

and affect copayment for an MDI. Even modest increases in out-of-pocket costs can be a tremendous burden for some families. Some insurance companies and health care providers are addressing the problem by reducing copayments for these medications or providing free sample medications. However, these remedies are not universally practiced and may not be beneficial for a given family. Many families may not know the effect of changing health care plans and the subtleties of pharmaceutical drug coverage at the time of enrollment or even have a choice if employed by a small business. Pharmaceutical drug samples may not be fully available to all practitioners and ultimately rely on the industry to subsidize.

The economic effect of changes caused by the transition is not restricted to low-income families. For the 3.6 million children with asthma who are insured, most participate in pharmaceutical plans that have copay rates of \$5 to \$10 per generic drug prescription to encourage generic medication use. In the near future, there will be no generic option, and patients will be forced to carry branded product copayments reaching anywhere from \$20 to \$50 per prescription for tier 1 to 3 products. This can amount to a 200% to 400% increase in out-of-pocket costs for an insured individual per prescription. In addition, because of classification issues of the MDIs, a patient's copayment may in some cases approach the total cash cost for the MDI product alone. This situation offers little savings for a family either purchasing medications through an insurance company plan or paying out of pocket. With increased use of high deductible medical plans, families are often forced to pay for many medications out of pocket until the deductible is met, creating further financial burden. Although some insurance companies are beginning to modify copay policies, families must assume the cost burden in the meantime. Frequently, children need multiple MDI inhalers to have them available at school, on the athletic field, and at home. MDIs generally must be replaced yearly. These factors point to potential increases in family expenses in copays alone for a child by \$100 to \$200 per year, assuming no refills of hydrofluoroalkane MDIs are needed. Unintended outcomes of the transition could include less availability of valuable medicines and/or use of less effective or convenient alternatives—for example, nebulized SABA delivery. Use of less than optimum therapies has been shown to affect urgent health care use and morbidity.¹⁰

Of course, the positive results of the hydrofluoroalkane transition for the environment are thought to be important. Further, the possibility of an increase in out-of-pocket costs of SABAs for families may encourage their more consistent use controller medications. However, patients may choose to use their limited financial resources to purchase immediate rescue medications at the expense of controller medications. Health care providers may have an additional argument when counseling patients that long-term controller use is a cost-effective approach to disease control. However, the lack of affordable rescue medicine potentially leading to the need for more urgent and costly care may detract from such an argument.

The transition from chlorofluorocarbon-based medication to hydrofluoroalkane propellant technology has been protracted and not entirely easy to accomplish. The leaders of the change are to be commended. However at this junction, it appears that gaps in practices of both the health care system and pharmaceutical industry may leave children with asthma stranded in ways not anticipated. Federal and private insurance systems should take steps to reduce the costs of hydrofluoroalkane medications for

vulnerable families to prevent the negative consequences of forced noncompliance or use of less effective therapies.

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Disclosure of potential conflict of interest: H. L. Leo has served as a grant reviewer for the National Alopecia Aerata Foundation, has received research support from the National Eczema Association and the Food Allergy and Anaphylaxis Network, and is on the speakers' bureau for the Food Allergy and Anaphylaxis Network. The rest of the authors have declared that they have no conflict of interest.

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doi:10.1016/j.jaci.2007.12.1177

Recall antigen reactions in patients with atopic dermatitis treated with tacrolimus ointment for 1 year

To the Editor:

Tacrolimus is an immunosuppressive drug that acts by inhibiting early T-cell activation. Topical treatment, indicated for atopic dermatitis (AD), is associated with systemic tacrolimus levels of only 3% to 4% of those seen in patients with systemic immunosuppression after organ transplantation.

Skin tests with recall antigens are an indirect measure of delayed-type hypersensitivity. Patients with active AD have impaired reactions compared with the normal population.¹ Apparently normal patients with multiple skin cancers also have impaired cell-mediated immunity.²

We studied the effect of 1-year topical tacrolimus treatment on T-cell reactions of the skin in patients with AD. Further impaired recall antigen test reactions could indicate an increased skin cancer or lymphoma risk.

A total of 48 adult patients (aged ≥ 16 years) with moderate-to-severe AD according to the Rajka and Langeland criteria were treated with 0.1% tacrolimus ointment in a 1-year, open-label, prospective clinical trial. Patients applied tacrolimus ointment twice daily to all areas affected by AD. Patients were instructed to apply ointment for 1 week after cessation of itch and to select new areas for treatment on the basis of the presence of itch. Other treatments for AD, except nonmedicated emollients, were not permitted during the study. The washout period for topical

TABLE I. Patient characteristics of the study groups

	AD patients treated with tacrolimus ointment 0.1%	Healthy controls
Patient numbers at baseline/1 y	48/45*	28/9
Males/ females, n	17/31	10/18
Mean age (y) at baseline	26,1	29,2
Mean affected BSA (%) at baseline	32,9	NA
Mean affected BSA (%) at 1 y	8,8	NA
Moderate/severe AD at baseline, n	33/15	NA
Anergic patients: baseline/1 year, n	15/1	0/0

AD, Atopic dermatitis; BSA body surface area.

*One patient discontinued after 6 months of treatment. For technical reasons, recall antigen testing could not be done in this patient and 2 others.

corticosteroids was 5 days, for systemic corticosteroids and immunosuppressants 4 weeks, and for UV light therapy 6 weeks. Less than 1 mg/d intranasal and/or inhaled corticosteroids, antihistamines, and antimicrobials was permitted during the study. This study was performed in patients participating in a multicenter, long-term safety study funded by Astellas Pharma (S. Reitamo et al, unpublished data, January 2008). The baseline control group consisted of 28 healthy volunteers.

Patients with AD were tested for recall antigens at baseline and after 1 year. Healthy controls were tested at baseline, and 9 were randomly chosen for retesting after 1 year to investigate whether multiple testing had an additive effect on the test results.

Baseline characteristics of the study groups are presented in Table I. Recall-antigen testing was performed by using the Multitest CMI (Institute Mérieux, Lyon, France). The Multitest applicator contained 7 antigens: tetanus, diphtheria, *Streptococcus* (group C), tuberculin, *Candida albicans*, *Trichophyton*, and *Proteus*, with glycerin as negative control. All applicators were purchased at the same time and were from the same batch. The test site was the volar side of the left forearm. In case of clear eczema on the left arm, the other arm or dorsal side was chosen. The arms were not treated in the morning before testing, and no topical treatments on the test site were allowed before reading of the test. The tests were read after 48 hours, with consecutive tests performed in the same way at the same site. A test reaction of at least 2 mm was considered positive, and for these the average diameter of induration (mm) was calculated. The results are presented as the median sum of average diameters (the Mérieux score) and also as the median number of positive antigens.

The study was approved by the Ethics Committee of Helsinki University Central Hospital. All patients gave written informed consent before the start of the study.

Statistical analyses were performed with the software package SPSS 11.0 for Windows (SPSS Inc, Chicago, Ill).

Baseline median (Q1, Q3) Mérieux score was 3.75 (0.00, 7.00) in the AD group and 14.75 (10.00, 18.88) in the control group (Mann-Whitney test, $P < .0001$), and after 12 months of treatment 10.00 (8.00, 13.00) in the AD group (Wilcoxon test, $P < .0001$ vs baseline; Fig 1). Baseline median (Q1, Q3) number of positive antigens was 1.00 (0.00, 2.00) in the AD group and 3.00 (3.00, 5.00) in the control group (Mann-Whitney test, $P < .0001$), and after 12 months 3.00 (2.00, 4.00) in the AD group (Wilcoxon test, $P < .0001$ vs baseline). Patients in the control group showed no increase in test reactions after the 1-year follow-up. The AD and control groups were comparable in age and sex ratio.

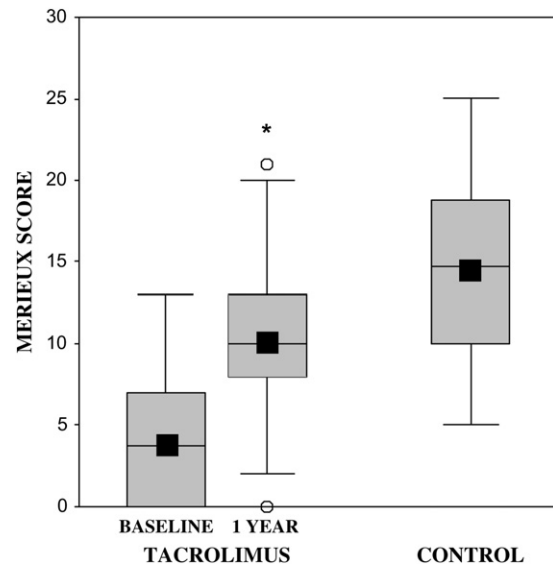


FIG 1. A normalization of the median Mérieux score was seen after 12 months of tacrolimus treatment (* $P < .0001$). The results are presented as box plots with the median value represented by a line across the box, and the mean by a small black box.

At baseline, 15 of the 48 patients with AD were anergic with no positive Multitest reactions. Baseline anergy was more common in severe disease than in moderate (Fisher exact test, $P = .004$), but sex or age did not affect anergy. None of the controls were anergic. After 1 year of treatment, only 1 patient with AD remained anergic (McNemar test, $P = .0005$). The mean eczema area declined from 32.9% at baseline to 8.8% after 12 months of tacrolimus treatment.

The results show a clear increase in both the number and the diameter of recall-antigen test reactions in the patients while the AD improves. This suggests that healing of the skin by tacrolimus ointment improves the skin immunity. Unfortunately, the patient number was small and the study design unblind. A larger, double-blind study is warranted in the future.

Multitest reactions have earlier been studied in patients with moderate-to-severe AD treated for 6 to 12 months with tacrolimus ointment. A slight but nonsignificant increase in the test reactions was seen. The results were interpreted to mean that tacrolimus ointment had no significant suppressive action on recall-antigen tests.³ The current study differs from the previous in that testing was performed in 1 center and results evaluated by a single investigator with long-term Multitest experience. Also, the time frame of reading was strictly adhered to. In the previous study, only 15 of 56 patients were evaluated at month 12.

Patients with active AD show many signs of decreased immunity of the skin, such as an increase in viral infections with herpes simplex virus and bacterial colonization with *Staphylococcus aureus*. *S aureus* colonization can be erased with topical tacrolimus treatment,⁴ and long-term studies suggest a decrease in herpes simplex virus infections.⁵ Microbial infections are controlled primarily by T cells of the T_H1 type, which are also needed to eliminate cancer cells. Recall-antigen reactions can be interpreted to be primarily of the T_H1 type. This fits well with the current findings.

The reversal of skin anergy after treatment with topical tacrolimus suggests a normalization of the T_H1 cell functions.

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Treatment with tacrolimus ointment, Multitest devices, and patient visits for the study were supported by Astellas Pharma.

Disclosure of potential conflict of interest: J. Mandelin has received research support from the Finnish Society of Dermatologists (SILY), Fujisawa GmbH, and Astellas Pharma. A. Remitz has received research support from Leo Pharma. S. Reitamo is on the speakers' bureau for Astellas Pharma and has received research support from Leo Pharma. H. Virtanen has declared that she has no conflict of interest.

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doi:10.1016/j.jaci.2007.12.1179