ORIGINAL ARTICLE

# One-Year Follow-up of Clinical and Inflammatory Parameters in Children Allergic to Grass Pollen Receiving High-Dose Ultrarush Sublingual Immunotherapy

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## Abstract

*Background:* In a previous double-blind placebo-controlled study, we analyzed a high-dose sublingual immunotherapy (SLIT) ultrarush protocol in asthmatic children monosensitized to grass pollen. In the present open-label study, we assessed the effect of SLIT on symptom score and nonspecific bronchial hyperreactivity in the same cohort followed for 1 subsequent year.
*Methods:* The study population comprised 35 children who were enrolled in our previous study. Placebo-treated patients were switched to active treatment; therefore, SLIT was administered for a further year to all patients. SLIT was considered effective if it reduced the severity of clinical symptoms and decreased the use of symptomatic medication. The effect of SLIT on nonspecific bronchial hyperreactivity (methacholine challenge test) was also measured.
*Results:* The symptom scores for asthma and rhinitis and medication score remained unchanged in the group who continued SLIT. We also observed further significant improvement in the results of the methacholine challenge test during the third year of treatment.
*Conclusions:* High-dose ultrarush SLIT reduced the severity of allergic symptoms in the first 2 grass pollen seasons but continuously improved bronchial hyperreactivity in children with asthma, suggesting that SLIT should be continued despite the lack of further improvement in clinical symptoms.

Key words: Asthma. Children. Immunotherapy. Rush. Sublingual.

## Resumen

*Antecedentes:* En un estudio previo con doble ciego controlado con placebo, se analizó un protocolo ultrarrápido de inmunoterapia sublingual (ITSL) administrada a dosis altas en niños asmáticos monosensibilizados al polen de gramíneas. En este estudio de diseño abierto, se evaluó el efecto de la ITSL en la puntuación de los síntomas y la hiperreactividad bronquial no específica en la misma cohorte sometida a seguimiento durante un año.
*Métodos:* En el estudio se incluyó a 35 niños que habían participado en el estudio previo. Los pacientes tratados con placebo cambiaron al tratamiento activo; por lo que se administró ITSL durante un año más a todos los pacientes. La ITSL se consideró eficaz si reducía la gravedad de los síntomas clínicos y disminuía el uso de medicación sintomática. Asimismo, se determinó el efecto de la ITSL en la hiperreactividad bronquial no específica (pruebas de provocación bronquial con metacolina).
*Resultados:* Las puntuaciones de los síntomas de asma y rinitis y la puntuación de la medicación no experimentaron cambios en el grupo que continuó con la ITSL. Asimismo, se observaron mejoras significativas en los resultados de la prueba de provocación con metacolina durante el tercer año de tratamiento.
*Conclusiones:* La ITSL ultrarrápida administrada a dosis altas redujo la gravedad de los síntomas alérgicos en las dos primeras estaciones polínicas de gramíneas, pero mejoró de forma continua la hiperreactividad bronquial en niños con asma, lo que indica que debe continuarse la ITSL pese a la ausencia de mejora en los síntomas clínicos.

Palabras clave: Asma. Niños. Inmunoterapia. Rápida. Sublingual.

## Introduction

Allergen-specific immunotherapy (SIT) is the only allergy treatment that modifies the immune response. SIT improves symptoms, prevents the onset of new sensitizations, and reduces the risk of developing asthma. Its clinical efficacy lasts many years [1]. Sublingual immunotherapy (SLIT) appears to be the most promising alternative to traditional injected immunotherapy, especially in children. SLIT is well-tolerated, safe, and effective [2-6]. Although much has been published on SLIT administered using a conventional induction phase, the literature contains little on ultrarush protocols. Furthermore, the number of trials in asthmatic children is limited. We previously performed a 2-season double-blind placebo-controlled study of high-dose ultrarush SLIT administered to asthmatic children monosensitized to grass pollen [7]. In the present open-label study, we assess the effect of SLIT on symptom scores and nonspecific bronchial hyperreactivity in the same cohort followed for 1 subsequent year.

## Materials and Methods

### Study Design

The study population comprised 35 pollen-allergic asthmatic children aged 6-17 years who had participated in our previous study [7]. SLIT was administered to all patients for 1 year; therefore, children initially assigned to placebo had SLIT for 1 year (first-year SLIT group), whereas those initially assigned to active treatment had SLIT for 3 years (third-year SLIT group). SLIT was administered from March to September.

The diagnosis of asthma was based on symptoms of asthma and on improvement in prebronchodilator forced expiratory volume ($FEV_1$) ≥12% after administration of salbutamol 200 µg. Patients with asthma and/or rhinitis who were allergic to perennial allergens and those with severe intermittent or persistent asthma were excluded. Patients for whom SIT was contraindicated according to EAACI guidelines [8] were also excluded. Systemic corticosteroids or immunosuppressive drugs must not have been taken within the 4 weeks preceding the study.

The efficacy endpoint was the reduction in the severity of clinical symptoms and the decrease in the use of symptomatic medication. The effect of SLIT on nonspecific bronchial hyperreactivity (methacholine challenge test) was also measured.

### Diary Card

The diary card included daytime symptoms (recorded at bedtime) and nocturnal awakening (recorded in the morning upon awakening) using scales that have been validated elsewhere [9]. In addition, the amount of as-needed $ß_2$-agonist (salbutamol) was recorded daily as the number of puffs. Daytime asthma symptoms and nocturnal awakenings were scored subjectively, as follows: 0, no symptoms during the day/night; 1, symptoms did not affect daily activities or nighttime sleep; 2, symptoms affected at least 1 daily activity or disturbed nighttime sleep; 3, symptoms affected 2 or more daily activities or disturbed sleep all night or most of the night. Use of $ß_2$-agonists was scored as follows: 0, none; 1, once a day; 2, between 2 and 3 times a day; 3, more than 3 times a day.

The minimum score for each day was 0 (no symptoms during the day, no symptoms at night, and no use of $ß_2$-agonists) and the maximum score was 9 (severe symptoms during the day and at night, and more than 3 administrations of $ß_2$-agonists). Additionally, ophthalmic symptoms (itching, blepharedema, epiphora) to a maximum of 9 per day, nasal symptoms (itching, congestion, sneezing, rhinorrhea) to a maximum of 12 per day, and medication (1 point for each permitted medication × the number of treatment days) were recorded [10].

### Methacholine Challenge Test

The methacholine challenge test was performed after the first year (October/November 2006) and after the second year (October/November 2007) of SLIT using the ZAN 200 ProvAir II dosimeter (nSpire Health Inc, Longmont, Colorado, USA). After the administration of physiological diluent, methacholine was delivered to a maximum of 8 cumulative doses: 0.04 mg, 0.08 mg, 0.17 mg, 0. 34 mg, 0.67 mg, 1.34 mg, 2.67 mg, and 5.34 mg. The challenge test was continued at 3-minute intervals between inspirations until $FEV_1$ fell by ≥20%. The $PD_{20}$ was calculated by linear interpolation on a logarithmic dose-response curve [11].

### Treatment

All patients were treated with Staloral 300 IR (Stallergenes SA, Antony, France) as a standardized extract of 5 grass pollens (*Dactylis glomerata, Anthoxanthum odoratum, Lolium perenne, Poa pratensis, Phleum pretense*). Verum (Stallergenes SA, Antony, France) was dispensed in the same glycerosaline diluents. All the children received ultrarush immunotherapy an average of 2 weeks before the pollen season (2006, 2007, and 2008), as follows: 1-3-6-12 (10-30-60-120 IR) drops separated by a 30-minute observation period (total of 240 IR). Every morning before breakfast they received 4 puffs (120 IR) for 6 months. To assess adherence to treatment, all patients were asked to bring empty vials to each visit. The pollen season was defined based on analysis of 3 previous pollen seasons in the region where the children lived. The season was defined as the first of 3 consecutive days with grass pollen counts ≥10 grains/$m^3$ until the last day before 3 consecutive days with a grass pollen count of <10 grains/$m^3$. A pollen count was performed throughout the study for the region of interest. During the pollen season, all children received budesonide 200 µg twice daily and salbutamol 100 µg/dose for quick relief. Other permissible treatments were standard treatments for infection and exacerbations of asthma and standard treatments for allergic rhinoconjunctivitis in the pollen seasons (local cromones, local and/or systemic antihistamines, and nasal corticosteroids).

### *Ethics*

The university ethics committee approved the experimental protocol and the parents signed an informed consent document before enrolment.

### *Statistical Analysis*

Changes in response to treatment within groups were compared using an analysis of variance with the Tukey-Kramer post hoc test. Variables exhibiting a heavily skewed distribution were compared within groups using the Kruskal-Wallis test followed by post hoc comparisons with the Dunn test. All analyses were performed on an intention-to-treat basis, with statistical significance set at 5%.

## Results

The number of patients continuing the study at the various follow-up visits is shown in Figure 1. All 35 patients completed the third year of the study. The average cumulative dose for each patient was 65 700 IR.

### *Symptom and Medication Scores*

The symptom scores for asthma and rhinitis and the medication score did not change in the third-year SLIT group, whereas they improved in children from the first-year SLIT group (Figure 2).

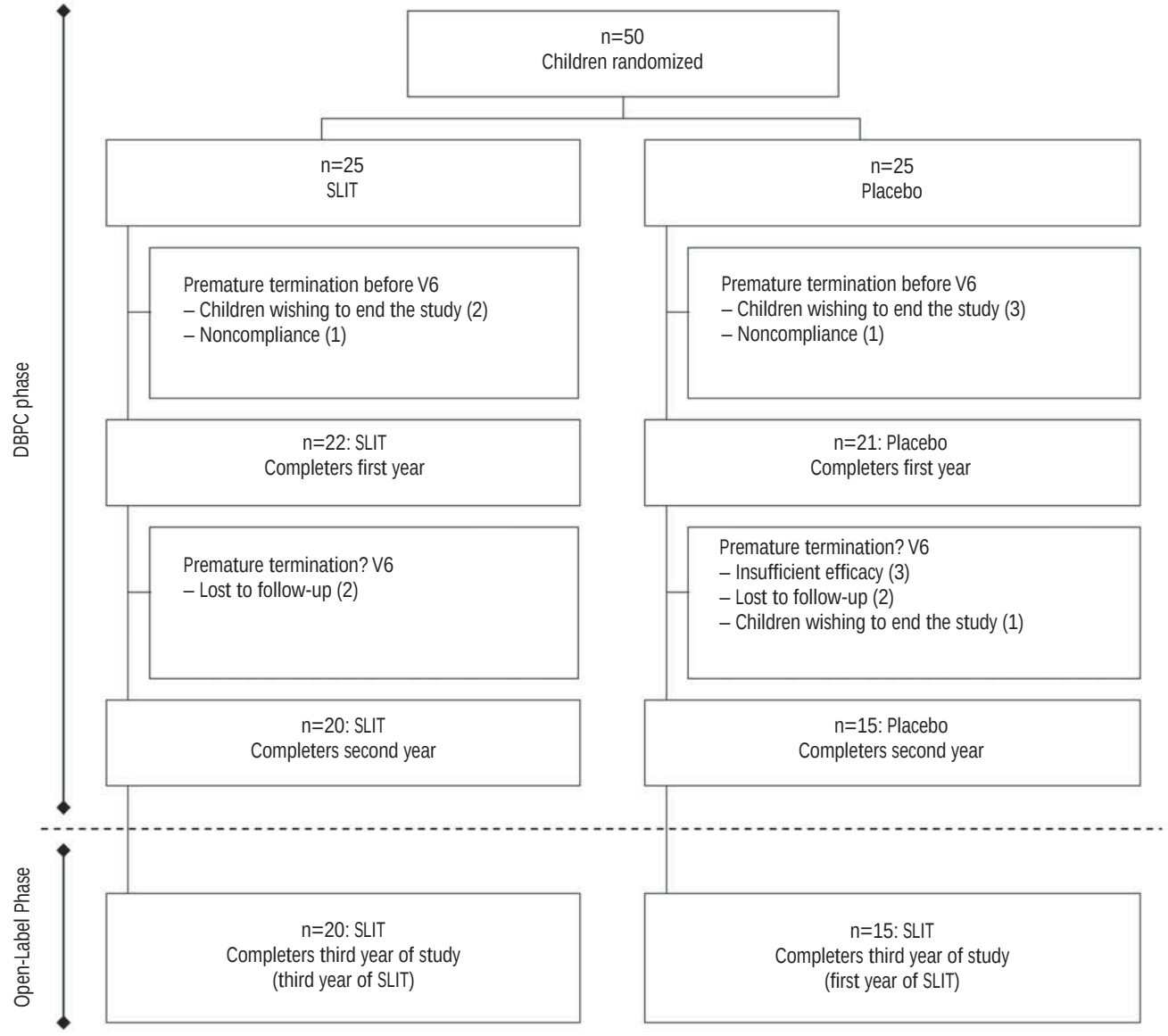


Figure 1. Numbers of participants in the double-blind placebo-controlled phase and open-label phase of the study. DBPC indicates double-blind placebo-controlled; SLIT, sublingual immunotherapy.

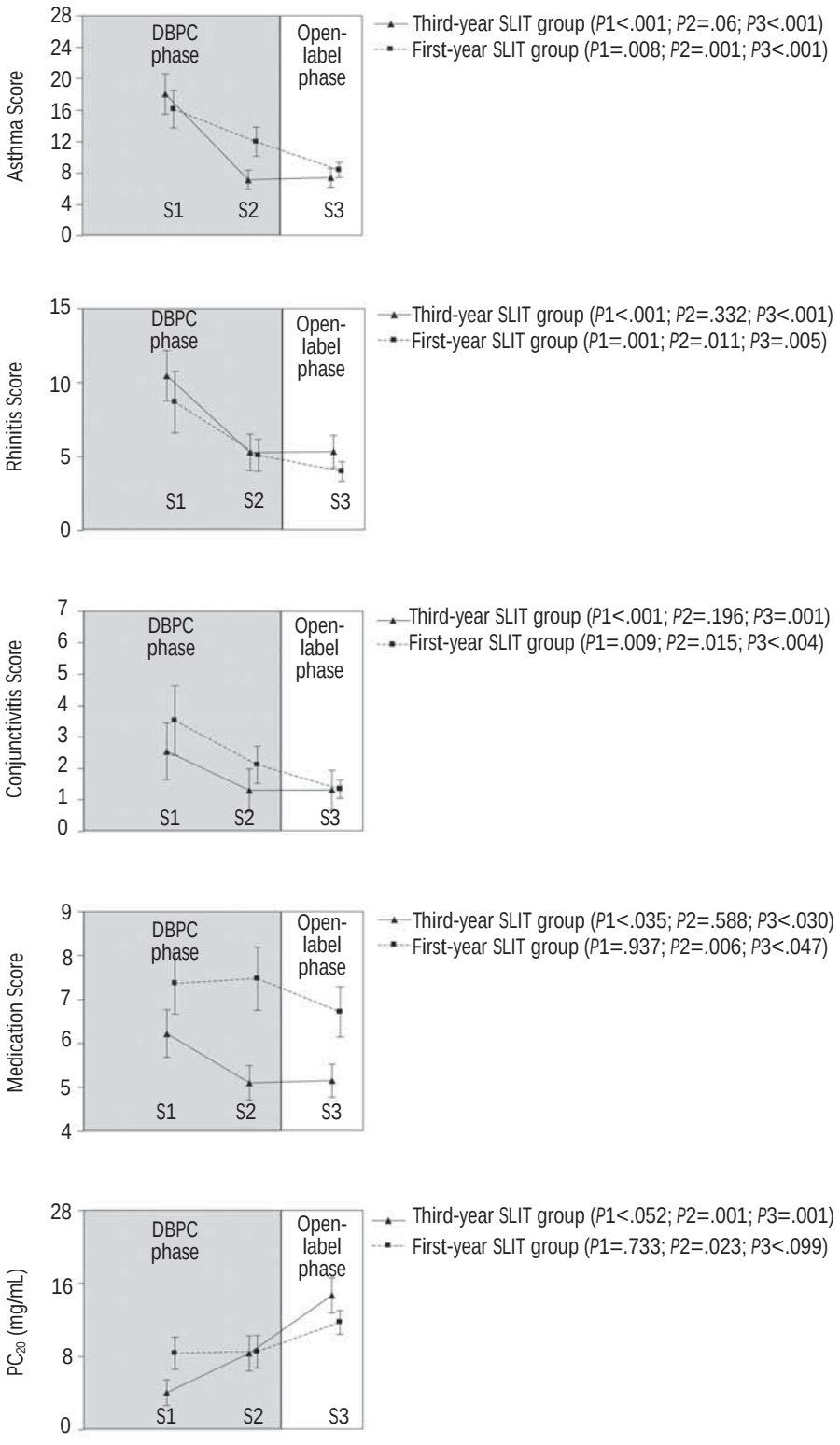


Figure 2. Within-group comparison of asthma, rhinitis, conjunctivitis, and medication scores and $PC_{20}$. All scores and $PC_{20}$ were compared within-groups between seasons (S): S2 vs S1 (P1), S3 vs S2 (P2), and S3 vs S1 (P3). All scores were adjusted to 1000 per $m^3$ and presented as mean with the standard error of the mean (whisker). Adjustment was calculated according to the following formula: mean weekly score/cumulative concentration of grass pollen during the season ×1000. DBPC indicates double-blind placebo-controlled; SLIT, sublingual immunotherapy.

 

### *Methacholine Challenge Test*

We observed a significant improvement in the results of the methacholine challenge test in both groups.

## Discussion

We show the results of a study that was initiated as a double-blind placebo-controlled course of SLIT in children with asthma monosensitized to grass pollen in whom clinical and immunological parameters were assessed. The results of the first 2 years of the study have been reported elsewhere [7]. The study continued open-label for an additional year, and SLIT was extended to all children. Symptoms and medication use improved during the first 2 years of SLIT and did not change during the third year. In the third-year SLIT group, we observed a significant improvement in nonspecific bronchial hyperreactivity during the double-blind placebo-controlled phase of the study [7], and this improvement continued in the third year of treatment. We observed an apparent discrepancy between the improvement in hyperreactivity and clinical symptoms. This phenomenon has never been observed in clinical settings. However, the present study does not directly explain whether further improvement in bronchial hyperreactivity in the third year follows the effect of the third year of SLIT. Contrary to the results of other studies [12], our data suggest that the efficacy of SLIT cannot be documented using clinical parameters only. In fact, it is very difficult to assess the significance of these findings, as a preseason baseline methacholine challenge test was not performed.

The effect of placebo in the double-blind placebo-controlled phase has been discussed elsewhere [7]; in the open-label phase, we observed a positive effect of SLIT on clinical parameters in this group of patients.

Our results are unexpected and have very important clinical implications. We conclude that high-dose ultrarush SLIT reduced the severity of allergic symptoms—mainly during the first 2 grass pollen seasons—and continuously improved bronchial hyperreactivity in our patients. Consequently, our SLIT regimen is effective in the treatment of grass pollen–allergic children with asthma and should be continued despite the absence of further improvement in clinical symptoms during SLIT.

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