

Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract

III. Systemic reactions during the rush protocol in patients suffering from asthma

J. Bousquet, MD, PhD, A. Hejjaoui, MD, H. Dhivert, MD, A. M. Clauzel, MD, and F. B. Michel, MD Montpellier, France

*Specific immunotherapy can induce severe systemic reactions (SRs), especially in patients with asthma. It also appears that potent standardized extracts may be more often involved in the generation of SRs than other extracts. Since these SRs may be potentially life threatening, it is desirable to predict their onset. A prospective study was carried out in 125 mite-allergic subjects with asthma ranging in age from 4 to 57 years to assess the incidence of SRs during a rush immunotherapy (RIT) protocol and maintenance injections and to attempt to predict the onset of the SRs. All patients received the same standardized extract of *Dermatophagoides pteronyssinus* with the same RIT and the same maintenance dose (3000 BU in subjects older than 10 years and 1500 BU in children younger than 10 years). Patients were carefully monitored during the RIT protocol, and possible SRs were followed for up to 2 hours after injections. Patients then received maintenance injections for a mean duration of 18.2 ± 5.6 months. During maintenance injections, patients were under supervision of a physician for 30 minutes. Within 2 weeks before the RIT, all patients older than 6 years had a pulmonary function test, skin prick test end point with the standardized *D. pteronyssinus* extract, and RAST. The severity of asthma was examined with the score of Aas. Forty-seven patients had an SR during the RIT protocol: four mild generalized urticaria, 35 asthma exacerbations, and eight anaphylactic shocks. None of the patients had to be admitted to an intensive care unit. Most SRs started within 15 minutes, and none of the SRs started 45 minutes or later after the last injection. The pulmonary function before immunotherapy had a predictive value for the onset of asthma, since 73.3% of patients with $FEV_1 < 80\%$ from predicted values developed asthma versus 12.6% with FEV_1 more than this threshold limit ($p < 0.0001$). The skin test end point was also predictive of SRs but to a lesser extent. During maintenance injections, the rate of SRs was low (4% per patient and 0.17% per injection). This study demonstrated that standardized extracts elicit a high rate of SRs in patients with asthma during RIT but that these extracts are safe during maintenance injections. Patients with severe asthma should not receive RIT with potent standardized extracts. (J ALLERGY CLIN IMMUNOL 1989;83:797-802.)*

Specific immunotherapy was introduced 70 years ago, and SRs occurred immediately. Life-threatening reactions and deaths were already observed in the 1930s, but immunotherapy appears to present a basic safety, since very few deaths have been reported during the past 20 years, although it is a very common therapeutic method.^{1,2} However, in October 1986, the

Abbreviations used

BU:	Biologic units
Dpt:	<i>Dermatophagoides pteronyssinus</i>
Dpt-IgE:	Dpt-specific IgE
RIT:	Rush immunotherapy
SR:	Systemic reaction

From the Clinique des Maladies Respiratoires, Centre Hospitalier Universitaire, Montpellier, France.

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Reprint requests: J. Bousquet, MD, Clin des Maladies Respiratoires, Centre Hospitalier Univ., Hôpital L'Aiguelongue, 34059 Montpellier Cedex, France.

Committee on Safety of Medicines of the United Kingdom published an article stating that immunotherapy is a dangerous treatment, should only be performed when full cardiorespiratory resuscitation equipment is available, and that the patient should be kept under

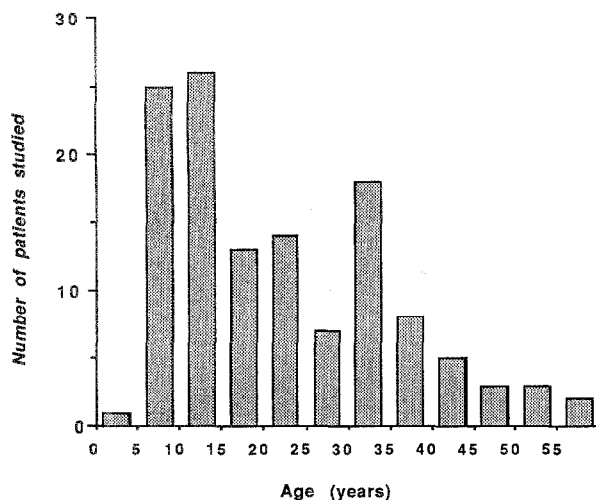


FIG. 1. Repartition of patients included in the study.

the supervision of a physician for 2 hours after treatment.³ The analysis of death certificates of recent fatal cases indicates clearly that (1) recent potent extracts are more dangerous than previous extracts and (2) patients observed with allergic asthma are more prone to develop life-threatening SRs.^{2,3}

A standardized and lyophilized *Dpt* extract has been available since 1980, and we have devised an RIT performed during 3 days, making it possible to reach the maintenance dose of 3000 BU in subjects older than 10 years, and 1500 BU in children younger than 10 years. The same RIT has been used for the past 6 years and has been demonstrated to alleviate significantly asthmatic symptoms in children and adults.^{4,5}

Because patients suffering from asthma more often develop SRs during immunotherapy, we attempted to determine whether these SRs could be predicted by studying 125 mite-allergic subjects with asthma ranging in age from 4 to 57 years who had RIT with a standardized *Dpt* extract.

MATERIAL AND METHODS

Patients

One hundred twenty-five patients ranging in age from 4 to 57 years (mean $\pm$ SD; 25.3 $\pm$ 11.2 years) (Fig. 1) were selected on the following criteria: (1) a definite history of perennial asthma, characterized according to the definition of the American Thoracic Society,⁶ and either a reversible bronchoconstriction after inhalation of 200 μ g of salbutamol or a significant sensitivity to carbachol, (2) a positive prick test and RAST to a *Dpt* standardized extract, and (3) no previous mite or house dust immunotherapy.

Extract

A standardized and lyophilized *Dpt* extract was prepared by Stallergenes Laboratories (Fresnes, France), according to the proposals of the allergen subcommittee of the Inter-

TABLE I. RIT protocol

	Hr	BU
Day		
1	9	30
	9, 30 min	150
	10	300
	11	600
	14	1200
2	9	1800
	11	2400
3	9	3000

national Unions of Immunological Societies. The preparation and standardization of this extract has been previously described in detail.⁴ A control of the potency of the extract was done by the manufacturer by RAST-inhibition and iso-electric focusing and compared with the internal standard standardized by in vivo and in vitro tests. The strength of the extract was expressed in BUs that were defined by comparing skin tests induced by a 9% codeine phosphate—positive control with serial dilutions of the *Dpt* extract. An arbitrary potency of 1000 BU was designated as the strength of *Dpt* extract that elicited a median wheal size identical to wheal size provoked by the positive control solution when both solutions were tested in parallel in 30 highly allergic subjects. The shelf life of *Dpt* extracts freshly reconstituted in 0.02% human serum albumin was assayed⁷ and determined to have a short life. This led to the preparation of single-dose vials of freeze-dried extracts. These vials were reconstituted the day of the injection and were then discarded. We also tested the batch-to-batch consistency of this *Dpt* extract by means of skin tests, according to the method of Dreborg.⁸

Immunotherapy schedule

The RIT consisted in a rapid increase of allergen doses that made it possible to reach the maintenance dose in 2 to 4 days, according to a protocol previously described⁴ (Table I). The maintenance dose was 3000 BU in individuals older than 10 years and 1500 BU in children younger than 10 years. The maintenance dose was administered weekly for 6 weeks, then bimonthly for the first year, and monthly after that time. When an SR occurred, the schedule was stopped, and the maintenance dose was reached more slowly.

Investigations of patients

Before immunotherapy, all patients were evaluated, and those patients who had an impaired pulmonary function received an adequate pharmacologic treatment. Then, within 2 weeks before immunotherapy, all patients had (1) an evaluation of the severity of asthma, according to the symptom-medication score of Aas⁹ that has been demonstrated to correlate with the activation of bronchoalveolar lavage cells,¹⁰ (2) a pulmonary function test with a Jaeger pneumoscreen (E. Jaeger, Würzburg, West Germany); normal

TABLE II. Characteristics of the patients according to the SRs observed during RIT

	No reaction	Severe SR	<i>p</i> Value*
No. of patients	85	43	
Age (yr)	24 ± 12	22 ± 11	NS
RAST score	3.4 ± 0.5	3.5 ± 0.4	NS
Severity of asthma (score of Aas)	3.1 ± 0.8	3.4 ± 0.6	NS
Skin test end point	4.3 ± 1.2	5.8 ± 1.2	<0.015
FEV ₁ (% from predicted values)	96.1 ± 16.2	83.2 ± 31.3	<0.001

Only patients with either severe SRs or no SRs were considered in this table. The four patients with mild urticaria were not studied.

Patients who had anaphylaxis and asthma were pooled.

**p* value by Student's *t* test.

values were obtained from Knudson et al.,¹¹ (3) a titration of serum *Dpt*-IgE by Phadebas RAST (Pharmacia Diagnostics AB, Uppsala, Sweden), according to the package insert, and (4) an end point skin prick test, according to a technique previously described in detail⁴ with eight threefold increasing concentrations of the standardized *Dpt* extract described above.

Study design

During the course of RIT, all patients were carefully monitored before and between each injection. Moreover, they were followed for up to 2 hours after the last injection. In particular, patients were always examined carefully before each injection and observed for possible wheezing. When an SR occurred, pulse rate and blood pressure were checked. Minor SRs, such as generalized urticaria, were treated with antihistamines and possibly systemic corticosteroids. Asthma was treated with theophylline infusion and intramuscular terbutaline. Finally, when symptoms of anaphylaxis were observed, subcutaneous and/or intramuscular epinephrine and sometimes oxygen were used.¹²

During maintenance immunotherapy, injections were administered by general practitioners or allergists. Each patient was kept under the supervision of a physician for 30 minutes after each injection, and the severity and time course of SRs were recorded on charts. All patients had been treated for up to 1 year, at least.

Statistical analysis was performed by means of Student's *t* test.

RESULTS

SRs during the RIT protocol

Anaphylaxis was characterized by severe symptoms, including tachycardia, hypotension, generalized urticaria, and/or angioedema, and possibly wheezing. All patients who presented with asthmatic reactions had an audible wheezing, and when it was possible, a peak flow was done. However, in the most severe asthmatic reactions, we preferred to treat the airway obstruction before performing a peak flow to confirm asthma. When a patient was observed with more than one SR, the patient was counted one time. Forty-three

patients (34.4%) had a severe SR requiring antiasthma treatment or epinephrine. Among these patients, 35 had asthma (peak flow monitored in 23 patients) and eight had anaphylaxis, which was immediately treated by subcutaneous or intradermal epinephrine (six subjects) or both epinephrine and oxygen therapy (two subjects). No patient had to be admitted to an intensive care unit. Only five patients had more than one SR; therefore, the rate of reaction per injection was 4.16%. Moreover, four other patients developed mild generalized urticaria. SRs were observed for doses ranging between 30 and 3000 BU.

Patients with mild SR had characteristics similar to patients who had no reactions, and since their number was low, they were no longer taken into consideration. The differences between reactors (patients with severe SR) and nonreactors (patients without SR) are presented in Table II and Fig. 2. Significant differences were only observed for the skin prick test end point and FEV₁ before RIT. It was observed that 73.3% of patients with FEV₁ <80% from predicted values developed asthma during RIT, whereas only 12.6% of patients with FEV₁ >80% from predicted values had bronchial symptoms (*p* < 0.0001). If patients with FEV₁ <80% had not been treated, the rate of severe SR would have been 19.7% per patient.

Most SRs started within 15 minutes after the last injection, and no SR started 45 minutes or later after the last injection (Fig. 3). No patient had a late onset SR. The quicker the onset of the SR, the more severe it was. SRs only occurred for doses >150 BU (Fig. 4).

SRs during maintenance injections

Patients were followed for a mean duration of 18.2 ± 5.6 months. A total of 5973 injections were received by the patients. Only five patients (4% SR per patient) had one to three SRs (0.17% SR per injection). Four SRs were characterized by asthma (in three of four patients, pulmonary function tests were

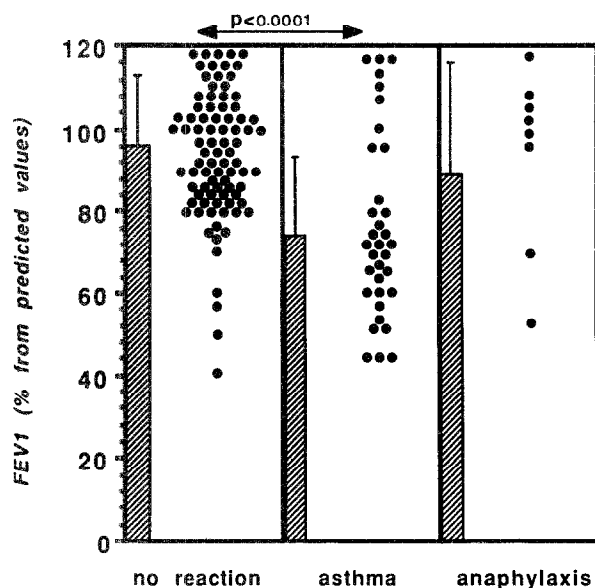


FIG. 2. Severe SRs according to the results of the pulmonary function statistical analysis by Student's *t* test.

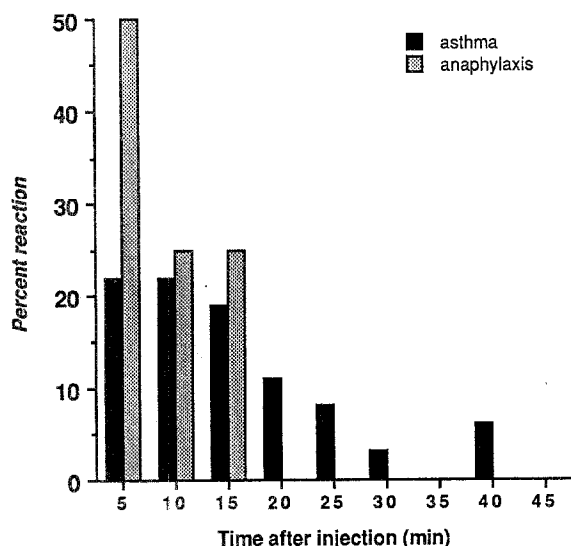


FIG. 3. Time of onset of SRs after injection of the standardized *Dpt* extract.

done and FEV₁ was decreased by 25%, 35%, and 40% from initial values), four SRs by a generalized urticaria, and one SR by anaphylaxis requiring epinephrine. All SRs occurred within 20 minutes after the injection.

DISCUSSION

Standardized extracts of *Dpt* used in RIT protocol were found to induce a high number of SRs in patients suffering from asthma. Asthma was particularly frequent in patients with an impaired pulmonary func-

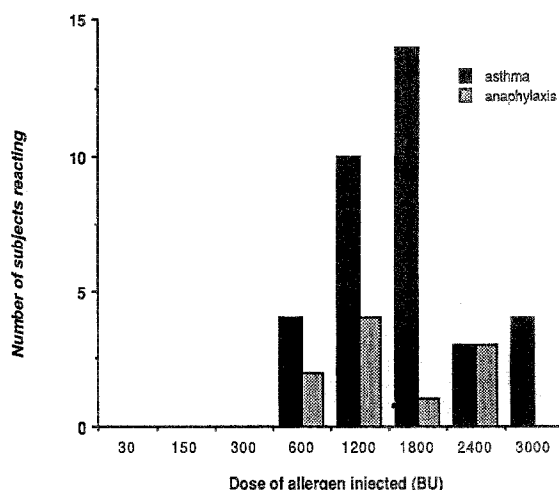


FIG. 4. Allergen doses inducing systemic reactions.

tion, and SRs were more often observed in highly sensitive subjects. In contrast, maintenance immunotherapy with this aqueous *Dpt* extract was found to be safer.

SRs occurred frequently during the RIT, but this rate is similar to that observed during RIT treatment with either pollens,¹³⁻¹⁵ animal danders,¹⁶ mites,¹⁷ or molds.^{18, 19} It is possible that RIT protocols expose patients to a higher incidence of SR,¹⁷ but this finding was not confirmed in our clinic with the same extract and the same maintenance dose. However, the cumulative dose of *Dpt* during the 48-hour period of RIT is greater than that administered during a maintenance injection period; that is, a larger dose is in fact being administered to the patients during a shorter period of time in comparison to a classic regimen. It must be pointed out that potent mite extracts induced a similar percentage of SRs when extracts were administered by a classic or clustered regimen.^{20, 21} Immunotherapy with standardized extracts differs from classic immunotherapy done in clinical practice with unstandardized extracts that elicit fewer SRs. Results from the literature indicate that the rate of SR ranges from one to 17 reactions per 1000 injections and is observed in 1% to 50% of the patients treated.²²⁻²⁵ With the same *Dpt* extract and RIT protocol, we subsequently tried to reduce the incidence of severe SR by (1) excluding patients with FEV₁ <80% from predicted values and (2) administering a preventive treatment to the patients (including corticosteroids, theophylline, and ketotifene) during the RIT. We have reviewed 110 patients and found a much lower rate of severe SRs (11%).²⁶

In the present study, only patients suffering from asthma were studied, and asthma was more often observed than anaphylaxis, especially in patients with a

bronchial obstruction. The latter finding agrees with findings of fatalities demonstrating that many deaths occurred in patients with asthma.^{2,3} This study and a previous study from our clinic⁵ suggest that patients with FEV₁ <80% from predicted values after an adequate pharmacologic treatment have less clinical benefits from RIT and have more asthmatic reactions during RIT; therefore, they should not receive RIT with a potent standardized mite extract. The sensitivity of the patients assessed by the skin prick test end point was also related to the rate of SRs, but we did not find any difference when RAST results were correlated to SR. This finding may be due to many factors, among which are the RAST scoring system and the fact that only highly allergic individuals receive immunotherapy.

During the RIT, all SRs occurred within 45 minutes after the last injection. This observation agrees with studies of anaphylactic shock after Hymenoptera stings.^{27,28} We had previously observed in pollen and mite RIT that very few mild SRs started between 45 and 90 minutes after the last injection²⁹ and that it does not appear necessary to keep patients under supervision for 2 hours,³ but 45 minutes of surveillance may be a safe compromise.

The low incidence of SRs during maintenance immunotherapy may be ascribed to the value of standardized extracts stored in stable form and only reconstituted the day of the injection, since it has been found that most SRs occurring during maintenance immunotherapy are observed when vials are changed.²² This study confirms pollen RIT with a standardized extract.^{14,15} We had already observed that when the maintenance dose is reached, subsequent injections are relatively safe. However, a few patients experienced SRs. All subjects undergoing maintenance immunotherapy should be kept under supervision of a trained physician for at least 30 minutes.

Standardized extracts usually induce more SRs than previous low potency extracts during the first phase of immunotherapy²² but were found, at least in the present study, to cause a low incidence of SRs during maintenance immunotherapy.

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High-molecular-weight kininogen is cleaved in active erythema multiforme

David M. Lang, MD, Sandra L. Sugimoto, BA, John G. Curd, MD,
Sandra C. Christiansen, MD, and Bruce L. Zuraw, MD La Jolla, Calif.

Erythema multiforme (EM) is an inflammatory disorder of the skin, which may include mucous membrane involvement, that features target (iris) lesions. Mediators specifically involved in EM are not well characterized; its pathogenesis remains enigmatic. In this study, evidence for participation of kinins in the pathophysiology of inflammation in EM was investigated by assessing cleavage of high-molecular-weight kininogen (HMWK) in plasma. These data were compared with analyses of plasmas from patients with serum sickness, chronic idiopathic urticaria/angioedema, and from normal control subjects. Patients with EM demonstrated significant levels of circulating cleaved HMWK in plasma during active disease ($p < 0.01$), which declined during remission/recovery. Plasmas from patients with EM obtained during active disease also demonstrated significant levels of 94 kd C1 inhibitor ($p < 0.01$) and C1 inhibitor-kallikrein complexes. Patients with serum sickness and chronic idiopathic urticaria/angioedema did not demonstrate these findings and did not differ from normal control subjects ($p = \text{not significant}$). Although the kininogenase responsible for HMWK cleavage in EM has not been conclusively demonstrated, these findings suggest that HMWK cleavage resulted from activation of the contact system and that some of the manifestations of EM in selected patients may in part be accounted for by inflammatory and proinflammatory actions of kinins. Based on these preliminary findings, it will be important to establish whether or not HMWK cleavage in EM is a general finding in patients with this disorder. Further investigation is needed to characterize more clearly kininogenase activity and elucidate the possible role of kinin generation in EM. (J ALLERGY CLIN IMMUNOL 1989;83:802-10.)

From the Divisions of Allergy and Immunology and Basic and Clinical Research, Scripps Clinic and Research Foundation, La Jolla, Calif.

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Reprint requests: David M. Lang, MD, Division of Allergy and Clinical Immunology, Henry Ford Hospital, 2799 West Grand Blvd., Detroit, MI 48202.

EM is an inflammatory cutaneous or mucocutaneous disorder characterized by distinctive target (iris) lesions. Rather than a specific disease, EM may be viewed as a cutaneous reaction pattern common to a variety of provoking factors and clinical disorders.¹ von Hebra² described EM in 1866 as an incorporation of erythema papulatum, erythema tuberculatum, erythema annulare, erythema iris, and erythema gyratum, all of which he recognized as dif-