Comparison of conventional and rush immunotherapy with Der PI in childhood respiratory allergy

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SUMMARY

Background: rush immunotherapy results obtained in Der PI-sensitive children with asthma and the changes in clinical and immunological parameters were investigated.

Methods: we studied 18 patients with Der PI sensitivity. Two groups were randomized: nine patients received RIT and nine patients received conventional immunotherapy (CIT) for three years. The RIT group reached the optimal maintenance dose at the end of one week. The CIT group reached the optimal maintenance dose in approximately three months. Symptom medication scores, lung function, side effects scores, skin-prick test, diluted skin-prick test with Der PI, bronchial provocation tests with Der PI, and Der PI-specific IgE and IgG4 were investigated in baseline conditions, at six months and at the end of the third year.

Results: there were no significant differences between groups in age, sex, and duration of illness. Treatment was tolerated very well. However, mean side-effect scores were higher in the RIT group than in the CIT group ($p < 0.005$). There were no significant differences between groups in the other parameters.

Conclusion: CIT is more advantageous than RIT in Der PI-sensitive children, although the maintenance dose was achieved more rapidly with RIT.

Key words: Dermatophagoides pteronyssinus. Rush immunotherapy. Conventional immunotherapy. Children. Bronchial provocation test.

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INTRODUCTION

Dermatophagoides pteronyssinus (Der PI) is the most common house-dust mite in Western Europe and Turkey and certainly is one of the most common allergens around the world. Trials with Der PI or Dermatophagoides farinea have been performed since 1970. Many conclusive trials have been carried out in children or adult subjects to treat asthma and/or rhinitis using either aqueous or tyrosine-adsorbed extracts, but most had to be long-term to demonstrate efficacy (1).

Many immunotherapy protocols have been proposed. In 1930, Freeman described three different protocols according to the frequency of allergen injections as the increment of doses weekly, daily, or " intensively" , and rush, consisting of five to six injections per day (1). In this study Freeman demonstrated the rapid effectiveness of treatment. Rush immunotherapy (RIT) had never been performed in Der PI allergy in children because severe systemic side effects might occur with under-standardized allergens. RIT programs with Der PI began when standardized lyophilized allergen extracts became available in 1980 (2).

In this study, the efficacy and safety of RIT with Der PI in children was investigated. For this purpose, symptom medication scores (SMS), bronchial challenge (BPT), pulmonary function tests (PFT), specific IgE (spIgE), and specific IgG4 (spIgG4) levels were evaluated at the beginning of the study, at six months and at three years. Results were compared to conventional (monthly) immunotherapy (CIT) with adsorbed material.

MATERIAL AND METHODS

Patients

This study was carried out prospectively between December 1994 and December 1999 in the Division

Table I

The protocol of rush immunotheraphy

Days	Hours	Volume (mL)	Vial (SQU/mL)	SQU/mL
1	09.00	0.1	1 (100)	10
1	09.30	0.4		40
1	10.00	0.8		80
1	11.00	0.2	2 (1.000)	200
1	12.00	0.4		400
1	13.00	0.7		700
1	14.00	0.1	3 (10.000)	1.000
1	15.00	0.2		2.000
2	09.00	0.2		2.000
2	10.00	0.3		3.000
2	12.00	0.5		5.000
2	14.00	0.8		8.000
3	09.00	0.8		8.000
3	10.00	0.1	4 (100.000)	10.000
3	12.00	0.2		20.000
3	14.00	0.3		30.000
4	09.00	0.3		30.000
4	10.00	0.4		40.000
4	12.00	0.5		50.000
4	14.00	0.6		60.000
5	09.00	1.0		100.000

of Pediatric Allergy and Immunology, Medical School of Çukurova University. Patients were examined and assessed by a single physician. The ages of eighteen patients ranged between 5-14 (mean age ± SD, 8.4 ± 3.1). Nine patients (7.7 ± 2.6) received RIT and nine patients (8.8 ± 3.7) received CIT.

All patients met the following criteria: (a) a history of mild or moderate asthma and/or rhinitis, (b) FEV1 > 80 %, (c) only positive skin prick test results with Der PI and/or positive RAST with Der PI, (d) positive bronchial provocation test with Der PI, (e) age range 4 to 16. Patients were excluded if they had an appreciable clinical history of sensitization to other allergens, or a history of other medical and immunological diseases.

Study desing and IT protocols

The study was performed after informed consent was obtained from parents. Eighteen patients were divided into two groups randomly. Group I (n = 9) received RIT with Aquogen ALK®. Group II (n = 9) received conventional IT (CIT) with depot extract adsorbed to aluminum hidroxide, Alutard ALK®.

RIT

RIT was performed according to the step protocol indicated in table I. The maintenance dose of 100,000 SQU was chosen based on the results of previous studies. After 5 days, this dose was administered at 2-week intervals for 6 months, then at monthly intervals.

Conventional IT

CIT was administered in incremental weekly doses for 3-4 months until the maximum tolerated dose (50,000-100,000 SQU/ml) was reached, and then used at monthly intervals (table II).

Skin prick test

The skin-prick test (SPT) was performed using a standard allergen panel of ALK (Soluprick SQ: ALK Laboratories, France). Glycerinated normal saline and histamine HCL 10 mg/mL were used as controls.

Diluted skin prick test

Because of the changes in skin sensitivity to Der PI, this test was performed in all patients who had only positive SPT with standardized Der PI. The diluted skin-prick test (DSPT) was performed with different concentrations of standardized Der PI

Table II

The schedule of adsorbed vaccine dose increase

Bottle	Week	Dose	Concentration	Total Volume (mL)	Frequency
	0	1	100 SQ/mL	0.20	weekly
1	1	2		0.40	
	2	3		0.80	
	3	4	1000 SQ/mL	0.20	weekly
2	4	5		0.40	
	5	6		0.80	
	6	7	10000 SQ/mL	0.20	weekly
3	7	8		0.40	
	8	9		0.80	
	9	10	100000 SQ/mL	0.1	weekly
	10	11		0.2	
	11	12		0.3	
4	12	13		0.4	
	13	14		0.6 or 0.8	
	14	15		1.0	

* IT was given once a month after reaching the maximum tolarated dose.

Table III

Asthma symptom medication score

Medication			Symptom	
No medication		0	None	
0				
Inhaled salbutamol	200 µg	1	Wheezing at expiration	1
Inhaled salbutamol	600 µg	2	Wheezing at inspiration and expiration	2
Inhaled cromolyn or nedocromil or oral ketotifen		3	High pitched wheezing also at rest	3
Inhaled steroid		4		
Inhaled steroid + oral aminophylline		5		
Oral steroid < 20 mg		6		
Oral steroid > 20 mg		7		

extract. The concentrations of solution were increased as 1,000, 3,000, 10,000, 30,000, 100,000 SQU/mL. After 15 minutes, the wheal was marked with a soft, fine-tipped pen and transparent adhesive tape was placed over the wheals. The tape was transferred to a record sheet and the area of the wheals was calculated. The dilution that produced as much induration as histamine was accepted as the cutaneous tolerance index.

Specific IgE and SpIgG4

Patients' sera were collected before initiating therapy, at 6 months, and at 3 years. Samples were stored at –40° C. Specific IgE and IgG4 were assayed in duplicate in a single session for the specimens collected before therapy, at 6 months, and at 3 years. Standard commercial tests were used. Specific IgE levels, expressed in Kua/L, were quantified in undiluted serum samples by a fluorimetric enzyme immunoassay (CAP System, Pharmacia, Uppsala, Sweden). Allergen-specific IgG4 antibodies were measured by a fluorimetric enzyme immunoassay (CAP system) in serum diluted 1:50. Results were expressed as a percent of the reference response by calculating the mean absorbancy of each sample and the mean absorbancy of the reference serum.

Symptom medication scores

The symptom-medication score (SMS) described by Bousquet et al (3) was used, with a small modification (table III). Most patients were followed-up by means of morning and evening peak flows, SMS before and after IT, at 6 months, and at 3 years. Before every injection, we obtained information on side effects and their symptoms at the time of each visit for injections. Side effects were recorded on a reaction score scale (4) (table IV).

Bronchial provocation test

A bronchial provocation test (BPT) was performed in subjects who had a baseline FEV1 value above 80% of the predicted value. Der PI extracts (Aquogen, ALK) were delivered by a nebulizer (Pari inhaler, West Germany). The concentrations of extract were increased as follows; 1000, 3000, 10,000, 30,000, 60,000, 100,000 SQ/mL. Forced expiratory maneuvers were performed 3 and 10 minutes after inhalation of each allergen solution. When FEV1 decreased by 20% or more, the test was stopped and the patient inhaled salbutamol immediately. Patients were kept under hospital observation for eight hours after BPT. Parents were called to check for late-phase reactions occurring the day after. No additional BPT were performed in patients who were hospitalized after the first BPT.

Statistics

Nonparametric statistical methods were used for calculations. Statistical analyses were performed using the SPSS-PC and BMDP+package. For differences between groups, the Kruskal-Wallas test, one-way analysis of variance (ANOVA), and repeated measures of analyses of variance were used. The Spearman correlation test was used for correlation analyses. The Chi-square test of independence was used to test the influence of one variable on another. The statistics of IgE, SPT, BPT, SpIgG4 levels and graphics were evaluated by geometric means.

Table IV

Reaction score scale

Local	
Enduration and/or erythema < 3 cm	0
Enduration and/or erythema > 3 cm	1
Systemic	
Generalized urticaria	2
Generalized pruritus and sneezing, nasal congestion	3
Wheezing, tachypnea, decrease of FEV1 and PEF	4
Anaphylaxis, hypotension, severe wheezing, laryngeal edema	5
Cardiopulmonary arrest	6

Table V

Evaluation of clinic and laboratory results of the patients in two groups before and after IT

First				6th Month			3rd Year		
	Mean	SD	Median*	Mean	SD	Median*	Mean	SD	Median*
SS	6.16	2.97		2.38	2.30	1.5(4.2)	1.11	1.76	0.0(2.0)
SPT	3.61	0.69		2.22	0.94		1.23	0.56	
DDT**	5666	9592	1000 (3750)	48388	38619		66000	37947	
BPT**	20470	25848	10000 (39000)	55294	36762				
SpIgE	4.66	1.81		4.94	0.89		5.06	0.99	
SpIgG4	8.00	4.78		87.02	48.44		156.00	23.69	

* IQR:Inter quarter range. ** SQ/mL.

RESULTS

Patients and tolerability

All of the patients completed the study. The evolution of the clinical and laboratory parameters of the patients before and after IT are shown in table V. The treatment was generally tolerated very well. The mean side-effect scores were 6.2 ± 1.6 in the RIT group and 0.8 ± 1.5 in CIT. There was a significant difference between groups ($p < 0.005$). Severe systemic side effects were not seen. Three patients had mild systemic reaction such as rhinorrhea, or mild bronchoconstriction within 30 min of injection. Generalized pruritis and urticaria were not seen.

Three patients developed local swelling larger than 3 cm, making it necessary to adjust updosing in CIT. These patients could not attain the optimum maintenance dose (100,000 SQ). One of them reached 20,000 SQ, the others reached 60,000 and 80,000 SQ.

In five patients, bronchospasm requiring hospitalization was diagnosed 6 to 8 hours after BPT at six months (three in the CIT group and two in the RIT group). Six patients tolerated 100,000 SQ and these tests were not repeated at 3 years. BPT improved significantly after six months of IT ($p = 0.01$). There was no significant difference between groups ($p = 0.4$). Tolerance to BPT significantly improved after IT in both groups ($p < 0.01$).

Allergy-specific parameters

A summary of the disturbance in allergen-specific parameters before and after SIT, compared to the baseline value, is shown in tables V and VI.

We found a significant reduction in specific cutaneous reactivity (shown as SPT) and an increase in IgG4 in both groups. Der PI-specific IgE levels did not vary significantly in either group, but there was a slight increase at end of 3 years. The Der PI-specific IgE levels were very similar in both groups after IT (tables VI and VII).

SMS and SPT were significantly reduced after the IT period in both groups ($p = 0.0003$, $p = 0.0007$). The patients treated with CIT had lower SMS and SPT than the RIT group but no significant differences. More significant improvement occurred in the RIT group, but there was no significant difference between groups ($p = 0.39$) (tables VII and

Table VI

The comparison of p value between before and after immunotherapy (Wilcoxon)

			6-12 month	0-3 year
CIT group	SS	0.0431	0.0679	0.0277
	SPT	0.0277	0.0679	0.0277
	DDT	0.1159	0.4652	0.117
	BPT	0.0796		
	SpIgE	0.4227	0.7853	0.4008
	SpIgG4	0.0277	0.2777	0.0277
RIT group	SS	0.0180	0.4227	0.0180
	SPT	0.0180	0.1775	0.0180
	DDT	0.0180	0.1088	0.0180
	BPT	0.3454		
	SpIgE	1.000	0.7874	1.000
	SpIgG4	0.0180	0.0425	0.0180
All patients	SS	0.0003	0.0251	0.0003
	SPT	0.029	0.0054	0.0003
	DDT	0.0009	0.3627	0.0007
	BPT	0.0110		
	SpIgE	0.5754	0.7897	0.4846
	SpIgG4	0.0004	0.0016	0.0002

Table VII

The comparison between groups (Mann-Whitney U)

	0 month	6 month	3 year
SS	0.6136	0.6106	0.3922
SPT	0.1715	0.4291	0.7353
DDT	0.8125	0.4950	0.3616
BPT	1.000	0.41155	
SpIgE	0.3591	0.0974	0.2936
SpIgG4	0.9430	0.7751	0.5661

VIII). SPT decreased after the IT period in both groups ($p = 0.0007$), but there was no significant difference between groups ($p = 0.36$).

There was no correlation between the increase in IgG4 and the decrease in cutaneous reactivity to Der PI at 6 months. We found a significantly negative correlation only between spIgG4 and cutaneous reactivity to Der PI (DSPT) at the end of 3 years ($p = 0.086$, $R = -0.4156$).

DISCUSSION

In this study, we analyzed the efficacy of RIT with mite allergens on specific and non-specific parameters, and compared with CIT in children.

In Turkey, Der PI is a major allergen (5). Specific IT with Der PI extracts was first proposed 70 years ago, but there is no general consensus about its efficacy and, at present, many different immunotherapy methods (1, 2).

RIT consists of a rapid series of injections of allergenic extracts that results in a rapid increase in allergen doses that makes it possible to reach the "maintenance" dose as soon as possible, thus reducing the "vulnerable" time between the induction of IgE and IgG responses.

We investigated changes in cutaneous and bronchial response, the level of Der PI-specific IgG4 and IgE associated with RIT and CIT, and the potential effectiveness. We demonstrated that RIT is clinically and immunologically specific for the allergen administered.

In this study, the efficacy of both types of IT was confirmed. In both groups, SMS improved, skin-prick test positivity increased, the maximum tolerated dose in BPT increased, and spIgG4 increased significantly after IT. There was no significant difference between groups.

After conventional allergen immunotherapy, there is an early decrease in end-organ responsiveness to allergen, which is not paradoxically associated with a decrease in allergen-specific IgE in serum (6). Mastrandrea also reported a highly significant reduction of Der PI and Der P2 IgE response only after the third year of treatment with RIT and CIT (7). Similarly, after both RIT and CIT we demonstrated decreased cutaneous and bronchial responses to Der PI in conjunction with no decrease in anti-Der PI IgE levels in serum. We found a consistent increase in specific IgG4 both groups. There was no correlation between the increase in IgG4 and the decrease in cutaneous reactivity to Der PI at 6 months. But we found that RIT may cause a rapid increase in anti-Der PI IgG4 level. We demonstrated a significantly negative correlation only between spIgG4 and cutaneous reactivity to Der PI (DSPT) at the end of 3 years ($p = 0.086$, $R = -0.4156$). We demonstrated that RIT can originate a rapid increase in anti-Der PI IgG4 level. Our findings confirm those of a previous study that demonstrated high IgG4 levels against house-dust mites shortly after RIT (8). There was no significant difference between groups in the increase in spIgG4 at 6 months and 3 years. Like most other specialists, we believe that the in vitro tests used (total serum IgE, spIgE, spIgG4) are not useful for evaluating the efficacy of IT in the follow-up (9, 10). Specific IgE is useful only in establishing the diagnosis; thus, we considered the serial determinations unnecessary (9). Specific IgG4 showed a significant increase during IT, but the meaning of this increase in relation to clinical improvement is still unclear (9, 11).

The side-effect score was significantly higher in the RIT group than in the CIT group. The frequency of adverse reactions observed confirms reports by other authors who perform RIT like we do (9,12). In our experience, there is no advantage in RIT over CIT in improving symptoms in the first year. RIT is not superior to CIT in routine practice with house-dust mites in children.

According to these results, CIT is more advantageous than RIT in Der PI-sensitive children, although the maintenance dose was achieved more rapidly with RIT.

RESUMEN

Objetivos: investigar los resultados de la inmunoterapia rápida en niños asmáticos sensibles a Der PI en relación con los cambios en los parámetros clínicos e inmunológicos.

Métodos: estudiamos a 18 pacientes con sensibilidad a Der PI. Se repartieron aleatoriamente en dos grupos. Nueve pacientes recibieron ITR y los

otros recibieron inmunoterapia convencional (ITC) durante tres años. El grupo de ITR alcanzó al final de una semana la dosis de mantenimiento óptima. El grupo de ITC alcanzó la dosis óptima aproximadamente al tercer mes. Fueron investigadas las puntuaciones por síntomas y administración de fármacos, función pulmonar, efectos secundarios, resultados de las pruebas cutáneas, pruebas cutáneas con Der PI diluido, pruebas de provocación bronquial con Der PI, IgE e IgG4 específicas de Der PI obtenidas en situación basal, en el sexto mes y al final del tercer año.

Resultados: no se encontraron diferencias significativas entre los grupos con respecto a la edad, sexo y duración de enfermedad. El tratamiento fue bien tolerado. Sin embargo, la puntuación media por efectos secundarios fue más elevada con la ITR que con la ITC ($p < 0,005$). No se encontraron diferencias significativas entre grupos en los otros parámetros.

Conclusión: la ITC tiene más ventajas que la ITR en niños con sensibilidad a Der PI, pero se alcanzó la dosis de mantenimiento más rápidamente con la ITR.

Palabras clave: Dermatophagoides pteronyssinus. Inmunoterapia rápida. Inmunoterapia convencional. Niños. Prueba de provocación bronquial.

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