ORIGINAL ARTICLE

Safety and Tolerability of Seasonal Ultra-rush, High-dose Sublingual-Swallow Immunotherapy in Allergic Rhinitis to Grass and Tree Pollens: An Observational Study in 193 Children and Adolescents

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Abstract

Objective: We conducted a large observational study in 193 children and adolescents with allergic rhinitis due to grass or tree pollens to evaluate the safety and tolerability of an ultrarush high-dose sublingual immunotherapy (SLIT) regimen reaching a maintenance dose of 300 index of reactivity within 90 minutes.
Methods: Children and adolescents aged 5 to 17 years with at least a 1-year medical history of allergic rhinitis with or without mild to moderate asthma due to tree pollens (birch, alder, hazel) or grass pollens (cocksfoot, meadow grass, rye grass, sweet vernal grass, timothy) were recruited. Standardized grass and tree pollen allergen extracts were used for ultrarush titration and subsequent coseasonal maintenance.
Results: During ultrarush titration, 60 patients (31%) reported 117 predominantly mild and local adverse events, which resolved within 150 minutes. During the maintenance phase, 562 adverse events were reported; the most frequent local events were oral pruritus, burning sensation, lip or tongue swelling, and gastrointestinal symptoms, and the most frequent systemic events were rhinoconjunctivitis and asthma. There was 1 clinically significant asthma event in an 11-year old boy with known asthma in whom SLIT was resumed after an interval of 4 days.
Conclusion: Ultrarush titration was safe and well tolerated. Pediatric patients with asthma should be carefully monitored and adequately trained to use their rescue medications.

Key words: Grasses. Trees. Ultrarush. Sublingual immunotherapy. Children. Safety. Allergic rhinitis. Asthma.

Resumen

Objetivos: Realizamos un gran estudio observacional con 193 niños y adolescentes con rinitis alérgica debido a gramíneas y pólenes de árboles para evaluar la seguridad y tolerancia de un régimen de inmunoterapia sublingual ultrarrápida a dosis alta (ITSL) alcanzando la dosis de mantenimiento de 300 índice de reactividad en 90 minutos.
Métodos: Se reclutaron niños y adolescentes entre 5 y 17 años con al menos 1 año de historia clínica de rinitis alérgica con o sin asma leve a moderado debido a pólenes de árboles (abedul, aliso, avellano) o gramíneas (dáctilo, poa común, lolium, grama de olor, hierba

timotea). Se emplearon extractos estandarizados de gramíneas, y de pólenes de árboles para la pauta ultra-rápida y la posterior dosis de mantenimiento coestacional.
Resultados: Durante la pauta ultra-rápida, 60 pacientes (31%) presentaron 117 reacciones adversas predominantemente leves y locales, que se resolvieron en 150 minutos. Durante la fase de mantenimiento, se notificaron 562 reacciones adversas; las más frecuentes fueron el prurito oral, sensación de ardor, inflamación de labios o lengua, y síntomas gastrointestinales, y las reacciones sistémicas más frecuentes fueron rinoconjuntivitis y el asma. Una reacción clínicamente significativa de asma ocurrió en un niño de 11 años de edad con asma conocida en el que la ITSL fue reiniciada tras un intervalo de 4 días.
Conclusión: La pauta ultra-rápida fue segura y bien tolerada. Los pacientes pediátricos con asma deberían monitorizarse cuidadosamente y ser entrenados adecuadamente para emplear su medicación de rescate.

Palabras clave: Gramíneas. Árboles. Ultra rápida. Inmunoterapia sublingual. Niños. Seguridad. Rinitis alérgica. Asma.

Introduction

Subcutaneous immunotherapy (SCIT) in allergic rhinitis has been linked to reduced development of later asthma and fewer symptoms in patients who already have asthma. [1,2]. The recommendation to use sublingual-swallow immunotherapy (SLIT) in children and adults with allergic rhinitis evolved over several years based on the following key publications: *a)* the World Health Organization (WHO) position paper on allergen immunotherapy [3], *b)* the Allergic Rhinitis and its Impact on Asthma (ARIA) Workshop Report in collaboration with the WHO (2001) [1] and its 2008 update [2], *c)* the Cochrane review of SLIT for allergic rhinitis based on 22 studies involving 979 children and adults [4], and *d)* a meta-analysis evaluating the efficacy of SLIT in the treatment of allergic rhinitis in children and adolescents aged 3 to 18 years [5]. Subcutaneous immunotherapy (SCIT), in contrast, while effective in children and adults, is burdened by the risk of side effects, which at times may be life threatening [2].

Allergen doses in SLIT have increased considerably over the past 10 years and are now up 500 times greater than those commonly administered with SCIT. A meta-analysis published in 2005 showed that the frequency of adverse events associated with SLIT was not dose dependent [6]. In the analysis, 25 controlled studies on SLIT were divided into 2 groups: 1 using low allergen doses (≤50 times the dose commonly administered with SCIT) (13 studies) and another with high allergen doses (>50 times the dose used with SCIT) (12 studies). While local side effects were observed more frequently in the low-dose group ($P<.0001$), there was no significant difference in the occurrence of systemic reactions. SLIT dosing regimens traditionally consisted of an induction phase lasting a couple of weeks followed by a maintenance phase lasting months or years. In 1995, a rush preseasonal treatment schedule designed to reach the maintenance dose in 15 days with twice-daily administrations in 34 adult patients with grass pollen–induced allergic rhinoconjunctivitis was shown to be safe and well tolerated [7]. A similar schedule (designed to reach the maintenance dose in 18 days with twice-daily administrations) in 30 adult patients with tree pollen–induced allergic rhinoconjunctivitis showed similar results [8]. More recently, an ultrarush high-dose SLIT regimen that reached a maintenance dose of 300 index of reactivity (IR) with *Juniperus ashei* allergen extract within 90 minutes (30–90–150–300 IR) proved to be safe in adult patients [9]; only local adverse events such as mouth and tongue itching were observed in both the SLIT group and the placebo group during the ultrarush titration phase.

In children, ultrarush high-dose SLIT regimens have been evaluated in 2 studies to date. In the first, a group of 28 children with allergic rhinitis (n = 18) or asthma (n = 10) due to grass or *Parietaria* pollens or house dust mites received ultrarush high-dose SLIT using a chemically modified allergen extract (monomeric allergoids) [10]. The patients (28 children and 77 adults) received doses of 100-300-600-1000-2000 allergenic units every 5 minutes. All the patients tolerated the treatment very well. In the second study, 100 children received ultrarush high-dose SLIT using allergen extracts from 2 different manufacturers; the extracts were grass pollens (43%), house dust mites (44%), *Parietaria* (9%), olive (3%), and *Alternaria* (1%) [11]. The ultrarush regimen used for one of the allergen extracts (Staloral) was 30–60–120–180–240 IR every 10 minutes. Thirteen (42%) of the patients (31 children and adolescents aged 6-17 y) experienced mild local adverse events. No severe events were observed.

We conducted a large observational study in 193 children and adolescents with allergic rhinitis due to grass or tree pollens to evaluate the safety and tolerability of an ultrarush high-dose SLIT regimen reaching a maintenance dose of 300 IR within 90 minutes (30-90-150-300 IR). The subsequent maintenance phase at 300 IR (once-daily dose) lasted up to 4 months, depending on the length of the pollen season.

Material and Methods

Patients and Study Design

Children and adolescents aged 5 to 17 years with at least a 1-year history of allergic rhinitis with or without mild to moderate asthma due to grass pollens (cocksfoot, meadow grass, rye grass, sweet vernal grass, timothy) or tree pollens (birch, alder, hazel) were recruited at 13 study centers (9 in Germany and 4 in Italy) between January and July 2004. Positive skin prick tests to tree or grass pollens were required. Patients fulfilling any of the following criteria were excluded: immunotherapy in the past 3 years, absolute or relative contraindications to immunotherapy, and the presence of a

condition which could compromise the patient's safety during the study. Written informed consent was obtained from children and their parents or caregivers. The study was approved by the ethics committee at the Lower Saxony Medical Council and the competent authority (Paul Ehrlich Institute, Langen, Germany).

Standardized mixtures of grass pollen (cocksfoot, meadow grass, rye grass, sweet vernal grass, and timothy) and tree pollen (birch, alder, and hazel) allergen extracts in aqueous solution were used for SLIT (Staloral; Stallergènes, Antony, France). The biological activity of the extracts was assessed in comparison with an internal standard in vitro and in vivo, and expressed as IR [12].

An ultrarush titration high-dose SLIT regimen reaching a maintenance dose of 300 IR within 90 minutes (30–90–150–300 IR) was used. During the titration phase, just before the next dose and 60 minutes after the most recent dose, patients were asked if they had experienced any adverse events and were also physically examined for the presence of local or systemic reactions. Forced expiratory volume in 1 second was measured in patients with asthma before titration. In addition, 3 consecutive peak flow rate (PFR) measurements (standing) were performed before each titration step. Following titration, patients received a once-daily maintenance dose of 300 IR for up to 4 months if they had reached this dose level during the titration phase. In most cases, SLIT was initiated after the beginning of the pollen season (coseasonal treatment for specific allergens).

During the maintenance period, safety was evaluated using patient diary cards on which patients and/or their parents were asked to report any adverse events. If an adverse event occurred, patients and/or their parents were required to inform the investigator before modifying the dose. At the end of the ultrarush titration phase, investigators and patients performed a global assessment of tolerability using a visual analogue scale (VAS) ranging from 0 (poor) to 100 (very good).

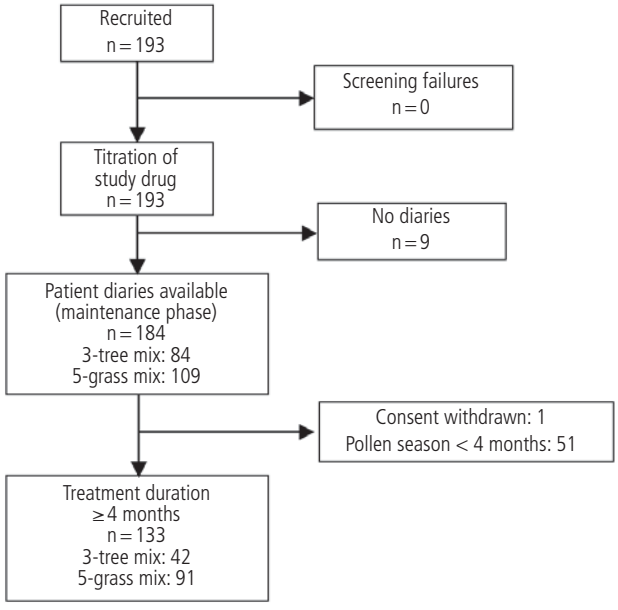

Figure 1. Study flow charts showing patient numbers.

The following symptomatic drugs were allowed to treat allergic reactions caused by pollen exposure or SLIT during titration and maintenance phases: oral loratadine or cetirizine, ocular and nasal azelastine, oral and rectal corticosteroids such as prednisolone, nasal fluticasone, corticosteroids for inhalation, selective $ß_2$-adrenoceptor agonists for inhalation, and, in case of emergency, adrenaline (self-injection kit).

Statistical Analysis

The primary endpoint was the frequency and intensity (mild, moderate, or severe) of expected local, gastrointestinal, and generalized adverse events. The secondary endpoint was the global assessment of tolerability by investigators and patients.

Adverse events were presented descriptively, along with intensity, relationship to study medication, action taken, and outcome. A serious adverse event was defined as any untoward event which resulted in death or persistent or significant disability or incapacity, required in-patient hospitalization or prolongation of existing hospitalization, or was life threatening or medically significant. Systemic reactions were graded according to guidelines published by the European Academy of Allergology and Clinical Immunology (EAACI) [13].

Most parameters were available as ordinal data. For these parameters, frequency counts and percentages were provided and presented graphically where appropriate. Score means were also calculated for ordinal data where appropriate. Nominal data, including dichotomous data, were described by frequency counts and percentages. Interval data, including VAS readings, were characterized by mean, SD, minimum, and maximum values, and 95% confidence limits of the mean.

The sample size selected for this observational study was based on previous experience of the frequency of adverse events during SLIT. With 100 patients, the power required to detect an adverse event in 1% of patients undergoing SLIT was found to be 84%, and the power to detect an adverse event in 1.6% of the patients was 95%.

Results

A total of 193 children and adolescents, 66 girls (34%) and 127 boys (66%), aged 5 to 17 years (mean age, 10.3 y), were enrolled in the study. Nearly all of the patients had allergic rhinitis (n = 182, 94%); 132 (68%) had concomitant allergic conjunctivitis and 110 (57%) had mild or moderate asthma. All of the patients were titrated to the 300 IR maintenance dose: 84 patients with tree pollen extracts and 109 patients with grass pollen extracts. Concomitant medication specified in the protocol was taken by most of the patients (n = 144, 75%).

During ultrarush titration, 60 patients (31%) reported a total of 117 adverse events, predominantly after the second dose (90 IR) at the 30-minute time point. Nearly all of the adverse events (n = 85, 73%) were mild and local; they included oral pruritus, burning sensation, lip or tongue swelling, and gastrointestinal symptoms such as abdominal pain, gastroenteritis, and nausea

Table 1. Frequency and Severity of Adverse Events Observed During Ultrarush Titration

Adverse Event	Mild		Moderate		Severe		Total	
	No.	%	No.	%	No.	%	No.	%
Local adverse events								
Oral pruritus/burning sensation	72	61.5	7	6.0	0	0.0	79	67.5
Lip/tongue swelling	9	7.7	3	2.6	0	0.0	12	10.3
Gastrointestinal events	4	3.4	0	0.0	0	0.0	4	3.4
Systemic adverse events								
Rhinoconjunctivitis	11	9.4	1	0.9	0	0.0	12	10.3
Asthma	0	0.0	0	0.0	0	0.0	0	0.0
Urticaria, erythema, pruritus	9	7.7	0	0.0	0	0.0	9	7.7
Nonspecific events (eg. tiredness)	1	0.9	0	0.0	0	0.0	1	0.9
Other events	0	0.0	0	0.0	0	0.0	0	0.0
Total	106	90.6	11	9.4	0	0.0	117	100

(Table 1). Mild rhinoconjunctivitis and urticaria were the most frequent systemic adverse events (Table 1). No severe events were observed during ultrarush titration and all events resolved within 30 to 150 minutes. Virtually all of the adverse events were considered to be at least possibly related to SLIT by the investigators.

The overall assessment of tolerability by the investigators and patients showed mean (SD) scores of 83.7 (13.7) and 85.9 (12.6), respectively. As the maximum VAS score was 100, these results demonstrated a good to very good tolerability of ultrarush titration.

Pulmonary function during ultrarush titration remained within the normal range in all of the patients with asthma.

A total of 184 patients received the planned daily maintenance dose of 300 IR at the beginning of the maintenance phase and 133 of these completed the 4-month treatment period.

During the maintenance phase, 139 patients reported 562 adverse events. The most frequently reported events were local events such as oral pruritus, burning sensation, lip or tongue swelling, and gastrointestinal symptoms (n=172, 31%), and systemic events such as rhinoconjunctivitis (n=147, 26%) and asthma (n=38, 7%) (Table 2). Most adverse events were mild (n=334, 60%) or moderate (n=190, 34%). A total of 38 (7%) severe adverse events were observed, predominantly application site-related events, rhinoconjunctivitis, and asthma (Table 2). Most adverse events (n=397, 71%) were assessed as at least possibly related to SLIT by the investigators. The majority of events (n=327, 58%) occurred during the first month of the maintenance phase (Figure 2). Only a few events (n=101, 18%) resulted in a reduced SLIT dose for the remainder of the maintenance phase, and virtually all of the events (n=537, 94%) had resolved by the end-of-study visit.

Only 1 of the 4 severe asthma events (graded according to EAACI guidelines [13]) was considered clinically significant (according to International Conference on Harmonization [ICH] guidelines [14] by the investigators). An 11-year old boy with a 4-year history of sensitization to birch, alder, hazel, grasses, and house dust mites for 4 years and a 2-year history of allergic asthma had normal PFR measurements at

Table 2. Frequency and Severity of Adverse Events Observed During the Maintenance Phase

Adverse Event	Mild		Moderate		Severe		Total	
	No.	%	No.	%	No.	%	No.	%
Local adverse events								
Oral pruritus/burning sensation	54	9.6	22	3.9	7	1.2	83	14.8
Lip/tongue swelling	31	5.5	27	4.8	2	0.9	60	10.7
Gastrointestinal events	20	3.6	8	1.4	1	0.2	29	5.2
Systemic adverse events								
Rhinoconjunctivitis	101	17.9	42	7.5	4	0.7	147	26.2
Asthma	21	3.7	13	2.3	4	0.7	38	6.8
Atopic dermatitis	2	0.4	3	0.5	0	0.0	5	0.9
Nonspecific events (eg. tiredness)	8	1.4	4	0.7	4	0.7	16	2.8
Other events	97	17.3	71	12.6	16	2.8	184	32.7
Total	334	59.4	190	33.8	38	6.8	562	100

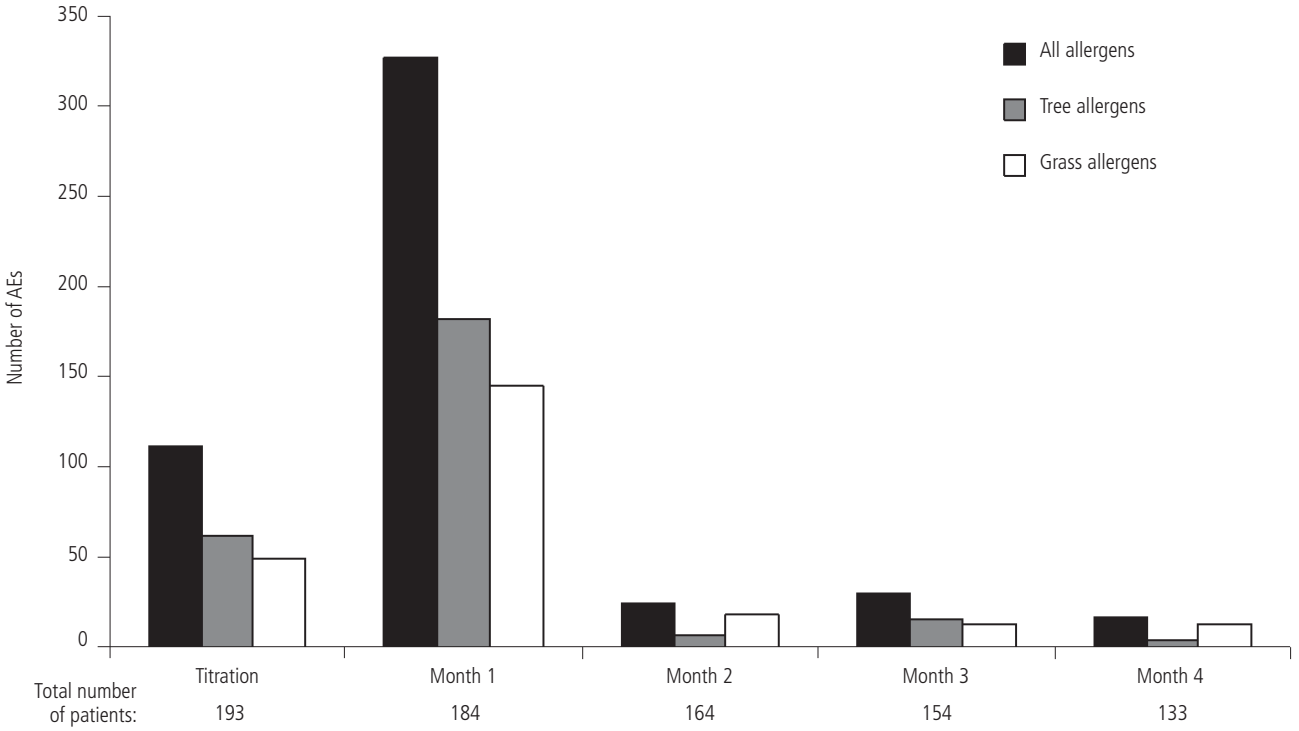

Figure 2. Number of adverse events during ultra-rush titration and 4-month maintenance phase. AEs indicates adverse events.

the beginning of the study. He experienced only mild local adverse events during ultrarush titration with grass pollen extract but developed dysphagia and dyspnea on day 4 of the maintenance phase, immediately after the 300 IR dose. Following intravenous remedial treatment with 100 mg of prednisone, clemastine, and 150 mg of theophylline, the boy recovered. Subsequent treatment consisted of rectal prednisone and epinephrine for inhalation. After 4 days, SLIT was resumed with gradually increasing doses up to 300 IR.

Discussion

This large observational study of 193 children and adolescents demonstrated that an ultrarush high-dose SLIT regimen reaching a maintenance dose of 300 IR within 90 minutes (30-90-150-300 IR) was safe and well tolerated. Similar results in adult patients using standardized *Juniperus ashei* allergen extracts from the same manufacturer have been previously reported [9]. Although ultrarush titration lasted only 90 minutes, the incidence and intensity of adverse events in this study were comparable to those reported in pediatric studies using traditional titration regimens [15-17]. In a recently published study using a 40-minute ultrarush titration regimen, 31 children and adolescents aged 6 to 17 years received allergen extracts from the same manufacturer used in this study [11]. A total of 13 patients (42%) experienced mild local adverse events and no severe events were observed. It is of note that, in contrast to most other studies, in which SLIT was started before the pollen season, we exposed most of the patients to coseasonal ultrarush titration.

During the maintenance phase, 1 clinically significant severe asthma event was observed. The event resolved after adequate remedial treatment and SLIT was resumed after 4 days. Overall, asthmatic exacerbations are rarely observed during SLIT. A rate of 1 in 498 patients was reported in a recent comprehensive review [18]. Rates reported in pediatric populations are comparable to ours [19-21] and in 1 case slightly higher [22]. Studies on SLIT in 65 and 126 younger children aged 3 to 7 and 3 to 5 years, respectively, did not detect any asthma events [23,24].

In conclusion, this ultrarush high-dose SLIT regimen was safe and well tolerated in children and adolescents aged 5 to 17 years at the start of and during the pollen season. Adverse events during ultrarush titration were mild or moderate and within the expected range for SLIT. They resolved rapidly and did not require extended medical supervision. Caution is, however, advised in children with asthma, who should be carefully monitored and adequately trained to use their rescue medications.

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