

Safety and Tolerability of Ultra-Rush Induction, Less than One Hour, of Sublingual Immunotherapy in Children

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Key Words

Sublingual immunotherapy, children · Ultra-rush induction

Abstract

Background: The safety and tolerability of sublingual immunotherapy (SLIT) has been documented in allergic patients both in the build-up phase as well as during maintenance, but only two studies have evaluated the occurrence of adverse reactions with an ultra-rush regimen of SLIT induction in a mixed paediatric/adult population. Moreover one of these two studies used a chemically modified extract (allergoid). The aim of the present study was to evaluate the occurrence of immediate or late adverse reactions in allergic children after a very fast (40 min) ultra-rush SLIT induction with two different allergen extract solutions. **Methods:** We studied 100 children (64 boys, mean age of 9.6 years, range 3.5–16.8), with a history of intermittent/persistent rhinitis and/or intermittent/mild persistent asthma due to inhalant allergens. The ultra-rush build-up phase involved the administration, every 10 min, of increasing doses of the highest-concentration vial of SLIT of two different manufacturers (Anallergo and Stallergènes). **Results:** All patients completed the treatment, side-effects have been recorded in 19% of the cases: 10% within 1 h after the

build-up phase, 7% within 48 h and 2% mixed. A major difference ($p = 0.0001$) was recorded between Anallergo (6 patients, 8.7%) and Staloral (13 patients, 41.9%), but all the reactions were mild: principally oral symptoms, in 1 case rhinorrhoea and cough, and delayed abdominal pain and diarrhoea in another patient. **Conclusions:** No severe adverse reactions were observed with this ultra-rush SLIT induction also in the paediatric age; statistical differences have been documented between the two different extracts.

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Introduction

Many studies have shown that sublingual immunotherapy (SLIT) may be considered a viable alternative to injection immunotherapy [1, 2]. SLIT has been shown to be a safe method in clinical trials in the phase of induction as well as during maintenance, both in adults and in children [3]. The phase of induction may differ from one SLIT to another, depending on various therapies; however, normally many days or weeks are required using vials with increasing concentrations [4]. So far only two studies have evaluated the occurrence of side-effects in allergic patients after a very fast regimen of SLIT build-up [5, 6], but both studied a mixed adult/paediatric pop-

Table 1. Demographic characteristics of subjects: percentage of pathologies, sensitizations, type of SLIT, side-effects and severity of reactions

	Total	Anallergo	Staloral 300	Anallergo vs. Staloral
Patients	100	69 (69)	31 (31)	
Age, years				
Mean	9.6	9.3	10.4	
Range	3.5–16.8	3.5–16.8	5.7–16.8	
Males	64	42 (61)	22 (71)	
Females	36	27 (39)	9 (29)	
Pathology				
Allergic rhinitis	71	49 (71)	22 (71)	
Asthma	62	42 (61)	20 (65)	
Allergic conjunctivitis	6	4 (6)	2 (6)	
Atopic dermatitis	5	2 (3)	3 (10)	
SLIT Allergens				
Grass pollen	43	21 (30)	22 (71)	p = 0.036
<i>Dermatophagoides</i>	44	37 (54)	7 (23)	
<i>Parietaria</i> spp.	9	8 (12)	1 (3)	
Olive	3	2 (3)	1 (3)	
<i>Alternaria</i>	1	1 (1)	0 (0)	
Side-effects				
Early (<1 h)	10	2 (33)	8 (62)	
Late (>1 and <48 h)	7	3 (50)	4 (31)	
Both	2	1 (17)	1 (8)	
Total side-effects	19	6 (8.7)	13 (41.9)	p = 0.0001
Main allergens				
Grass pollen		2 (9.5)	10 (45.5)	p = 0.055
<i>Dermatophagoides</i>		3 (8.1)	2 (28.6)	
Severity				
Mild	19	6 (100)	13 (100)	
Therapy necessary (oral antihistamine)		3/6	2/13	

Figures in parentheses indicate percentages.

ulation and the results for the paediatric subjects could not be extracted. Moreover Gammeri et al. [6] used a chemically modified extract (monomeric allergoid), well tolerated also in very young children [7].

The aim of our study was to evaluate the safety and the tolerability in children of a rapid induction phase, in 40 min, of SLIT with two different native allergen extract solutions.

Materials and Methods

During the period from March 2004 to June 2005 we tested 100 children, with an average age of 9.6 years (range 3.5–16.8), 64 boys and 36 girls (table 1). At the study entry, the pathologies suffered were: allergic rhinitis (71%), either intermittent or persistent based on ARIA criteria [8], intermittent/mild persistent asthma (62%), according to Global Initiative for Asthma [9], allergic conjunctivitis (6%) and atopic eczema (5%). Patients who had re-

ceived previous courses of immunotherapy, with anatomical abnormalities of the upper respiratory tract or suffering from malignancies or systemic immunological disorders were excluded from this study.

Atopic status was assessed by skin prick tests carried out with a standard panel of commercial extracts (Stallergènes SA, Antony, France). The panel included: *Dermatophagoides pteronyssinus*, grass pollen, *Parietaria judaica*, *Cynodon dactylon*, *Artemisia vulgaris*, olive, dog and cat dander, and *Alternaria*, plus a positive (histamine 1%) and a negative (isotonic saline) control.

The majority of the patients was monosensitized, but 39% of patients had a positive skin test to at least 2 inhalant allergens. The diagnosis of allergy to these allergen sources was based on the correlation of clinical history and positive skin tests, and all patients were treated with a monotherapy (i.e. one inhalant allergen extract) for the most clinically relevant allergen, paying special attention to potential allergens in the patient's own environment, according to a WHO position paper [10].

For the therapy, we utilized standardized allergen extract solutions from Anallergo (Florence, Italy) and Staloral 300 from Stallergènes. These two SLIT are native allergen extracts prepared as a

Table 2. Concentration ($\mu\text{g/ml}$) of SLIT major allergens of the two different manufacturers

	Anallergo allergen extract	Staloral 300
Timothy major allergen, Phl p 5	5	24
Mite major allergen, Der p 1	12	25
<i>Parietaria</i> spp. major allergen, Par j 1	5	210

Table 3. Immunotherapy protocol with allergen extract solution

Time min	Anallergo		Stallergènes	
	drops	dose of allergen solution, RAST units	pressures	dose of allergen solution, IR
0	1	500	1	30
10	2	1,000	2	60
20	3	1,500	4	120
30	4	2,000	6	180
40	5	2,500	8	240
Total	15	7,500 ¹	21	630 ²

Drops were kept under the tongue for at least 2 min before swallowing. IR = Index of reactivity. RAST units and IR are 'in-house references'.

¹ Cumulative dose administered: 7,500 RAST units containing 3,75 μg of Phl p 5 or 9 μg of Der p 1.

² Cumulative dose administered: 630 of IR containing 50,4 μg of Phl p 5 or 52,5 μg of Der p 1.

glycerinated solution, to be administered as sublingual drops, and standardized on the basis of different 'in-house references' (i.e. Anallergo, 10,000 RAST units/ml; Stallergènes, 300 IR/ml; IR = index of reactivity). As declared by the manufacturers [5], at least for the available data, the amounts of major allergens are very different for the two products (table 2).

Considering these data, we started, for safety reasons, this new ultra-rush build-up method using Anallergo extracts because of their lower concentration of major allergens. In a second period, after a preliminary evaluation of the safety, tolerability and absence of systemic severe reactions of this rapid induction phase of SLIT, we decided to use the more concentrated Staloral 300 extracts, too.

This explains the different numbers of treated patients with the two products (69% with Anallergo extracts and 31% with Staloral 300) and the different percentage of SLIT with dust mite, grass pollen and *Parietaria* spp. pollen in the two groups (table 1).

The allergens used for SLIT were: grass pollen (43%), *Derma-tophagoides* (44%), *Parietaria* spp. (9%), olive (3%), *Alternaria* (1%). All pollen-sensitive patients were submitted to the rush therapy protocol independently of the pollen season.

After informed consent of the parents and clinical examination about the well-being of the children, we started SLIT induction with the highest-concentration vial, increasing the quantity every 10 min (table 3). Drops had to be kept under the tongue for at least 2 min before swallowing. We monitored possible side-effects for at least 1 h after the last administration; parents at home monitored eventual symptoms (sneezing, nasal itching and obstruction, rhinorrhoea, lacrimation, conjunctival itching and hyperaemia, cough, wheezing, chest tightness, abdominal pain, diarrhoea, vomiting, urticaria, angio-oedema and worsening of eczema) for a further 48 h filling in a special form. In case of emergency, parents could contact us by mobile phone. All patients were asked to continue with the maintenance doses recommended by the manufacturer.

Frequency comparisons between the two groups were examined by the χ^2 test (Fisher's exact test when appropriate). Student's t test was used for mean comparisons.

Results

All children completed ultra-rush SLIT and tolerated the treatment well. Statistical analysis of the patients treated with the two different SLIT was not significant for sex, age and pathologies. Due to the absence of any randomization of the patients, different percentages of grass pollen, dust mite and *Parietaria* spp. between the two SLIT products were found, but only for grass pollen allergen was this statistically significant (Staloral 300 = 71%, Anallergo = 30%, $p = 0.036$).

Side-effects were recorded in 19% of the cases (19 patients): 10% immediate, i.e. during the induction of SLIT or within 1 h after the administration; delayed in 7% of the cases (>1 h, <48 h), and both in 2% of the cases. A major difference was recorded ($p = 0.0001$) between Anallergo (6 patients, 8.7%) and Staloral (13 patients, 41.9%) though only mild local symptoms were registered (scale 0–3) for both products. Most of the reactions were self-limiting in few minutes, only for precautionary measures, we administered oral cetirizine in 3/6 patients treated with Anallergo and 2/13 treated with Staloral 300 ($p = \text{n.s.}$). In most cases we noticed itch of the oral mucosa, in 1 case we registered rhinorrhoea and cough, and in another patient abdominal pain and only once running stool when at home. All the patients continued maintenance therapy without any problem. Between the 2 main allergens used (grass pollen and mites) from the different producers, only a trend ($p = 0.055$) was demonstrated of major reactivity for Staloral 300 grass pollen compared to Anallergo and this independently of the pollen season (data not shown).

Discussion

In our study, the cumulative dose after 40 min was several times the dose administered during the conventional schedule. Even so, the adverse event rate we observed was not different from previously reported data [3]. No serious adverse event was reported and our methodology of ultra-rush induction has been proven to be safe in the paediatric age. The majority of mild local symptoms spontaneously disappeared within 30 min, suggesting that an observation period of 1 h should be sufficient.

Patients and parents accepted very well this ultra-rush build-up since it simplifies and shortens the SLIT initial phase.

The difference of the adverse effects using the 2 products may be explained by the higher concentration of major allergens in Stallergènes extracts, especially for grass pollen ($p = 0.055$), bearing in mind furthermore that Staloral 300 grass pollen has been used more. Indeed, the cumulative dose administered of Phl p 5 and Der p 1 was, respectively, 3.75 and 9 μg with Anallergo and 50.4 and

52.5 μg with Staloral 300. However, for dust mite any available comparison cannot be drawn due to bias in the numbers of treated patients (Anallergo = 37, Staloral = 7).

The main points of the study were the safety and the tolerability of this ultra-rush method, but a preliminary analysis of efficacy (data not shown) for those patients (only 30) who have been treated, until now, by SLIT for at least 1 year, is not different from those patients who have had a traditional induction method of the therapy.

Considering the high level of safety and tolerability, our ultra-rush induction could be indicated when we have a delay in starting with the SLIT with respect of the pollen season, as well as taking up again the therapy after interruption and even for pre-/co-seasonal schemes [11].

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