

Short Communication

Safety of ultra-rush titration of sublingual immunotherapy in asthmatic children with tree-pollen allergy

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The recommendation to use sublingual-swallow immunotherapy (SLIT) in children and adults with allergic rhinitis has been established over the past decade. Recently, ultra-rush titration of SLIT has become more and more common, raising concerns about its safety in children with asthma. Fifty-four children with asthma and adolescents aged 6–14 with documented allergic disease because of tree pollen (birch and possibly alder and/or hazel) from 14 study centers in Germany participated in a randomized, double-blind, and placebo-controlled study. Twenty-seven were randomized to receive SLIT with standardized birch pollen allergen extract and the other 27 to receive placebo. An ultra-rush high-dose SLIT titration regimen reaching the maintenance dose of 300 index of reactivity (IR) within 90 min (30–90–150–300 IR) was used. The difference in mean PFR changes during ultra-rush titration between SLIT and placebo was not significant ($p = 0.056$). A 95% probability that SLIT does not decrease PFR during ultra-rush titration was demonstrated. Neither anaphylactic shock nor else serious systemic reactions to the study drug occurred. No serious adverse event assessed by the investigator as related to study drug treatment was reported.

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The recommendation to use sublingual-swallow immunotherapy (SLIT) in children and adults with allergic rhinitis evolved over several years (1–5). In contrast, subcutaneous immunotherapy (SCIT) is effective in children and adults, but it is burdened by the risks of side effects (2). These side effects may be life-threatening (2).

Over 80% of asthmatics have rhinitis, and 10–40% of patients with rhinitis have asthma (2). The fact that most patients with asthma have rhinitis (6) suggests the concept of ‘one airway one disease’ although there are differences between rhinitis and asthma (7, 8).

Over the past 10 yr, the allergen doses used for SLIT have been up to 500 times higher than the doses commonly administered with SCIT.

Traditional SLIT dosing regimens consisted of an induction phase lasting a couple of weeks followed by a maintenance phase of months or years. More than 10 yr ago, a rush preseasonal treatment schedule reaching the maintenance dose in 15 days with twice-daily administrations was studied in 34 adult patients with grass pollen-induced allergic rhinoconjunctivitis and shown to be safe and well tolerated (9). In children and adolescents, ultra-rush high-dose SLIT titration regimens were evaluated in three studies so far (10–12).

Lung function testing is helpful in diagnosing and monitoring asthma and in assessing the efficacy of therapy (13). Above the age of 5 yr, conventional lung function testing is possible in

most children. This includes measures such as peak flow rate (PFR) (13).

We conducted a randomized, double-blind, placebo-controlled study in 116 children and adolescents with allergic rhinitis because of tree pollens to evaluate the safety of an ultra-rush high-dose SLIT titration regimen reaching the maintenance dose of 300 IR within 90 min (30–90–150–300 IR). In this short communication, we focus on PFR changes during ultra-rush titration in the subpopulation of children with asthma.

Methods

Study design

This was a randomized, double-blind, placebo-controlled study. From October to December 2004, out of the birch pollen season baseline skin prick test, total and tree-pollen-specific immunoglobulin E (IgE), Retrospective Rhinoconjunctivitis Total Symptom Score (RRTTS) for the 2004 pollen season, and lung function tests in children with asthma were performed. The RRTTS consisted of the six symptoms sneezing, rhinorrhea, nasal pruritus, nasal congestion, ocular pruritus, and watery eyes with mild, moderate, and severe intensity of the individual symptom scored as 1, 2, and 3, respectively. Lung function tests in children with asthma were repeated before each titration step on the day of randomization. Written informed consent was obtained from children and their parents or caregivers. The study was approved by the Ethics Committee of the Charité University in Berlin and the competent authority (Paul Ehrlich Institute, Langen, Germany).

Patients

In total, 138 children and adolescents aged 6–14 with a medical history of allergic rhinitis or rhinoconjunctivitis with or without mild to moderate asthma because of tree pollens (birch and possibly alder and/or hazel) were recruited at 14 study centers in Germany. Positive skin prick tests and presence of specific IgE ≥ 0.7 kU/L to the respective tree pollens were required, as well as a RRTTS of ≥ 8 . Patients fulfilling any of the following criteria were excluded: previous immunotherapy within the past 3 yr, perennial allergic rhinitis, perennial allergic asthma, absolute or relative contraindications to immunotherapy, or any other condition which could compromise the patient's safety during the study. In December 2004, 116 patients were randomized to receive either SLIT with standardized birch pollen

extract or placebo and treated for 6 months during the entire 2005 birch pollen season.

Immunotherapy and concomitant treatments

Standardized birch pollen (*Betula alba*) allergen extract in aqueous solution was used for SLIT (Staloral[®], Stallergènes, Antony, France). Biological activity of the extract was assessed in comparison with an internal standard *in vitro* and *in vivo* and expressed as index of reactivity (IR) (14). Ultra-rush high-dose SLIT titration regimen reaching the maintenance dose of 300 IR within 90 min (30–90–150–300 IR) was used in an ambulatory setting under close medical supervision until 60 min after the last dose. Modifications were restricted to severe local and at least mild generalized reactions.

The following symptomatic drugs were allowed for the treatment of allergic reactions during titration: local (nasal and ocular) levocabastine (step 1), oral cetirizine (step 2), nasal fluticasone (step 3), and eventually an oral corticosteroids (step 4). In patients with asthma, the previous medication with corticosteroids for inhalation and/or selective beta₂-adrenoceptor agonists for inhalation was continued at the same dose.

Lung function test

Three consecutive peak flow rate (PFR) measurements (standing) were performed in children with asthma at baseline and before each titration step of ultra-rush titration.

Laboratory safety data

The following hematology and blood chemistry parameters were determined: RBC, hemoglobin, hematocrit, platelets, WBC including differential, Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), bilirubin, Lactate dehydrogenase (LDH), and C-reactive protein (CRP).

Statistical analysis

Demographic and baseline data as well as PFR data were compared between groups, using the non-parametric Mann–Whitney U test. Differences were considered statistically significant at a p value of < 0.05 .

Results

Out of the total study population of 116 children and adolescents (60 treated with SLIT and 56 with placebo), 54 patients had mild to moderate

allergic asthma (27 treated with SLIT and 27 with placebo). The patients of this subpopulation were well matched at baseline (Table 1).

Safety

Safety assessment was achieved by the evaluation of the physical examination data, laboratory results, and adverse events. Vital signs and laboratory safety data were well within normal ranges during the period of the regimen. The most frequent symptoms were 'application site itching' and 'application site paresthesia'. Neither anaphylactic shocks nor other serious systemic reactions to the study drug occurred. No serious adverse event assessed by the investigator as related to study drug treatment was reported.

Peak flow rate

Figure 1 displays the mean PFR of children with asthma during ultra-rush titration. Mean PFR slightly increased in both groups. The difference in mean PFR changes between SLIT and placebo was not significant ($p = 0.056$). Figure 2 displays mean slopes and 95% confidence intervals of PFR changes during ultra-rush titration. The

Table 1 Demographic and clinical characteristics of the asthmatic patient subpopulation at baseline

	SLIT group	Placebo group	p
Sex (m/f)	10/17	18/9	0.059
Age (mean $\pm$ s.d.; years)	10.2 $\pm$ 2.64	10.5 $\pm$ 2.55	0.647
Height (mean $\pm$ s.d.; cm)	144.8 $\pm$ 17.90	145.0 $\pm$ 15.62	0.924
Weight (mean $\pm$ s.d.; kg)	38.2 $\pm$ 13.52	39.6 $\pm$ 12.34	0.634
PFR (mean $\pm$ s.d.; l/min)	290.7 $\pm$ 107.7	298.7 $\pm$ 90.52*	0.548

SD, standard deviation.

*In the placebo group, PFR was measured in 23 of 27 patients only.

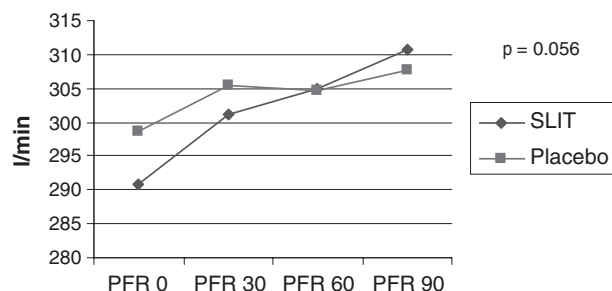


Fig. 1. Mean peak flow rates of children with asthma during ultra-rush titration (PFR 0, PFR 30, PFR 60, and PFR 90 are the peak flow rates measures at 0, 30, 60, and 90 min after start of ultra-rush titration, i.e. before each of the titration steps (30–90–150–300 IR). The difference in mean PFR changes during ultra-rush titration between SLIT and placebo was not significant ($P = 0.056$)).

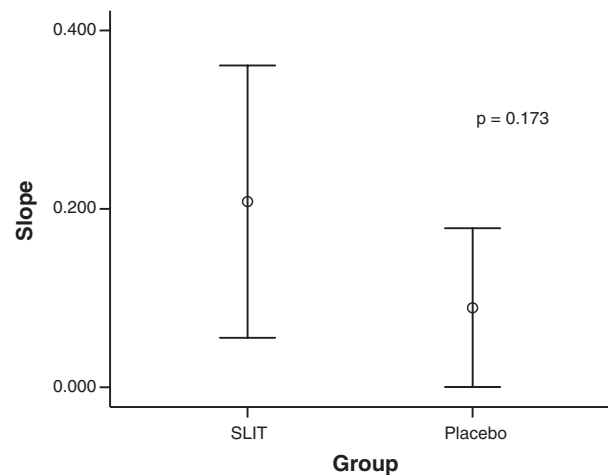


Fig. 2. Mean (95% confidence interval) of the slope of changes in peak flow rates of asthmatic children during ultra-rush titration (The slope of the change in peak flow rates at 0, 30, 60, and 90 min after start of ultra-rush titration, i.e. before each of the titration steps (30–90–150–300 IR) was calculated for both groups. The difference in mean PFR slopes during ultra-rush titration between SLIT and placebo was not significant ($P = 0.173$)).

lower limit of the 95% confidence interval was above zero demonstrating a 95% probability that SLIT does not decrease PFR. The difference of mean slopes between SLIT and placebo was not significant ($p = 0.173$).

Discussion

In this randomized, double-blind, placebo-controlled study, the safety of an ultra-rush high-dose SLIT regimen with standardized birch pollen allergen extract reaching the maintenance dose of 300 IR within 90 min (30–90–150–300 IR) was assessed. PFR changes during ultra-rush titration could be helpful in monitoring asthma. A 95% probability that SLIT does not decrease PFR during ultra-rush titration was demonstrated. There was no specific risk of ultra-rush titration detected in children with asthma and adolescents aged 6–14 allergic to tree pollens.

In a large observational study in 193 children and adolescents aged 5–17 with allergic rhinitis and/or asthma, an ultra-rush high-dose SLIT regimen with grass and/or tree pollen allergen extracts of the same manufacturer using the same ultra-rush regimen was assessed (12). During ultra-rush titration, 60 patients (31%) reported 117 predominantly mild and local adverse events, which resolved within 150 min. The only moderate systemic reaction was moderate rhinoconjunctivitis in one patient.

In 31 children and adolescents aged 6–17 with allergic rhinitis and/or asthma, an ultra-rush

high-dose SLIT titration regimen with grass pollen, *Parietaria* pollen and/or *Dermatophagoides* allergen extracts of the same manufacturer was used reaching the maintenance dose of 240 IR within 40 min (30–60–120–180–240 IR) was assessed (11). In this group and a parallel group of patients aged 4–17 receiving allergen extracts of another manufacturer, only mild and predominantly local reactions were detected. As most local reactions spontaneously disappeared within 30 min, an observation period of 1 h was suggested.

In 28 children and adolescents as well as 77 adults with allergic rhinitis and/or asthma, a 20-min ultra-rush high-dose SLIT titration regimen with grass pollen, *Parietaria* pollen and/or *Dermatophagoides* allergoid extracts was used (10). Only a single gastrointestinal adverse event in a single patient was reported.

In conclusion, our results determined in a randomized, double-blind, placebo-controlled study design are in line with previously published safety data from uncontrolled studies on ultra-rush SLIT regimens in children and adolescents. No specific risk of ultra-rush titration or SLIT itself was detected in children with asthma with respect to PFR in this study.

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