

Vernal keratoconjunctivitis: Result of a novel therapy with 0.1% topical ophthalmic FK-506 ointment

To the Editor:

Vernal keratoconjunctivitis (VKC) is a serious childhood ophthalmologic condition. Despite its limited natural course with disease activity subsiding upon reaching pubertal age, significant morbidity was observed.^{1,2} Histologically, eosinophilic infiltration is seen within giant conjunctival follicles and in the limbal "Trantas dot." CD4+ T cells are found abundantly in conjunctival scrapings and biopsy specimens.³ These CD4+ cells had been cloned and were demonstrated to exhibit T_H2 phenotypes.⁴

The therapy of VKC includes cold compress, natural tears, avoidance of specific/nonspecific triggers, and application of topical ophthalmic preparations ranging from antihistamines and mast cell stabilizers to periodic use of topical corticosteroids for exacerbations.⁵ By far, none of these treatments yields a complete relief to affected patients.² Such findings suggest that the treatment of VKC should be targeted toward reduction of the T_H2 activity. We report the result of our open-label trial of 0.1% topical tacrolimus ointment in 10 patients with recalcitrant VKC (9 boys and 1 girl; mean age, 9.12 ± 2.45 years). The diagnosis of VKC was based on its characteristic eye symptoms (intense itching, tearing, mucous secretion, photophobia) and the presence of upper tarsal giant papilla or the gelatinous limbal infiltrates—the Trantas dot.^{2,3} Mean duration of disease before the enrollment was 3.96 ± 1.96 years (range, 1.5 to 7 years). All patients failed to respond satisfactorily to sufficient trial of conventional VKC treatment (cyclosporine, 7; lodoxamide, 3; olopatadine, 6; sodium cromoglycate, 3; and emedastine, 3). Nine patients had concomitant allergic rhinitis and 2 had asthma. Skin prick tests were positive in 9 patients (house dust mites, 7; acacia, 2; cat, 1; cockroach, 1; and grass pollen, 1). Written informed consent was obtained from all patients and/or their parents. Previous topical ocular medications were discontinued during a 1-week run-in period. Rescue treatment allowed during the entire study was natural tears. Oral antihistamine was allowed only in those who had previously taken the drug before enrollment (5 of 10 patients).

Physical and ophthalmologic examination was carried out before the run-in and then at weekly intervals during the treatment period. At the end of the 1-week run-in, patients were begun on topical 0.1% FK-506 eye ointment prepared by our hospital pharmacy (oral tacrolimus capsules, Prograf, Fujisawa, Japan) mixed with ophthalmic base containing 80% paraffin, 10% liquid paraffin, and 10% lanolin). The ointment was packed under sterile condition into a 5-g ophthalmic tube dispenser. This ophthalmic preparation was initially applied in a Phase-I trial (applying once per week and proceeding to twice per week and then daily in 1 patient with VKC) without any significant side effects.

FK-506 ointment, at 0.5 cm (in length), was applied to the lower conjunctival sac of both eyes, once or twice

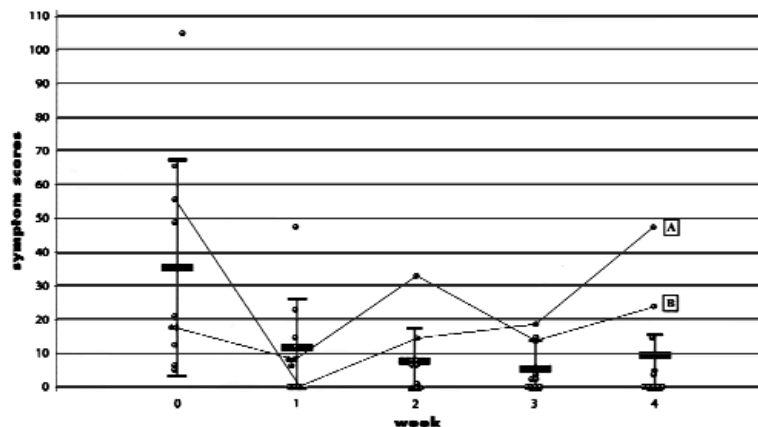


FIG 1. Dot-plot showing individual symptom scores at various time points of treatment (one dot represents one patient), with bars indicating mean score (and standard deviation) at various time points. The two line graphs are symptom scores of the two patients with higher scores (patient A and patient B, see text for details). Comparison of symptom scores at baseline and at 1 week of treatment was statistically significant ($P < .05$).

daily, according to disease severity, for 4 weeks. Patients recorded their daily eye symptoms in diary cards (eye itching, tearing, photophobia, discharge, blepharospasm, and foreign body sensation on a scale of 0 to 3, with 0 = no symptom, 1 = noticeable discomfort on an occasional basis, 2 = frequent discomfort, and 3 = constant discomfort throughout the day) during the run-in and throughout the treatment period. Adverse effects were recorded on the scorecard. Objective ophthalmologic findings including hyperemia, papillary size, punctate keratitis, and Trantas dots were scored on a scale of 0 to 3 (none, mild, moderate, and severe). External ocular photography of everted upper tarsal conjunctiva was taken at the beginning and at the end of treatment. Patients' compliance was checked from the diary card and by inspection of the remaining drug at each visit. Data of this open-label trial are reported with the permission from the Human Ethic Review Committee of the Siriraj Hospital.

Three patients had run-in weekly eye symptom scores of >50 , whereas 2 had scores between 20 and 50 and 5 had scores <20 . Superficial corneal punctate keratitis was noted in 6 cases and Trantas dot in 1 case. FK-506 was used once daily in 6 patients and twice daily in 4 patients.

Fig 1 depicts weekly eye symptom scores (with mean $\pm$ SD) of all patients during the run-in and week 1 through 4 of treatment. All patients responded rapidly to the treatment, with a mean score at the end of the first week reaching 31% of their baseline (11.8 ± 14.5 vs 35.4 ± 32.5 , $P = .015$, Wilcoxon signed-rank test). At the end of the therapy, the mean symptom score was 20% of baseline. Patient A had an increase in his eye symptoms on the second week as the result of his existing corneal scar, requiring corneal debridement on the third week. His symptoms persisted despite an improvement in objective findings. Patient B had an increase in symptoms at the end of the first week, necessitating a change of his treatment regimen from single to twice daily, to which he responded satisfactorily.

Mean size of tarsal papilla at the end of the study was significantly reduced as compared with baseline (right eye, 1.09 ± 0.64 mm vs 0.63 ± 0.57 mm; left eye, 1.19 ± 0.97 mm vs 0.57 ± 0.51 mm, $P < .05$). Fig 2 (a and b) illustrates the appearance of upper tarsal conjunctiva of patient C, who showed the greatest response to FK-506. There was a significant reduction in chemosis, conjunctival swelling, and injections at the end of the treatment period ($P = .046$).

The only adverse effect observed was transient eye stinging (7 patients). One patient had infectious conjunctivitis, which responded satisfactorily with the addition of topical antibiotics.

There was no significant change of CBC, BUN, creatinine, SGOT, and SGPT at the end of the study compared with baseline. Mean blood level of FK-506 (Tacrolimus-II, Abbott Laboratories) drawn at the completion of the study was 0.29 ± 0.38 ng/mL (range, 0 to 0.9 ng/mL). Significant eosinophilia (0.5 to 4+) from upper tarsal conjunctiva scrapings noted in 4 patients at the beginning of the study completely disappeared at the end of the therapy.⁶ In contrast, basophilic metachromatic cells persisted in conjunctival scrapings in most patients (8 in 9 patients). Patients and physician preferences assessed at the end of treatment indicated a high preference for treatment (score, 4/5).

The results of this initial trial of FK-506 in the treatment of VKC indicated a highly favorable response. In a recent trial with 2% cyclosporine, symptom scores up to 26% of baseline were observed at the end of the 4-month period.⁷ The persisting burning sensation from 2% cyclosporine is bothersome; the use of FK-506 may be more preferable for the lack of such problem.

Patients with tarsal VKC, with giant papilla, were found to be less responsive to cyclosporine compared with those with limbal VKC.⁷ Tarsal VKC is a disease with conjunctival follicles and giant papilla.⁵ Papilla are formed by accumulation of more chronic inflammatory

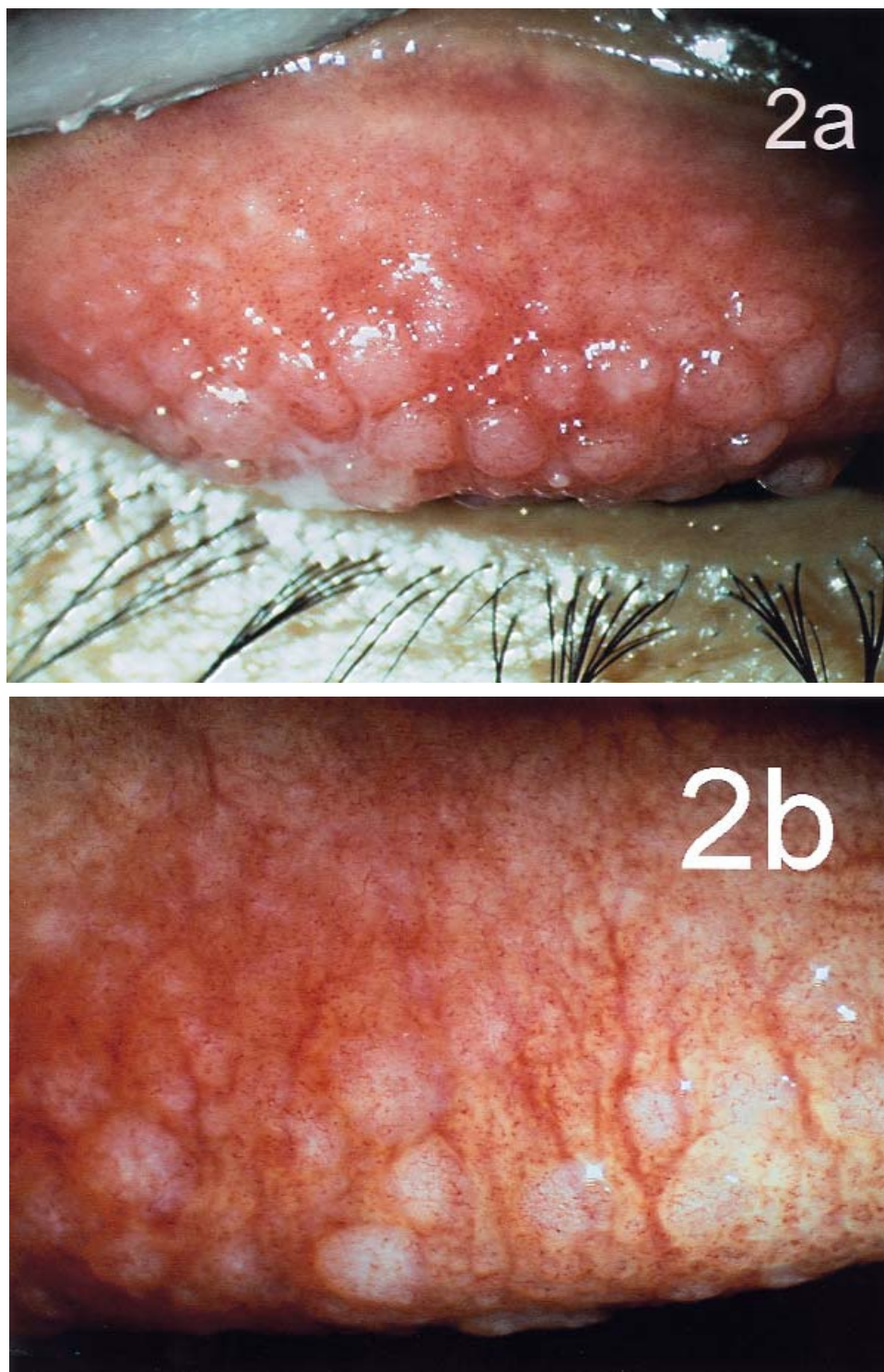


FIG 2. External ocular photography of everted upper tarsal conjunctiva of right eye from patient C at baseline (a) and at the end of the 4-week treatment with FK-506 (b).

cells of varying stages including fibroblasts, with hyperproduction of collagen type I and III, and with mucous metaplasia³ resembling the remodeling process of the lung in asthma⁸ and of skin in atopic dermatitis.⁹ FK-506 ointment was found to be highly effective in the treat-

ment of atopic dermatitis.¹⁰ Such a finding has led to our rationale of using FK-506 in severe VKC. The concentration of FK-506 in our study (0.1%) was based entirely on the dose response determined in patients with atopic dermatitis.¹⁰ Since the response to 0.1% FK-506 in this

study was quite dramatic, it is possible that lower concentration of FK-506 ophthalmic ointment could be tried in future studies. Absorption of FK-506 from conjunctiva was negligible, as observed from skin of patients with atopic dermatitis.¹⁰ A randomized, controlled trial comparing the use of FK-506 with placebo and with other conventional agents to verify the efficacy demonstrated in this initial report is urgently needed.

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