Rush Immunotherapy with House Dust Extract in Patients with Mild Extrinsic Asthma

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HIROKAWA, Y., KONDO, T., KOBAYASHI, I. and OHTA, Y. *Rush Immunotherapy with House Dust Extract in Patients with Mild Extrinsic Asthma*. Tohoku J. Exp. Med., 1996, **178** (4), 371-380 — Rush immunotherapy (RIT) with house dust extract was given to 15 patients with mild extrinsic or mixed asthma. Every patient was strongly positive for IgE on the radioimmunosorbent test and sensitive to house dust extract on the scratch skin test. Nine patients were positive on the bronchial provocation test to house dust extract and 6 could not be examined. All patients did not drop out and got to house dust extract solution 10^{-1} within 1 week. The symptom-medication scores decreased significantly after RIT. During RIT 1 patient developed a mild asthmatic attack and 3 patients developed generalized skin reaction. Eight weeks later, the threshold for house dust-provoked bronchoconstriction increased in 9 patients, but did not in 3 patients. The blood eosinophil count and blood histamine level significantly decreased. We conclude that RIT is able to raise antigen concentrations for a short periods and effective but not risky for mild asthma. ——— anaphylaxis; eosinophils; histamine; bronchial hypersensitivity

The specific immunotherapy has been used to treat allergic disease since 1910 (Noon and Cantab 1911), including bronchial asthma (Brun 1949). Although immunotherapy is effective in many patients with extrinsic asthma, failure of such therapy has also been reported (Hill et al. 1982). During the course of immunotherapy, patients must visit a medical facility once a week for several months or years. The symptoms of bronchial asthma may be improved or deteriorated by psychogenic factors, seasonal causes, or alteration of treatment content. Therefore the assessment of this therapy in terms of the efficacy may be influenced adversely by these factors in the long therapeutic time. These adverse factors may also have hindered investigation of the mechanism of immunotherapy. Thus, the efficacy, safety and even the mechanism of immunotherapy for bronchial asthma remain to be fully investigated.

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Rush immunotherapy (RIT) was first introduced by Miller and Manamann (1971). The RIT is performed by injecting a specific allergen 3 to 6 times daily at increasing concentrations until the maintenance level is reached in a few days. In RIT this may lead the benefit that only a minimum number of subjects discontinue the therapy before the maintenance concentration is reached, and seasonal deterioration or modification of anti-asthmatic drugs is less likely to occur during such accelerated therapy. Therefore, we consider RIT to be an excellent method for assessing the efficacy and safety of immunotherapy for bronchial asthma. In the present study we further investigated the mechanism of RIT action by comparing laboratory parameters measured before and after RIT.

SUBJECTS AND METHODS

We studied 15 patients with mild asthma. We obtained informed consent from all of them before RIT. Subjects included 6 men and 9 women with a mean age of 26 years (range, 14 to 48 years). The diagnosis of bronchial asthma was made according to the standards of the American Thoracic Society (1986). Six of the 15 patients were atopic, the remaining 9 had mixed asthma (Table 1). All the patients were strongly positive for house dust-specific IgE (RAST Score 3-4) and on scratch skin testing for house dust extract. Each patient was also on xanthine and a β -agonist, however, oral or inhaled corticosteroid was not given before or during RIT.

RIT was performed according to Miller's methods (Miller and Manamann 1971). The allergen (Torii, Tokyo) was injected subcutaneously 3 to 6 times a

TABLE 1. *Characteristics of patients*

Patient No.	Age (years)	Sex	Type
1	15	M	Mixed
2	16	F	Mixed
3	23	F	Mixed
4	25	M	Mixed
5	25	F	Mixed
6	31	F	Mixed
7	43	M	Mixed
8	46	F	Mixed
9	48	F	Mixed
10	15	F	Atopic
11	17	F	Atopic
12	17	M	Atopic
13	22	F	Atopic
14	22	M	Atopic
15	29	M	Atopic

day as its concentration was increased until the maintenance level was achieved. The maintenance concentration was determined as more than 10^{-1} and no one had any general adverse effects (Nagata et al. 1989).

Every patient was asked to record his/her symptoms in a diary from which the symptom-medication scores (Horst et al. 1990) were calculated. The scores obtained during, 2 weeks before and 8 weeks after RIT were compared.

Each patient was admitted to the hospital before undergoing RIT. Bronchodilators were discontinued at least 24 hr before admission and all tests were performed on admission day. A skin test on the forearm with house dust extract was performed, and then the bronchial provocation test (Chai et al. 1975) was conducted with house dust extract. Bronchial provocation test with the sensitizing allergen was performed according to the method described by Makino et al. (1982). Bronchial provocation test is widely used for assessing the efficacy of asthmatic medication including immunotherapy (Bousquet et al. 1985a; Thomas et al. 1988 Emanuele et al. 1991; Sullivan et al. 1994;). The initial concentration of the allergen on the bronchial provocation test was one tenth of the threshold observed on the skin test. The patient inhaled aerosol of house dust extract solution for 2 min and spirometry (Model 298, Chest Co., Tokyo) was performed 10 min after the inhalation. This procedure was repeated immediately with increasing antigen concentration as long as the FEV_1 did not decrease by 15% or more of the control value. When the FEV_1 fell by 15–19% of the control value this procedure was repeated with the same antigen concentration after 15 min. When the FEV_1 fell by 20% of the control value, the concentration of antigen used was considered as the threshold concentration. Spirometry was repeated every 2 hr after cessation of antigen inhalation. If the FEV_1 decreased to less than 80% of the control value at 3–8 hr after the inhalation test, the patient was regarded as positive for a late asthmatic response (LAR).

We measured non-specific IgE antibody (RIST, SRL Lab., Tokyo), peripheral blood cell counts, house dust-specific IgE antibody (RAST, SRL Lab.) and plasma histamine levels. Tryptase and eosinophil cationic protein (ECP) levels in sputum were also measured (Mitsubishi Yuka, Tokyo). Eight weeks after the RIT every patient was admitted again and the same tests were repeated.

During the RIT period, inhalational disodium cromoglycate (DSCG) was given 4 times a day and an oral anti-histamine was given daily to prevent any allergic reaction (Nagata et al. 1989). The maintenance concentration of the subcutaneous allergen was determined as follows. If there was no side effect, the maintenance dose reached was $10^{-1} \times 0.5$ ml. If there was any side effects, the concentration used before developing the side effect was taken as the maintenance concentration. After reaching the maintenance concentration each patient visited the hospital every 2 weeks for subcutaneous injection of the allergen of the maintenance concentration.

The data were analyzed by the Wilcoxon ranked sum test. For any $p < 0.05$,

we judged the difference to be statistically significant.

RESULTS

Every patient reached a concentration of at least 10^{-1} (1 : 10) in 6 to 8 days (mean, 7 days). Three patients did not complete the asthma diary, and thus we studied the remaining 12 patients in this study. Fig. 1 shows the symptom-medication scores before and at 8 weeks after RIT. The mean scores before RIT was 8.8 points and that after RIT was 7.4 points. The decrease in average daily symptom-medication scores after RIT was statistically significant ($p=0.008$).

The FEV_1 in the 12 patients was 2.32 ± 0.68 l (mean $\pm$ S.D.) before RIT, and was 2.58 ± 0.78 l after RIT. The FEV_1 did not increase significantly after RIT. The bronchial provocation test was applied in 9 of the 12 patients. In the remaining 3 patients the provocation test was not done because a mild attack developed on admission day. The threshold on the bronchial provocation test was expressed as the logarithm of provocative dose of house dust causing a 20% fall of $FEV_{1.0}$ (log PD_{20}) (Fig. 2). The log PD_{20} significantly ($p=0.045$) increased 8 weeks after RIT. The LAR was also assessed after the house dust provocation test. The LAR disappeared after RIT in 5 of the 9 patients while the LAR persisted in the remaining 4 patients.

The mean serum IgE was 716 ± 619 IU/ml before RIT and was 840 ± 476 IU/ml after RIT. Although the serum IgE appeared to increase slightly after RIT, this increase was not statistically significant. In 8 of the 12 patients, the house

Fig. 1. The symptom-medication scores before and at 8 weeks after RIT. The average daily symptom-medication scores was significantly decreased ($p=0.008$) after RIT.

Fig. 2. The thresholds of the bronchial responsiveness to inhaled house dust extract expressed as the log PD₂₀. The log PD₂₀ significantly ($p=0.045$) increased 8 weeks after RIT.

Fig. 3. The blood eosinophil counts before and at 8 weeks after RIT. The blood eosinophils significantly decreased ($p=0.03$) at 8 weeks after RIT.

Fig. 4. The blood histamine before and at 8 weeks after RIT. The plasma histamine significantly decreased ($p=0.008$) at 8 weeks after RIT.

dust-specific IgE points exceeded 17.5 (i.e., upper limit of the scale) before and after RIT. Therefore, this change in house dust specific IgE level could not be assessed.

Fig. 3 shows the changes in blood eosinophil levels occurring as a result of RIT. The mean blood eosinophils was $542.4 \pm 194.4 \text{ mm}^3$ before RIT and was $336.2 \pm 169.5 \text{ mm}^3$ after RIT. The counts of blood eosinophils in all the 12 patients decreased significantly ($p=0.03$) after RIT. The tryptase and ECP in the sputum was measured in 7 of the 12 patients as the other 5 patients could not present the sputum. The sputum ECP was $853.8 \pm 1,307.2 \text{ ng/ml}$ before RIT and was $2,500.4 \pm 5,258.8 \text{ ng/ml}$ after RIT. In one of the 7 patients, the sputum ECP increased from 200 ng/ml to 16,800 ng/ml after RIT, and this patient developed intractable nasal symptoms.

Fig. 4 shows the changes in blood histamine before and after RIT. The blood histamine was $69.4 \pm 18.0 \text{ ng/ml}$ before RIT and was $61.1 \pm 19.8 \text{ ng/ml}$ after RIT. The blood histamine concentration decreased significantly after RIT ($p=0.008$). The mean sputum tryptase concentration was 12.6 ± 4.0 arbitrary units/ml before RIT and was 14.3 ± 6.0 arbitrary unit/ml after RIT. Therefore the sputum tryptase level did not significantly change after RIT.

The adverse effects of RIT were assessed in each of the 15 patients. In 1 patient, an asthma attack developed approximately 15 min after subcutaneous injection of antigen at the maximum concentration (i.e., 10^{-1}). The provoked mild attack was treated successfully by administration of intravenous aminophylline and of subcutaneous adrenaline. With treatment the attack subsided in

several hours. No one developed moderate or major asthmatic attack. In 3 patients, a generalized eruption developed approximately 15–30 min after injection of 10^{-1} antigen. These subjects were treated with intravenous antihistamine (Restamine calcium, Kowa, Tokyo). One patient developed intractable nasal symptoms after RIT, however, her symptoms subsided gradually over the period of 1 year.

DISCUSSION

We found that subject's symptoms evaluated by symptom-medication score improved at 8 weeks after RIT. Previous studies (Brun 1949; Mcallen et al. 1967; Smith 1971) also assessed the efficacy of immunotherapy on bronchial asthma from the scores counted from asthmatic diary. These studies indicated some evidence of beneficial clinical effect. In our study, the improvement was further supported by a decrease in bronchial responsiveness to house dust-extract. Therefore, we speculate that the effect of RIT on asthmatic symptom may be exerted by a decrease in bronchial responsiveness. Despite our expectation, the FEV₁ did not increase significantly after RIT. However, Baumann et al. (1986) has reported that the FEV₁ does not always recover with symptoms in mild asthma.

Mechanism of RIT

During the course of RIT, the serum IgE level increased, although not significantly. Several investigators (Kjellman et al. 1977; Creticos et al. 1984) have suggested that during conventional immunotherapy the serum IgE increases for several months and then decreases gradually. This can explain a slight increase in IgE levels observed in the present study. In contrast, it has been reported (Lichtenstein et al. 1973) that the serum IgE level does not correlate with improvement of asthma symptoms. Presumably the serum IgE does not play a significant role in mediating the effect of immunotherapy.

Histamine, the major mediator of asthma, is stored in the secretory granules of human mast cells and basophils (Riley and West 1953). In our study the plasma histamine level decreased significantly after RIT. It has been reported (Borowska et al. 1986) that such a decrease in plasma histamine may reflect a decrease in the histamine content of human mast cells and basophils. It has also been reported (Isersky et al. 1983) an in vitro study in which repetitious antigen stimulation decreased the degranulation rate in mast cells. We speculated that rapid progression of therapeutic effects in RIT is caused partly by this rapid decrease in mast cell histamine content. But this speculation should be confirmed by a further study on mast cell level.

Eosinophils are responsible for allergic inflammation in airways (Kay 1987). Since ECP is contained in the matrix of eosinophils (Peters et al. 1986), the sputum ECP reflects the activity of eosinophils in the airways of asthmatic patients (Numao et al. 1991). In our study neither peripheral eosinophil count

nor sputum ECP significantly decreased after RIT. However, these findings do not necessarily eliminate the role of eosinophil activity in the immunotherapy. It is possible that in a particular patient with possible RIT-provoked allergic rhinitis this disease may have masked significant decreases in peripheral eosinophil count and in the sputum ECP. Changes in eosinophil activity after RIT remained to be investigated.

Increases in the PD_{20} observed after RIT suggested a decrease in house dust-specific airway hypersensitivity after RIT. It was reported (Warner et al. 1978) that PD_{20} correlated with the number of eosinophils in peripheral blood. In our study the observed decrease in the eosinophil count may be related to an increase in PD_{20} . Therefore, we suspect that eosinophils are affected very early after RIT.

Usefulness of RIT

It has been suggested (Bousquet et al. 1985b) that RIT has a stronger and more rapid effect than does conventional immunotherapy. It has also been reported (Norman et al. 1968) that RIT permits administration of a higher maintenance dose and is more effective than conventional immunotherapy. Since the maintenance dose is reached very rapidly, patients tend not to discontinue the therapy prematurely. RIT was not compared to conventional immunotherapy in the present study. But all patients medicated with RIT did not drop out and reached house dust extract solution (HD) 10^{-1} . We speculate that RIT may have more advantages than conventional immunotherapy in treating mild asthma.

In RIT, the concentration of injected allergen extract was increased every few days. Therefore, the immunological reaction in RIT would be expected to exceed that in conventional immunotherapy. Our study demonstrated this by showing that 3 of 12 patients developed a generalized eruption. However, this side effect was treated easily with topical anti-histamines. None of our patients developed a severe anaphylactic reaction. During RIT a mild asthmatic attack developed in only 1 patient, however, this side effect was soon improved by administration of intravenous xanthine and subcutaneous β -agonist. Therefore, RIT therapy is not risky. However, we can not eliminate completely the risk of anaphylaxis in RIT. We recommend that RIT should be performed while the patient is observed closely in the hospital.

In conclusion, RIT is an effective but not risky therapy for patients with mild extrinsic asthma. The mechanism of RIT may either decrease in eosinophil activity or decreases in eosinophil chemotaxis. Histamine, too, may play a significant role in RIT.

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