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Ultrarush schedule of subcutaneous immunotherapy with modified allergen extracts is safe in paediatric age

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Background: Traditional subcutaneous immunotherapy up dosing with allergenic extracts has been shown to be associated with frequent adverse reactions. In recent studies it has been demonstrated that using modified extracts, namely allergoids, it is a safe and effective procedure particularly on accelerated schedules. However data assessing its safety in paediatric age is scarce.
Objective: To evaluate the safety profile in paediatric population of using modified allergen extracts, in an ultrarush schedule, to reach the maintenance dose in the first day.
Methods: We included children undergoing treatment with subcutaneous immunotherapy during a five-year period, using modified aeroallergen extracts, depigmented, polymerized with glutaraldehyde and adsorbed on aluminium hydroxide using an ultrarush induction phase. The type of adverse reactions during the ultrarush protocol was recorded.
Results: We studied 100 paediatric patients (57 males) with a mean age of 11.6 years (5 to 18 years; standard deviation, 3.3), all with moderate to severe persistent rhinitis, with or without allergic conjunctivitis, asthma and atopic eczema, sensitized to mites and/or pollens. All reached the maintenance dose of 0.5 mL in the first day, except 1 child. During the ultrarush protocol the total number of injections was 199. There were 21 local adverse reactions in 11 patients, 11 immediate and 10 delayed; from those, had clinical relevance 1 immediate and 4 delayed. Systemic reactions were recorded in 2 cases, both immediate and mild.
Conclusion: The ultrarush protocol, without premedication, was a safe alternative to be used in paediatric age during the induction phase of subcutaneous immunotherapy using allergoid depigmented extracts.

Key words: Adverse Events; Allergens; Allergoids; Immunotherapy; Pediatrics; Safety

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INTRODUCTION

Antiallergic vaccination or specific immunotherapy is the only therapeutic method that can change natural history of allergic disease [1]. It is indicated for the treatment of multiple IgE-mediated allergic diseases, such as asthma, rhinitis and allergic conjunctivitis, allowing a significant improvement in both symptomatology and quality of life, and simultaneously reducing the overall costs [1, 2].

Allergen immunotherapy (AIT) may be administered by subcutaneous, sublingual or oral routes, with different administration schedules, such as the classical, the cluster, or the accelerated schedules, as rush or ultrarush. The accelerated schedules enable a faster administration, reaching the maintenance phase in less than 1 hour, can improve the patient compliance and accelerate the onset of the beneficial effect of this specific treatment [1, 2].

Subcutaneous administration of specific immunotherapy (SCIT) raises some safety concerns, due to its risk of adverse reactions, namely in the paediatric age group. Adverse reactions may be local or systemic, ranging from erythema, pruritus, and/or edema at the injection site to life-threatening systemic reactions [2-4]. In several studies of conventional SCIT, systemic reactions have been reported to occur in 0.8% to 46.7% of patients [5]. Frew et al. [6], in a multicenter study of SCIT in patients with rhinoconjunctivitis sensitized to pollens, reported a grade 3 systemic reactions rate of 4.4%, in the highest dose group.

The occurrence of adverse reactions has been reported in studies using physically (semidepot) or physically and chemically (allergoids) modified aqueous extracts, often requiring premedication with antihistamines and corticosteroids [1, 2].

Recently, allergenic extracts submitted to methods to reduce allergenicity have been made commercially available. These consist of depigmentation in combination with glutaraldehyde polymerization (polymerized allergoids) [7-10].

Previous, randomized, double blind, placebo-controlled studies in patients with asthma [7, 8] and rhinitis [9, 10] have shown the clinical efficacy and safety of the administration of mite- [7, 8] and pollen-polymerized depigmented allergoid extracts [9, 10], using a conventional SCIT schedule. Pfaar et al. [11] in a prospective, randomized, double-blind, placebo-controlled, 2-year study, comparing the clinical and immunological efficacy of depigmented and polymerized grass pollen extracts, using a rush preseason schedule, in patients with allergic rhinoconjunctivitis sensitized to grass pollens, concluded that the use of these extracts was clinically and immunologically effective and extremely safe, as no serious reactions have been identified.

Similarly, Brehler et al. [12] examined patients with allergic rhinoconjunctivitis sensitized to grass pollens, tree pollens, and house dust mites. A subgroup of this study population was submitted to a conventional SCIT schedule and other subgroup was submitted to a rush schedule using a polymerized depigmented allergoid with no premedication. In his assessment, no statistically significant differences were observed in adverse reactions, between the rush group and the classical administration group, regardless of the implicated allergen. Nevertheless, the clinical significance of these differences may be debatable.

There are few studies using the rush schedule to administer polymerized depigmented allergoids in paediatric age. The purpose of this observational study was to assess the safety in children and adolescents of an ultra-rush induction schedule of SCIT using polymerized depigmented allergoids.

MATERIALS AND METHODS

All paediatric patients examined by the authors during 5 years (from May 2007 to June 2012), in our Allergy Center, submitted to SCIT initiated with an induction phase using an ultrarush schedule with mite- or pollen-modified allergenic extract (depigmented, glutaraldehyde-polymerized, and adsorbed on aluminium hydroxide), and that maintained the treatment for at least 1 year, were enrolled into this study.

Their demographic data (age and sex), background of allergic disease and sensitization to aeroallergens were recorded, as well as the type of adverse reactions occurring during the ultrarush induction phase of the subcutaneous AIT, and the respective management.

Treatment with subcutaneous immunotherapy has been proposed to patients with moderate to severe persistent allergic rhinitis, defined according to Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines [1], with moderate to severe symptoms and quality of life impairment present more than 4 days a week and for more than 4 consecutive weeks, with or without conjunctivitis, asthma and/or atopic eczema, sensitized to mites and/or pollens (skin prick tests with commercial aeroallergen extracts [Laboratorios LETI, S.L., Madrid, Spain] and specific IgE

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determinations performed through the ImmunoCAP method [Thermo Fisher, Upssala, Sweden]). Treatment was initiated according with the vaccine manufacturer recommendations (Laboratorios LETI, S.L.), with the vial containing the maximum recommended concentration of the modified allergens(s) (100 depigmented polymerized per mL [DPP/mL] for mite extracts and 1,000 DPP/mL for pollen extracts), according to the manufacturing process and potency that has already been described in previous publications [7-12]. The induction phase protocol consisted of the administration, of 0.2- and 0.3-mL doses in alternate arms, 30 minutes apart, reaching the maximum dose (50 DPP for mite extracts and 500 DPP for pollen extracts) from the first day. All administrations of the ultrarush schedule were made by one of the authors, allergy specialist, at the Day Care Unit, under medical surveillance and following a minimum monitoring period of 60 minutes after the last dose, recording and treating possible adverse reactions. No patient received premedication at the day of the procedure, namely antihistamines.

To all patients the phone number of the medical staff was given, to report late reactions after the induction phase or any event occurred during the maintenance phase. After induction, medical contact or examination has been scheduled and the appropriate treatment was prescribed for any late reaction.

The local Ethics Committee approved the study and informed consent from the healthcare providers has been obtained in order to allow their children to be enrolled into this observational study.

Assessment of adverse reactions

Adverse reactions have been classified according to their location (local or systemic) and time emergence (immediate, within the first 30 minutes after the administration, or late, when occurring after this period). The local presence of discomfort, edema, pain and pruritus has been evaluated. Local reactions were classified by measuring the larger diameter of the reaction. Immediate reactions <5 cm in diameter and late reactions <10 cm in diameter have been deemed clinically not relevant [1, 2, 13]. Systemic reactions were retrospectively classified according to The World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System, which defines 5 grades of severity [3].

For the treatment of local reactions, the application of cold was recommended and, depending on the severity, topical corticosteroids and nonsedating oral antihistaminic drugs were also prescribed. The treatment of systemic reactions followed the recommendations of the European Academy of Allergy and Clinical Immunology [14].

RESULTS

One hundred paediatric patients (57 males) with a mean age of 11.6 years (5–18 years; standard deviation, 3.3) were included.

All had moderate to severe persistent allergic rhinitis, 60% had allergic conjunctivitis, 62% asthma, and 25% atopic eczema. Overall 90,3% (56 of 62 patients) had persistent asthma, and all of them were under controlled therapy namely inhaled steroids. At the beginning of specific immunotherapy treatment, asthma was clinically and functionally controlled in all patients. Regarding the aeroallergen sensitization profile, 74% of the patients were sensitized to mites, 77% to grass pollens and 60% to tree pollens; 21% were sensitized to mites only, 26% to grass and/or tree pollens only, and 53% simultaneously to mites and pollens.

All patients had both a positive skin prick test and serum-specific IgE determination to the allergen(s) included in the composition of their antiallergic vaccine, selected as major allergen(s) for being the most clinically relevant ones. Specific immunotherapy with modified pollen extracts was initiated before or after the peak pollen season. The composition of the administered allergen extracts is described in Table 1.

All patients reached the 0.5-mL maintenance dose at the induction day, except 1 child, who received the 0.2-mL dose only, due to the occurrence of an immediate local reaction leading to the protocol suspension (as described above). The total number of subcutaneous vaccines administered during the ultrarush phase was 199.

During the induction phase 21 local adverse reactions occurred in 11 patients; 11 immediate reactions (9 to *Dermatophagoides pteronyssinus* extract, 2 to grass pollens) and 10 late reactions (4 to *D. pteronyssinus* extract, 6 to grass pollens). Table 2 shows the number and the severity of these reactions, while Table 3 describes all cases. All 11 immediate local reactions were <5 cm in diameter.

In 1 case (patient number 1 of Table 3), the 2.5-cm immediate local reaction occurred after the administration of 0.2 mL causing a local discomfort with pruritus, edema and pain; therefore, as per the child and parents' will, it was decided to suspend the protocol. The local reaction has been treated with

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Table 1. Distribution of antiallergic vaccines by number of children, according to its allergenic composition

Aeroallergens	No. (%)
Mites	
D. pteronyssinus	25 (51.0)
D. pteronyssinus + *D. farinae*	3 (6.1)
D. pteronyssinus + *L. destructor*	13 (26.5)
L. destructor	4 (8.2)
Other mites (mix)	4 (8.2)
Total of mite-specific immunotherapy	49 (100)
Pollens	
Grass pollens (mix)	27 (52.9)
Grass pollens (mix) + *Olea europaea*	15 (29.4)
Grass pollens (mix) + *Platanus acerifólia*	1 (2.0)
Grass pollens (mix) + *Olea europaea* + *Platanus acerifolia*	1 (2.0)
Grass pollens (mix) + *Parietaria judaica*	1 (2.0)
Grass pollens (mix) + *Plantago lanceolate*	1 (2.0)
Parietaria Judaica	1 (2.0)
Olea europaea	4 (7.8)
Total of pollen-specific immunotherapy	51 (100)

D. pteronyssinus, *Dermatophagoides pteronyssinus*; *D. farinae*, *Dermatophagoides farinae*; *L. destructor*, *Lepidoglyphus destructor*.

oral nonsedative antihistaminic and local ice application. The child has been discharged 2 hours later, under surveillance, as per indications; a telephone contact was made 6 hours later, due to the worsening of the child's condition, with a late local reaction >10 cm in diameter. Considering this evolvement, treatment has been suspended and the situation was reported to the Pharmacovigilance Department of Laboratorios Leti. After the vaccine has been analysed, it was concluded that the concentration was within the normal parameters. As the child and the parents were unavailable to restart specific immunotherapy using a conventional schedule, sublingual specific immunotherapy was proposed. The other 5 patients with immediate local reactions <5 cm in diameter continued to receive the 0.5-mL maintenance dose, with a good tolerability.

As to late reactions, the occurrence of two late local reactions >10 cm in diameter were reported (patient number 2 of Table 3) and it has been decided to transitorily suspend specific immunotherapy. This case was also reported to the Pharmacovigilance Department of Laboratorios Leti and, after analysis, the concentration of the vaccine has been proved to be within the normal parameters. Subsequently, the patient restarted specific immunotherapy using a conventional induction schedule, with no adverse reactions and showing a good tolerability in the maintenance phase. In another patient, two late local reactions with 5 to 10 cm have been reported (patient number 3 of Table 3). It was decided to reduce the maintenance dose to 0.3 mL, which was sustained during the pollen season, being afterwards progressively increased until the 0.5-mL maintenance dose was reached, with good tolerability. Two late reactions <5 cm in diameter have also occurred (patient number 4 of Table 3) after the ultrarush schedule, however worsening of the condition was observed with the subsequent maintenance doses, with late local reactions measuring 5 to 10 cm being reported, and these reactions matched with grass pollen atmospheric peak. Therefore dose was reduced to 0.3 mL during the pollen season for patient comfort, being afterwards progressively increased to 0.5 mL, showing a good tolerability. In the other two patients with late local reactions <5 cm in diameter the 0.5-mL maintenance dose was sustained, with good tolerability.

Local reactions were treated with local cold application and, depending on the severity, with topical corticosteroids and nonsedating oral antihistamines as well.

Concerning the systemic reactions (Table 4 shows the number and the severity of these reactions; Table 5 shows a description of the reports), 2 cases were reported, both immediate and mild (grade 1) reactions, after the 0.5-mL cumulative dose of mite-polymerized depigmented allergoid extract. In 1 case (patient number 1 of Table 5), erythema of the face with pruritus was reported and, in the other (patients number 2 of Table 5), near syncope/vasovagal reaction was reported. In both patients hospitalization was not required. In those 2 cases, it was decided that the next dose would be administered after 30 days, under the allergist surveillance, when the maintenance phase would be initiated. In the first case, ultrarush schedule was repeated (0.2 mL + 0.3 mL), while in the second case the 0.5-mL maintenance dose was administered, with no adverse reaction. Both patients remained in the maintenance phase, showing good tolerability.

DISCUSSION

Clinical efficacy of specific immunotherapy depends on the dose of the allergen administered; however, high doses may

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Table 2. Ultrarush schedule: number and severity (mm in diameter) of local reactions (100 patients, corresponding to 199 injections)

Diameter (cm)	Local reactions								
	0.2-mL dose	% Per patient	% Per injection	0.3-mL dose	% Per patient	% Per injection	Total	% Per patient	% Per injection
Immediate									
<5	6	6.00	3.01	5	5.00	2.51	11	11.00	5.52
5–10	0	0	0	0	0	0	0	0	0
>10	0	0	0	0	0	0	0	0	0
Total	6	6.00	3.01	5	5.00	2.51	11	11.00	5.52
Late									
<5	3	3.00	1.51	3	3.00	1.51	6	6.00	3.02
5–10	1	1.00	0.50	1	1.00	0.50	2	2.00	1.00
>10	1	1.00	0.50	1	1.00	0.50	2	2.00	1.00
Total	5	5.00	2.51	5	5.00	2.51	10	10.00	5.02

Table 3. Ultrarush schedule: description of local reactions

Patients (n=11)	Age (yr)	Sex	Diagnosis	Composition of the vaccine	Reaction (n=21)	Mean diameter of the edema (cm)	Dose (mL)
1	14	F	RC, A	Depigoid, Dpt 100%	Immediate	<5	0.2
2	11	M	RC, A	Depigoid, Dpt 100%	Late	>10	0.2
					Late	>10	0.3
3	14	M	RC, A	Depigoid, Gra 100%	Late	5–10	0.2
					Late	5–10	0.3
4	17	F	RC, A	Depigoid, Gra100%	Late	<5	0.2
					Late	<5	0.3
5	11	F	RC, A	Depigoid, Dpt 100%	Late	<5	0.2
					Late	<5	0.3
6	9	M	RC	Depigoid, Gra100%	Immediate	<5	0.2
					Immediate	<5	0.3
7	6	M	RC	Depigoid, Gra100%	Late	<5	0.2
					Late	<5	0.3
8	10	M	RC, A	Depigoid, Dpt 100%	Immediate	<5	0.2
					Immediate	<5	0.3
9	11	F	R, A	Depigoid, Dpt 100%	Immediate	<5	0.2
					Immediate	<5	0.3
10	16	F	RC	Depigoid, Dpt 100%	Immediate	<5	0.2
					Immediate	<5	0.3
11	8	M	RC, A	Depigoid, Dpt 100%	Immediate	<5	0.2
					Immediate	<5	0.3

R, rhinitis; RC, rhinoconjunctivitis; A, asthma; Dpt, *Dermatophagoides pteronyssinus*; Gra, grass pollens.

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Table 4. Ultrarush schedule: number and severity of systemic reactions (100 patients, corresponding to 199 injections)

Type of reaction	Systemic reactions					
	Immediate			Late		
	Total	% Per patient	% Per injection	Total	% Per patient	% Per injection
Mild (grade 1)	2	2.00	1.00	0	0	0
Moderate to Severe (grades 2–5)	0	0	0	0	0	0
Total	2	2.00	1.00	0	0	0

Table 5. Ultrarush schedule: description of systemic reactions

No.	Age (yr)	Sex	Diagnosis	Composition of the vaccine	Reaction	Grade	Description	Dose (mL)
1	13	F	RC	Depigoid, Dpt 50%, Lep 50%	Immediate	1	Erythema of the face and pruritus	0.5
2	13	F	RC, AE	Depigoid, Dpt 34%, Lep 33%, Blomia 33%	Immediate	1	Near syncope	0.5

RC, rhinoconjunctivitis; AE, atopic eczema; Dpt, *Dermatophagoides pteronyssinus*; Lep, *Lepidoglyphus destructor.*

cause safety problems, due to the risk of adverse reactions [15]. The glutaraldehyde-polymerized depigmented allergen extracts show a significant decrease in specific IgE binding capacity, being more immunogenic and less allergenic, thus allowing the treatment to be initiated with higher doses, compared to the unmodified extracts, and a maintenance dose to be reached in a short period of time, potentiating the earlier onset of efficacy [16]. Several studies have shown the safety and early clinical efficacy of SCIT, using vaccines containing modified allergen extracts (depigmented and polymerized) in children and adults with allergic rhinoconjunctivitis and/or asthma with mite- and/or pollen-sensitization, most of them using conventional or cluster schedules [9, 17-25].

In the literature, there are few studies using rush or ultrarush schedules in paediatric age. Our study shows that SCIT induction using the ultrarush schedule is applicable and safe in the paediatric age, as this is the common practice at our Center. In this 5 years study, we report the ocurrence of local reactions in 11% of paediatric patients submitted to an ultra-rush schedule, with only one immediate local reaction and four late local reactions of clinical relevance. As to the systemic reactions, only 2 cases were reported, corresponding to 1% of all administered doses during the induction phase, both mild immediate reactions. No patient required hospitalization. It should be stressed that in our population, 62% of the patients had asthma, and keeping it controlled was absolutely necessary, as this is one of the main risk factors for severe systemic reactions [26].

Our results are consistent with those of previous studies, which have also concluded that ultrarush schedule is highly safe, causing no severe reactions [11, 12]. In fact, Pfaar et al. [11], in a prospective, randomized, double-blind study in 195 patients aged between 11 and 69 years (mean age, 33 years), with allergic rhinoconjunctivits, grass pollen-sensitized, administered with depigmented, polymerized grass pollen extract, using a rush preseasonal schedule (n = 135) versus placebo (n = 60), found the occurrence of local reactions in 70% (n = 95) versus 40% (n = 24) of patients, respectively, but with no need to reduce the administered dose or to suspend the protocol. Mild systemic reactions have also been reported in 16 patients of the active group versus 7 patients in the placebo group; however, no severe reactions were reported. Brehler et al. [12] examined 303 adult patients with allergic rhinoconjunctivits, grass pollen-, tree pollen-, and house dust mite-sensitized, receiving the conventional versus the rush subcutaneous schedule of immunotherapy and using a polymerized depigmented allergoid. Six percent of systemic reactions and 32% of local reactions were reported in the rush group, with no statistically significant differences relative to the classical administration, regardless of the implicated allergen.

Casanovas et al. [13] conducted a prospective, observational, multicenter study in 1,068 patients, from whom 33.2% were aged between 3 and 18 years, with rhinoconjunctivitis and/or asthma, sensitized to mites and/or to pollens, to assess the safety of a vaccine including in its composition depigmented

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and polymerized, mites or pollens allergen extract, using a rush schedule. In this study, only seven local relevant reactions and eight systemic reactions were reported, none of which was severe. This latter study reports a lower incidence of adverse reactions, compared to Pfaar et al. [11] and Brehler et al. [12] studies, being consistent with our study, and also including a great number of paediatric patients.

We can describe many advantages of using the rush schedule in children: greater convenience of fewer administrations, particularly relevant in this age group; reducing the number of visits to the health facilities; better compliance and a faster onset of clinical benefits; less direct and indirect costs, compared to the conventional schedule.

It should be noted that besides prescription, SCIT induction should be only performed under the supervision of the allergy specialist, and always where the necessary facilities for the treatment of local and systemic reactions are available, always following the guidelines and recommendations for good clinical practice [1, 2].

In conclusion, this study showed that, when performed by allergists, the SCIT with depigmented polymerized allergoid extracts using an ultrarush schedule is safe in paediatric population, reaching the maintenance dose on the first day of treatment, without significant local or systemic adverse reactions.

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