

Selective enhancement of production of IgE, IgG4, and Th2-cell cytokine during the rebound phenomenon in atopic dermatitis and prevention by suplatast tosilate

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Background: Atopic dermatitis is a chronic inflammatory skin disease, which is commonly treated with topical steroids. It is, however, associated with rebound after therapy has been discontinued.

Objective: This study was designed to elucidate the mechanisms of the rebound phenomenon, and to test the effect of an oral anti-allergic medication, suplatast tosilate, on atopic dermatitis.

Methods: This is a randomized, placebo controlled study. Patients with atopic dermatitis who had been treated with strong steroid ointment (dexamethasone valerate) for several years were divided into two groups. One group (the control group, $n = 15$) was treated with a non-steroid anti-inflammatory ointment (bufexamac ointment), while the other group (the suplatast tosilate group, $n = 17$) was treated with the anti-allergic medications, suplatast tosilate and bufexamac ointment. In each group, in vitro production of immunoglobulins and cytokines before and after 2 weeks of treatment was measured.

Results: In the control group, 15 of the 15 patients experienced rebound and mean production of IgE, IgG4, IL-4, IL-5, IL-10, and IL-13 was enhanced after 2 weeks. In contrast, only 2 of the 17 patients in the suplatast tosilate group experienced rebound. There was no enhancement of production of immunoglobulins and cytokines after 2 weeks of treatment.

Conclusion: Enhanced production of the Th2-cell cytokines, which selectively induces IgE and IgG4 production, may be involved in the pathogenesis of the rebound phenomenon, and that suplatast tosilate may prevent the rebound phenomenon by down-regulating the production of these cytokines.

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INTRODUCTION

Atopic dermatitis is a chronic inflammatory skin disease of wide prevalence characterized by severe itching.¹ Steroid ointment is commonly used for its treatment; however, it is associated with relapse after discontinuation of prolonged use of steroid ointment.^{2,3} Usually, this relapse occurs within several days after discontinuation of steroid ointment, and it is defined

as exacerbation of atopic dermatitis sometimes associated with facial swelling and is called “rebound phenomenon”.⁴ The exact mechanisms of the rebound phenomenon remain to be elucidated, and its preventive therapy has not been previously reported. I therefore measured the production of immunoglobulins and cytokines during the rebound phenomenon. I also studied the effect of an oral anti-allergic medication, suplatast tosilate, which down-regulates production of IgE, IL-4, and IL-5, but not IgG or IFN- γ .⁵

SUBJECTS AND METHODS

Thirty-two patients with atopic dermatitis who had been treated with strong

steroid ointment (dexamethasone valerate), but not with oral corticosteroids or antihistamines, for several years were enrolled in this study after obtaining informed consent. The diagnosis was based on the criteria of Hanfin and Rajka.¹ The patients were randomly divided into two groups. One group of patients (the control group) was treated with non-steroid anti-inflammatory ointment (bufexamac ointment), while the other group (the suplatast tosilate group) was treated with suplatast tosilate (400 mg/day) and bufexamac ointment.^{6,7} As shown in Table 1, two groups were similar at admission with respect to mean age, duration of treatment with steroid ointments, sex distribution, presence of other allergic diseases, mean serum IgE and IgG4 levels, allergens, and inflammation of atopic dermatitis determined by our skin score.^{3,8} Peripheral blood was drawn before and after 2 weeks of treatment, and mononuclear cells were separated. They were cultured ($2 \times 10^5/0.2$ mL/well) with medium alone for 7 days, and the amount of in vitro spontaneous production of immunoglobulins and cytokines was determined by ELISA as previously reported.^{3,6} The culture medium was DME, supplemented with Ham's nutrient (DME/F-12; Sigma Chemical Co), 0.5% BSA, and 50 μ g/mL transferrin.⁵ Statistical analysis was done by Student's *t* test.

RESULTS

In the control group, 15 of the 15 patients experienced the rebound phenomenon after 2 weeks. To elucidate the immunologic mechanisms of the

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Table 1. Subject Characteristics

	Group	
	Control	Suplatast Tosilate
Age, yr	18–39 (29)*	17–43 (30)
Sex		
Male	7†	8†
Female	8†	9†
Duration of treatment with steroid ointments, yr	4–11 (8)	4–12 (8)
Other allergy		
Asthma	3†	3†
Rhinitis	6†	7†
Conjunctivitis	4†	5†
Serum IgE levels, IU/mL	639–12620 (5375)	712–14340 (5832)
Serum IgG4 levels, mg/dL	43–92 (52)	39–103 (56)
Allergens		
House dust	15†	17†
<i>Dermatophagoides pteronyssius</i>	15†	17†
Pollen	12†	14†
Cat dander	7†	8†
Skin scores for inflammation	12–23 (19)	14–25 (20)

* Figures in parenthesis present means.

† Number of patients.

rebound phenomenon, production of immunoglobulins and cytokines was measured. As shown in Table 2, during the rebound phenomenon, production of IgE and IgG4 was significantly enhanced without affecting production of IgG1, IgG2, IgG3, IgM, IgA1, or IgA2. In the suplatast tosilate group, however, only 2 of the 17 patients experienced the rebound phenomenon after 2 weeks of treatment. Further, production of IgE, IgG4, and other immunoglobulins was not enhanced. I and others have previously reported that production of IgE and IgG4 was

regulated by Th1-cell and Th2-cell cytokines^{2,6,9}; therefore, cytokines were measured. As shown in Table 3, in the control group, production of IL-4, IL-5, IL-10 and IL-13, but not IL-2 or IFN- γ , was enhanced during the rebound phenomenon. In contrast, production of these cytokines in the suplatast tosilate group was not enhanced.

DISCUSSION

It has been reported that Th2-cell cytokines, IL-4, IL-5, IL-10, and IL-13 induce IgE and IgG4 production.^{2,6,9} The present results indicate that pro-

duction of IgE and IgG4 was selectively enhanced during the rebound phenomenon. Subsequent study revealed that production of Th2-cell cytokines, IL-4, IL-5, IL-10, and IL-13, was also enhanced during the rebound phenomenon. In contrast, production of Th1-cell cytokines, IL-2 and IFN- γ , was not enhanced. It is possible that enhanced production of Th2-cell cytokines may induce IgE and IgG4 production.

In contrast, in the suplatast tosilate group, the rebound phenomenon was prevented, and production of IgE, IgG4, and other immunoglobulins and various cytokines was not enhanced. It has been reported that suplatast tosilate downregulates production of IgE, IL-4 and IL-5, but not IgG or IFN- γ .⁵ In addition, suplatast tosilate reduced IL-5-driven eosinophilia in patients with bronchial asthma.⁷ It is possible that suplatast tosilate may downregulate enhanced production of IL-4, IL-5, IL-10, and IL-13, thus resulting in counteracting the enhancement of IgE and IgG4 production. It should be mentioned that although rebound phenomenon occurred in 2 out of 15 patients in the suplatast tosilate group after 2 weeks, it was not so severe as was observed in the control group. Further, treatment with suplatast tosilate for another 2 weeks significantly improved rebound phenomenon in these 2 patients. In contrast, in the control group, rebound phenomenon was not significantly improved after another 2 weeks in 15 of 15 patients.

Table 2. Comparison of the Immunoglobulin Production in the Control Group and the Suplatast Tosilate Group

Group	Immunoglobulin Production, ng/mL							
	IgE	IgG4	IgG1	IgG2	IgG3	IgM	IgA1	IgA2
(A) Control (n = 15)								
Before	5 $\pm$ 2	25 $\pm$ 9	287 $\pm$ 41	132 $\pm$ 23	36 $\pm$ 10	210 $\pm$ 42	87 $\pm$ 29	13 $\pm$ 6
After	22 $\pm$ 5*	78 $\pm$ 21*	279 $\pm$ 56	147 $\pm$ 48	32 $\pm$ 10	202 $\pm$ 39	90 $\pm$ 25	11 $\pm$ 4
(B) Suplatast tosilate (n = 17)								
Before	6 $\pm$ 3	28 $\pm$ 7	297 $\pm$ 53	121 $\pm$ 30	33 $\pm$ 9	221 $\pm$ 30	79 $\pm$ 14	12 $\pm$ 5
After	5 $\pm$ 3	24 $\pm$ 7	292 $\pm$ 57	116 $\pm$ 27	35 $\pm$ 7	215 $\pm$ 38	83 $\pm$ 18	13 $\pm$ 5

In each group, immunoglobulin production by peripheral blood mononuclear cells was determined before and after 2 weeks of treatment. Values are the means $\pm$ SD.

* $P < .001$ versus before treatment.

Table 3. Comparison of the Cytokine Production in the Control Group and the Suplatast Tosilate Group

Group	Cytokine Production, ng/mL					
	IL-4	IL-5	IL-10	IL-13	IL-2	IFN- γ
(A) Control (n = 15)						
Before	305 $\pm$ 82	245 $\pm$ 52	157 $\pm$ 40	179 $\pm$ 33	167 $\pm$ 41	104 $\pm$ 38
After	879 $\pm$ 215*	748 $\pm$ 202*	538 $\pm$ 119*	634 $\pm$ 124*	179 $\pm$ 39	101 $\pm$ 33
(B) Suplatast tosilate (n = 17)						
Before	321 $\pm$ 76	267 $\pm$ 62	179 $\pm$ 33	193 $\pm$ 32	159 $\pm$ 41	110 $\pm$ 29
After	331 $\pm$ 70	249 $\pm$ 59	182 $\pm$ 41	169 $\pm$ 51	162 $\pm$ 51	103 $\pm$ 34

In each group, cytokine production by peripheral blood mononuclear cells was determined before and after 2 weeks of treatment. Values are the means $\pm$ SD.

* $P < .001$ versus before treatment.

In summary, these results suggest that enhanced production of Th2-cell cytokines, IL-4, IL-5, IL-10 and IL-13, may be involved in the pathogenesis of the rebound phenomenon, and that suplatast tosilate may prevent the rebound phenomenon by downregulating the production of these cytokines.

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