

Use of Systemic T-lymphocyte Signal Transduction Inhibitors in the Treatment of Atopic Keratoconjunctivitis

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Purpose: Topical immunomodulators such as tacrolimus have revolutionized the treatment of atopic dermatitis. Because T lymphocytes are integral to the pathogenesis of atopic dermatitis, systemic treatment with T-lymphocyte signal transduction inhibitors should ameliorate both the dermatologic and ocular manifestations. We describe the successful treatment of 6 patients with severe atopic keratoconjunctivitis (AKC) resistant to conventional therapies.

Methods: Retrospective observational case series. The charts of patients with AKC assessed by 1 of the authors were reviewed to identify those treated with systemic T-cell signal transduction inhibitors. Visual acuities, previous treatments, and the response to systemic signal transduction inhibitors were observed and reported in 6 patients.

Results: The patients had a mean duration of AKC of 21 years. Topical corticosteroids and antihistamines had failed to control signs and symptoms of the disease in all patients, and in some patients, systemic corticosteroids and topical cyclosporine were ineffective. Three patients were treated with systemic cyclosporine, and 3 were treated with systemic tacrolimus. One patient was subsequently treated with daclizumab in addition to tacrolimus. All 6 patients experienced complete remission of their AKC and an increase in visual acuity.

Conclusions: Selective systemic immunosuppression of T lymphocytes with cyclosporine or tacrolimus has proved effective in the treatment of both atopic dermatitis and atopic keratoconjunctivitis. We advocate the consideration of systemic therapy in cases that are resistant to conventional treatment to resolve inflammation and preserve vision. Further studies in this area are advocated.

Key Words: atopic keratoconjunctivitis, tacrolimus, T cell, immunosuppressive agents, signal transduction

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Atopic keratoconjunctivitis (AKC) is a chronic and potentially blinding immune-mediated ocular surface inflammatory disease that occurs in association with atopic dermatitis. It is estimated that between 25% and 42% of patients with eczema develop AKC, which eventually progresses to involve both eyes.^{1,2}

Severe AKC may result in a progressive cicatrizing conjunctivitis with secondary keratopathy and neovascularization, which can result in significant visual impairment. Other conditions associated with visual morbidity in patients with AKC include retinal detachments, keratoconus, cataract, staphylococcal blepharitis, meibomian gland dysfunction, and herpes simplex keratitis.^{3–6}

Conventional therapy for mild AKC includes the avoidance of allergens and the use of topical mast cell stabilizers and antihistamine preparations. A new class of agents, the topical immunomodulators, such as tacrolimus and pimecrolimus, were approved by the U.S. Food and Drug Administration for the treatment of atopic eczema and heralded a revolution in the treatment paradigm of this condition and a move away from topical corticosteroids and their adverse effects.^{7–9} In more severe cases, topical treatment is ineffective, and systemic corticosteroids with their inherent adverse side effect profile have been used for inflammatory control. Topical tacrolimus has been reported to be effective in the treatment of eyelid dermatitis. Furthermore, the use of systemic tacrolimus has been used to good effect in the treatment of experimental allergic/immune-mediated blepharoconjunctivitis in animal models.¹⁰

We report a case series of the use of T-lymphocyte signal transduction inhibitors in the treatment of AKC in patients who had failed conventional or other immunomodulatory therapy.

MATERIALS AND METHODS

Approval from the institutional review board was obtained for this study. The charts of patients with AKC assessed by 1 of the authors (C.S.F.) between 2000 and 2007 were reviewed to identify those patients who were treated with systemic T-cell signal transduction inhibitors. Clinical data such as visual acuities, slit-lamp biomicroscopic findings, previous treatments, and the response to systemic signal transduction inhibitors were recorded and are reported here for 6 patients.

Table 1 summarizes the characteristics of all 6 patients.

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TABLE 1. Clinical Features of all Patients

Variable	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Duration of AKC (y)	16	40	12	21	14	25
Ocular presentation	Corneal hydrops, scarring, epithelial defect, and stromal ulceration	Corneal neovascularization, keratoconus with peripheral thinning, and superficial punctate keratitis	Conjunctival injection, mucus discharge, and superficial punctate keratitis	Corneal scarring and neovascularization	Corneal ulcer	Corneal neovascularization
Ocular associations	Keratoconus	Keratoconus	Intraocular hypertension	—	Keratoconus	—
Dermatological associations	Eczema	Eczema	Eczema	Eczema	—	Eczema
Previous topical therapy	Loteprednol, moxifloxacin, cyclosporine, artificial tears	Prednisolone	Tobramycin, prednisolone, tacrolimus	Prednisolone, cyclosporine, loteprednol	Moxifloxacin, fluorometholone, cyclopentolate	Pred Forte, artificial tears
Previous systemic therapy	Prednisone, cyclosporine	Cyclosporine	—	Prednisone, pseudoephedrine	Doxycycline, loratadine	—
Side effects	Nephropathy/hypertension (prior cyclosporine)	Flulike syndrome, nephropathy (prior cyclosporine)	—	—	Hypertension (current tacrolimus)	Breast tenderness, cold intolerance (current cyclosporine)
T-cell inhibitor therapy	Tacrolimus	Tacrolimus	Cyclosporine	Cyclosporine	Tacrolimus	Cyclosporine
Initial visual acuity	20/200 OD HM OS	20/400 OD 20/100 OS	20/50 OD 20/40 OS	20/70 OD 20/60 OS	20/125 OD 20/80 OS	20/30 OD 20/70 OS
Final visual acuity	20/60 OD (scarring after hydrops) 20/20 OS	20/30 OD 20/60 OS	20/20 OU	20/20 OU	20/20 OD 20/40 OS	20/25 OD 20/70 OS
Conjunctival findings pretreatment	3+ injection OU	1+ injection OU	2+ injection OU	3+ OD, 2+ OS injection Chemosis OU	Follicular conjunctivitis 1+ 2+ injection OS	4+ injection OU
Conjunctival findings posttreatment	0	0	Trace injection OD, 0 OS 1+ papillary conjunctivitis	0.5+ injection OU No chemosis	No conjunctivitis 0 injection	0 injection
Duration of treatment	2 y	2 y	2 y	4 y	4 mo	6 mo

HM, hand motion.

The degree of conjunctival inflammation (hyperemia and injection) was recorded by using a standardized grading scale reported elsewhere.¹¹

RESULTS

Six patients with long-standing histories of AKC, who had failed conventional or other immunomodulatory treatments, were identified. These patients were subsequently treated with the systemic T-cell signal transduction inhibitors tacrolimus ($n = 3$; Prograf; Fujisawa Healthcare, Deerfield, IL) or cyclosporine ($n = 3$; Neoral or Sandimmune; Novartis Pharmaceuticals, East Hanover, NJ). The clinical features and treatment histories of these patients have been tabulated in Table 1.

Patient 1

A 31-year-old man with a history of chronic bilateral ocular discomfort associated with tearing, photophobia, and

mucous discharge for several years was referred. He had recently developed a persistent corneal epithelial defect with stromal ulceration in his right eye.

The patient related a 16-year history of atopic dermatitis and exercise-induced asthma. Medications at presentation included 60 mg of systemic prednisone daily with topical tacrolimus and triamcinolone creams to skin lesions. He was also using topical loteprednol, moxifloxacin, artificial tears, and cyclosporine 0.05% eyedrops. This patient had developed nephropathy and hypertension in response to previous systemic cyclosporine therapy.

Examination showed active eczema of the face and chest. Visual acuities were 20/200 OD and hand motion OS, with physiologic intraocular pressures. Slit-lamp biomicroscopy showed bilateral keratoconus, with 3+ conjunctival injection, and corneal hydrops OS.

Serologies showed markedly elevated serum immunoglobulin E levels (2650 IU/mL; upper limit of normal, 248 IU/mL).

We started systemic tacrolimus 4 mg/d. In view of his disease severity, we also started this patient on concomitant daclizumab (Zenapax; Roche Pharmaceuticals, Nutley, NJ) therapy at an initial infusion frequency of 75 mg intravenously biweekly.

After a series of 5 daclizumab infusions, the patient's ocular and dermatologic symptoms were dramatically improved, with improvement in visual acuities to 20/60 OD and 20/20 OS. He had no conjunctival injection at his last follow-up visit. The patient continues this treatment regimen, with excellent control and minimal symptoms from his AKC 2 years after presentation.

Patient 2

A 45-year-old woman with a 40-year history of eczema and AKC presented with ocular discomfort, irritation, and poor vision. She also related a history of abdominal cramping, decreased urinary output, and flulike symptoms. She had been taking 200 mg of cyclosporine daily for the past 1 month. Her medical history included asthma, hay fever, and frequent sinus infections. The patient's visual acuities were 20/400 OD and 20/100 OS. External examination showed chronic bilateral eczema of the eyelids, with scaling and crusting of the lid margins (atopic eyelid disease). An ocular examination showed +1 conjunctival injection with papillae present in both superior and inferior tarsal conjunctivae. The corneas showed superficial punctate keratitis, neovascularization, scarring, peripheral thinning, and keratoconus.

The cyclosporine therapy was discontinued, and systemic tacrolimus was started at a dose of 4 mg daily. Two months later, the patient showed significant improvement with no conjunctival injection and improvement in visual acuity to 20/100 OD and 20/80 OS. She related no side effects from the tacrolimus therapy. This patient's signs and symptoms remained controlled on tacrolimus therapy and she underwent staged lamellar tectonic corneal grafts. Subsequent bilateral penetrating keratoplasties with amniotic membrane grafting after complete resolution of all AKC-related inflammation were performed. Postsurgery resurgence of symptoms led to frequent eye rubbing that caused multiple dislocations of the protective bandage contact lens. This finding suggested ineffective disease control, and the tacrolimus dose was increased to 5 mg/d. The patient's visual acuities improved to 20/30 OD and 20/60 OS because of adequate disease control after the increased dose of tacrolimus, and her AKC remains well controlled (with no conjunctival injection) 2 years after initial presentation.

Patient 3

A 41-year-old man presented to the emergency ward with a 3-day history of red swollen eyelids, itching, burning, and a yellowish discharge in both eyes. The patient had a 12-year history of AKC and eczema. He was using topical tobramycin for both eyelids, in association with topical prednisolone acetate OU 2 times a day and tacrolimus ointment for the affected facial skin.

Presenting acuities were 20/50 OD and 20/40 OS, and the patient's intraocular pressures were 29 mm Hg OD and 30 mm Hg OS. Slit-lamp biomicroscopy showed bilateral eyelid

thickening with 1+ papilla formation. The patient had severe, bilateral meibomian gland dysfunction, 2+ conjunctival injection, and superficial punctate keratitis. Preliminary diagnoses of rosacea-associated blepharitis, steroid-induced glaucoma, and AKC were made.

Physical examination showed severe periorbital erythema with scaling, excoriations, and mild edema. The patient also had scaly erythematous patches on his face, ears, and chest. A diagnosis of atopic dermatitis and AKC was made. In view of the elevated intraocular pressures, we discontinued the topical corticosteroids, and the patient was treated with ocular hypotensives. Systemic cyclosporine therapy was initiated at a dose of 200 mg/d, and within 6 weeks, there was a remarkable improvement in both the patient's skin and ocular condition. There was an ~80% reduction in the eczematous skin lesions with corrected visual acuities of 20/20 bilaterally. This patient's condition is maintained in remission on cyclosporine therapy 2 years after presentation. He continues to have mild (1+) papillary conjunctivitis, but the conjunctival injection has resolved.

Patient 4

A 47-year-old woman was referred for evaluation of a 21-year history of AKC, which was previously treated with topical and systemic corticosteroids and topical cyclosporine without significant benefit. At presentation, she was using loteprednol 4 times a day OU, artificial tears, and oral pseudoephedrine.

This patient's medical history included multiple chronic allergies, asthma, eczema, and psoriasis. On examination, the facial skin was dry and scaly, with striae on the lips. Visual acuities were 20/70 OD and 20/60 OS with normal intraocular pressures. Slit-lamp examination showed thickened lids with blepharitis OU, 3+ injection of the OD conjunctiva, and 1 1/2+ OS with chemosis OU. There was bilateral peripheral scarring of the corneas.

Serologies were significant only for elevated serum immunoglobulin E (650 IU/mL). Systemic cyclosporine therapy was initiated at 200 mg/d. The patient was also started on topical olopatadine twice daily, and all previous treatments were discontinued. On reexamination 1 month later, the patient reported symptomatic improvement in both eyes, with visual acuities of 20/60 OD and 20/20 OS. She tolerated the cyclosporine well, and her condition has remained in remission on that medication. Her acuities have improved to 20/20 OU 4 years after presentation. At the last follow-up visit, she showed 0.5+ injection OU.

Patient 5

A 45-year-old woman with hypertension was referred for evaluation of a corneal ulcer in her left eye. Her medical history included a 14-year history of eczema. This corneal ulceration represented a recurrence, and on presentation, the patient was taking topical moxifloxacin, fluorometholone, and cyclopentolate, along with systemic doxycycline, loratadine, and atenolol. Visual acuities were 20/125 in the right eye and 20/80 in the left eye, and intraocular pressures were normal. Slit-lamp examination showed keratoconus with apical thinning in the right eye, a shield ulcer in the left eye, and bilateral

eyelid dermatitis. She also had significant meibomian gland dysfunction, 1+ follicular conjunctivitis, nuclear sclerotic cataracts, and 2+ conjunctival injection in the left eye.

General physical examination showed eczematous skin lesions, and review of systems was positive for pruritus. A diagnosis of atopic dermatitis and coexisting atopic and vernal keratoconjunctivitis was made. Serologies showed an immunoglobulin E level of 6869 IU/mL. Immunomodulatory therapy with tacrolimus 5 mg/d in conjunction with topical cyclosporine was started. Topical moxifloxacin, fluorometholone, and artificial tears were continued. A bandage contact lens was placed on the left eye. One month later, the patient related symptomatic improvement but was found to be systemically hypertensive. Hydrochlorothiazide was prescribed. At the last follow-up visit, 6 months after presentation, the patient's follicular conjunctivitis and corneal ulcer had resolved, and her eczema was under control. Conjunctivae were quiet. Visual acuities had improved to 20/20 (with the bandage contact lens) and 20/40.

Patient 6

A 52-year-old female patient was referred to us for evaluation of her bilateral atopic keratoconjunctivitis and a request by the referring ophthalmologist to evaluate the patient for the necessity for limbal stem cell grafting. The patient had bilateral cataract surgery 1 month before presentation and was using prednisolone acetate 1% drops and daily-wear scleral contact lenses. The patient's medical history showed a 25-year history of eczema.

On examination, her visual acuities were 20/30 and 20/70, and intraocular pressures were normal. External examination showed eyelid erythema with meibomian gland dysfunction, 4+ injection of both conjunctivae, and neovascularization and pannus formation in both corneas. Serologies showed elevated immunoglobulin E levels (275 IU/mL). We believed that limbal stem cell transplantation would fail if performed without first controlling the patient's AKC. Immunomodulatory therapy was started with cyclosporine 100 mg/d in an effort to control the underlying inflammatory disease.

On follow-up 1 month later, the patient had improved subjectively and objectively (decreased conjunctival injection and better vision), and her eczema had subsided. Two months later, the right eye had no injection, but the left eye continued to show inflammation. The cyclosporine dose was increased to 100 mg 4 times a day, and topical cyclosporine and loteprednol were added. This patient continues to be monitored. Her acuities at last follow-up were 20/25 and 20/70, and there was no conjunctival injection.

DISCUSSION

We described the therapeutic benefit of systemic T-lymphocyte signal transduction inhibitors in the treatment of AKC. In AKC, the conjunctiva contains increased concentrations of T cells. Helper T cells are the primary mediators or effectors of tissue damage in AKC and recruit other cell types, including mast cells, eosinophils, lymphocytes, and basophils, which secrete various allergic and inflammatory mediators. The chronically elevated levels of these cells and the mediators

derived from them, such as eosinophil cationic protein from eosinophils, contribute significantly to the chronic damage seen in AKC.^{12,13}

Three patients were treated with systemic tacrolimus, and 3 patients were treated with systemic cyclosporine. These agents' mechanism inhibits calcineurin, a calcium/calmodulin-dependent phosphatase, which normally activates nuclear factor of activated cells, which causes proliferation and activation of T cells. Inhibition of calcineurin activity by cyclosporine and tacrolimus—calcineurin inhibitors—inhibits the second messenger pathway involved in signal transduction from surface receptors to nucleus and thus inhibits proliferation, activation, and the production of cytokines by T cells (which attract other effector cells). This action inhibits the chronic inflammatory process. All of these patients had failed prior conventional therapy, and in some cases, previous immunomodulatory therapy, and hence reflect a subgroup of patients with severe sight-threatening disease.

Of our 3 patients who were treated with systemic tacrolimus (patients 1, 2, and 5), 2 had previously failed cyclosporine therapy, developing iatrogenic complications such as nephropathy, hypertension, and decreased urine output. The subsequent use of systemic tacrolimus in these patients produced a favorable clinical response with minimal side effects. One of these patients (patient 1) was concomitantly treated with systemic intravenous daclizumab because of the extreme severity of his disease at presentation.

Our 3 patients who were treated with systemic cyclosporine (patients 3, 4, and 6) responded positively with a decrease in ocular and systemic symptoms and improvement in visual acuities. A minimum of 12 weeks of therapy with systemic cyclosporine is needed for therapeutic benefit.¹⁴ One of our patients needed only 6 months of therapy with cyclosporine for disease control.

There have been a few reports of topical cyclosporine and tacrolimus therapy for atopic blepharitis and eyelid disease,^{9,15} but there is a paucity of reports describing the use of these calcineurin inhibitors in the treatment of AKC. Hoang-Xuan et al¹⁶ described 4 patients who were refractory to, or dependent on, systemic corticosteroid therapy and were treated with systemic cyclosporine. Inflammation was successfully controlled in 3 patients, with 1 patient showing a partial response. Dose-dependent renal toxicity developed in 1 patient. Some patients who may not tolerate 1 calcineurin inhibitor may tolerate another. More recently, Stumpf et al¹⁷ showed the therapeutic benefit of low-dose systemic tacrolimus in 3 patients with severe and refractory AKC and advocated this therapy as safe and effective. Tacrolimus, however, has potential side effects, and these need to be monitored for, just as with cyclosporine, with regular blood counts, blood pressure monitoring, renal function, and liver enzyme assays.

It is extremely unlikely that a prospective randomized multicenter placebo-controlled trial would be feasible for the study of calcineurin inhibitor therapy for AKC, because of the few patients who experience severe and recalcitrant AKC. However, this report, coupled with other small case series from the literature, can guide us in our treatment of this difficult subgroup of patients in our effort to prevent significant visual morbidity.

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