

LETTER TO THE EDITOR

Treatment of atopic keratoconjunctivitis in patients with atopic dermatitis: is ocular application of tacrolimus an option?

Editor

Atopic dermatitis (AD) is a common chronic inflammatory skin disease; ocular involvement has been described in 25–40% of patients¹ and usually starts with atopic blepharitis (eyelid dermatitis), followed by conjunctivitis and sometimes keratitis. The most visual threatening type is atopic keratoconjunctivitis (AKC) (Fig. 1). Adequate treatment of the eyelid dermatitis and early recognition and treatment of eye symptoms in AD patients may reduce the risk of severe ocular complications such as AKC.²

Treatment of eyelid dermatitis in AD is often inadequate.³ This is mainly due to fear of using periocular corticosteroids. Recent studies showed beneficial effects of topical applied newer immunosuppressive drugs such as tacrolimus on the exterior side of the eyelids⁴. This however is often insufficient to prevent corneal and conjunctival involvement; treatment should also involve the palpebral conjunctiva. Therefore, we performed a literature search on

the therapeutic value of ocular applied tacrolimus in patients with AKC. Five articles with interesting conclusions were found. The results are summarized in Table 1.

Ohashi *et al.*⁵ performed a prospective randomized controlled trial comparing tacrolimus 0.1% eye drops twice daily to placebo in 41 patients with AKC. After 2 and 4 weeks, a significant reduction was found in objective ocular signs and subjective symptoms in the tacrolimus group compared with placebo. In the tacrolimus group, one patient developed a de-novo herpetic keratitis. The most common side-effect in the tacrolimus group was mild ocular irritation (42.9%).

In a small prospective open study, Wakamatsu *et al.*⁶ treated nine eyes of nine patients with moderate-to-severe AKC with 0.1% tacrolimus eye drops twice daily. After 1 month, the corneal fluorescein staining, conjunctival injection and conjunctival oedema scores were significantly reduced. Papillary formation did not show significant reduction. None of the patients reported side-effects, and there were no significant changes in intraocular pressure or development of cataract.

Miyazaki *et al.*⁷ treated five patients (nine eyes) with AKC with tacrolimus 0.02% dermatological ointment 1–4 times daily in both eyes. Treatment with steroids was continued during this study. All patients noted decreased symptoms within 2–4 weeks, and the inflammation score (irritation of the conjunctivae) dropped with

Table 1 Results

Article	+	–
Ohashi <i>et al.</i> ⁵ 41 patients	Significant reduction in objective ocular signs after 2 and 4 weeks, respectively, –4.4 (SD $\pm$ 3.4 P = 0.012) and –5.4 (SD $\pm$ 4.2 P = 0.008) No development of cataract, glaucoma or visual loss	One patient developed herpes keratitis Ocular irritation in 42.9%
Wakamatsu <i>et al.</i> ⁶ patients	Significant reduction in corneal fluorescein staining scores: 5.50 $\pm$ 4.14–0.28 $\pm$ 0.75 (P = 0.016) Significant reduction in conjunctival injection scores: 2.89 $\pm$ 0.33–1.00 $\pm$ 0.53 (P = 0.004) Significant reduction in conjunctival oedema scores: 2.78 $\pm$ 0.67–1.00 $\pm$ 0.92 (P = 0.016) No side-effects reported No increase in intraocular pressure or development of cataract	
Miyazaki <i>et al.</i> ⁷ patients	Inflammation scores reduced with a mean of 2.0 ($\pm$ 0.7 range 1–3) Clinical parameter scores reduced with a mean of 1.11 ($\pm$ 0.87 range 0–3) Mean intraocular pressure reduced by 9.33 mmHg ($\pm$ 5.35 range 2–20) No development of cataract	There was simultaneous use of ocular corticosteroids; however, this was stopped by 4/5 (80%) of the patients. Ocular irritation in 90%
Joseph <i>et al.</i> ⁸ 1 patient		One patient developed herpes keratitis
García <i>et al.</i> ⁹ 1 patient	Reduction of symptoms 70% reduction in the number of giant papillae under the eyelids after 8 weeks No visual loss	



Figure 1 Patient with atopic keratoconjunctivitis.

Table 2 Clinical parameters

Skin involvement	Ocular involvement
1. Redness and scaling of the eyelids	1. Burning sensation
2. Severe eyelid oedema	2. Excessive tearing
3. Crusting and maceration of the eyelids	3. Loss of cilia
4. Lichenification of the lid crease	4. Redness of conjunctiva
5. Protruding (or ectropion) of the eyelids	5. Opacification of the cornea with decreased visual acuity

a mean of 2.0 (SD $\pm$ 0.7 range 1–3). Topical application of corticosteroids was stopped by 4/5 patients (80%). The mean intraocular pressure reduced by 9.33 mmHg ($\pm$ 5.35, range 2–20). The incidence of ocular irritation was 90%.

Joseph *et al.*⁸ treated one patient with AKC with tacrolimus 0.03% dermatological ointment twice daily on the ocular surface. Treatment was complicated by a de-novo herpetic keratitis in the left eye after 1 week. Switching to trifluridine eye drops in the left eye leads to disappearance of the herpes keratitis.

Finally, García *et al.*⁹ reported on a patient with chronic, recurrent AKC with giant papillae, who was treated with tacrolimus 0.03% dermatological ointment twice daily in both eyes. After 2 months, symptoms had significantly reduced and the size of the giant papillae was reduced by 70%. Visual acuity remained stable and the patient remained asymptomatic after 8 months.

The results of the above-mentioned studies demonstrate the efficacy of ocular application of tacrolimus in patients with AKC. However, the study groups were small, there was a short follow-up and only Ohashi⁵ and Wakamatsu⁶ applied a prospective study design.

Overall, two patients with AKC (3.5%) developed a herpes keratitis after ocular application of tacrolimus. Herpes keratitis is more often noted in patients with AD.¹⁰ Because of this predisposition in combination with the immunosuppressive effect of tacrolimus, it is important to conduct an adequate follow-up by an ophthalmologist. Ocular irritation seems to be the most common side-

effect of topically applied tacrolimus. Among the reviewed studies, 38.6% of patients suffered from these side-effects.

In conclusion, AKC is a serious ophthalmic disorder occurring relatively frequent in patients with AD. Inadequate treatment of eyelid dermatitis/blepharitis may lead to the sequel of conjunctivitis/AKC and thereby lead to corneal damage, eventually causing permanent blindness. Therefore, early recognition and adequate treatment of eyelid dermatitis are important. Dermatologists have an important role in recognizing symptoms of AKC and should not hesitate to refer to an ophthalmologist. Table 2 gives important clinical parameters for a dermatologist to refer. Regarding the current limited data from literature, ocular application of tacrolimus 0.1% 0.03% and 0.02% seems effective in treating patients with AKC; however, ocular irritation may limit its use. Because of the risk of development of herpes keratitis, adequate follow-up is advised.

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