patients with AKC.⁵

Because there is no commercially available ocular preparation for tacrolimus, we now report on a retrospective study of 3 patients with severe AKC where the disease was refractory to conventional therapy and they were therefore treated with low-dose systemic tacrolimus as an adjunct to their existing treatment.

MATERIALS AND METHODS

The patients in this study attended the Bristol Eye Hospital with severe AKC not controlled with conventional treatment between 2002 and 2004. Severe AKC was defined as characteristic chronic signs including photophobia, eyelid

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swelling and erythema, conjunctival hyperemia, giant tarsal conjunctival papillae, and follicles with mucus secretion and corneal superficial punctate epithelial erosions. These signs were present despite the use of topical steroids, and they significantly affected the patient's quality of life and required continuous ophthalmic intervention. All the patients in this series fitted this definition.

After full discussion of the risks and potential benefits of adjunctive low-dose systemic tacrolimus therapy, patients were treated for at least 1 year to control the symptoms.

The patients were screened before starting tacrolimus and during treatment. This included assessment of weight, blood pressure, urinalysis, chest x-ray (baseline only), full blood count, renal function (urea, electrolytes, creatinine, and magnesium), liver function, glucose, and lipids. Pregnant women were excluded.

Patients were started on a dose of 0.03 to 0.08 mg/kg of tacrolimus, and the dose was titrated to symptoms and blood trough levels. Patients were monitored for response to treatment and side effects by clinical examination and studies as above.

RESULTS

Patient 1

A 32-year-old woman with asthma first presented at the age of 11 with AKC. Her symptoms were controlled over the years on various regimens of topical medication until she was diagnosed with keratoconus at the age of 23 years. Unfortunately, she became intolerant to both rigid gas-permeable and keraSoft contact lenses over the next 5 years. Her best spectacle-corrected vision was 6/9 in the right and 6/18 in the left eye, and she therefore had left penetrating keratoplasty (PKP). Despite perioperative oral prednisolone in addition to topical steroids, she developed vascularization of the graft and loosening of the superior sutures after 4 weeks. Topical CsA (2%) was added, but she became intolerant of it within 3 weeks. She was changed to systemic CsA (2 mg/kg/d), but after a further 4 weeks, she developed mild hallucinations, numb gums, and paresthesia in her hands and feet. She was therefore started on tacrolimus at a dose of 2 to 4 mg/d (0.02–0.05 mg/kg/d). Two years later, she is on predsol 0.5% once a day in addition to tacrolimus, and her best spectacle-corrected visual acuity is 6/5 in the left eye. The average trough tacrolimus level was 3.34 ng/mL, with a range between 3 and 7.2 ng/mL. There has been no clinically significant change in the systemic clinical parameters to monitor for toxic side effects, and she complained only of intermittent minor cramps and paresthesia but is not willing to discontinue her treatment. Her symptoms in the fellow eye also markedly improved, where subsequently she also had a penetrating keratoplasty.

Patient 2

A 29-year-old woman with asthma and eczema initially presented in our unit at the age of 21 years with symptoms of AKC for more than 2 years. In the 6 years before starting tacrolimus, she required 62 ophthalmic outpatient consultations in a corneal and external eye disease subspecialty clinic and 2 admissions for a shield ulcer and microbial keratitis. Her

best-corrected vision ranged between 6/4 and 6/6 in the right and left eyes, respectively, at best and 6/9 and 6/36, respectively, at worst. Vision was maintained only with topical prednisolone 1% because she did not tolerate topical CsA 2%. She was started on systemic tacrolimus at a dose of 2 to 4 mg/d (0.04–0.08 mg/kg/d) to reduce her dependency on topical steroids. The average trough tacrolimus level was 2.12 ng/mL, with a range between 3 and 5 ng/mL. There was no clinically significant change in the systemic clinical parameters to monitor for toxicity. Although she was still dependent on prednisolone drops 0.5% once a day, her symptoms markedly improved with no relapses during treatment and with maintenance of good vision. After 1 year, she noticed some difficulty concentrating, which she attributed to the tacrolimus and decided to stop treatment herself. Incidentally, her eczema also improved while on tacrolimus. There was 1 minor relapse of symptoms 6 months after discontinuation of tacrolimus, which was easily treated with a short increase in her topical steroid.

Patient 3

A 43-year-old man with type 2 diabetes mellitus first presented at the age of 35 years with a 10-year history of painful red eyes. Over the years, he was treated with topical steroids and antibiotics for rosacea blepharitis and staphylococcal keratoconjunctivitis by general ophthalmologists. He had surgery for bilateral cataracts, which were attributed to the chronic use of steroids (diabetes was diagnosed just before starting tacrolimus). Despite treatment and vision of 6/9 in both eyes, he complained of regular episodes of bilateral watering, burning, photophobia, and stickiness. He was referred for a cornea/external eye disease opinion and on examination had signs including eyelid swelling, conjunctival hyperemia, giant tarsal conjunctival papillae with copious mucus secretion, and superficial punctate epithelial erosions over both corneas. The diagnosis was changed to AKC, and he was started on systemic tacrolimus at a dose of 4 to 8 mg/d (0.03–0.07 mg/kg/d) to reduce his symptoms and dependency on topical steroids. The average trough tacrolimus level was 3.38 ng/mL, with range between 3 and 10 ng/mL during the 18-month treatment period. The patient noticed a marked improvement in his symptoms and claims that the eyes are more comfortable than they have been for 18 years, and he was able to participate in sporting events for the first time since his eye problems started. There was no clinically significant change in the systemic clinical parameters to monitor for toxic side effects, and he has been able to maintain good glycemic control on oral hypoglycemics. Although the patient has noticed a slight reduction in memory, neuropsychologic testing revealed only mild reduction in visual memory. Considering the benefit to his eyes, the patient feels that this does not warrant stopping the tacrolimus.

A comparison of the patients' clinical details are summarized in Table 1.

DISCUSSION

Severe AKC is a relatively rare but potentially sight-threatening ocular allergic condition. The management is often

TABLE 1. Summary and Comparison of the Patients' Clinical Details

	Case 1	Case 2	Case 3
Age (yr)	32	29	44
Sex	Female	Female	Male
Age at presentation (yr)	11	21	35
Duration of symptoms at presentation (yr)	0	>2	>10
Associated ocular pathology	Keratoconus requiring bilateral PKPs for contact lens intolerance	Shield ulcer and microbial keratitis	Blepharitis and rosacea
Number of medications before systemic tacrolimus	12	6	5
Date of commencement of systemic tacrolimus	March 2002	October 2002 (stopped November 2003 because of disease remission)	October 2002
Dose of tacrolimus	2–4 mg/d (0.02–0.05 mg/kg)	2–4 mg/d (0.04–0.08 mg/kg)	4–8 mg/d (0.03–0.07 mg/kg)
Blood tacrolimus levels (mean/range [ng/mL])	3.34/<3–7.2	2.12/<3–5	3.38/<3–10
Number of medications after systemic tacrolimus	6	1	2
Clinical and laboratory monitoring of tacrolimus side effects	No change from baseline	No change from baseline	No change from baseline
Minor side effects	Cramps and paraesthesia	Difficulty concentrating	Reduced visual memory
Comments from patients	Happy with eyes and sight and not willing to stop treatment	Eyes back to “normal” after 1 year of treatment with tacrolimus	Eyes are the best they have been in 18 years and now able to play sports again

difficult and prolonged as shown by the 3 cases above. In these patients, topical antihistamines, mast cell stabilizers, and topical steroids were all used as the main form of treatment before tacrolimus, but these therapies did not provide satisfactory results, and despite reliance on topical steroids, these patients continued to experience symptoms that impinged significantly on their employment and quality of life.

We first used systemic tacrolimus for AKC with patient 1, where the quality of life was affected by her conditions (AKC, keratoconus, and contact lens intolerance). The only way to improve her vision was to perform a relatively high-risk corneal graft. After the graft and despite systemic prednisolone, there was significant deterioration of the ocular surface, with loosening of sutures and corneal vascularization. The patient became intolerant of both topical and systemic CsA but responded well to systemic tacrolimus with significant symptomatic improvement in both eyes.

This positive response to tacrolimus in both eyes prompted us to try it with the other 2 patients, with a view to reducing their dependency on topical steroids and possibly putting them into disease remission. Although no formal scoring was used, all the patients on low-dose systemic tacrolimus in this series noted subjective clinical improvements in terms of improved and long-term stability of functional visual acuity, as well as symptom relief. Although continuous monitoring is required during tacrolimus treatment, minimal ophthalmologic interventions were required in this period.

In comparison with patients on tacrolimus for the prevention of allograft rejection, the doses required to achieve symptomatic relief were much lower (trough blood levels of approximately 3 ng/mL for AKC and 10 ng/mL for allograft

rejection). In addition, at the dose used to control AKC, there were only minor side effects, and the patients tolerated the medication well over the time that they were on the treatment. Furthermore, there was no rebound in symptoms after cessation of treatment in the second patient.

This report shows the therapeutic benefits of systemic tacrolimus in some severe and refractory cases of AKC. Systemic tacrolimus should be considered when sight-threatening AKC fails to respond to conventional therapy. Nevertheless, various adverse effects may be associated with its use, and the therapy needs to be monitored by experienced clinicians. Although the number of patients suffering from this condition is relatively small, a prospective randomized multicenter placebo-controlled clinical trial with both objective and subjective disease scoring scales and a quality-of-life questionnaire would determine the long-term efficacy and safety of the treatment.

REFERENCES

1. Bielory L. Ocular allergy guidelines: a practical treatment algorithm. *Drugs*. 2002;62:1611–1634.
2. Hingorani M, Calder VL, Buckley RJ, et al. The immunomodulatory effect of topical cyclosporin A in atopic keratoconjunctivitis. *Invest Ophthalmol Vis Sci*. 1999;40:392–399.
3. Iwamoto H, Yoshida H, Yoshida O, et al. Inhibitory effects of FK506 on the development of experimental allergic/immune-mediated blepharoconjunctivitis in Lewis rats by systemic but not by topical administration. *Graefes Arch Clin Exp Ophthalmol*. 1999;237:407–414.
4. Rikkers SM, Holland GN, Drayton GE, et al. Topical tacrolimus treatment of atopic eyelid disease. *Am J Ophthalmol*. 2003;135:297–302.
5. Reinhard T, Reis A, Mayweg S, et al. [Topical Fk506 in inflammatory corneal and conjunctival diseases. a pilot study.] *Klin Monatsbl Augenheilkd*. 2002;219:125–131.