

RUSH IMMUNOTHERAPY WITH THE STANDARDISED GRASS-POLLEN EXTRACT IN CHILDREN WITH MILD ALLERGIC ASTHMA. A COMPARISON OF TWO PREMEDICATION REGIMENS.

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A b s t r a c t

Rush immunotherapy (RIT) is a variant of the initial phase of allergen-specific immunotherapy. The build-up phase is shortened to several days, but this can be accompanied by systemic adverse reactions to the allergen administered. Grass-pollen allergens cause systemic reactions most often. The aim of our study was to evaluate systemic reactions to different doses of allergen and to different premedication regimens (with or without a middle dose of oral steroids) during a four-day RIT in children with mild asthma. Twenty nine children underwent RIT with a standardised vaccine of 6 grass-pollen and rye extracts. The target dose for children 6 to 15 years old was 40 000 SQ-U during 4 days. Two regimens of premedication were used to prevent systemic reactions as follows: fifteen children with mild asthma were given loratadine and SR theophylline and the control group of fourteen children received, in addition, prednisone at a daily dose of 1 mg/kg. SR theophylline was administered at a dose that resulted in a therapeutic serum level of 8–20 mg/l. A dose of 2 000 SQ-U was achieved in all children without any adverse reaction. Twelve children (41%) had a systemic reaction, but they all continued the maintenance therapy. The incidence of systemic reactions per injection was 2.6%. The numbers of urticarious and asthmatic reactions were 10 (34%) and 6 (21%), respectively. There were no anaphylactic or severe asthmatic reactions. Premedication with a middle dose of oral corticosteroids did not influence the number of systemic reactions.

Key words

Rush immunotherapy, Grass and rye pollen, Systemic reaction, Children, Asthma bronchiale, Premedication

INTRODUCTION

Allergen-specific immunotherapy (SIT) is an effective treatment for patients with allergic rhinitis/conjunctivitis, allergic asthma and allergic reactions to stinging insects. Standardised vaccines allow us to reach a maintenance dose of the major allergen in a range of 5 to 20 µg. Such doses correlate with therapeutic efficacy (1). The major immunological mechanism of SIT is the induction of specific anergy, possibly by IL-10, in peripheral T cells and the subsequent reactivation of distinct cytokine patterns (Th₀-Th₁ type profile). Continuous treatment with high doses of

allergens for several years finally decreases IgE antibody levels. SIT starts with the initial phase in which gradually increasing quantities of an allergen vaccine are administered until the maintenance dose is reached. However, during the initial phase of treatment, specific serum levels of IgE increase along with IgG₄. Increasingly secreted IL-10 appears to counter-regulate IgE synthesis and, within a few weeks, the ratio of specific IgE to IgG₄ rapidly decreases (2, 3, 4).

The initial (build-up) phase of SIT is associated with a higher risk of the systemic adverse reaction in comparison with the maintenance phase (5). Immunotherapy protocols of the initial phase of SIT are conventional, cluster and rush. Rush immunotherapy (RIT) shortens the initial treatment from months to days, but systemic adverse reactions appear more often (6). In order to decrease the risk of complications, it is necessary to use premedication especially if pollen extracts are administered (5,7). Previous studies on children included older types of antihistamines, theophylline used without checking its serum level and high doses of corticosteroids (7, 8). In our work we evaluated a RIT protocol, using the standardised mixture of grass and rye pollens in children with mild asthma bronchiale. Lotaradine and sustained-release (SR) theophylline at therapeutic serum levels were used as premedication. Prednisone was added to premedication in the control group of children. Systemic adverse reactions were evaluated in relation to the dose of the extract administered and the premedication applied.

MATERIALS AND METHODS

PATIENTS

Twenty-nine children, 10 girls and 19 boys (median age, 9.7±3.2 years; range, 5 to 17 years) underwent RIT. Three patients were 5 years old and two patients were older than 15 years. Twenty-six children had allergic bronchial asthma, three children had allergic rhinoconjunctivitis and eczema. Their clinical signs were typical of summer allergy to grass pollens and rye. The diagnosis was confirmed by skin prick tests and by specific serum IgE levels. Children with asthma used beta₂-agonists intermittently or took cromones. Their condition was defined as mild asthma. Some of them used inhaled corticosteroids on rare occasions. The children were divided into two groups according to the premedication used. Group A consisted of 15 children, age 9.5±3.2 years, with allergic asthma who received loratadine and SR theophylline premedication. Group B (control) comprised 14 children, age 9.9±3.1 years, of which eleven patients had allergic asthma and three had allergic rhinoconjunctivitis and eczema. They used premedication with loratadine, SR theophylline and prednisone at a daily dose of 1 mg/kg.

METHODS

The allergen immunotherapy was based on an aqueous solution of allergen extracts from six grass pollens (*Dactylis glomerata*, *Lolium perenne*, *Alopecurus pratensis*, *Phleum pratense*, *Poa pratensis*, *Festuca pratensis*) and rye pollen (*Secale cereale*), i.e., the Alk Wasserig SQ 200 vaccine produced by Epipharm, ALK-ABELLÓ Group. The activity of the extract was given in standardised quality units (SQ-U/ml). The content of the major grass-pollen allergen was 12 µg per 100 000 SQ-U. For 4 days, gradually increasing doses were applied. On the 5th day, the patients were given a depot injection of the maintenance dose and were discharged from hospital 3 h later (Table 1).

In 5-year-old children, the target dose was 5 000 SQ-U, i.e., 0.5 ml of the 10 000 SQ-U/ml concentration. Children aged 6 to 15 years had a target dose of 40 000 SQ-U, i.e., 0.4 ml of the

Table 1
Schedule for dose increment

Day	SQ-U/ml	Dose (ml)	Dose (SQ-U)	
1st	100	0.1	10	
		0.4	40	
		0.8	80	
	1000	0.2	200	
		2nd	1000	200
		0.4	400	
		0.7	700	
	10000	0.1	1000	
3rd	10000	0.1	1000	
		0.2	2000	
		0.3	3000	
		0.5	5000	
		0.8	8000	
4th	100000	0.08	8000	
		0.1	10000	
		0.2	20000	
		0.3	30000	
		0.4	40000	
		0.5	50000	

100 000 SQ-U/ml concentration. Two children older than 15 years were given a target dose of 50 000 SQ-U, i.e., 0.5 ml of the 100 000 SQ-U/ml concentration. The application sites for injections were as follows: right forearm, left arm, left forearm, right arm. The injections were applied subcutaneously.

For 3 days before starting the treatment, the children were given loratadine (Claritine) tablets (10 mg) and SR theophylline (Uni-Dur SR) tablets (Schering-Plough Labo, Belgium). Claritine was applied at a dose of 1/2 tablet (weight under 30 kg) or 1 tablet (weight over 30 kg). Uni-Dur SR was given at doses of 200, 300 or 400 mg according to the body weight (approximately 10 mg/kg) once a day in the evening. The serum level of theophylline was checked on the 3rd day of administration, i.e., on the day when RIT was started. It was set at a therapeutic level of 8 to 20 mg/l. The children who had not reached this level were excluded from the study. All of the children were given loratadine and theophylline tablets at the same dosage for 14 days after completing RIT.

In group B children (controls), prednisone was administered in addition to loratadine and theophylline. The prednisone administration (1 mg/kg/day) continued during RIT for 5 days.

After the last application of ALK Wasserrig SQ 200, the therapy continued on the following day with an Alutard SQ 200 depot injection at a concentration tolerated on the last day of the initial phase; the patient was then kept on maintenance therapy lasting several years. The depot vaccine was applied every 4 to 8 weeks. If the patient had an adverse systemic reaction during RIT, the maintenance dose was equal to the highest vaccine concentration that the patient tolerated without adverse effects.

RESULTS

All children reached at least 2 000 SQ-U per dose without systemic adverse reactions. Of the 29 children, 12 (41%) presented with systemic adverse reactions. All children reached a concentration at least 200% higher than was the initial dose of 10 SQ-U. The vaccine dose that started a systemic reaction was in a range of 3 000 SQ-U to 20 000 SQ-U. The children were without any problems and without side reactions on the 1st and 2nd days after vaccine application. Reactions appeared after the 11th injection on the 3rd day of RIT. The 5-year-old children had no systemic reaction; they reached a maintenance dose of 5 000 SQ-U, which was not further increased. A topical reaction appeared only in one patient. A wheal, 20x20 mm in size, appeared around the puncture point after a dose of 10 000 SQ-U was applied and persisted for 120 minutes. The dose then was not increased.

Systemic reactions appeared in 11 children at 45 to 120 min after vaccine application. Only in one case, there was both a urticarious and a conjunctival reaction 15 min after the application. A total of 462 injections of the standardised vaccine were given. The incidence of systemic reactions was 2.6 % per injection (12 systemic reactions). Urticaria appeared in 10 cases (34%) and symptoms of mild asthma in 6 cases (21 %). There were no anaphylactic reactions, no symptoms of severe asthma or cardiovascular reaction. Systemic reactions for the whole patient sample are shown in *Fig. 1* (total number of reactions), *Fig. 2* (urticarious episodes) and *Fig. 3* (asthmatic episodes).

Premedication with prednisone did not influence the number of general adverse responses. Out of 15 children in group A, six showed systemic reactions (40%) and all were urticarious reactions; in addition, three (20%) children also had an asthmatic reaction but no severe asthma. In group B (14 children) which was given prednisone, six children had a systemic reaction (43%); of these, four had urticarious episodes and three had mild asthmatic difficulties (21%). Group B differed from group A only in the number of urticarious reactions, which was lower (*Table 2*).

The children with a systemic reaction were treated with hydrocortisone administered intravenously. A daily dose of loratadine was repeated or antihistamine (Methiaden-Ca) was applied intravenously. The children with a bronchial reaction also received beta₂-agonists by inhalation of aerosol and, eventually, theophylline intravenously. In all these patients, allergic reactions ceased within a few hours.

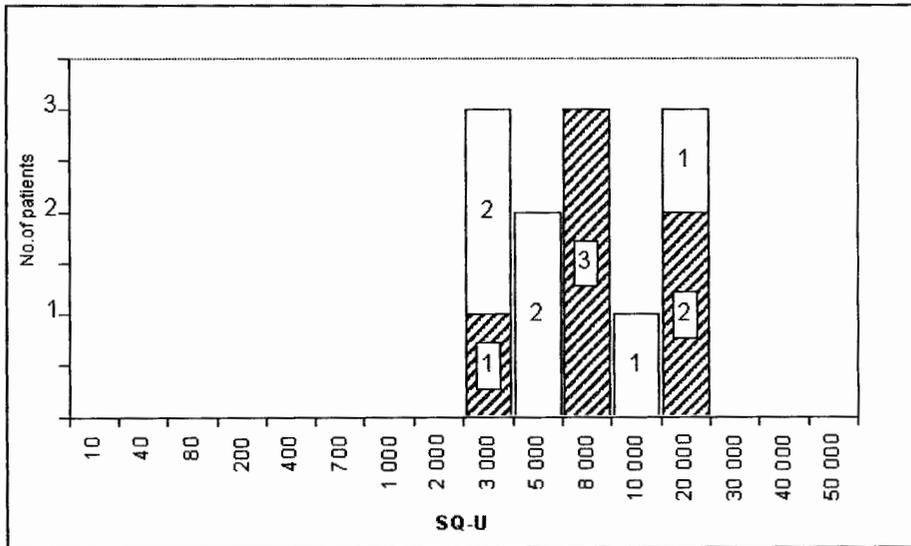


Fig. 1

Systemic reactions in patients in relation to increasing doses of vaccine (SQ-U). Shaded area, group A patients given premedication without prednisone. White area, group B patients whose premedication included prednisone. 1,2,3, numbers of patients who had systemic reactions.

The allergen immunotherapy continued the next day after RIT had been completed with a maintenance dose of the depot vaccine in all children. This dose corresponded to the dose tolerated the day before, i.e., this dose was one degree lower than the dose that started the systemic reaction.

Claritine was well tolerated in all children during the whole treatment without any side reaction. No symptoms of sedation or change in psychic conditions were observed. No abdominal pain or headache appeared.

Uni-Dur SR was without side effects in group A children who did not receive prednisone. The situation in group B, in which prednisone was given, was more complicated. Two children reacted by stomach pain the last day of prednisone administration. One child had hypokalemia the last day of prednisone administration, which was treated by infusion therapy. Two children in this group also had fatigue.

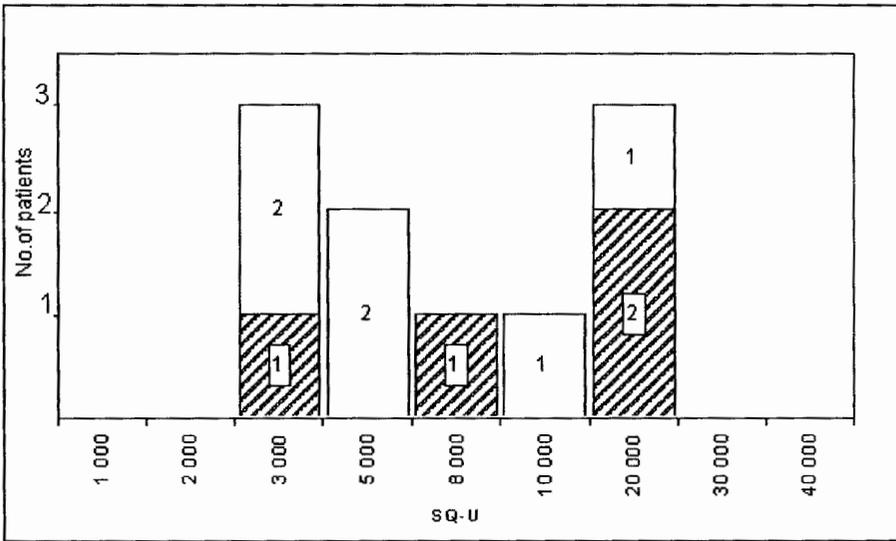


Fig. 2

Urticarious episodes in patients in relation to increasing doses of vaccine (SQ-U). Shaded area, group A patients given premedication without prednisone. White area, group B patients whose premedication included prednisone. 1,2,3, numbers of patients who had urticarious episodes.

DISCUSSION

RIT is a variant of the initial phase of SIT. SIT is indicated for the treatment of asthma bronchiale in children above 5 years of age; for severe and non-controlled forms of asthma bronchiale it is not recommended (9,10). Our sample included children with a mild form of asthma; only three children in the control group (B) had allergic rhinoconjunctivitis with eczema. A shortening of the initial phase of SIT can be recommended for several reasons. First, children with asthma bronchiale often suffer from respiratory infections during autumn and winter seasons and, therefore, an achievement of high doses of vaccine can be complicated. Second, the effective concentration of the vaccine can be achieved during a short period right before the pollen season. Third, patients living far from medical care facilities sometimes ask for fewer visits at their specialist than is necessary for the conventional form of SIT.

The initial phase of SIT can be shortened by rush or cluster schedules. We used a four-day model of RIT associated with two regimens of premedication, either with or without oral corticosteroids, and both with antihistamine and SR theophylline. The maximum dose of allergen was dependent on the age of the

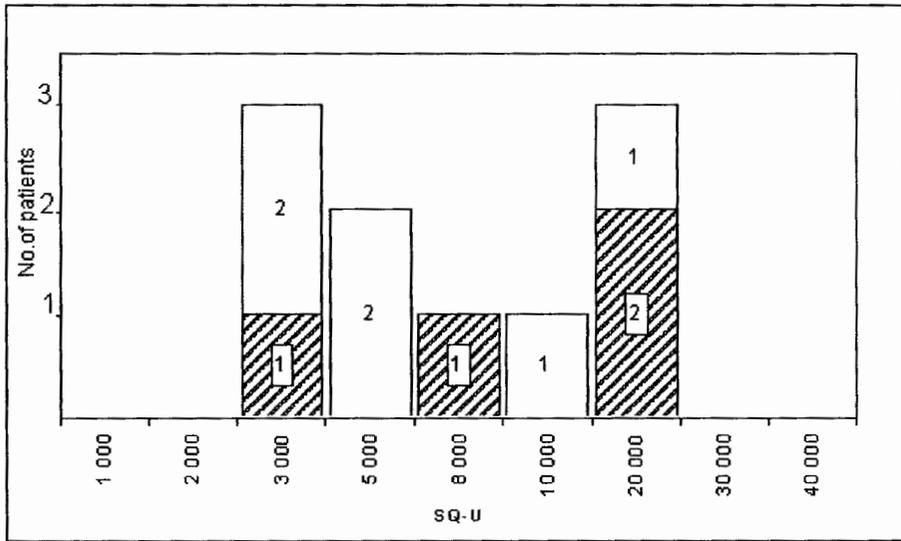


Fig. 3

Asthmatic episodes in patients in relation to increasing doses of vaccine (SQ-U). Shaded area, group A patients given premedication without prednisone. White area, group B patients whose premedication included prednisone. 1,2,3, numbers of patients who had asthmatic episodes.

Table 2

Systemic reactions in the patients on two different premedication regimens

Patient characteristics	Group A	Group B
No. of patients	15	14
Systemic reactions	6	6
Asthmatic episodes	3	3
Urticarious episodes	6	4
No. of injections	246	216
Incidence of SRs per injection	2.4 %	2.8 %
Incidence of SRs per patient	40 %	43 %

Premedication treatment in group A consisted of loratadine and theophylline. Premedication for group B included loratadine, theophylline and prednisone. Treatment with prednisone did not reduce the number of systemic adverse reactions. SRs, systemic reactions.

child. At the end of RIT, each child was given a depot vaccine at the highest concentration that was tolerated during RIT. We evaluated the number of systemic reactions and compared their occurrence in relation to the two premedication regimens.

SIT is accompanied by slight alterations in immunological parameters of T and B lymphocytes that are related to the reactivation of Th₀-Th₁ type cytokines and changes in IgG (11, 12). A change in affinity of IgG has been reported during RIT (13, 3, 4). High doses of corticosteroids (2 mg/kg/day) have a marked suppressive effect on bone marrow and T lymphocytes; therefore, they are not suitable for the use in SIT. We used a lower dose of corticosteroids (1 mg/kg/day) to prevent allergic reactions during RIT but we did not find any decrease in the number of systemic reactions in the group treated with corticosteroid premedication; only urticarious reactions were less frequent. However, adverse reactions (fatigue, stomach pain, poor tolerance of theophylline) caused by these corticosteroids were observed.

The number of systemic reactions in RIT is lowest for insect venom immunotherapy (VIT). *Brehler et al.* reported 10.7% of systemic reactions after application of VIT during hospitalisation without corticosteroid administration; RIT was shortened to two days (14). Similarly, RIT for hypersensitivity to imported fire ant stings (IFA) in the USA has been described. *Tankersley et al.* also tested a protocol without corticosteroids and reported 4.8% of systemic reactions during a two-day RIT with the IFA vaccine (15).

When a mixture of several antigens is involved in the application of grass-pollen allergens, adverse reactions are more frequent than when a single-allergen vaccine is used. The ratio of systemic reactions to a pollen mixture to those to a Hymenoptera vaccine was 2.75 : 1 for a conventional SIT (5). We used a maximum of 6 grass-pollen allergens enriched with a rye allergen for our model situation. The systemic reactions in children given premedication with loratadine and theophylline were late and were not severe so that all children could start maintenance treatment. A late topical reaction appeared in one patient after administration of a concentration of 10 000 SQ-U and this dose was not increased.

Loratadine and SR theophylline were administered for another two weeks after the termination of RIT as a preventive treatment because the children discharged from hospital went home where they were exposed to different concentrations of allergens in the air than in the hospital. Loratadine (Claritin) was well tolerated, theophylline (Uni-Dur SR) caused gastrointestinal symptoms in two children on the 5th day of use with prednisone.

Loratadine is a non-sedative antihistamine with antiallergic effects (16). Theophylline causes bronchodilatation and, in our study, its level was kept at a therapeutic value of 8 to 20 mg/l. At this concentration, it also has immunosuppressive and antiallergic effects (17, 18). Loratadine may reduce skin

and nasal reactions. A similar effect of fexofenadine on a decrease in urticarious skin reactions during an ultra-rush immunotherapy for adults has been recorded (19). No decrease in the number of systemic reactions was seen when antileukotrienes (zileuton and montelukast) were used during premedication in RIT (20).

RIT with the standardised grass-pollen vaccine was described by *Hejjaoui et al.* They reported 31.3% of systemic reactions per patient and 5.5% per injection when no premedication was used. However, there were 14.7% of systemic reactions per patient and 5.5% per injection after the use of premedication (methylprednisone, ketotifen, theophylline). The doses of vaccine were reduced to half for children under ten (8). In our study, only the children under six received a reduced dose. The number of systemic reactions per patient was higher (41.3%) and the incidence per injection was lower (2.6%). *Dolz et al.* report 25% (7/28) of the systemic reactions to three grass-pollen ALK allergens in adults (21). *Portnoy et al.* treated children with grass-pollen allergens and used premedication with prednisone, astemizole and ranitidine during a two-day RIT. They described 27% (3/11) of the systemic reactions (7). During first two days, the children in our study were without systemic reactions but the doses they reached were lower (2000 SQ-U).

We evaluated the doses that initiated systemic reactions. All children tolerated the vaccine amount up to a dose of 2000 SQ-U. This fact has been used in a cluster schedule for dust mites (22), cat (23) grass and birch pollen extracts (24) where the 1000 SQ-U level of the ALK allergen has been reached after application of the third injection. *Winther et al.* used only one grass-pollen allergen in a cluster schedule and observed 45% of systemic reactions without using premedication in adults with seasonal rhinitis (24). The current trend leads to a cut-down of the number of injections and to a reduction of a cumulative dose of allergen (14,23). On the basis of our results, a two-day, semi-rush protocol or a cluster immunotherapy schedule involving a mixture of grass-pollen extracts can be designed for treatment of out-patients with a dose up to 2000 SQ-U.

In conclusion, it is possible to perform RIT with 6 grass-pollen and rye extracts (ALK Wasserig SQ) up to a dose of 2000 SQ-U, including premedication with loratadine and SR theophylline. Higher vaccine doses can be accompanied by systemic adverse reactions that cannot be prevented by adding a middle dose of oral corticosteroids to the premedication.

RYCHLÁ IMUNOTERAPIE SE STANDARDIZOVANÝM EXTRAKTEM LETNÍCH TRAVIN
U DĚTÍ S MÍRNÝM ASTMA BRONCHIALE . SROVNÁNÍ DVOU SCHEMAT
PREMEDIKACE

Souhrn

Rychlá imunoterapie (RIT) je variantou počáteční fáze alergen-specifické imunoterapie. Vzestupná fáze je zkrácena na několik dní, ale může být provázena systémovými vedlejšími reakcemi na podaný alergen. Alergeny letních travin způsobují tyto reakce nejčastěji. Cílem studie bylo zhodnotit systémové reakce během čtyřdenní RIT u dětí s lehkým astmatem v závislosti na dávce alergenu a při různých schématech premedikace (při užití středních dávek perorálních steroidů a bez nich). Dvacet devět dětí podstoupilo RIT se standardizovanou vakcinou pylů šesti letních travin a žita. Děti ve věku 6–15 let dosahovaly cílovou dávku vakciny 40 000 SQ-U během 4 dní. Byly užity dvě schémata premedikace k prevenci vedlejších reakcí: patnáct dětí s lehkým astma bronchiale dostávalo loratadine a teofylin, u kontrolní skupiny 14 dětí byl přidán prednison 1 mg/kg/den. Sérové hladiny teofylinu byly na terapeutických hodnotách 8–20 mg/l. Všechny děti dosáhly nejméně dávku 2000 SQ-U. Dvanáct dětí (41%) mělo systémovou reakci, ale všechny pokračovaly další den dávkou vakciny, která byla snášena bez vedlejší reakce. Incidence systémové reakce na počet injekcí byla 2,6%. Úrtikariální reakce se vyskytla u 10 dětí (34%), astmatická reakce u 6 dětí (21%). Premedikace se středními dávkami perorálních kortikosteroidů neovlivnila počet systémových reakcí.

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