ARTICOLO ORIGINALE
ORIGINAL ARTICLE

Safety of Ultra-Rush (two hours) Sublingual-Swallow Immunotherapy in Allergic Patients

Sicurezza dell'immunoterapia sublinguale ultra-rapida (in due ore) in pazienti allergici

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Key words

Sublingual-swallow immunotherapy • Rhinoconjunctivitis Asthma • Grass pollen • Mites • Birch pollen • Tryptase

Parole chiave

Immunoterapia sublinguale • Rinocongiuntivite • Polline di graminacee • Asma • Acari • Polline di betulla • Triptasi

Summary

Objectives

The safety of sublingual immunotherapy (SLIT) with conventional regimens has been demonstrated, but no published study considered as yet ultra-rush protocols. This study evaluated the safety of ultra-rush SLIT with four commercial allergen extracts in allergic patients.

Methods

Ninety-one patients took part in trials of specific ultra-rush SLIT for the treatment of IgE-mediated rhinitis and asthma. The buildup ultra-rush phase was performed by the administration of increasing doses every twenty minutes for two hours. Saliva tryptase was assessed before and after SLIT. 87/91 patients tolerated the treatment very well.

Results and Conclusions

Four patients had mild adverse reactions. Two events involved the oral cavity, one patient had gastro-intestinal symptoms, and one patients had rhinitis lasting 48 hours.
The baseline levels of saliva tryptase were low before and after sublingual allergen administration in all patients but one, who had no symptoms (3.50 U/l before and 32.4 U/l after).
No severe adverse reactions were observed during ultra-rush SLIT, demonstrating its excellent safety profile.

Riassunto

Obiettivi

La sicurezza dell'immunoterapia sublinguale (SLIT) è stata dimostrata con i convenzionali regimi di somministrazione, ma nessun studio ha finora considerato un protocollo ultra-rapido di somministrazione. Il presente studio valuta la sicurezza del regime ultra-rapido di somministrazione della SLIT in pazienti allergici.

Metodi

91 soggetti affetti da rinite e asma IgE mediate hanno preso parte allo studio e sono stati trattati con SLIT in regime ultra-rapido. La fase di induzione è stata ottenuta attraverso somministrazioni di dosi crescenti ogni venti minuti nell'arco di due ore. Sono stati valutati i livelli di triptasi salivare prima e 60 minuti dopo l'ultima dose di vaccino sublinguale. 87 su 91 pazienti hanno tollerato il trattamento molto bene.

Risultati e conclusioni

Quattro pazienti hanno presentato reazioni avverse lievi. In due casi è stato osservato un coinvolgimento della cavità orale; un paziente ha presentato sintomi gastrointestinali; un paziente ha manifestato rinite per 48 ore. I livelli di triptasi salivare valutati prima e 60 minuti dopo la somministrazione di vaccino sono risultati bassi, tranne in un paziente asintomatico (3,5 U/l prima, 32,4 U/l dopo).
Ricorrendo all'induzione ultra-rapida di SLIT non è stata documentata alcuna reazione grave, confermando l'eccellente profilo di sicurezza.

Introduction

Specific immunotherapy, which is the only form of allergy treatment acting on causes and not simply on symptoms, is the practice of administering increasing doses of the responsible allergens to allergic patients in order to induce allergen-specific non responsiveness [1]. The World Health Organization (WHO) Position Paper on allergen immunotherapy states that sublingual route may represent a viable alternative to subcutaneous injection therapy for allergic diseases [2]. During the last 12 years, a consistent number of randomized controlled clinical trials with sublingual immunotherapy (SLIT) were performed [3-13]. From these studies emerged an excellent safety of SLIT, which was confirmed in lar-

ge populations trials [14 15]. Several studies [15-17] have shown that adverse events fell into four main categories: respiratory, cutaneous, gastro-intestinal and buccolingual. Commonly, such events appear a few minutes after the administration of the allergen extract dose. Respiratory effects (sneezing, dyspnea) are generally mild and short-lasting, as well as cutaneous symptoms (itching, urticaria). Buccopharyngeal reactions (e.g. labial and/or buccal tickling, edema in the oral cavity) are the main side effects documented in treated patient. Also gastrointestinal effects, such as diarrhea, may occur.
According to the schedules used in the cited studies, the current therapeutic approach consists of a 2-14 week incremental dose period. This, probably, may represent a compliance's problem for many patients.
The objective of the present study is to evaluate the occurrence of adverse reactions in allergic patients treated by an ultra-rush SLIT regimen of administrations of allergen extracts with a buildup period during two hours, rather than the commonly used 2-14 weeks.

Material and methods

Patients

Ninety-one patients (mean age: 27 years; range 8-64 years) with a history of mite and pollen induced IgE-mediated rhino-conjunctivitis with or without asthma were selected and enrolled in the trial from December 2001 to March 2002. A small proportion (11, i.e. 12%) of the patients suffered from moderate asthma. The diagnosis of allergy to mites, birch-, and grass-pollen was done by clinical history, positive skin prick tests with standardized allergen extracts (ALK Abello, Madrid, Spain) and serum specific IgE measured by the CAP System® (Pharmacia Upjohn Diagnostics, Uppsala, Sweden) (Tab. I).

Treatment

Patients were divided in four groups (IA, IB, II, III) each of which received four different therapeutic allergen extracts of three different manufacturers.
Group IA and Group IB were respectively composed by 37 and 14 patients, and were treated with a standardized timothy grass pollen and mite extract (Staloral 100® and Staloral 300®, Stallergénes SA, Antony, France). As declared by the manufacturer the amount of the timothy major allergen Phl p 5 in 100 IR/ml extracts was 8.5 µg/ml, the amount of mite major allergen Der p1 in 100 IR/ml extract was 9.6 µg/ml, and the amount of the birch major allergen Bet v 1 in 100 IR/ml extract was 20 µg/ml. The in-house reference extract has a biological potency of 100 IR/ml, which is defined as the concentration inducing a 7 mm wheal to a skin prick test using a Stallerpoint® needle in 30 subjects sensitized to the specific allergen.
The treatment was performed by a 20-minute progression during two hours (Tab. II), during which the extract was given as sublingual drops (Group IA) or 100 µl aliquots (Group IB). When the top dose, consisting of 20 drops from the 100 IR/ml vial (Group IA) and 10 aliquots (1000 µl, i.e. 1 ml) from the 300 IR/ml vial (Group IB) was reached the induction phase was stopped. The maintenance dose was 20 drops of 100 IR/ml vial (Group IA) and 1 ml of the 300 IR/ml vial, three times a week. The immunotherapy protocol of Group IA and Group IB is depicted in Table I.
Group II was composed by 27 subjects; SLIT was performed using three different standardized allergen extracts containing timothy grass pollen-, or birch-, or mite-extracts (Pangramin®, ALK-Abello, Madrid, Spain); the concentrations of the solutions were 2.5 µg/1000 STU of Phl p 5; 22.5 µg/1000 STU of Bet v 1; 4 µg/1000 STU of Der p 1, 2 µg/1000 STU of Der p 2 and 4 g/1000 STU of Der f 1, 2 µg1000 STU of Der f 2 µg1000 STU (a mix of *D. pteronissinus* and *D. farinae* extract was used), respectively. In the case of Pangramin, we administered a top dose fourfold the top dose recommended by the manufacturer (20 drops instead of 5 drops). This choice was made with the aim of administering and comparing similar amounts of major allergens for those treatments where their concentration was declared by the manufacturer. A schedule of increasing doses was used, with drops to be taken by the sublingual route with a 20-minute progression of doses, increasing from 1 to 20 drops of the maximal concentration allergen extracts (Tab. III). The maintenance dose recommended was 10 drops three times a week.
Group III was composed by 13 subjects. All patients were undergoing to SLIT with a monomeric allergoid in orosoluble tablets (LAIS®, Lofarma SpA, Milan, Italy). The product was titrated in allergenic units (AU) and standardized according to the in-house reference preparation. The buildup ultra-rush phase of two hours involved the administration every twenty minutes of increasing doses (100, 300, 600, 1000, 2000 AU). After two hours the cumulative dose administered was 4000 AU. As suggested by manufacturer, the maintenance dose recommended was 2000 AU once a week.
All patients in the four groups (or one parent for minors), signed informed consent forms before starting the SLIT.

Measurement of salivar tryptase

Tryptase levels were determined by the ELISA (UniCAP Tryptase System FEIA, Pharmacia, Uppsala, Sweden) before and 60 minutes after the administration of the top dose.

Tab. I. Demographic and clinical characteristics of patients.

	Group IA	Group IB	Group II	Group III
Number of patients	37	14	27	13
Age years (Median, 25-75th p.)	27 (16-35)	26 (19-35)	27 (17-34)	29 (18-36)
Diagnosis				
RC	29 (78.4%)	9 (64.3%)	18 (66.71%)	10 (76.9%)
RC+BA	4 (10.8%)	2 (14.3%)	4 (14.8%)	1 (7.7%)
Previous SIT*	4 (10.8%)	3 (21.4%)	5 (18.5%)	2 (15.4%)
OAS	3		2	

Specific IgE kUA/l geometric mean (SD)

	Group IA			Group IB			Group II			Group III		
Phl p 1	n = 27	5.5	(39.2)	n = 9	9.5	(38.8)	n = 25	11.9	(37.5)	n = 13	7.4	(26.2)
Phl p 2	n = 21	1.1	(14.5)	n = 6	2.0	(24.5)	n = 18	2.1	(7.7)	n = 9	2.5	(11.8)
Phl p 4	n = 26	4.5	(33.5)	n = 9	13.4	(30.5)	n = 23	4.6	(13.0)	n = 11	9.6	(25.9)
Phl p 5	n = 22	3.7	(37.8)	n = 8	3.0	(25.5)	n = 21	7.5	(35.0)	n = 10	9.4	(36.0)
Phl p 6	n = 20	1.2	(19.2)	n = 7	2.0	(15.0)	n = 19	2.3	(22.9)	n = 9	2.3	(16.2)
Phl p 7	n = 3	0 < 0.35	(0.8)	n = 1	< 0.35	(7.9)	n = 2	< 0.35	(28.5)	n = 0	< 0.35	(–)
Phl p 11	n = 16	1.3	(11.3)	n = 6	0.9	(5.6)	n = 14	0.5	(7.7)	n = 6	1.3	(7.5)
Phl p 12	n = 10	< 0.35	(2.3)	n = 5	0.5	(2.7)	n = 8	0.3	(1.6)	n = 4	< 0.35	(0.5)
Bet v 1	n = 3	21.8	(57.9)	n = 2	0.4	(1.2)	n = 2	> 100	(–)		–	
D 1	n = 5	20.3	(54.4)	n = 3	1.8	(4.5)	n = 4	3.9	(45.6)	n = 3	3.6	(62.2)

n = number of positive sera; D1, *Dermatophagoides pteronissinus* extract; SIT, subcutaneous immunotherapy (* mean duration of SIT at SLIT starting: 34.6 months); RC, rhino-conjunctivitis; BA, bronchial asthma; OAS, oral allergy syndrome to apple in 5 patients allegic to birch.

Tab. II. Immunotherapy protocol of patients treated with 100 IR/ml (Group IA) and 300 IR/ml (Group IB) allergen extracts (Staloral®, Stallergenes SA, Antony, France). Allergen extracts had to be kept under the tongue for at least two minutes before swallowing.

Incremental dosing	Drops containing 100 IR/ml (Group IA, n = 37)	100 µl aliquots containing 300 IR/ml (Group IB, n = 14)
0 min	1	100
20 min	2	200
40 min	4	400
60 min	8	600
80 min	12	800
120 min	20	1000

Cumulative dose administered: 235 IR(Staloral® 100) and 930 IR(Staloral® 300) after two hours
n, number of patients

Results

Most patients tolerated the treatment well, while four patients developed at least one adverse reaction.
In a patient allergic to grass pollen with asthma and rhino-conjunctivitis, rhinitis symptoms (sneezing) appeared a few minutes after the administration of eight drops of the 100 IR/ml concentration of timothy grass pollen extract from Stallergénes, and continued for 48 hours, requiring antihistamine treatment (cetirizine). One patient, suffering from rhinitis to mites, had diarrhea and abdominal complaints lasting 24 hours. However, this patient decided to continue the SLIT. In this case, the allergen extract used was the 300 IR/ml of mites from Stallergénes. Another patient, treated with the 300 IR/ml timothy pollen extract, presented buccal tickling not during the buildup phase of SLIT, but during maintenance treatment, namely three days after starting, and occurring a few minutes after each allergen extract administration. The adverse event disappeared when dose administered was adjusted at 30 IR, corresponding to one 100 µl aliquot. The fourth patient, allergic to grass pollen, also had bucco-pharyngeal effects (itching in mouth, labial swelling) after the administration of eight drops containing 1.3 µg of Der p 1 and 0.6 µg of Der p 2/1000 STU from Alk-Abello. No adverse events were noted after administration of the monomeric allergoid in tablets.
The baseline levels of saliva tryptase were low (data not shown) before and after sublingual allergen administration in all patients, but one. In this subject, who had no reaction to SLIT, the level of saliva tryptase was 3.5 U/L before receiving the allergen extract, and 32.4 U/L 60 minutes after the administration of the cumulative allergen dose.

Tab. III. Immunotherapy protocol of patients treated with timothy- or mite- or birch- extracts (Pangramin®, ALK-Abello SA, Madrid, Spain).

Incremental dosing	20 drops of solution containing 2 µg/ml of Phl p5; or 3.2 µg/ml of Der p 1 and 1.6 µg/ml of Der p 2, 3.2 of Der f 1 and 1.6 µg of Der f 2; or 13.2 µg/ml of Bet v 1, respectively.
0 min	1
20 min	2
40 min	4
60 min	8
80 min	12
120 min	20

Cumulative administered after two hours: 4.7 µg of Phl p 5; 7.5 µg of Der p 1, 3.7 µg of Der p 2, and 7.5 µg of Der f 1, 3.7 µg of Der f 2; 31 µg of Bet v 1.

Discussion

Only a few studies have focused on clinical efficacy and safety of rush SLIT[5,8], but no published paper is thus far available on ultra-rush SLIT regimens.
The main implication of our study is that SLIT was very well tolerated and accepted by the patients. The ultra-rush schedule was easy to manage because the build-up phase took only 120 minutes and the very rapid dosage increase did not elicit serious adverse reactions. Moreover, SLIT was well tolerated also in five patients with oral allergy syndrome to apple, confirming a previous report on the safety of this treatment in such patients[18]. It is noteworthy that three of the four reported side-effects were of no clinical relevance since only one patient required a dose adjustment from 300 to 30 IR, while the others continued the treatment with no more adverse reactions.
In our experience the conventional dosing period, requiring a number of weeks, together with the self-administration of SLIT, seem to represent a practical problem in some patients. These ultra-rush schedules for SLIT seem to be an interesting therapeutic approach because the build-up phase is directly managed by the physician. In fact, only the dose established by the allergist during ultra-rush-SLIT regimen must be effectively assumed by patients at home, thus facilitating the compliance.
In agreement with previous findings[19,20] we did not observe an involvement of mucosal tissue mast cells, since no increase of saliva tryptase could be demonstrated after ultra-rush SLIT, even at the cumulative dose of 260 μg of Phl p 5 (9 patients), or 243 μg of Bet v 1.
This is clinically confirmed by the fact that the five patients with oral allergy syndrome did not suffer from buccopharyngeal symptoms after administration of high allergen doses.
Langerhans-like dendritic cells present in mucosa are likely to play a pivotal role in desensitization through the sublingual or oral route due to their interactions with other cells. (i.e. naive T cells)[21-23]. Moreover, mast cells and eosinophils may be involved in this process. However, Marcucci et al.[19] found no increase of tryptase after the administration of SLIT, thus giving serious reasons to doubt that an allergic reaction could occur in the mouth.
We may conclude that, in our hands, the safety profile of ultra-rush SLIT is favorable. Further studies are needed to establish the efficacy and safety of ultra-rush schedules for SLIT to transfer them to routine treatment.

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