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The proactive treatment of atopic dermatitis with tacrolimus ointment in Korean patients: a comparative study between once-weekly and thrice-weekly applications

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MADAM, Atopic dermatitis (AD) typically runs a chronic course of flares and remissions. A proactive approach, with long-term treatment of AD using low-dose, intermittent, topical anti-inflammatory agents has been shown to control acute disease and prevent relapses.^{1,2} Tacrolimus ointment is a topical calcineurin inhibitor (TCI) that has been demonstrated to be efficient in the treatment of AD; the effectiveness of proactive treatment with tacrolimus has been confirmed in previous clinical trials.^{3–6} To date, no study has compared the efficacy and tolerability of different proactive treatment regimens, such as the frequency of tacrolimus ointment application. We compared the effectiveness of proactive treatment with tacrolimus ointment administered either once weekly or thrice weekly in delaying and reducing the occurrence of AD exacerbations.

During the stabilization phase (phase I), patients with moderate-to-severe AD applied tacrolimus ointment 0.1% (Protopic®; Astellas Pharma US Inc., Deerfield, IL, U.S.A.) to all affected areas twice daily for 4 weeks. When an Investigator Global Assessment (IGA) score of ≤ 2 (0, clear; 1, almost clear; 2, mild; 3, moderate; 4, severe; 5, very severe) was achieved, the patient then began the maintenance phase (phase II) and was randomly assigned to apply tacrolimus ointment once

daily, either once weekly or thrice weekly for 40 weeks to areas previously affected. Disease exacerbations (DEs, defined as an IGA score >2) were treated with tacrolimus ointment twice daily until an IGA of ≤ 2 was regained, after which the randomized treatment was restarted. Statistical analyses were performed using SPSS 18.0 (SPSS, Chicago, IL, U.S.A.). A P-value of <0.05 was considered statistically significant.

A total of 275 patients were enrolled for phase I of the study. Of these patients, 142 completed phase I and the remaining 133 were excluded. The primary reason for exclusion was an IGA score >2 at the completion of phase I (77.4%). In total, 142 patients were randomly assigned to phase II, with 78 patients in the once-weekly group and 64 patients in the thrice-weekly group. There were no significant differences between the two treatment groups in demographic and baseline characteristics. Eighteen patients (23%) in the once-weekly group and 10 patients (16%) in the thrice-weekly group were excluded during phase II. The common reasons for early exclusion were voluntary withdrawal ($n = 12$, once weekly; $n = 7$, thrice weekly) and follow-up loss ($n = 6$, once weekly; $n = 3$, thrice weekly).

Primary endpoint analysis showed that the median time to the first relapse was not significantly different between the once-weekly group [110 days, 95% confidence interval (CI) 100–120] and the thrice-weekly group (106 days, 95% CI 96–116; $P = 0.79$) (Fig. 1a). The number of DEs was also not significantly different between the two groups ($P = 0.49$) (Fig. 1b). The mean length of treatment time for DE in the thrice-weekly group was longer than that of the once-weekly group, but this was not significantly different between the once-weekly and thrice-weekly groups (mean $\pm$ SD: 26.19 $\pm$ 19.79 vs. 31.93 $\pm$ 16.25 days; $P = 0.38$) (Fig. 1c). The IGA scores for the first DE in the once-weekly group were IGA 4 in 50% of patients and IGA 5 in 50%. The IGA scores for the first DE in the thrice-weekly group were IGA 3 in 2% of patients, IGA 4 in 48% and IGA 5 in 50% ($P = 0.57$) (Fig. 2a). The mean Eczema Area and Severity Index scores during the maintenance phase (phase II) were similar between the once-weekly and thrice-weekly groups and were not significantly different ($P = 0.93$) (Fig. 2b). During phase II, there were no significant differences between the two treatment groups in the incidence of application-site adverse events, such as burning sensation, pruritus and erythema.

Immunological justification of maintenance treatment is based on the fact that normal-appearing skin in patients shows barrier defects and subclinical inflammation.⁷ Thus, maintenance therapy applied to previously involved skin is essential to prevent disease relapse. To the best of our knowledge, this is the first study to evaluate the efficacy and tolerability of different proactive regimens using tacrolimus ointment. There were no significant differences in efficacy and safety between the once-weekly and thrice-weekly proactive regimens. Therefore, patients with AD should apply tacrolimus ointment regularly at least once weekly to enhance patient compliance. In phase I of our study, 48.4% of the patients dropped out prior to entering proactive therapy. This was mostly due to lack of

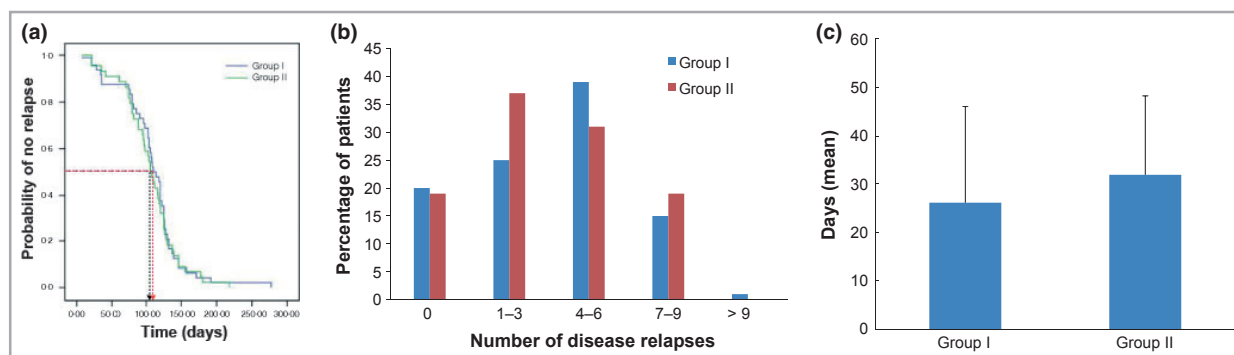


Fig 1. (a) Kaplan-Meier plot of the probability of remaining free of relapse. The median time to first relapse was 110 days for the once-weekly group (Group I) and 106 days for the thrice-weekly group (Group II) ($P = 0.79$). (b) Number of disease relapses. The number of disease relapses was not significantly different between the once-weekly and thrice-weekly groups ($P = 0.49$). (c) Mean treatment length for disease relapse during phase II. The mean number of treatment days for disease exacerbations in the thrice-weekly group was greater than that of the once-weekly group, which was not significantly different between the once-weekly and thrice-weekly groups (26.19 ± 19.79 vs. 31.93 ± 16.25 days; $P = 0.38$).

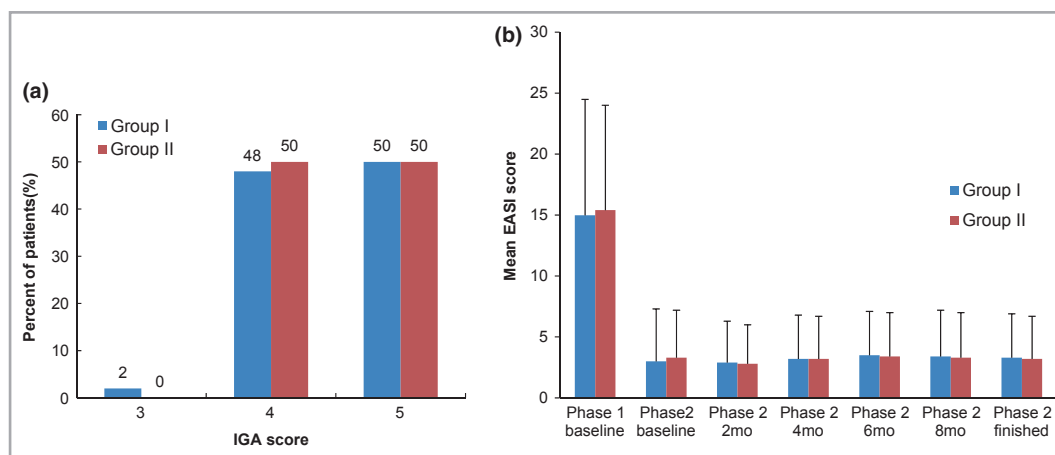


Fig 2. (a) Investigator Global Assessment (IGA) scores at the first disease relapse. The IGA scores for the first disease relapse did not significantly differ between the once-weekly (Group I) and thrice-weekly groups (Group II) ($P = 0.57$). (b) The mean Eczema Area and Severity Index (EASI) scores during maintenance phase (phase II) were similar between the once-weekly group and the thrice-weekly group and did not differ significantly ($P = 0.93$).

drug efficacy. This dropout rate is the highest reported for all proactive trials in AD, possibly resulting in trial data that are valid for a subpopulation of patients with mild AD only. The short stabilization period (phase I) might have resulted in selection of a population with milder disease. Thus, future studies with a large sample size are needed to confirm our results.

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Repigmentation of the epidermis around the acrosyringium in piebald skin: an ultrastructural examination

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MADAM, Piebaldism (MIM 172800) is an autosomal dominant disorder characterized by congenital poliosis and leucoderma on the frontal scalp, forehead, ventral trunk and extremities.

Piebaldism is caused by a mutation in the *KIT* protooncogene, which encodes the tyrosine kinase transmembrane cellular receptor that binds stem cell factor.¹ In general, the leucoderma associated with piebaldism is stable throughout life, and there are few or no melanocytes in the regions of affected skin. However, the appearance of a new pigmented region in piebald skin has been reported in several cases.^{2,3} This report describes evidence for repigmentation in piebald skin arising from a periacrosyringium region, based on ultrastructural observations.

A 3-month-old Japanese boy presented with aberrant hair and skin coloration. A physical examination revealed poliosis on the frontal scalp, and leucoderma on the forehead, ventral trunk, knee and elbows (Fig. 1a). There was no family history of genetic disorders or parental consanguinity. We performed a gene-sequence analysis of the *KIT* gene in a peripheral blood sample according to a previous report,⁴ after obtaining the informed consent from the patient's parents. The protocol was conducted according to the Declaration of Helsinki principles and was approved by the Genetic Ethics Committee of the University of Toyama and Kinki University Faculty of Medicine. A heterozygous substitution (p.G664R) was identified in exon 13 of the *KIT* gene. This mutation was previously reported by Spritz.⁵ The patient was therefore diagnosed with piebaldism. As he aged, several pigmented regions gradually appeared and extended within the piebald skin without any treatments. At 4 years of age, a histological examination of skin from a repigmented region was performed (Fig. 1b).

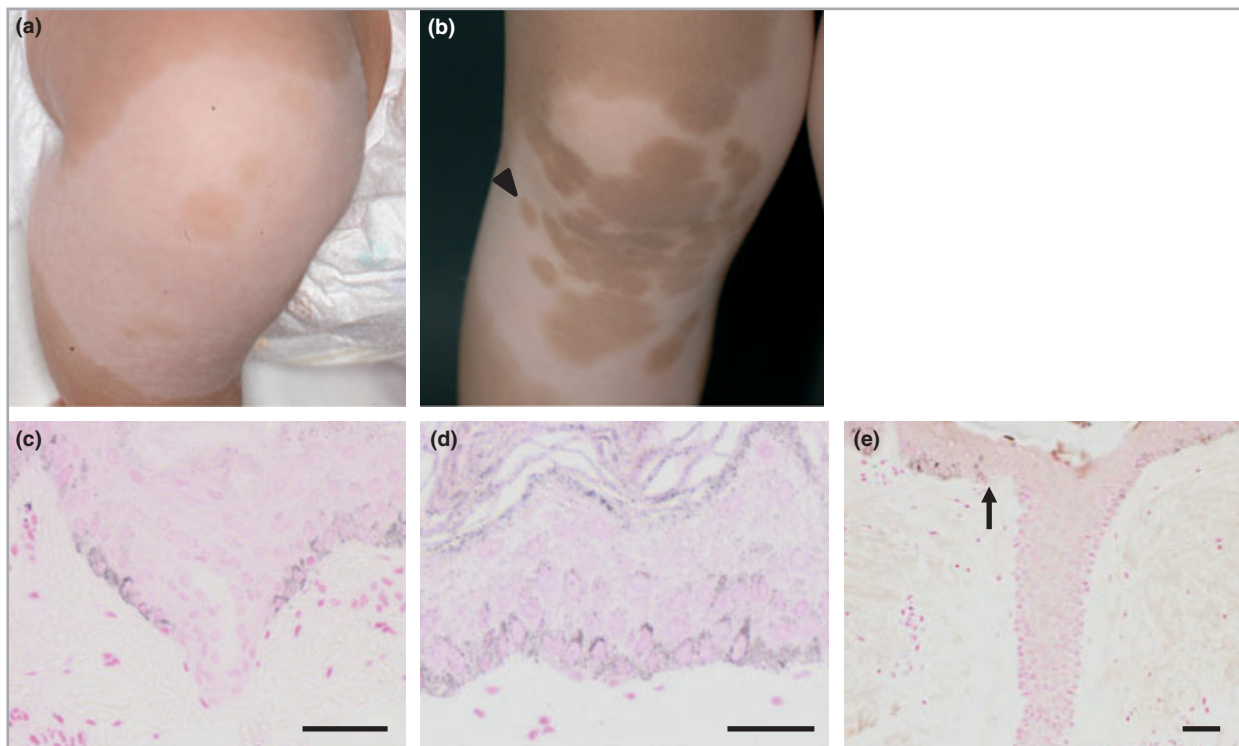


Fig 1. Clinical features of the right knee at 3 months of age (a) and 4 years of age (b). The arrowhead indicates the skin region that was excised for a histological examination. Fontana–Masson staining of the epidermis around the acrosyringium (c), intrafollicular epidermis (d) and hair follicles (e). The arrow indicates the discontinuous melanin distribution in the intrafollicular epidermis. The scale bar is 50 µm.