

Expert Opinion

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Increasing long-term safety of seasonal grass pollen sublingual immunotherapy: the ECRIT study

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Objective: The usual build-up phase of days or weeks in allergen-specific immunotherapy entails inconveniences for individuals with symptoms only during the pollen season. Additionally, affected individuals often appear for treatment shortly before the expected start of the season without enough time for titration. This double-blind, placebo-controlled study evaluated the safety of ultra-rush grass pollen immunotherapy with sublingual drops (Staloral)[®] in co-seasonal treatment over three consecutive seasons.

Methods: 209 patients with grass pollen allergic rhinitis received ultra-rush titration (30, 90, 150 and 300 index of reactivity (IR)) of a five grass pollen mixture or placebo every 20 min at the start of the season, followed by 300 IR daily or placebo until the end of the respective season for three consecutive years. Adverse events were documented.

Results: Mean treatment duration varied between seasons (81.8 - 92.7 days). No systemic or anaphylactic reactions were reported and no unexpected adverse events were observed. Adverse events included application site irritation, oedema, abdominal pain and diarrhoea. Fourteen patients discontinued treatment due to adverse events (placebo: four (6%) patients, verum: ten (7%) patients). Adverse events decreased in frequency over each consecutive year of treatment.

Conclusion: Seasonal sublingual immunotherapy with ultra-rush titration is well tolerated even when administered as co-seasonal treatment. It may be a valuable option for patients who present late.

Keywords: allergic rhinitis, co-seasonal treatment, grass pollen extract, sublingual immunotherapy, tolerability, ultra-rush titration

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1. Introduction

Sublingual immunotherapy (SLIT) is now recognised by meta-analyses [1] and guidelines [2-4] as an effective treatment for allergic rhinitis in both adults [1] and children [5]. More recent data demonstrate that, at the appropriate dose, it is effective from the first treatment season for the treatment of allergic rhinoconjunctivitis in adults [6] and children [7].

SLIT was originally developed as an alternative to subcutaneous immunotherapy (SCIT), with the advantage of more convenient administration and a superior safety profile [8]. In double-blind, placebo-controlled clinical studies, SLIT was well tolerated by the vast majority of patients [9], and it seems to be associated with a lower incidence of systemic reactions than SCIT [10]. For SLIT, the most commonly observed side effects were local reactions in the administration site or gastrointestinal effects, which were self-limiting or manageable by a temporary dose reduction and generally mild.

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SLIT is usually initiated during a build-up (titration) phase over several days or weeks [3] with the usage of bottles containing different allergen concentrations. Such a build-up phase entails certain inconveniences for individuals who only have symptoms for 3–4 months per year during the pollen season. An additional challenge is that affected individuals often appear for treatment only shortly before the start of the pollen season not leaving enough time for a long titration phase before the expected start of the season. This issue is intended to be solved by simplifying the administration schedule for SLIT by compressing the titration phase from several days [11], into < 2 h [12,13] or even omitting it [14].

We have previously shown that SLIT containing pollens of five grass species was effective in reducing symptoms of rhinitis and conjunctivitis in patients with grass pollen-induced allergic rhinoconjunctivitis over three seasons of treatment in the 'Efficacy, safety and tolerability of Co-seasonal ultra-Rush sublingual ImmunoTherapy' (ECRIT) study [15]. The presentation of safety data was limited to an overview about adverse events (AEs) without detailed information about specific AEs. This paper presents detailed information on the safety and tolerability of this treatment over three seasons with a focus on the severity and frequency of AEs and the dynamics of the incidence over the seasons.

2. Patients and methods

2.1 Study design

This was a randomised, double-blind, placebo-controlled, parallel-group, multi-centre study in patients with grass pollen allergic rhinitis.

2.2 Patients

Two hundred and sixty-six patients (aged 7.9–64.7 years) with grass pollen allergic rhinoconjunctivitis were screened, 11 of whom were < 18 years old. The diagnosis was based on clinical history (≥ 2 years of grass pollen allergy), confirmed by a positive skin prick test (wheal diameter ≥ 3 mm) (Stallergenes SA, France) and the presence of timothy grass pollen-specific serum IgE reaching a level of at least 0.70 kU/l corresponding to class 2 in the utilised detection system (CAP[®] System; Phadia, Uppsala, Sweden). The skin prick test included pollens of five grass species (orchard grass, *Dactylis glomerata*; meadow grass, *Poa pratensis*; perennial rye grass, *Lolium perenne*; sweet vernal grass, *Anthoxanthum odoratum*; and timothy grass, *Phleum pratense*). Patients had to suffer from persistent allergic rhinitis (> 4 weeks/year) with a severity requiring treatment and providing the indication for specific immunotherapy [3]. All patients had these symptomatic treatments during the previous pollen season and had planned treatment for the first study season with oral cetirizine, ocular or nasal azelastine, oral or ocular prednisolone, nasal beclomethasone or inhaled salbutamol.

Exclusion criteria were: perennial allergic rhinitis and/or perennial allergic asthma, a total serum IgE level > 2000 kU/l,

chronic non-allergic rhinitis or sinusitis, atopic dermatitis, severe asthma (mild asthma GINA grade 1–2 was accepted) [16], any immunotherapy in the previous 5 years and the usual contraindications to immunotherapy [17]. Patients were screened with a panel of clinically relevant allergens. House dust mite sensitivity, that is, positive prick test and/or specific IgE without clinical symptoms, was not an exclusion criterion.

All patients or their guardians gave their written informed consent to participate in the study, which was conducted in accordance with the International Conference on Harmonisation guidelines on good clinical practice and approved by the local ethics committees and competent authorities.

2.3 SLIT extracts and treatment

Of the screened patients, 213 were randomised (2:1) to receive either SLIT for the treatment period and placebo in the follow-up period, or placebo during both the treatment and follow-up periods. All patients visited their study centre at the beginning and at the end of the first pollen season (baseline visit) to assess the use of symptomatic medication in the absence of SLIT. The starting date for treatment was the first day of the pollen season estimated by local pollen calendars. The evaluation period during the pollen seasons was defined as the period from the first day with relevant pollen exposure (≥ 100 pollen grains/m³) until the last day with at least 50 pollen grains/m³ plus 7 days.

During the next three pollen seasons, patients received study medication or placebo, as randomised. A mixture of pollen extracts of five grass species (orchard, meadow, perennial rye, sweet vernal and timothy grasses; Staloral[®], Stallergenes SA) was used at a concentration of 300 index of reactivity (IR)/ml (equivalent to 21 µg/ml of Phl p 5; *P. pratense* major allergen) and administered as sublingual drops. Rush titration was performed under diligent supervision. On day 1, patients took four increasing doses of SLIT, corresponding to 30, 90, 150 and 300 IR, at 20-min intervals (0, 20, 40 and 60 min), followed by a daily intake of 300 IR for the duration of the pollen season. In the event of a severe drug reaction (a reaction unacceptable to the patient), titration was interrupted and repeated the next day. If the reaction continued to be severe, the patient was discontinued from the study. These side effects were considered as adverse drug reactions and were documented in the study results as AEs. Rescue medications were offered to all patients.

Compliance was checked by counting the returned vials of SLIT.

The final pollen season, without treatment, was the follow-up period. All patients visited the study centre before and at the end of each respective treatment pollen season.

2.4 Safety measurements

Safety assessments included documentation of the frequency and severity of AEs by the investigators with a focus on the date of onset, occurrence, duration, intensity, action taken, outcome and causative relation to the study drug.

Gastrointestinal and oral symptoms were graded as 1 = mild, 2 = moderate and 3 = severe. Systemic reactions were graded as 0 = no symptoms, 1 = unspecific symptoms, 2 = mild systemic symptoms, 3 = non-life-threatening symptoms and 4 = anaphylactic shock. Side effect symptoms, weekly frequency and intensity were additionally documented by the patients in their diaries every 14 days (frequency: 0 = never, 1 = during 1 – 4 days, 2 = during 5 – 8 days, 3 = during 9 – 12 days, 4 = nearly every day, 5 = every day).

2.5 Immunological measurements

Blood samples for the determination of specific IgE and IgG4 levels were taken before treatment, after each of the three treatment seasons and after the follow-up season. Timothy grass-specific IgE and IgG4 antibodies were determined by CAP® (Pharmacia, Uppsala, Sweden). The pollen mixture of five grass species was used as the antigen. Sera were incubated as specified by the manufacturer and analysed on a Pharmacia ImmunoCAP® 250 measuring unit.

2.6 Statistical analysis

An exploratory analysis was performed on the number of patients with at least one AE in the SLIT and placebo groups using the two-sided Fisher's exact test.

3. Results

3.1 Study population

In all, 213 patients were randomised in this study, and 209 patients were consistently treated with SLIT ($n = 142$) or placebo ($n = 67$) until the end of their participation in the study.

3.2 Pollen seasons

Pollen seasons were of 2.5 – 3 months duration, depending on location of the study centre. Patients began their treatment 13 – 28 days before the first day of the evaluation period of the treatment pollen seasons. Mean treatment duration varied by season, from 81.8 to 92.7 days. The mean cumulative dose of SLIT was ~ 22,000 IR per season (corresponding to 1500 µg of the group 5 major allergen).

3.3 Adverse events

As previously reported, the titration and maintenance phases of SLIT were well tolerated [15]. No systemic or anaphylactic reactions were reported and no unexpected AEs were observed.

The ultra-rush titration was tolerated well without severe systemic or anaphylactic reactions. Seven patients withdrew from the study at the first day due to symptoms self-assessed as severe (four nausea, one diarrhoea, two unspecific). Two patients experienced nausea at the first titration day but tolerated the repeated titration at the next day well and continued the treatment.

Most AEs reported during the entire study (1-year baseline, 3-year treatment and 1-year follow-up periods) were mild or

moderate in intensity (Table 1). There was no statistically significant difference between the number of patients reporting AEs in the placebo and SLIT groups ($p = 0.50$, Table 1).

The most frequently reported AEs, that is, in ≥ 3 patients of the SLIT group during the entire study, are summarised in Table 2. The pattern of AEs is typical for a study population with grass pollen allergic rhinitis observed over 5 consecutive years.

All serious AEs were assessed as 'not related' or 'unlikely related' to study medication or rescue medication, and there was no statistically significant difference in the number of patients with serious AEs between SLIT and placebo groups ($p = 0.160$).

Fourteen patients discontinued treatment due to AEs, four (6%) patients of the placebo group and ten (7%) of the SLIT group (Table 1); from those in the SLIT group, four AEs were considered 'definitely' or 'likely' related to study medication. Those AEs were predominantly local reactions or gastrointestinal reactions.

Treatment-emergent AEs (TEAEs) reported during the 3-year treatment period are summarised in Table 3. There was no statistically significant difference between the number of patients reporting TEAEs in the placebo and SLIT groups during any of the three pollen seasons of the treatment period ($p = 0.65, 1.00, 0.69$; Table 3). It is to be noted that the number of patients with any TEAE decreased substantially over time in the SLIT group and, although to a lower extent, in the placebo group (Table 3). This was particularly true for patients in the SLIT group reporting any local reaction (Table 3) and reflected in the self-assessment of the patients in their diaries (Figure 1).

4. Discussion

Although the evidence for efficacy and safety of SLIT has increased over the past decade, long-term studies and, therefore, reports of long-term safety of SLIT remain scarce. Most of the available long-term studies are either not randomised, placebo-controlled studies [18] or contain only small numbers of patients [19]. Except the ECRIT study, only one randomised, double-blind, placebo-controlled long-term study on SLIT has been published [14].

Previously, we have published efficacy data of the ECRIT study demonstrating that co-seasonal treatment initiated as ultra-rush titration was effective over 3 years and was effective from the first pollen season with continued efficacy on symptoms after treatment cessation [15]. In this paper, we show that such treatment is increasingly well tolerated as shown by the self-assessment of the patient regarding the frequency of events which is in line with the number of TEAEs.

The most frequently observed AEs during the titration and maintenance phases were mild-to-moderate and limited to the site of administration, including local itching and burning in the oral cavity. In each consecutive year of treatment the

Table 1. Summary of AEs reported during the entire study (1-year baseline, 3-year treatment and 1-year follow-up periods).

AEs	Patients with AE (n (%))		p Value
	SLIT (n = 142)	Placebo (n = 67)	
Any AE	98 (69)	42 (62.7)	0.5
Any serious AE	11 (7.8)	5 (7.5)	1
Any treatment-emergent AE leading to premature discontinuation of study medication	10 (7)	4 (6)	1
Any treatment-emergent local or systemic reactions*	24 (16.9)	12 (17.9)	0.24
Intensity of AEs	Number of AEs [n (%)]		
Mild	146 (39.4)	66 (43.4)	-
Moderate	197 (53.1)	70 (46.1)	-
Severe	25 (6.7)	12 (7.9)	-

*Symptoms in the oral cavity, allergic rhinitis or asthma, urticaria. AE: Adverse event; SLIT: Sublingual immunotherapy.

Table 2. Most frequently reported AEs (in ≥ 3 patients of the SLIT group) during the entire study (1-year baseline, 3-year treatment and 1-year follow-up periods).

AEs (MedDRA preferred terms)	Patients with AE* (n (%))	
	SLIT (n = 142)	Placebo (n = 67)
Nasopharyngitis	31 (21.8)	12 (17.9)
Headache	8 (5.6)	2 (3)
Bronchitis	7 (4.9)	1 (1.5)
Gastritis	7 (4.9)	2 (3)
Pregnancy	6 (4.2)	4 (6)
Acne	6 (4.2)	1 (1.5)
Asthma	6 (4.2)	3 (4.5)
Influenza	6 (4.2)	2 (3)
Diarrhoea	5 (3.5)	2 (3)
Eczema	5 (3.5)	4 (6)
Sciatica	5 (3.5)	0 (0)
Cystitis	4 (2.8)	3 (4.5)
Sinusitis	4 (2.8)	3 (4.5)
Back pain	4 (2.8)	2 (3)
Dental treatment	4 (2.8)	0 (0)
Intervertebral disc protrusion	4 (2.8)	2 (3)
Gastrointestinal disorder	3 (2.1)	2 (3)
Application site irritation	3 (2.1)	1 (1.5)
Application site pruritus	3 (2.1)	1 (1.5)
Ligament injury	3 (2.1)	1 (1.5)

*Differences between groups not significant. AE: Adverse event; SLIT: Sublingual immunotherapy.

frequency of TEAEs diminished, and no severe systemic or anaphylactic AEs or serious AEs related to study medication were observed. Therefore, although it is optimal to start SLIT before the pollen season, our data suggest that in patients who present late (at or after the start of the pollen season) to their practitioner SLIT is well tolerated, without the risk of anaphylaxis.

The patients had to document adverse effects in a 2-week interval in their diaries. This may have lead to a recall bias, but it has been shown for symptom scores in allergic rhinitis that a retrospective documentation may overestimate effects but is still sensitive enough for discrimination [20]. We are thus confident that the data support our conclusions.

Previously we have shown that both IgE and IgG4 levels increased markedly in the first season of SLIT and IgE decreased thereafter [15]. By comparison, both markers remained constant in patients receiving placebo. These data are in agreement with current understanding of mechanisms underlying immunotherapy, suggesting that efficacy is at least partially due to the downregulation of IgE-mediated signalling pathways in inflammatory cells, which occur after repeated application of allergens. The time pattern of IgE levels in the treatment groups appears to be similar to the time pattern of side effects. It remains to be evaluated whether the decrease in the number of TEAEs over consecutive years is caused by induction of hypo-responsiveness through IgG4-mediated desensitisation.

This study is part of growing evidence suggesting that a long build-up phase of SLIT is not necessary. The rationale underlying the long build-up phase resulted from the risk factors for systemic reactions associated with SCIT, and included extremely high sensitivity, co-seasonal allergen exposure, a history of previous systemic reactions and the presence of bronchial asthma [21,22]. To avoid induction during co-seasonal allergen exposure, treatment of pollen allergies with SCIT, and by default SLIT, is currently initiated before the expected start of the pollen season. At least for SLIT, the rationale for a long build-up phase is not based on appropriate data. Nonetheless, an increased risk for systemic adverse reactions when starting SLIT without titration [23] cannot be discarded, as shown recently when two cases of anaphylactic reactions were reported after the first dose of grass pollen SLIT [24].

Due to the small number of children recruited (n = 11), this study cannot give further insight into the safety in

Table 3. Summary of TEAEs reported during the 3-year treatment period.

TEAEs	Patients with AE (n (%))		p Value
	SLIT (n = 142)	Placebo (n = 67)	
Number of patients with any TEAE*	55 (36.6)	27 (40.3)	0.65
First year	33 (23.2)	16 (23.9)	1
Second year	22 (15.5)	12 (17.9)	0.69
Third year	12 (8.5)	7 (10.4)	0.62
Number of patients with any local reaction	8 (5.6)	0 (0)	0.06
First year	7 (4.9)	0 (0)	0.09
Second year	1 (0.7)	0 (0)	1
Third year	0 (0)	0 (0)	-
Number of patients with any gastrointestinal reaction	1 (0.7)	1 (1.5)	0.54
First year	1 (0.7)	0 (0)	1
Second year	0 (0)	1 (1.5)	0.32
Third year	0 (0)	0 (0)	-
Number of patients with any skin reaction	2 (1.4)	4 (6)	0.08
First year	1 (0.7)	0 (0)	1
Second year	1 (0.7)	3 (4.5)	0.1
Third year	0 (0)	1 (1.5)	0.32

*All TEAEs including, but not limited to, local, gastrointestinal and skin reactions. AE: Adverse event; SLIT: Sublingual immunotherapy; TEAE: Treatment-emergent adverse event.

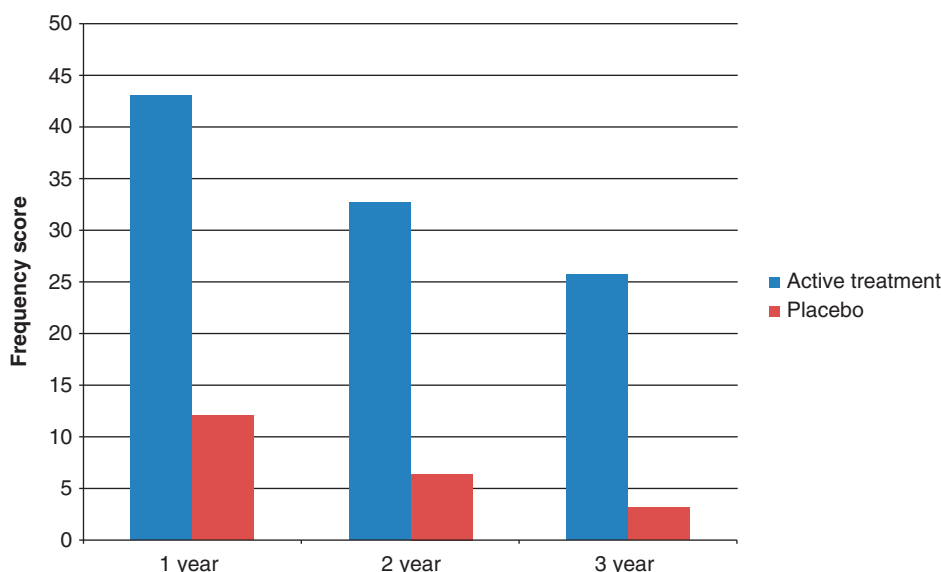


Figure 1. Frequency sum score for local side effects self-assessed by patients in their diary over the consecutive treatment seasons. Frequency score (documented on all 14 days during the pollen season): 0 = never, 1 = on 1 – 4 days, 2 = on 5 – 8 days, 3 = on 9 – 12 days, 4 = nearly every day, 5 = every day.

this age group beyond that already provided by existing studies [25,26].

In conclusion, SLIT with a standardised grass pollen extract was well tolerated when administered during pollen exposure. Even with a rushed titration the treatment was well tolerated, and with each consecutive year of treatment the frequency and intensity of TEAEs decreased. The safety profile of seasonal treatment with ultra-rush titration was comparable to that of

standard SLIT, as shown in meta-analyses [9,27], and also for seasonal SLIT.

5. Conclusion

Seasonal SLIT with ultra-rush titration is well tolerated even when administered as co-seasonal treatment. It may be a valuable option for patients who present late.

Declaration of interest

This study was sponsored by Stallergenes GmbH, Germany. J Sieber is an employee of Stallergenes GmbH. M Neis

declares no conflict of interest. The remaining authors have been speakers or consultants or have received research or other funding from several pharmaceutical companies including Stallergenes.

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