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A SHORT-TERM TRIAL OF TACROLIMUS OINTMENT FOR ATOPIC DERMATITIS

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ABSTRACT

Background Tacrolimus (FK 506) is an effective immunosuppressant drug for the prevention of rejection after organ transplantation, and preliminary studies suggest that topical application of tacrolimus is effective in the treatment of atopic dermatitis.

Methods We conducted a randomized, double-blind, multicenter study that compared 0.03 percent, 0.1 percent, and 0.3 percent tacrolimus ointment with vehicle alone in patients with moderate-to-severe atopic dermatitis. The ointment was applied twice daily to a defined, symptomatic area of 200 to 1000 cm² of skin for three weeks. The primary end point was the change in the summary score for erythema, edema, and pruritus between the first and last days of treatment.

Results After three weeks of treatment, the median percentage decrease in the summary score for dermatitis on the trunk and extremities was 66.7 percent for the 54 patients receiving 0.03 percent tacrolimus, 83.3 percent for the 54 patients receiving 0.1 percent tacrolimus, 75.0 percent for the 51 patients receiving 0.3 percent tacrolimus, and 22.5 percent for the 54 patients receiving vehicle alone ($P < 0.001$). The results for the face and neck were similar. The differences among the three tacrolimus groups were not statistically significant. A sensation of burning at the site of application was the only adverse event that was significantly more frequent with tacrolimus than with vehicle alone ($P < 0.001$). Throughout the study, most patients in all three tacrolimus groups had blood concentrations of tacrolimus below 0.25 ng per milliliter. The highest concentration was 4.9 ng per milliliter, which was reported in the group receiving 0.3 percent tacrolimus.

Conclusions The short-term application of tacrolimus ointment is effective in the treatment of atopic dermatitis, with the sensation of burning being the main side effect. (N Engl J Med 1997;337:816-21.)

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ATOPIC dermatitis, an inflammatory skin disease with a chronically relapsing course, is characterized by episodes of intense pruritus, lichenification, severely dry skin, and a susceptibility to cutaneous infections.¹⁻³ There is currently no safe alternative to the topical application of corticosteroids for the control of acute episodes of atopic dermatitis. Although topical corticosteroids are generally well tolerated, they commonly

cause skin atrophy and less frequently cause hypopigmentation, secondary infections, and acne.⁴ Topical cyclosporine has been investigated as an alternative treatment in patients with atopic dermatitis and other dermatoses, but these studies have met with little success, presumably because of inadequate penetration of the drug into the skin.⁴⁻⁶ One study did show a significant effect of a cyclosporine gel as compared with a placebo gel after two weeks of treatment, but the differences between the dermatitis scores for the study groups were small.⁷

Tacrolimus (FK 506) is an effective and well-tolerated primary immunosuppressant drug used in solid organ transplantation.⁸ Although its mode of action is similar to that of cyclosporine, its molecular weight is lower and its potency in inhibiting T-cell activation is 10 to 100 times greater.⁹ Moreover, topically applied tacrolimus appears to penetrate the skin sufficiently to effect local immunosuppression. Topical tacrolimus inhibits experimentally induced allergic contact dermatitis,¹⁰ and preliminary studies have suggested that the drug is effective in the treatment of atopic dermatitis.¹¹⁻¹³

To assess the efficacy and safety of topical tacrolimus in patients with atopic dermatitis, we compared ointments containing 0.03, 0.1 and 0.3 percent tacrolimus with vehicle alone. The primary end point was a combined score for erythema, edema, and pruritus. The study was carried out at 16 centers in Europe between April 1995 and March 1996.

METHODS

Study Design

This was a phase 2, randomized, double-blind, multicenter study. A three-week treatment phase, during which ointment was

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applied to a defined symptomatic area of 200 to 1000 cm² of skin, was preceded by a one-week washout phase and followed by a one-week follow-up phase. The study was conducted in compliance with guidelines for good clinical practice from the Committee for Proprietary Medicinal Products of the Commission of the European Communities.

Patients

Male and female patients, 13 to 60 years of age, with a confirmed diagnosis of moderate-to-severe atopic dermatitis, according to the criteria of Rajka and Langeland,¹⁴ were recruited for the study. All patients gave informed consent, and the study was approved by the ethics committee at each participating center. Patients were excluded if they had received any therapy for atopic dermatitis, other than emollients or antihistamines, within three weeks before the start of the washout phase. The criteria for entry into the treatment phase were a symptomatic area of at least 200 cm² of skin on the trunk or extremities or both, and no evidence of hypersensitivity to the ointment base (tested by daily application during the washout phase).

At the start of the treatment phase, 200 to 1000 cm² of affected skin was selected for treatment. The affected area could be noncontiguous and could include the trunk, extremities, face, and neck, but at least 200 cm² had to be on the trunk or extremities. Investigators were instructed to select the lesions with the worst erythema and edema.

Treatment

Patients were assigned to receive 0.03, 0.1, or 0.3 percent tacrolimus ointment (Fujisawa) or vehicle alone (the ointment base) on the basis of a 1:1:1 randomization scheme stratified by center. The ointment base was an oil-oil emulsion containing propylene carbonate, white wax, mineral oil, paraffin, and petrolatum. Every week, during the treatment phase, eight 10-g tubes were dispensed to each patient. The patients were instructed to apply the ointment to the selected area twice daily, with each application separated by about 12 hours. The investigators, patients, and study monitors were not aware of the treatment assignments.

No concurrent treatment, other than emollients or bath oil, was allowed during the study. Explicitly prohibited were other experimental treatments, tranquilizers and sleeping pills, and systemic, topical, or inhaled corticosteroids, antihistamines, and antimicrobial drugs.

Assessments

At base line, the patient's overall disease was assessed. Total-body involvement was estimated with the use of transparent shapes of 100 to 1000 cm² or by the rule of nine, which assigns standard measurements to body parts on the basis of the size of the body part.¹⁴ The total-body score was the sum of the individual scores, on a scale of 0 to 3, for erythema, edema, pruritus, oozing or crusting, excoriation, and lichenification of all involved skin, dryness of noninvolved skin, and sleep loss.

The area selected for treatment was assessed at base line (the day on which the patient was assigned to a treatment group); after three days and one, two, and three weeks of treatment; and one week after the completion of treatment. The investigator graded the area selected for treatment, on a scale of 0 to 3, for the severity of erythema, edema, oozing or crusting, excoriation, and lichenification of involved skin and dryness of noninvolved skin. The patient graded the pruritus of the selected area on a 10-cm visual-analogue scale, with severe at the bottom and absent at the top; this grade was converted to a score of 0 to 3 for analysis. At the end of the treatment phase, an overall assessment of the condition of the treated area (symptoms completely resolved, markedly improved, moderately improved, slightly improved, unchanged, or worse) was performed by both the investigator and the patient. To ensure consistency in the assessments of efficacy, all the investigators received a manual and participated in a one-day, centralized training course, as well as on-site training.

Adverse events were recorded at all study intervals, whether or not the events were thought to be related to the study drug. Laboratory tests were performed at base line and after one, two, and three weeks of treatment; these included assessments of hematologic variables, serum electrolytes, renal and hepatic function, blood glucose, and serum total IgE. For a retrospective analysis of any potential toxic effects, whole-blood concentrations of tacrolimus were also measured at these intervals, as well as three days after the start of treatment.

End Points

The primary end point was the change in score 1 (the sum of the scores for erythema, edema, and pruritus in the treated area) from base line to the completion of treatment. Score 1 was chosen as the primary end point because pruritus is always present in patients with atopic dermatitis^{1,2} and because we anticipated that erythema and edema would be reliable markers of active disease. Secondary end points were the change from base line in score 2 (score 1 plus the sum of the scores for oozing or crusting, excoriation, and lichenification of involved skin and dryness of noninvolved skin in the treated area) and the overall assessments of the treated area by the investigator and the patient.

Statistical Analysis

For scores 1 and 2, absolute and percentage changes from base line to day 3 and weeks 1, 2, and 3 of treatment were calculated. The Jonckheere test was used to test the hypothesis of no differences among the distribution functions for the four treatment groups against the alternative hypothesis of ordered distribution functions.¹⁵ If the scores at the week 3 visit were missing, the last scores available during treatment were substituted. Separate analyses were performed for the trunk and extremities and the face and neck. To test the primary end point for a center effect, base-line effect, and treatment effect, an area under the time curve was calculated from each patient's score 1 data, and an analysis of variance was performed.

RESULTS

Patients

A total of 250 patients were screened, and 215 were randomly assigned to a treatment group. After randomization, two patients were excluded: one who never received treatment and one for whom only base-line data were available. Thus, 213 patients were included in the intention-to-treat analysis: 54 received 0.03 percent tacrolimus, 54 received 0.1 percent tacrolimus, 51 received 0.3 percent tacrolimus, and 54 received vehicle alone. The four groups were well matched with regard to demographic and base-line characteristics (Table 1). In all four groups, the mean area selected for treatment (approximately 800 cm²) was about a fifth of the mean total affected area. The reasons for withdrawal from the study were similar among the treatment groups, except that more patients in the vehicle group than in any of the tacrolimus groups were withdrawn because of the use of prohibited therapy (Table 1).

Scores 1 and 2

For both the trunk and extremities and the face and neck, a significant difference was observed among the treatment groups in the change in score 1 (the

TABLE 1. DEMOGRAPHIC AND BASE-LINE CLINICAL CHARACTERISTICS OF THE PATIENTS AND REASONS FOR WITHDRAWAL FROM THE STUDY.*

VARIABLE	0.03% TACROLIMUS (N=54)	0.1% TACROLIMUS (N=54)	0.3% TACROLIMUS (N=51)	VEHICLE (N=54)
Mean age — yr	30±12	28±9	27±10	29±11
Female sex — no. (%)	28 (52)	32 (59)	32 (63)	28 (52)
White race — no. (%)	52 (96)	51 (94)	48 (94)	53 (98)
Mean total-body involvement — cm ²				
Trunk and extremities	3848±3680	3452±4361	3367±3654	3453±3730
Face and neck	307±341	354±331	344±327	404±364
Median total-body score†	13.5	13.0	14.0	14.0
Area selected for treatment				
Mean area — cm ²	809±273	778±271	821±254	821±260
Median score 1‡	6.0	6.0	6.0	6.0
Withdrawal from study — no. (%)	7 (13)	7 (13)	7 (14)	21 (39)
Reason for withdrawal — no. (%)				
Use of prohibited therapy	2 (4)	0	3 (6)	13 (24)
Adverse event	1 (2)	4 (7)	3 (6)	5 (9)
Other	4 (7)	3 (6)	1 (2)	3 (6)

*Plus-minus values are means ±SD.

†The total-body score was calculated as the sum of the scores for erythema, edema, pruritus, oozing or crusting, excoriation, and lichenification of involved skin, dryness of noninvolved skin, and sleep loss (range of possible scores, 0 to 24).

‡Score 1 was calculated as the sum of the scores for erythema, edema, and pruritus (range of possible scores, 0 to 9).

sum of the scores for erythema, edema, and pruritus in the treated area) between base line and the end of the treatment period ($P<0.001$, by the Jonckheere test, for both the absolute and percentage changes). The median percentage decreases in the scores for the trunk and extremities were 66.7, 83.3, and 75.0 percent for the groups that received 0.03, 0.1, and 0.3 percent tacrolimus, respectively, and 22.5 percent for the vehicle group. For the face and neck, the values were 71.4 percent, 83.3 percent, 83.3 percent, and 25.0 percent, respectively. Improvement in symptoms was apparent three days after the start of treatment (Fig. 1). An analysis of variance confirmed a treatment effect ($P<0.001$) and showed a significant difference between each of the tacrolimus groups and the vehicle group ($P<0.001$), with no significant interaction between treatment and the participating center and no significant baseline differences between the treatment groups. Although the median percentage decreases in scores 1 and 2 over time were greater in the groups receiving 0.1 and 0.3 percent tacrolimus than in the group receiving 0.03 percent tacrolimus, an analysis of variance with pairwise comparisons showed no significant differences among the three tacrolimus groups. A separate analysis, in which data related to protocol violations were excluded, yielded similar results.

Changes between base line and the end of the treatment period in score 2 (the sum of score 1 and the scores for oozing or crusting, excoriation, and lichenification of involved skin and dryness of non-

involved skin) also differed significantly among the four treatment groups ($P<0.001$, by the Jonckheere test, for both the absolute and percentage changes). For the trunk and extremities, the median decreases from base line to the end of treatment were 61.5 percent, 71.4 percent, and 70.0 percent for the groups that received 0.03, 0.1, and 0.3 percent tacrolimus, respectively, and 21.8 percent for the vehicle group. The values for the face and neck were 70.6 percent, 75.0 percent, 77.8 percent, and 27.3 percent, respectively. The median percentage decreases over time were similar to those for score 1 (data not shown).

Overall Assessments

According to the investigators' overall assessments of the treated areas, a significantly higher proportion of patients in each of the tacrolimus groups than in the vehicle group had completely resolved or markedly improved symptoms ($P<0.001$ by the chi-square test) (Fig. 2). The results were similar for the patients' overall assessments ($P<0.001$ by the chi-square test; data not shown).

Adverse Events

There were no significant differences among the treatment groups in the overall incidence of adverse events. Thirty-two of the 54 patients receiving 0.03 percent tacrolimus, 33 of the 54 receiving 0.1 percent tacrolimus, 32 of the 51 receiving 0.3 percent tacrolimus, and 23 of the 54 receiving the vehicle

Figure 1. Median Percentage Decreases in Score 1 from Base Line to the End of Treatment in Patients with Atopic Dermatitis Who Received Tacrolimus (0.03 Percent, 0.1 Percent, or 0.3 Percent) or Vehicle Alone.

Score 1 was calculated as the sum of the scores for erythema, edema, and pruritus in the treated area. The median percent decreases in score 1 were larger in each of the tacrolimus groups than in the vehicle group ($P < 0.001$ by the Jonckheere test). The bars denote interquartile ranges.

alone had at least one adverse event. The sensation of burning at the site of application was the only event with a significantly higher incidence in the tacrolimus groups than in the vehicle group ($P < 0.001$ by the chi-square test); 20 patients receiving 0.03 percent tacrolimus, 25 receiving 0.1 percent tacrolimus, and 25 receiving 0.3 percent tacrolimus reported a burning sensation, as compared with 8 patients receiving the vehicle alone. The two other most frequently reported events at the site of application were pruritus (reported by 7, 2, 7, and 4 patients in the four treatment groups, respectively) and erythema (reported by 3, 6, 6, and 3 patients in the four treatment groups, respectively). The most frequent

Figure 2. Overall Assessments of the Treated Areas after Three Weeks of Treatment.

The proportion of patients whose symptoms were completely resolved or markedly improved, according to the investigators' assessments, was higher in each of the tacrolimus groups than in the vehicle group ($P < 0.001$ by the chi-square test).

event involving untreated areas was an exacerbation of atopic dermatitis, which was reported by 4, 4, 2, and 7 patients in the four treatment groups, respectively.

In the tacrolimus groups, all adverse events that led to withdrawal from the study occurred at the site of application of the ointment. One patient with folliculitis in the 0.03 percent group, three patients with burning and one with pruritus in the 0.1 percent group, and two patients with burning and one with a suspected viral skin infection in the 0.3 percent group were withdrawn from the study. In the vehicle group, two patients with adverse events at the site of application (burning and pruritus, respectively) were withdrawn, as well as three patients with adverse events unrelated to the site of application (exacerbation of atopic dermatitis in all three cases).

Whole-Blood Concentrations of Tacrolimus

Overall, whole-blood concentrations of tacrolimus were very low during the study. A large proportion of the patients had values below the detection limit of the assay (0.05 ng per milliliter) at all intervals, and only a small number of patients had concentrations higher than 1 ng per milliliter (Table 2).

Clinical Laboratory Assessments

The median values for all clinical laboratory variables were similar in the four treatment groups and

TABLE 2. BLOOD CONCENTRATIONS OF TACROLIMUS DURING THE TREATMENT PHASE.*

TACROLIMUS GROUP AND CONCENTRATION	TIME FROM BASE LINE			
	3 DAYS	1 WEEK	2 WEEKS	3 WEEKS
0.03% Group				
<0.05 ng/ml — no. (%)	19 (49)	18 (43)	18 (49)	13 (38)
0.05 to <0.25 ng/ml — no. (%)	12 (31)	15 (36)	15 (41)	16 (47)
0.25 to 1.0 ng/ml — no. (%)	8 (21)	9 (21)	4 (11)	5 (15)
>1.0 ng/ml — no. (%)	0	0	0	0
Maximum — ng/ml	1.0	0.6	0.5	0.5
0.1% Group				
<0.05 ng/ml — no. (%)	7 (19)	11 (26)	10 (24)	9 (24)
0.05 to <0.25 ng/ml — no. (%)	12 (32)	17 (40)	17 (40)	22 (58)
0.25 to 1.0 ng/ml — no. (%)	13 (35)	11 (26)	15 (36)	6 (16)
>1.0 ng/ml — no. (%)	5 (14)	3 (7)	0	1 (3)
Maximum — ng/ml	2.4	3.3	0.8	1.1
0.3% Group				
<0.05 ng/ml — no. (%)	6 (18)	7 (19)	5 (15)	7 (25)
0.05 to <0.25 ng/ml — no. (%)	11 (32)	12 (32)	16 (48)	7 (25)
0.25 to 1.0 ng/ml — no. (%)	7 (21)	17 (46)	11 (33)	14 (50)
>1.0 ng/ml — no. (%)	10 (29)	1 (3)	1 (3)	0
Maximum — ng/ml	4.9	1.9	1.6	1.0

*Measurements were made in 39, 42, 37, and 34 of the patients in the 0.03 percent group at 3 days, 1 week, 2 weeks, and 3 weeks, respectively. The comparable numbers in the 0.1 percent group were 37, 42, 42, and 38, and in the 0.3 percent group they were 34, 37, 33, and 28.

did not change appreciably during the study. Similarly, there were no apparent differences in the frequency of individual changes in any given variable.

DISCUSSION

In this controlled study, each of the three tacrolimus ointments was more effective than the vehicle alone. There were no statistically significant differences among the active treatments, although there was a trend toward an advantage with 0.1 percent tacrolimus over 0.03 percent tacrolimus. However, the numbers of patients in the three groups were too small to conclude that there were no differences among the active treatments.

An acceptably safe range of systemic exposure to tacrolimus has not been established in patients with atopic dermatitis. In patients with psoriasis who received oral tacrolimus, toxicity was not apparent with a median trough blood concentration of 10 ng per milliliter over a nine-week period.¹⁶ In organ-transplant recipients, levels are generally kept below 20 ng per milliliter to reduce the risk of toxicity.¹⁷ Systemic exposure was low in our study, and the decrease in trough concentrations over time is consistent with the results of a recent study, which showed that the absorption of tacrolimus into the bloodstream decreased as skin healed in patients with atopic dermatitis, with no absorption through the skin of healthy controls.¹³ Thus, systemic exposure to tacrolimus seems to depend on a compromised barrier function and should be brief in the small

number of patients with substantial blood concentrations at the beginning of treatment. Our data also suggest a dose-response relation with regard to blood concentrations. However, the design of the study does not allow an analysis of pharmacokinetic characteristics. Blood was obtained at different times in relation to the application of the ointment, and blood samples were not obtained from all patients at each visit.

The sensation of burning at the site of application appears to have been the only drug-related adverse event. Since a large proportion of the patients who received the vehicle alone also reported this event, the burning may have been caused in part by the vehicle. In many patients, the sensation of burning decreased or ceased altogether as the skin healed, but this effect has not been systematically evaluated.

For patients who have lesions on the face, neck, or regions of flexure, where the skin is particularly thin, providing an alternative to topical corticosteroids that does not produce atrophy is crucial. At a concentration that had an efficacy similar to that of 0.13 percent clobetasol propionate (a superpotent corticosteroid that causes atrophy) in treating an inflammatory reaction in pigskin, topical tacrolimus did not cause atrophy.¹⁸ Skin atrophy was also not observed in our study, but the period of treatment was too short for clinical signs of atrophy to become apparent.

Whereas oral cyclosporine therapy in patients with atopic dermatitis causes increased serum urea, creat-

inine, and bilirubin concentrations,^{19,20} there were no changes in any clinical laboratory values during our study. The absence of nephrotoxicity would be an important advantage of topical tacrolimus therapy. Only short-term therapy is advisable with oral cyclosporine because of nephrotoxicity, and most patients have a relapse within six weeks after the withdrawal of the drug.²¹

We conclude that tacrolimus ointment is effective in the treatment of atopic dermatitis and that the only drug-related adverse event appears to be the sensation of burning at the site of application. In the special circumstances of our study, in which tacrolimus ointment was applied to a restricted area of skin and the period of treatment was limited to three weeks, the treatment had an acceptable safety profile. It will be important to obtain data on the safety of tacrolimus administered to a larger area of skin for a longer period.

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APPENDIX

In addition to the authors, the following investigators participated in the European Tacrolimus Multicenter Atopic Dermatitis Study Group: E. Wassmer (Heinrich Heine University, Düsseldorf, Germany); A. Wollenberg (Ludwig Maximilians University, Munich, Germany); W. Czech and J. Mueller (Albert Ludwigs University, Freiburg, Germany); I. Hartmane and R. Gutmane (Latvian Medical Academy, Riga, Latvia); L. Kemény (Albert Szent-Györgyi Medical University, Szeged, Hungary); P. Spuls (University of Amsterdam, Amsterdam); M. Blaszczyk (Dermatology Clinic, Warsaw, Poland); J. Berth-Jones (George Eliot Hospital, Nuneaton, United Kingdom); C. Larsen (Marselisborg Hospital, Århus, Denmark); M. Doliwo (Saint Joseph Hospital, Paris); P. Pigatto (University of Milan, Milan, Italy); A. Remitz and H. Granlund (Helsinki University Central Hospital, Helsinki, Finland); J. Ring and D. Abeck (Technical University, Munich, Germany); R. Camp and H. Shahidullah (Leicester Royal Infirmary, Leicester, United Kingdom); L. Fry and J. Garioch (St. Mary's Hospital, London); and G. Burg and R. Brinkhaus (University Hospital, Zurich, Switzerland).

REFERENCES

1. Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. *Acta Derm Venereol Suppl* (Stockh) 1980;92:44-7.
2. Merk H. Clinical symptoms of atopic eczema. In: Ruzicka T, Ring J, Przybilla B, eds. *Handbook of atopic eczema*. Berlin, Germany: Springer-Verlag, 1991:27-30.
3. Beltrani VS. The clinical manifestations of atopic dermatitis. In: Leung DYM, ed. *Atopic dermatitis: from pathogenesis to treatment*. Austin, Tex.: R.G. Landes, 1996:1-39.
4. Boguniewicz M, Leung DYM. Management of atopic dermatitis. In: Leung DYM, ed. *Atopic dermatitis: from pathogenesis to treatment*. Austin, Tex.: R.G. Landes, 1996:185-220.
5. De Rie MA, Meinardi MM, Bos JD. Lack of efficacy of topical cyclosporin A in atopic dermatitis and allergic contact dermatitis. *Acta Derm Venereol* 1991;71:452-4.
6. Thompson AW, Aldridge RD, Sewell HF. Topical cyclosporin in alopecia areata and nickel contact dermatitis. *Lancet* 1986;2:971-2.
7. de Prost Y, Bodemer C, Teillac D. Double-blind randomized placebo-controlled trial of local cyclosporine in atopic dermatitis. *Acta Dermatol* 1989;125:570.
8. Fung JJ, Todo S, Starzl TE. Tacrolimus in solid organ transplantation. In: Lieberman R, Mukherjee A, eds. *Principles of drug development in transplantation and autoimmunity*. Austin, Tex.: R.G. Landes, 1996:183-90.
9. Goto T, Kino T, Hatanaka H, et al. FK 506: historical perspectives. *Transplant Proc* 1991;23:2713-7.
10. Lauerma AI, Maibach HI, Granlund H, Erkkö P, Kartamaa M, Stubb S. Inhibition of contact allergy reactions by topical FK506. *Lancet* 1992;340:556.
11. Nakagawa H, Etoh T, Ishibashi Y, et al. Tacrolimus ointment for atopic dermatitis. *Lancet* 1994;344:883.
12. *Idem*. Effects of tacrolimus (FK506) ointment for facial atopic dermatitis. *Allergy* 1995;50:Suppl 26:368. abstract.
13. Kawashima M, Nakagawa H, Ohtsuki M, Tamaki K, Ishibashi Y. Tacrolimus concentrations in blood during topical treatment of atopic dermatitis. *Lancet* 1996;348:1240-1.
14. Rajka G, Langeland T. Grading of the severity of atopic dermatitis. *Acta Derm Venereol Suppl* (Stockh) 1989;144:13-4.
15. Jonckheere AR. A distribution-free *k*-sample test against ordered alternatives. *Biometrika* 1954;41:133-45.
16. The European FK 506 Multicentre Psoriasis Study Group. Systemic tacrolimus (FK 506) is effective for the treatment of psoriasis in a double-blind, placebo-controlled study. *Arch Dermatol* 1996;132:419-23.
17. Kershner RP, Fitzsimmons WE. Relationship of FK506 whole blood concentrations and efficacy and toxicity after liver and kidney transplantation. *Transplantation* 1996;62:920-6.
18. Meingassner JG, Stütz A. Immunosuppressive macrolides of the type FK 506: a novel class of topical agents for treatment of skin diseases? *J Invest Dermatol* 1992;98:851-5.
19. Sowden JM, Berth-Jones J, Ross JS, et al. Double-blind, controlled, crossover study of cyclosporin in adults with severe refractory atopic dermatitis. *Lancet* 1991;338:137-40.
20. van Joost T, Heule F, Korstanje M, van den Broek MJ, Stenveld HJ, van Vloten WA. Cyclosporin in atopic dermatitis: a multicentre placebo-controlled study. *Br J Dermatol* 1994;130:634-40.
21. Granlund H, Erkkö P, Sinisalo M, Reitamo S. Cyclosporin in atopic dermatitis: time to relapse and effect of intermittent therapy. *Br J Dermatol* 1995;132:106-12.