

Letter to the Editor

Topical tacrolimus in the treatment of atopic dermatitis—does it benefit the airways? A 4-year open follow-up

To the Editor:

The mechanism by which skin symptoms often precede the respiratory symptoms in childhood is poorly understood. Bronchial hyperresponsiveness (BHR) represents one of the main pathophysiological features in asthma.¹ Atopic dermatitis (AD) and allergic rhinitis are risk factors for BHR and asthma.² Sensitization of the skin with a protein antigen may lead to BHR in mice when the sensitizing antigen is used for respiratory challenge.³ Currently it is not known whether treatment of the established skin disease could have an effect on BHR or other respiratory symptoms.

Therefore, 64 patients with moderate-to-severe AD,⁴ age 25.2 (13–56) years, undergoing a 4-year, prospective, open-label, uncontrolled safety study with intermittent tacrolimus 0.1% ointment monotherapy,⁵ were followed for respiratory symptoms, BHR, and serum IgE.

The treatment response for AD was evaluated by body surface area, serum IgE, flow-volume spirometry for FEV₁, and a dosimetric histamine challenge test⁶ in which the provocative dose of inhaled histamine producing a decrease of 15% in FEV₁ was measured, were performed at baseline and after 12 months of treatment. In the histamine challenge test, a dose less than 1.6 mg was considered to represent increased BHR. The result was expressed in terms of the log slope of the dose response curve. The occurrence of physician-diagnosed asthma and allergic rhinitis was estimated by a validated questionnaire and the degree of asthma and rhinitis symptoms by a visual analog scale (VAS) from 0 to 10 cm at baseline, 12 months, and 48 months. A result of at least 2 cm was interpreted to represent active symptoms. Skin prick tests (SPTs) were performed at baseline for birch, timothy, mugwort, cat, dog, horse, cow, house dust mite, *Cladosporium herbarum*, and natural rubber latex.

An intention-to-treat analysis with last observation carried forward was performed as required by the distribution of the variable in question by using *t* test, Wilcoxon signed-rank test, or χ^2 test with the SAS Statview program (SAS Institute, Cary, NC).

Lifetime prevalence of physician-diagnosed asthma was 42% and of allergic rhinitis, 45%. Inhaled corticosteroids were used by 10 and intranasal corticosteroids by 3 patients at a stable dose of as much as 1 mg/d during the study. None of the patients used long-acting β -agonists before or during the study. The treatment with topical tacrolimus was well tolerated and resulted in good clinical response in AD. The main results are presented in Table I.

The number of patients with increased BHR decreased significantly ($P < .0001$). A total of 13 (39%) of the 33 patients who showed BHR at baseline did not show it at 12 months. Three (10%) of the patients with normal bronchial responsiveness at baseline, all with active respiratory

symptoms, showed mild BHR at 12 months. The log slope of the dose-response curve of histamine challenge test decreased significantly in patients with increased BHR at baseline ($P = .015$), that is, presenting a significant alleviation of BHR. The improvement was most clear in patients with moderate-to-severe BHR at baseline (4.86 ± 0.92 vs 3.58 ± 1.53 ; $P < .02$; $n = 11$). BHR improved particularly in patients with no asthma medication or patients using bronchodilating agents as needed only but not in the patients using inhaled corticosteroids. Asthma and rhinitis symptoms decreased significantly ($P < .005$ and $P < .02$), especially in patients with active symptoms at baseline ($P < .003$ and $P < .002$). One asymptomatic patient developed active respiratory symptoms but not BHR during the follow-up. There was no marked change in FEV₁.

A total of 82% of the patients showed at least 1 positive (≥ 3 mm) reaction in the SPT. The mean number of positive reactions was 3.9 and sum 21.2 mm. SPT reactivity and level of serum IgE were significantly correlated ($P < .001$). An almost significant decrease in serum IgE was seen in a subgroup of patients with elevated serum IgE at baseline and a sustained good treatment result in AD throughout the study (3690 ± 3490 vs 2233 ± 2121 ; $P = .06$; $n = 25$), whereas in patients with less favorable AD response, serum IgE tended to increase (3497 ± 5138 vs 4226 ± 4775 ; $P = .10$; $n = 22$).

Respiratory symptoms and BHR decreased in patients with moderate-to-severe AD treated with tacrolimus ointment monotherapy for 12 months. The result is limited by lack of a control group. The current study population was not ideal because it included adolescents and adults with already established respiratory disease. The effects of this kind of intervention on the actual atopic march would be best investigated in young children with newly diagnosed AD before the development of respiratory disease. However, to our knowledge, this is the first follow-up study on the effect of topical treatment of AD on respiratory symptoms.

Mild BHR can be found in as many as 16% of healthy individuals.⁶ Moderate or severe BHR is usually considered compatible with asthma diagnosis.¹ Clinical remission of childhood asthma in the teenage years is usual, but the patients may still show BHR and elevated exhaled nitrogen oxide levels as signs of persistent airway inflammation that may be a risk for asthma relapse later in life. Some fluctuation in BHR over time is possible, for example, as a result of respiratory tract infections or seasonal allergies. In population studies, BHR seems to decrease along with linear growth during adolescence; in adults, BHR is usually stable and is more likely to increase with age, especially in association with smoking, but not atopy.⁷

In the current study, the BHR measurements were performed between late October and early January and were thus not confounded by upper airway infections or the pollen season. The study included subjects from a wide

TABLE I. Results of lung function tests, respiratory symptoms, and serum IgE of 64 patients with AD treated with topical tacrolimus

	N	Baseline	12 mo	48 mo
Body surface area (%)	64	30.6 ± 25.3	10.6 ± 17.1**	9.5 ± 14.9**
Sustained good treatment response	36	28.6 ± 26.6	2.20 ± 4.50**	5.2 ± 14.8**
FEV ₁ (L/s)		3.79 ± 0.76	3.77 ± 0.75	
BHR (log slope)		2.37 ± 1.52	2.10 ± 1.43	
Increased BHR at baseline	33	4.36 ± 1.19	2.88 ± 1.38†	
Asthma symptoms (cm/VAS)		1.91 ± 2.20	1.41 ± 2.10*	1.28 ± 2.23*
Active symptoms at baseline	24	4.09 ± 1.60	2.43 ± 2.5*	2.36 ± 2.77†
Rhinitis symptoms (cm/VAS)		2.82 ± 2.97	2.01 ± 2.70†	1.93 ± 2.90*
Active symptoms at baseline	38	5.19 ± 2.39	3.36 ± 2.91*	3.33 ± 3.02*
Serum IgE (kU/L)		2701 ± 4377	2260 ± 3469	

P* < .01.†*P* < .05.*P* < .0001.

age range, and linear growth of adolescence could explain BHR improvement in only 1 patient. The reproducibility of the BHR measurement used in this study has been very good.⁶ The improvement of BHR was seen mainly in patients without ongoing inhaled or nasal corticosteroids. Therefore, the long-term effects of antiasthmatic medication are an unlikely cause of the changes in BHR during the follow-up. The simultaneous decrease of the respiratory and nasal symptoms supports the improvement of BHR and makes the results clinically more significant. Altogether, it seems that effective long-term treatment of skin inflammation in AD is associated with reduction of BHR and other respiratory signs beyond what can be expected from the natural variability of the disease. In the current study, the changes in FEV₁ and BHR did not correlate, suggesting that the improvement in BHR could be more likely caused by improvement of inflammation than increase of the airway caliber.

Studies in animal models suggest that epicutaneous antigen exposure can promote specific IgE-production and T_H2-type immune responses.³ This may be a result of the disturbed barrier function of AD skin caused by several genetic and environmental reasons, such as mutations of the filaggrin gene, as well as by inflammation.^{8,9} AD is characterized by both T_H2-type and T_H1-type inflammation. T_H2 cell migration from the skin to the airways has been considered to explain the atopic march from AD to asthma.² Tacrolimus inhibits T-cell activation and proliferation as well as production of inflammatory cytokines. Clearing of the skin inflammation may also improve the skin barrier function. Systemic exposure to topical tacrolimus is not likely to explain the current results because it diminishes along with skin improvement, and measurable blood concentrations are rare.⁵

The effects of topical tacrolimus on the skin could decrease the absorption of antigens and their systemic effects on the airways. Our finding that the weakened or anergic recall antigen reactions improve in tacrolimus-treated patients with AD also suggests normalization of the T-cell profile (Mandelin et al, unpublished data, January 2004). This would also explain the decrease of

serum IgE levels in the patients with a sustained good improvement in AD.

We conclude that effective long-term treatment of moderate-to-severe AD may improve respiratory symptoms. This preliminary observation calls for controlled trials in pediatric patients with AD before the onset of the respiratory disease.

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REFERENCES

- Guidelines for the diagnosis and management of asthma: update on selected topics, 2002. National Institutes of Health. *J Allergy Clin Immunol* 2002;110(suppl):141-218.
- Spergel J, Paller A. Atopic dermatitis and the atopic march. *J Allergy Clin Immunol* 2003;112(suppl):118-27.
- Spergel J, Mizoguchi E, Brewer J, Martin T, Bhan A, Geha R. Epicutaneous sensitization with protein antigen induces localized allergic dermatitis and hyperresponsiveness to methacholine after single exposure to aerosolized antigen in mice. *J Clin Invest* 1998;101:1614-22.
- Rajka G, Langeland T. Grading of the severity of atopic dermatitis. *Acta Derm Venereol* 1989;144(suppl):13-4.
- Reitamo S, Remitz A, Kyllönen H, Saarikko J, Granlund H. Topical non-corticosteroid immunomodulation in the treatment of atopic dermatitis. *Am J Clin Dermatol* 2002;3:381-8.

6. Sovijärvi ARA, Malmberg LP, Reinikainen K, Ryttilä P, Poppius H. A rapid dosimetric method with controlled tidal breathing for histamine challenge: repeatability and distribution of bronchial reactivity in a clinical material. *Chest* 1993;104:164-70.
7. Chinn S, Jarvis D, Luczynska C, Ackermann-Liebrich U, Antó J, Cerveri I, et al. An increase in bronchial responsiveness is associated with continuing or restarting smoking. *Am J Respir Crit Care Med* 2005;172: 956-61.
8. Cork MJ, Robinson DA, Vasilopoulos Y, Ferguson A, Moustafa M, Mac-Gowan A, et al. New perspectives in epidermal barrier dysfunction in atopic dermatitis: gene-environment interactions. *J Allergy Clin Immunol* 2006;118:3-21.
9. Homey B, Steinhoff M, Ruzicka T, Leung DYM. Cytokines and chemokines orchestrate atopic skin inflammation. *J Allergy Clin Immunol* 2006; 118:178-89.

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