# Sublingual immunotherapy in pollen-induced seasonal rhinitis and conjunctivitis: a randomized controlled trial

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ABSTRACT

**Background:** Sublingual immunotherapy (SLIT) is a recognized and safe treatment for allergic rhinitis and conjunctivitis. The aim was to evaluate the efficacy and safety of tablets for grass and rye pollen–induced rhinitis and conjunctivitis.
**Methods:** A double-blind, randomized, placebo-controlled trial was carried out over 9 months. 105 patients received a standardized grass/rye mix extract or a placebo using sublingual drops during the build-up phase. Drops were replaced by sublingual tablets during the maintenance phase (300 IR/daily).
**Results:** In patients that received active treatment, a significantly lower total symptom score (rhinitis and conjunctivitis) compared to the placebo group was observed ($p = 0.038$). The investigators' assessment revealed a significant improvement in favor of the active treatment group ($p = 0.018$). Skin reactivity to grass and rye pollen was significantly reduced in the active treatment group ($p < 0.05$). No statistical difference was observed between the two groups for serum-specific IgG4 levels. Side effects were local and mild, and no severe systemic reactions were reported.
**Conclusion:** This study indicates that tablet-based sublingual immunotherapy was safe and significantly improved grass/rye pollen-induced rhinoconjunctivitis symptoms. It was also associated with a significant inhibition of the immediate skin response.

KEY WORDS

**rhinoconjunctivitis, seasonal, allergic, immunotherapy, sublingual, grass pollen, rye pollen, hay fever**

## Introduction

Sublingual immunotherapy (SLIT) has been previously investigated with the overall aim of improving the safety and convenience of immunotherapy. According to the current literature, strong evidence points towards the efficacy of SLIT in pollen-induced rhinitis and rhinoconjunctivitis (1–13).

To be effective, SLIT must be administered as a high-dose extract, which in fact does not compromise the good safety profile of the sublingual route. A substantial improvement in patient compliance (a critical issue) could be achieved by the use of sublingual tablets instead of drops because it makes intake easier. Two studies have provided evidence for the efficacy and safety of SLIT tablets in patients with grass and ragweed pollen–induced rhinoconjunctivitis (1, 8).

In this placebo-controlled study in patients suf-

Table 1: Main clinical efficacy variables: Symptom score and medication score
Data represent the area under curve (AUC) (median and 95% CI) for the clinical efficacy variables

| **Clinical scores** | SLIT ($n$ = 48) | Placebo ($n$ = 53) | Treatment differences§ | 95% CI * | $P^{\#}$ |
|---|---|---|---|---|---|
| Over the 10-week pollen season | | | | | |
| **Total symptoms** | 180 | 277 | 90 | (5, 181) | 0.038 |
| **Rhinitis** | 142 | 190 | 49 | (- 7, 112) | 0.084 |
| **Conjunctivitis** | 36 | 86 | 41 | (10, 750) | 0.003 |
| **Rescue medication** | 13 | 26 | 0 | (- 4, 22) | 0.64 |
| **Symptoms/medication score** | 195 | 322 | 103 | (- 1, 204) | 0.051 |
| During the 2-week peak pollen season | | | | | |
| **Total symptoms** | 15 | 39 | 16 | (0, 36) | 0.03 |
| **Rhinitis** | 12 | 29 | 10 | (0, 24) | 0.04 |
| **Conjunctivitis** | 2 | 10 | 5 | (0, 13) | 0.005 |
| **Rescue medication** | 0 | 0 | 0 | (0, 10) | 0.13 |
| **Symptoms/medication score** | 22 | 46 | 17 | (0, 45) | 0.04 |

*§: Hodges-Lehmann estimate for treatment difference between medians (placebo* versus *active drug).*
** 95% CI: Confidence interval for the difference between medians. # Wilcoxon rank sum test.*

fering from seasonal rhinoconjunctivitis, we assessed the efficacy and safety of SLIT using high doses of grass/rye pollen extract.

# *Materials and methods*

## *Patients*

105 patients (18–50 years old) were recruited from 14 German allergy clinics. All patients had a history of seasonal allergic rhinoconjunctivitis for at least 2 years, positive skin-prick tests to grass and rye pollen extracts, and timothy pollen–specific IgE (0.35 kU/l). Patients with perennial rhinitis, receiving immunotherapy within the previous 2 years, or because of routine contraindication for immunotherapy, were excluded. Patients with mild seasonal asthma controlled with inhaled β2-agonists could be included in the investigation. The present investigation was a multicenter, double-blind, randomized, placebo-controlled study. Following enrollment from September to December 1997, treatment was started in January 1998 and conducted until September 1998.

## *Immunotherapy protocol*

For immunotherapy, an extract containing a mixture of grass and rye-pollen extracts prepared according to a previously described method was used (8). It was standardized in IR units, in which a concentration of 100 IR/ml was defined as the concentration eliciting a mean skin prick wheal diameter of 7 mm in 30 patients. The active study medication was a solution (Staloral(r) (Stallergenes, Antony, France)) and a tablet (freeze-dried pollen extract). The up-dosing, up-titration phase started with 1 drop and increased to 10 drops of 1 IR/ml, followed by 1 drop and increasing to 10 drops of 10 IR/ml, then 1 drop to 20 drops of 100 IR/ml. Patients then switched to tablets (100 IR), taking 1 tablet/day for 1 week, 2 tablets/day for 1 week, and finally 3 tablets daily for 1 week. The maintenance dose remained at 3 tablets daily (i.e., 300 IR) for 30 weeks. The cumulative dose was 47,643 IR (3,500 µg Phl p 5). The solution was kept under the tongue for 2 minutes before swallowing. The tablets were kept under the tongue until dissolved (approximately 2 minutes), and then swallowed as well. Placebo tablets and drops appeared identical to the active extract concerning the shape, taste, and color.

## *Symptom and medication scores*

Patients were asked to complete diary cards during the maximal pollination period (from 15 April to 1 July) evaluating nasal symptoms (sneezing, blocked nose, rhinorrhea, itching), ocular symptoms (redness, itching, tearing), and medication intake. Each symptom was graded on a 0–3 scale, with 0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms, and 3 = severe symptoms. The maximum possible daily score was 21. Rescue medication allowed included H1-antihistamines (levocabastine eye drops and nasal spray, cetirizine tablets) and beta-sympathomimetics (salbutamol). Nasal steroid (flunisolide) was allowed only if symptoms were not relieved with H1-antihistamines. Oral steroids (pred-

Table 2: Secondary efficacy variables: Results of the grass and rye pollen quantitative skin prick test and the allergen-specific $IgG_4$ and IgE levels
Data represent the changes compared to baseline (median values)

| **GRASS AND RYE POLLEN QUANTITATIVE SKIN PRICK TEST** | | | | | | |
|---|---|---|---|---|---|---|
| | **Grass pollen skin test** | | | **Rye pollen skin test** | | |
| **Allergen concentration** | SLIT ($n$ = 48) | Placebo ($n$ = 53) | *p values** | SLIT ($n$ = 48) | Placebo ($n$ = 53) | *p values** |
| 1 IR/ml | - 0.1 | - 0.3 | NS | - 1.0 | 0.2 | NS |
| 10 IR/ml | - 0.6 | 0.6 | 0.03 | - 1.5 | - 0.3 | NS |
| 30 IR/ml | - 1.1 | - 0.1 | 0.04 | - 0.2 | 0.0 | NS |
| 100 IR/ml | - 1.4 | 0.5 | 0.0007 | - 0.8 | 0.0 | 0.04 |
| 300 IR/ml | - 1.2 | 0.5 | 0.003 | - 1.1 | - 0.4 | 0.03 |
| Allergen-specific $IgG_4$ and IgE levels | | | | | | |
| | **Grass pollen (timothy)** | | | **Rye pollen** | | |
| **Specific IgE and $IgG_4$** | SLIT ($n$ = 48) | Placebo ($n$ = 53) | *p values** | SLIT ($n$ = 48) | Placebo ($n$ = 53) | *p values** |
| IgE | 0.9 | 0.7 | 0.6 | 0.1 | - 1.1 | 0.001 |
| $IgG_4$ | 8.8 | 4.9 | 0.053 | 0.6 | 4.7 | 0.07 |

** Wilcoxon rank-sum test; NS: not significant*

nisolone 1 mg tablet) were permitted only in the case of severe persistent symptoms. Each puff, drop (per nostril/eye), or tablet counted as one point. The mean weekly rhinitis score, conjunctivitis score, and medication score as well as a combined total symptom score (rhinitis score plus conjunctivitis score) and a combined symptom/medication score were calculated for each week. At the end of the study, physicians were also requested to record an overall assessment of the efficacy of SLIT on a four-point scale.

### *Skin tests*

Before treatment and after the pollen season, quantitative skin-prick tests were performed with five grass and rye-pollen extract solutions at dilutions of 1 IR/ml, 10 IR/ml, 30 IR/ml, 100 IR/ml, and 300 IR/ml (Stallergenes, Antony, France). The tests were performed in duplicate on the forearms. Skin reactions were recorded after 15 minutes, and then the wheal reaction was outlined and transferred to adhesive tape. The mean wheal diameter (maximum and perpendicular diameter) was recorded.

### *Immunological parameters*

Venous blood was taken before treatment and after the pollen season. Blood was analyzed for allergen-specific IgE and IgG4 to timothy and rye extract. Specific IgE was measured in kU/I (RAST-CAP System, Pharmacia Diagnostivs, Uppsala, Sweden), and specific IgG4 was expressed as a binding percentage compared with a standard serum. Grass pollen counts were obtained from the pollen monitoring station in Kiel, Germany.

## *Results*

A total of 105 patients were recruited at the 14 trial centers. Three patients were excluded because they did not fulfill the inclusion criteria or because they met an exclusion criterion. 102 patients were randomized and 101 patients were included in the intent-to-treat (ITT) population (48 active, 53 placebo). 90 patients continued treatment until the end of the study (42 active, 48 placebo). No significant differences were found between the two groups in inclusion for age, gender, allergen-skin test reactivity, or allergen-specific IgE levels.

### *Symptom scores*

The median AUC (area under curve) of the total symptom score (nasal + ocular) was 35% lower in the actively-treated group; this difference was statistically significant ($p$ = 0.038). Conjunctivitis symptoms were significantly reduced in the actively-treated group; the total ocular score was 58% lower in the SLIT group compared with the placebo group ($p$ = 0.003). Rhinitis symptom scores (sneezing, rhinorrhea, and nasal blockage) were lower in the actively-treated group ($p$ = 0.084) 2-week peak pollen period (Table 1). Data for the first 2-week peak pol-

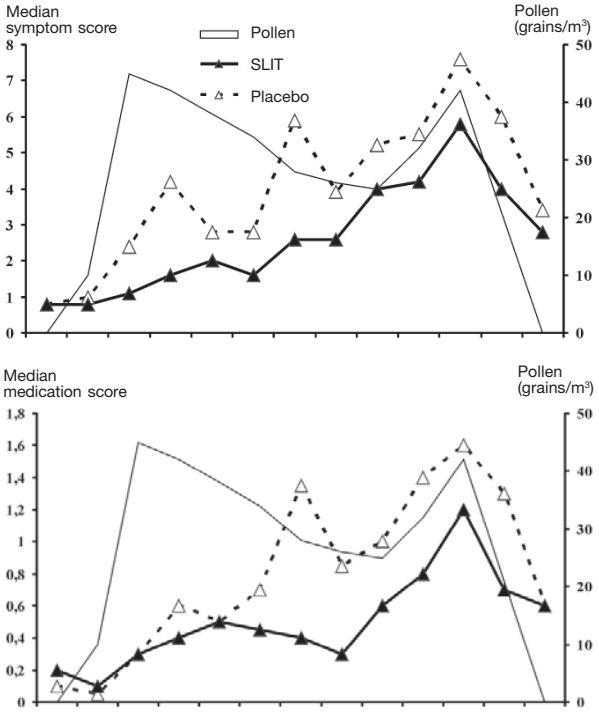


**Figure 1: Course of symptom and medication scores during the grass pollen season**

len period of the season are displayed in the lower part of Table 1.

## *Medication score*

Approximately one half of patients on placebo and one quarter of patients on SLIT-tablets took rescue medication. However, this difference was not statistically significant. The combined symptom/medication score was 39% lower in the SLIT group compared to the placebo group, but not significant. For both groups, the presence of symptoms and the use of rescue medication closely paralleled the second pollen peak (Figure 1). During the first pollen peak, medication use in the placebo group did not correlate to the symptom levels probably because these patients were not nasally primed at the beginning of the season. The investigators' assessment (Fig. 2) showed a higher degree of satisfaction with SLIT therapy (success and partial success) in 73% (35/48 patients) of patients in the SLIT group compared to 41% (22/53 patients) of patients in the placebo group; this difference was statistically significant ($p = 0.018$).

Table 3: Side effects reported during the study

| Side effects | Active (n = 48) N (%) | Placebo (n = 53) N (%) |
|---|---|---|
| Oral itching / burning | 19 (39.6) | 1 (1.9) |
| Mouth / lip swelling | 6 (12.5) | 0 (0) |
| Rhinitis | 10 (20.8) | 8 (15.1) |
| Conjunctivitis | 8 (16.7) | 9 (17) |

## *Skin tests*

The skin test responses to grass and rye pollen at the two highest concentrations (100 IR/ml and 300 IR/ml) were significantly reduced in the actively treated group (Table 2). Moreover, an increase in skin test reactivity was observed in the placebo group.

## *Immunological parameters*

Timothy-specific IgE increased in both groups without a significant difference between the two groups (Table 2). Rye-specific IgE increased slightly in the SLIT group but decreased surprisingly in the placebo group. Allergen-specific IgG4 levels increased an average of twofold in the actively-treated group with no significant difference between groups.

## *Safety assessment*

Local buccal side effects such as oral itching or burning were reported significantly more frequently ($p < 0.001$) in the SLIT treated patients, whereas the frequency of rhinitis and conjunctivitis was similar in both groups (Table 3). Most adverse events were mild to moderate and occurred during the up-titration phase. There were no serious adverse events.

# *Discussion*

Our data assessed the safety and efficacy of a standardized grass/rye mix pollen extract administered by the

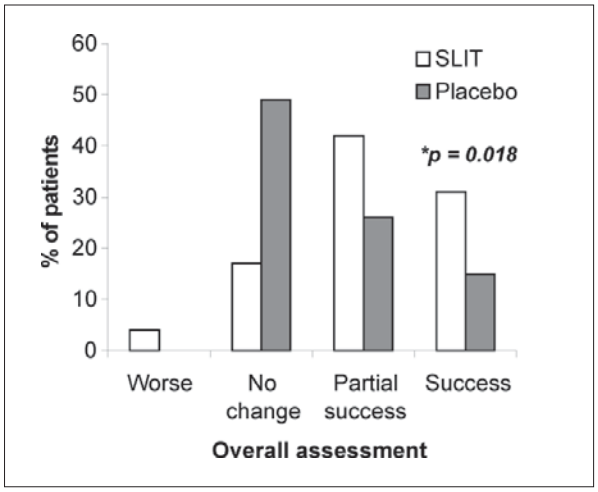


**Figure 2: Overall investigators' assessments – percentage of patients**

** Cochran-Mantel-Haenszel test placebo versus SLIT*

sublingual swallow route. The total symptom score in patients treated with SLIT improved significantly compared to patients under placebo during the pollen season. Medication scores were somewhat lower in the SLIT-treated group, but this difference was not significant.

The efficacy of SLIT in rhinitis and conjunctivitis has previously been evaluated in randomized controlled trials (1, 4–8, 10–12, 14, 17). For studies involving seasonal allergens, a recent meta-analysis (13) concluded that SLIT significantly differed from a placebo in reducing symptoms and the need for medication during the pollen season. A characteristic of our study was the high cumulative dose administered (550 times the subcutaneous immunotherapy doses), which was used in another grass pollen SLIT trial (6). A significant reduction in the need for rescue medication and/or in symptom score was also reported in former studies (14, 17, 19, 20). The magnitude of the efficacy is partly dose-dependent, as reported recently in a study using various dosages of ragweed pollen extract (8), in which significant efficacy was demonstrated in patients treated with high doses compared to patients treated with low doses or a placebo.

The significant reduction in immediate allergen skin sensitivity reported in our study was not demonstrated in other SLIT studies, probably reflecting a variation in the dose administered (1, 6, 8). The induction of allergen-specific IgG4 antibodies during specific immunotherapy is considered evidence of immunological stimulation. In this study, despite the high dose administered, the increase of IgG4 by SLIT did not reach significance in comparison to the placebo group.

Previous SLIT studies have shown contradictory results concerning the induction of IgG4, probably linked to the various doses used. Adverse events were frequent in the SLIT group with every second patient experiencing local side effects of minor severity. However, despite the high daily dose administered in our study, no increase in the severity of systemic adverse events was seen in the SLIT group. This is in accordance with previously published safety analyses (15, 16) and the recent meta-analysis (13) showing that the majority of adverse events were mild and local at the site of the administered allergen extract.

One characteristic of our study was the administration of the maintenance dose with sublingual soluble tablets. These tablets have advantages over drops in terms of compliance. In the majority of the SLIT studies, allergen extracts were administered as drops, which may raise the problem of patient acceptability. Indeed, they must be kept under the tongue for 2 minutes before being swallowed, which is not easy, considering that the volume of one intake generally amounts to 1 ml. It appears that the availability of a solid form (tablet) allowing progressive sublingual dissolution could represent progress in terms of acceptability for the patient and thus improve compliance. To date, few studies using tablets in SLIT have been published. They were performed with ragweed (1) or grass-pollen (6, 16–20) extracts and showed a good safety profile and efficacy. Our study corresponds well with the previous one in terms of efficacy, safety, and patient compliance.

## Conclusion

Our findings demonstrate that grass/rye pollen high-dose SLIT is safe and effective in patients with seasonal allergic rhinitis and conjunctivitis. Clinical efficacy, and better possibilities for detection and for handling adverse events open new possibilities for SLIT. In addition to a positive risk/benefit ratio, the present study showed the advantages of sublingual tablets in terms of easy use and improved compliance.

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