

Short communication

Safety and tolerability of grass pollen tablets in sublingual immunotherapy – a phase-1 study

Background: A single-centre, randomized, double-blind, placebo-controlled study.

Aims: To compare the safety and tolerability of four different sublingual immunotherapy (SLIT) regimes in grass pollen allergic rhinitis.

Methods: Thirty subjects sensitized to grass pollen were enrolled and allocated to four groups. Sublingual immunotherapy was administered in tablets daily for 10 days. Groups 1 and 2 received incremental sublingual doses of 100, 200, 300, 400 and 500 IR, Group 1 daily and Group 2 increments every second day. Repeated constant dose regimens of 300 IR and 500 IR were administered in Groups 3 and 4 respectively. Safety assessments included adverse events (AE), vital signs, electrocardiogram (ECG) and clinical laboratory tests.

Results: Sublingual immunotherapy 300 IR (Group 3) administered in a constant dose and incremental doses up to 500 IR (Groups 1 and 2) were generally well tolerated. The majority of AEs were mild to moderate, the most common being oral pruritus, throat irritation and swollen tongue. Severe local AEs (swelling of throat) were observed only for Group 4. No serious systemic AEs were reported. There were no relevant changes in clinical laboratory, vital signs and ECG data.

Conclusion: Adverse events were mostly local (sublingual), were not severe and resolved rapidly. Using a 5-day induction regimen high-dose treatment up to 500 IR could be administered without important side-effects, in contrast to initiating with a constant dose of 500 IR. The data indicate that a short dose increase phase may reduce the incidence of AEs when high-dose SLIT is administered.

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The prevalence of allergic diseases is increasing to almost 25% of the population. Allergic rhinitis is the most frequently observed allergic disease, and the risk of developing asthma is three times higher in patients with rhinitis than among the general population. The clinical efficacy of conventional subcutaneous immunotherapy (SCIT) is well documented (1), but the risk of severe systemic side-effects has lead to a search for safer forms of immunotherapy, e.g. sublingual immunotherapy (SLIT). In a report analysing the frequency of systemic side-effects during SLIT, most reactions were mild and transient requiring either no or minimal symptomatic treatment (2). Adverse events (AEs) include oral/sublingual itching or swollen lips/tongue and rarely mild, self-limiting abdominal pain. The safety of SLIT was reported in eight European double-blind, placebo-controlled trials, in which 357 were treated with active allergens and 343 received placebo. Different allergens were used, the length of maintenance treatment ranged from 4 months to 2 years. 145 AEs were reported in the treatment group vs 79 in the placebo group. Neither

serious adverse events (SAEs) nor anaphylactic reactions were recorded (3). Sublingual immunotherapy is considered a viable alternative to SCIT by the EAACI position paper (2), WHO (4) and ARIA position paper (5) based upon the clinical efficacy of SLIT studies with, e.g. grass pollen (6). In a randomized, placebo-controlled study it was concluded that side-effects were fewer during SLIT treatment and that the efficacy of SLIT and SCIT was not statistically different (7). Moreover, a reduced induction phase, using the rush-protocol, has been reported to be safe (8, 9). The purpose of the present study was to investigate the safety of high-dose SLIT without a dose-escalation phase.

Material and methods

Patients

Thirty patients aged 18–50 years allergic to grass pollen and otherwise healthy were enrolled (Table 1). The diagnosis of grass pollen

Table 1. Demographic characteristics of patients included in the trial

	Immunotherapy (Group 1)	Group 2	Group 3	Group 4	Placebo
Patients	6	6	6	5	7
Sex					
Male	4	4	3	4	3
Female	2	2	3	1	4
Age (years)					
Mean $\pm$ SD	33 $\pm$ 9	30 $\pm$ 11	30 $\pm$ 4	27 $\pm$ 6	29 $\pm$ 7
Range	23–44	20–47	27–37	20–35	22–43
Duration of rhinitis (mean; years)	22	13	15	13	18
Grass pollen skin test – wheal, mm (mean $\pm$ SD)	8.2 $\pm$ 2.6	8.3 $\pm$ 2.4	8.6 $\pm$ 2.2	7.7 $\pm$ 2.2	6.1 $\pm$ 2
Specific immunoglobulin (Ig)E to grass pollen (mean)	8.1	41.1	39.7	19.5	14.1

allergy was based on clinical history, positive skin prick test (wheal diameter ≥ 3 mm) to a standardized pollen extract and serum-specific immunoglobulin (Ig)E levels > 0.7 kIU/l.

Exclusion criteria were important past or present disease, history of life-threatening asthma, oral steroids within 12 weeks of screening and immunotherapy with grass pollen within the last 5 years.

All patients gave their written informed consent to participate in the study, which was conducted according to the International Conference on Harmonisation (ICH) guidelines on good clinical practice (GCP) and approved by the local Ethics Committee.

Allergen extracts

A mixture of five grass pollen allergens (*Anthoxanthum odoratum*, *Dactylis glomerata*, *Lolium perenne*, *Phleum pratense*, *Poa pratensis*) from Stallergènes (Antony, France), was used. Sublingual immunotherapy tablets containing freeze-dried allergen extracts of five grasses of the strengths 100, 300 and 500 IR together with matching placebo were used for the study.

Immunotherapy

Thirty-five patients were screened and 30 patients were included and sequentially allocated to four groups. Within Groups 1 and 2, two subjects were randomized to receive placebo and six to receive SLIT. In Group 3, one subject received placebo and six received SLIT, in Group 4 two subjects received placebo and five had active treatment. The treatment was administered double-blinded. The study run for 2 weeks omitting treatment in the weekends (10 treatment days in total). Group 1 received incremental doses, repeating each of the concentrations 100, 200, 300, 400 and 500 IR for 2 days or 10 single doses of placebo. Group 2 received single daily incremental doses of 100, 200, 300, 400 and 500 IR and then a further five doses of 500 IR or 10 single doses of placebo. Groups 3 and 4 received 10 single sublingual doses of 300 IR or 500 IR, respectively, or 10 single doses of placebo.

After the inclusion visit subjects visited the investigational site 10 times for treatment and once for follow up 5–10 days after the last dose.

Immunological measurements

Skin tests were performed in duplicates at screening and at follow up, with a standard panel of 10 allergens from ALK-Abelló (Hørsholm, Denmark). Skin reactions were recorded after 15 min (10).

Allergen-specific IgE (Pharmacia CAP system, Uppsala, Sweden) towards standard panel allergens and allergen-specific IgG1 and IgG4 were performed at screening and follow up (11).

Safety and compliance

Safety assessments included physical examinations, 12-lead electrocardiogram (ECGs), pregnancy tests and conventional laboratory tests.

Adverse Events were reported focusing on the date of onset, occurrence, duration, intensity, action taken, outcome and relationship to study drug. The definition and grading of allergic side-effects was according to WHO (4).

Compliance with treatment was evaluated by intake of tablets surveyed by the investigators.

Statistical analysis

Descriptive statistics were performed for all safety and tolerability data as well as for levels of IgE, IgG and response to skin prick tests.

Results

Thirty adult patients were included (see Table 1), two patients were withdrawn because of AEs, treatment compliance was good for all patients.

Safety results

Ninety-one AEs were reported during treatment, 85 in the four SLIT groups and six in the placebo group (Fig. 1). Adverse events were considered local if they occurred in oropharynx and systemic if they occurred in the eyes, nose, stomach or on the skin. Except for two AEs, all were considered allergy-like and considered possibly related to treatment. The AEs most often occurred on the first treatment day.

Group 1 had 29 AEs. Six subjects receiving SLIT had AEs of mild intensity, three also of moderate intensity. One subject receiving placebo had AEs of mild intensity (Fig. 2, Group 1). *Group 2* had 26 AEs in the SLIT group. All of the six subjects had mild intensity AEs, two also

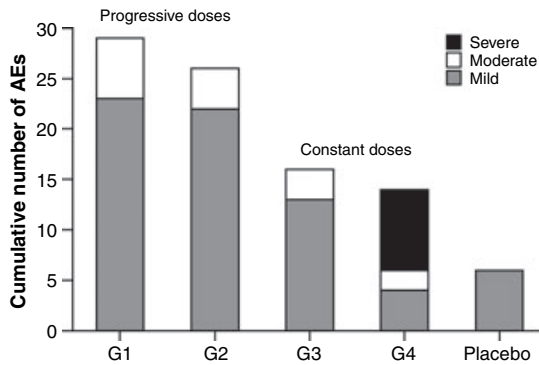


Figure 1. Distribution of adverse events related to treatment group and intervention (G1–4 = actively treated groups). Adverse events are graded in severity as severe, moderate or mild according to the protocol.

had moderate intensity AEs (Fig. 2, Group 2). Group 3 had 16 AEs in the SLIT group. All four subjects had AEs of mild intensity, two also of moderate intensity. The

most common mild intensity AEs were oral pruritus, throat irritation and swollen tongue occurring immediately after administration of SLIT and resolving spontaneously before the next administration of SLIT. The most common moderate intensity AEs were pruritus, eye redness, swelling face, dry throat, throat irritation, oral pain and fatigue (Fig. 2, Group 3).

Group 4 had 14 AEs in actively treated patients. All six subjects experienced mild intensity AEs, two subjects receiving SLIT also had moderate intensity AEs and two subjects receiving SLIT had a total of eight severe intensity AEs. Thus, Group 4 was the only group presenting AEs of severe intensity. Subject 028 was withdrawn because of a mild common cold on day 10, unrelated to treatment. However, this subject also reported severe intensity AEs related to treatment, occurring intermittently over 7–8 days and resolving without intervention. Subject 031 was withdrawn on day 3 because of a severe intensity local AE being throat irritation, oropharyngeal swelling, ear pruritus, swollen tongue and tongue blistering occurring about

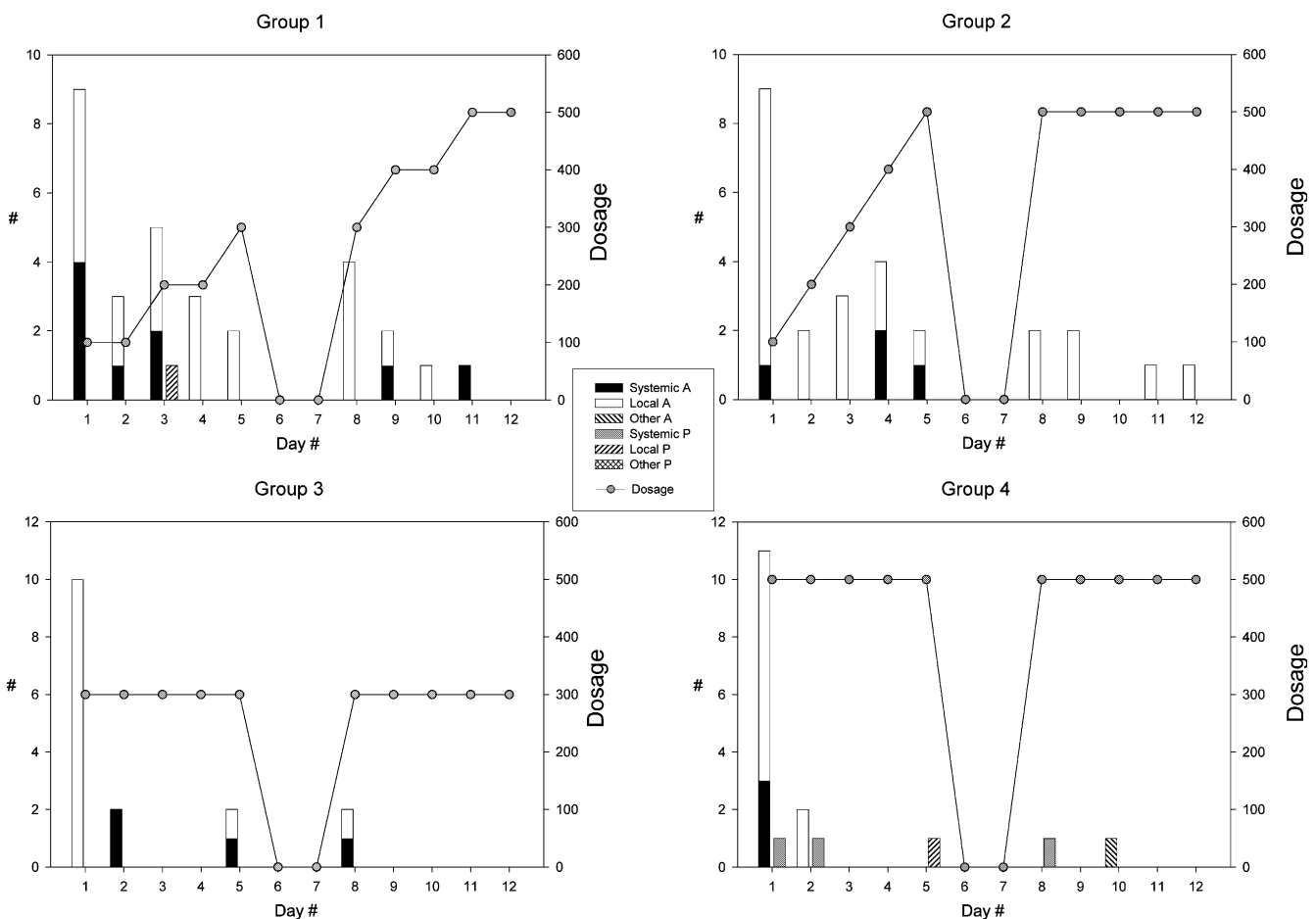


Figure 2. The bars show the distribution of adverse events (AE) in each treatment group related to allergen extract dosing (or placebo). Adverse events are subdivided in local AE, systemic AE and other AE showing the relationship to active or placebo treatment. The dots indicate the allergen dosing for actively treated patients.

5 min after treatment and requiring treatment with 50 mg prednisolone and 180 mg fexofenadine hydrochloride to relieve postdose swelling of the tongue. The AE resolved after 13 h (Fig. 2, Group 4).

Pharmacodynamic results

Specific IgE. There were no significant differences at screening and follow up and no obvious relationship with treatment groups.

Immunological markers. There was no consistent pattern comparing active and placebo treatment for each group, to suggests a drug effect on IgG1 or IgG4 measurements from the predose to postdose samples.

Skin tests and other data

There was no obvious change in skin prick test size with any of the allergens in any of the treatment groups at screening and at follow up. There were no relevant changes in clinical laboratory, vital signs and ECG data.

Discussion

During the last few years sublingual tablet or spray-under-the-tongue immunotherapy (SLIT) has been investigated. It has been shown that the side-effects are fewer

using SLIT, even when using rush-therapy with a reduced induction phase, and the clinical effect is not statistically different from the effect of SCIT.

The present study confirms the safety of SLIT treatment even when using a very short induction phase. In this study SLIT administered up to and including a dose of 300 IR daily for 10 days was generally well tolerated. Adverse events were most common at the site of administration (sublingual), and resolved rapidly without intervention. No SAEs were reported. Most reactions were mild, AEs of severe intensity only occurred in the group receiving a constant dose of 500 IR leading to rescue treatment and withdrawal of one patient. Except a common cold, all AEs were considered allergy-like and possibly related to treatment. The AEs mostly occurred on the first treatment days indicating some kind of adaption.

Using a 5-day induction regimen high-dose treatment of 500 IR could be administered without important side-effects in contrast to initiating treatment using a constant dosing of 500 IR. The data indicate that a short dose-escalation phase may reduce the incidence of AEs when high-dose SLIT is administered.

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