



SHORT COMMUNICATION

PILOT STUDY OF IFN- γ -INDUCED SPECIFIC HYPOSENSITIZATION FOR HOUSE DUST MITES IN ATOPIC DERMATITIS: IFN- γ -INDUCED IMMUNE DEVIATION AS A NEW THERAPEUTIC CONCEPT FOR ATOPIC DERMATITIS

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IFN- γ /IL-4 imbalance is a central immunologic defect which is responsible for increased IgE antibody response in atopic dermatitis. Effects of hyposensitization were controversial in atopic dermatitis. Reversed IFN- γ /IL-4 balance was induced using IFN- γ in atopic dermatitis and specific hyposensitization with house dust mites (HDM) was tried in the status of IFN- γ -induced immune deviation. A total of 58 atopic dermatitis patients who had obvious allergy to HDM were selected in this study. IFN- γ -induced hyposensitization for HDM was tried in 10 patients. Twenty-two patients received IFN- γ therapy and six were treated by simple hyposensitization. Twenty were enrolled as control subjects. The clinical severity scores decreased effectively only by IFN- γ -induced hyposensitization for HDM. Specific hyposensitization for HDM in the status of IFN- γ -induced immune deviation successfully improved atopic dermatitis. HDM might play a pathogenic role in subpopulation of atopic dermatitis.

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Interferon (IFN)- γ /interleukin (IL)-4 imbalance from Th₁/Th₂ dysregulation is the central immunopathobiology in atopic dermatitis (AD).¹ This immunologic abnormality leads patients to increased IgE antibody responses.² With these findings, IFN- γ therapy has been tried with limited success.³

Hyposensitization has been tried by repeated injection of increasing doses of allergens in allergic disease.⁴ However, its effect has been controversial in several reports.⁵ Especially, hyposensitization with house dust mites (HDM) was unsuccessful in improving AD.⁶ Reversed IFN- γ /IL-4 balance was induced by exogenous IFN- γ . Hyposensitization with HDM was

tried in the status of IFN- γ -induced immune deviation as a new therapeutic concept for AD.

RESULTS

Clinical responses

By IFN- γ -induced hyposensitization with HDM, clinical severity scores decreased from 576.5 ± 241.0 to 134.7 ± 134.6 in this group ($P=0.0007$) (Fig. 1). However, by IFN- γ therapy, their clinical severity scores slightly changed from 353.1 ± 121.3 to 311.1 ± 129.6 ($P=0.005$). By simple hyposensitization, the clinical severity scores were insignificantly changed from 470.8 ± 283.0 to 479.2 ± 243.1 ($P=0.765$). In the control group, no patient showed clinical improvement and the clinical severity scores changed from 565.0 ± 216.5 to 560.0 ± 213.1 ($P=0.309$). Abrupt aggravation episodes disappeared only after IFN- γ -induced hyposensitization.

Serum IgE levels and blood eosinophil fraction

Serum IgE levels increased significantly by IFN- γ -induced hyposensitization from 1679.5 ± 1323.5 IU/ml to 2934.6 ± 2250.8 IU/ml ($P=0.014$) (Fig. 1). By IFN- γ

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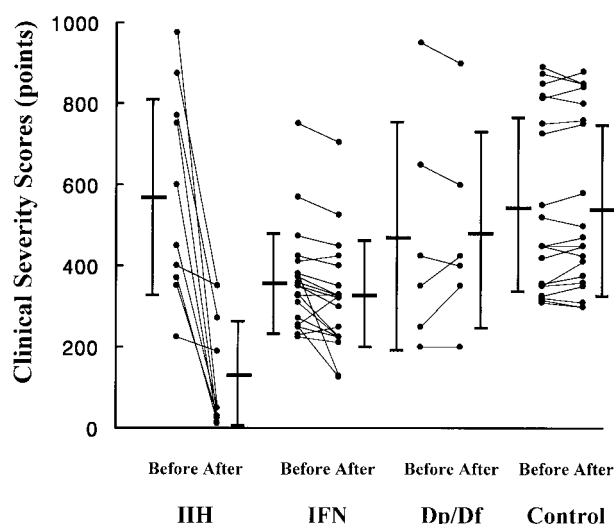


Figure 1. Changes of clinical severity scores by IFN- γ -induced hyposensitization, by IFN- γ therapy, and by hyposensitization as well as in the control group.

IHH, interferon-induced hyposensitization group; IFN, interferon-treated group; Dp/Df, simple hyposensitization group; Control, control group; Before, before treatment; After, after treatment.

therapy, serum IgE levels changed insignificantly from 1276.5 ± 1333.5 IU/ml to 1456.1 ± 1446.2 IU/ml ($P > 0.05$). By hyposensitization, serum IgE levels markedly increased from 1652.0 ± 962.2 IU/ml to 1790.0 ± 1351.2 IU/ml ($P > 0.05$). In the control group, serum IgE levels changed insignificantly from 1278.4 ± 1105.3 IU/ml to 1505.4 ± 1510.8 IU/ml ($P > 0.05$). There were no significant changes in blood eosinophil fractions to white blood cell (WBC) counts in all groups.

DISCUSSION

Specific hyposensitization with HDM in the status of IFN- γ -induced immune deviation effectively improved the clinical symptoms of AD (Fig. 2). AD patients showed also significant improvements by simple IFN- γ therapy. However, these improvements were too minimal to be beneficial for the patients, clinically. Abrupt aggravation episodes were remained even after simple IFN- γ therapy. Therefore, the clinical results of IFN- γ -induced hyposensitization for HDM were not the simple pharmacologic effects of exogenous IFN- γ . Currently, a consensus on a provocation test, which is similar to ordinary exposure to HDM, has not been made, and the pathogenic role of HDM in AD remains controversial.⁹ From our results, HDM was strongly suspected to play a pathogenic role in AD.

Hyposensitization with HDM was not beneficial as reported in many reports.⁶ Simple hyposensitization

was ineffective in AD in this study, too. Interestingly, IFN- γ -induced hyposensitization showed dramatic clinical improvement in this study and these improved states were well maintained for at least 8 weeks after finishing the therapy.

Serum IgE levels remarkably increased even though clinical severity scores were markedly improved. In our previous study, serum IgE levels did not change or were rather increased by IFN- γ therapy for AD.¹⁰ Serum IgE levels also increased by simple hyposensitization. Hyposensitization procedure is the process of allergic stimulation. This allergenic stimulation seemed to result in remarkable elevation of IgE in this study.

Conclusively, IFN- γ -induced hyposensitization for HDM was remarkably beneficial in HDM-sensitized AD. A new concept of IFN- γ -induced immune deviation may be effective in treating AD. HDM possibly plays pathogenic roles in a subgroup of AD.

MATERIALS AND METHODS

Patient selection

Fifty-eight AD patients were enrolled in this study who fulfilled the criteria of Hanifin and Rajzka⁷ and the following criteria; (1) recalcitrant clinical course, (2) strong positive skin-prick test results with HDM and high serum levels of HDM-specific IgE by MAST with/without weak positive results for other allergens, (3) frequent episodes of abrupt severe aggravation after exposure to a daily living space—of a classroom, an office, a room, or a certain space—which were suspected to offer HDM allergens in spite of complete diet elimination before entering study, (4) typical skin involvement on exposure area (Fig. 2).

Study design

Ten patients were treated with IFN- γ -induced hyposensitization (male:female ratio=6:4, mean age=14.7 $\pm$ 5.3 years). Twenty-two patients were treated only with IFN- γ therapy (male:female ratio=8:14, mean age=15.6 $\pm$ 10.3 years). Six patients simply were received hyposensitization (male:female ratio=4:2, mean age=12.8 $\pm$ 10.4 years). Twenty patients were enrolled as the negative control group (male:female ratio=6:14, mean age=10.9 $\pm$ 8.0 years) and did not receive any of the above treatments. To exclude the dietary effects concerning food allergy, complete diet elimination was performed for 8 weeks before and after the study as suggested by EAACI.⁸ Complete blood count (CBC) and total IgE were examined in all patients before and after treatment. All patients were tested with MAST and skin-prick test to identify causative allergens. All patients were informed about the study on their initial visit and all studies were approved by Ethical Committee of Samsung Cheil Hospital.

Therapeutic results were evaluated by (1) decrease of clinical severity scores and (2) the disappearance of aggravation episodes which were present before treatment. Grading

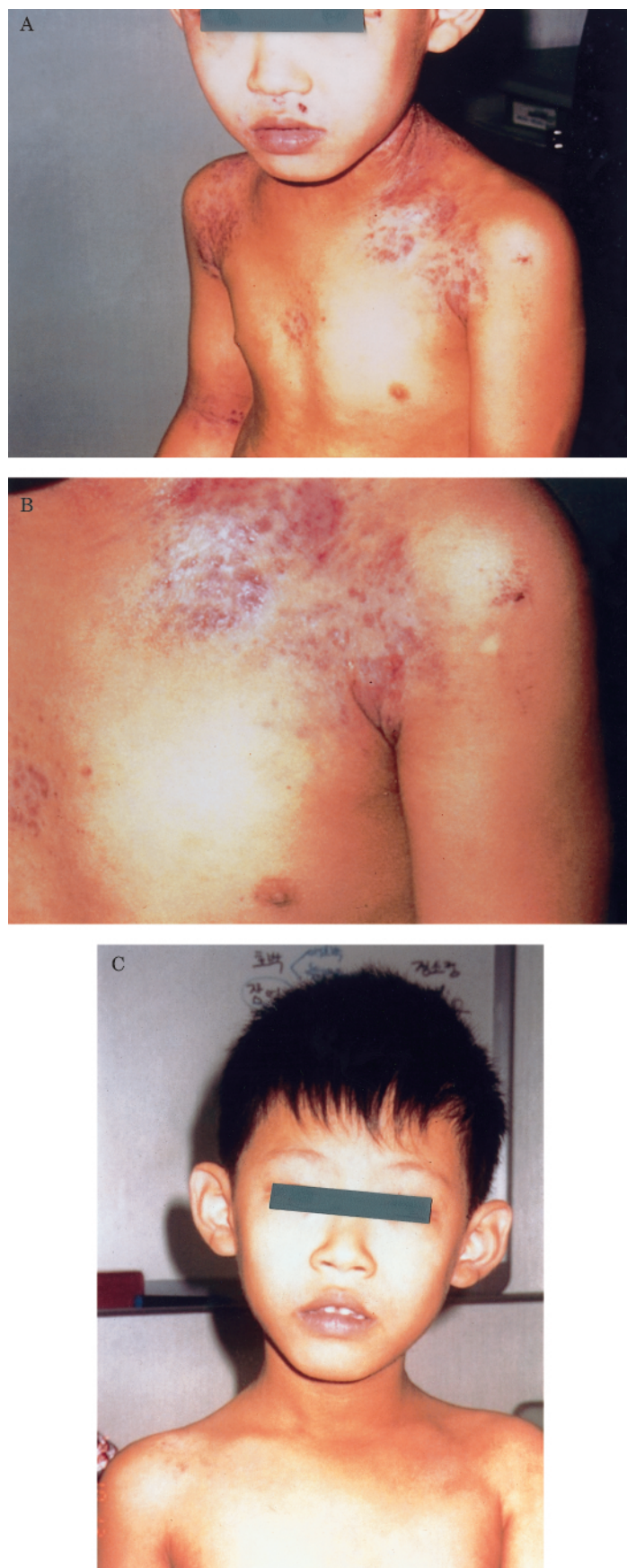


Figure 2. Typical skin involvement in a case.

(a) skin lesions on face, neck, axilla, antecubital fossa, and anterior chest before treatment, (b) magnified shoulder lesions before treatment, (c) dramatically improved skin lesions on face, neck, axilla, antecubital fossa, and anterior chest after IFN- γ -induced hyposensitization with house dust mites.

TABLE 1. Clinical Severity Scoring System**(a) Pruritis Scoring****A-1. Day****<Duration>**

100	:All day
75	:Over two-thirds of day time but less than all day
50	:Over one third of day time and less than two-thirds
25	:Occasionally (less than one third of day time)
0	:None

<Grade>

0.	No itching or no scratch
1.	Feel of itching to tolerable itching or unconsciousness scratch
2.	Mild interference in day work by scratching or itching
3.	Moderate interference in day work by scratching or itching
4.	Severe interference in day work
5.	Complete interference

A-2. Night**<Duration>**

100	:All night
75	:Over two-thirds of sleep but less than all night
50	:Over one third of sleep and less than two-thirds
25	:Occasionally (less than one third of sleep)
0	:None

<Grade>

0.	No itching or no scratch (well sleep)
1.	Feel of itching to tolerable itching or unconsciousness scratch during sleep
2.	Some sleep disturbance by scratching or itching (Mild)
3.	Sleep disturbance by scratching or itching (Moderate)
4.	Some sleep during almost all awakening by scratching or itching (Severe)
5.	Complete awakening by scratching or itching

(b). Skin lesion scoring**<Grade>**

0.	No lesion or no scar or no pigmentation
1.	Pigmentation or depigmentation or scar only
2.	Redness (erythema) or coarseness of skin
3.	Scaly change or scratch wound
4.	Papular or vesicular eruption, desquamation
5.	Bleeding, woozing, infection, exudation of pus, lichenification

(c) Clinical severity score

Day pruritis score=Day duration $\times$ Grade

Night pruritis score=Night duration $\times$ Grade

Pruritis score=(Day pruritis score+Night pruritis score)/2

Skin lesion score=Sum of (Skin lesion % $\times$ Lesion grade)

Clinical severity score=Pruritis score+Skin lesion score.

the clinical severity of atopic dermatitis was assessed by the scoring system (Table 1).

For hyposensitization, HDM allergen extracts (Alavac-S, Bencard, Brentford, UK) which consisted of three steps of antigen concentration, were used. The first step and second step were 1/100th and 1/10th dilutions, respectively, of the third step. Each step consisted of 10 injections of allergens with increasing doses from 0.1 ml to 1.0 by 0.1 ml. In the first step, patients received ten injections for 10 consecutive days. In the second step, patients received three injections per week for over 3 weeks. In the third step, patients received two injections per week for 5 weeks.

IFN- γ induced hyposensitization was performed according to hyposensitization schedule with simultaneous injections of IFN- γ with every Alavac-S injections. IFN- γ therapy group received only the IFN- γ injections, without an Alavac-S injection, following a schedule similar to the hyposensitization schedule. In IFN- γ therapy group, injections

were given for 5 consecutive days during the first week, followed by three injections per week for 3 weeks, and then followed by two injections per week for the last 5 weeks. Simple hyposensitization procedures without IFN- γ injection were performed as scheduled.

To evaluate the significance of the test, Wilcoxon matched-pair signed-ranks test was used in this study. Differences associated with a probability of $P < 0.05$ were considered significant.

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