

Once Daily Sublingual Immunotherapy without Updosing – A New Treatment Schedule

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Key Words

Allergy · Asthma · Immunotherapy · Rhinitis · Sublingual immunotherapy · Tolerability · Updosing

Abstract

Background: Treatment regimens with specific immunotherapy include updosing. Due to excellent tolerance of sublingual immunotherapy (SLIT), it was hypothesized that administration of once-daily SLIT could be initiated safely without updosing. The objective was to evaluate tolerability of SLIT administered once daily without updosing. **Methods:** 135 patients suffering from allergic rhinitis with/without asthma were included in a double-blind, placebo-controlled, parallel-group study. Patients were randomized into two groups. Group 1 (n = 69) received active treatment throughout the study, including 10 days updosing (T1), 20 days maintenance treatment (T2), and 2 consecutive months on maintenance treatment (T3 and T4). Group 2 (n = 66) obtained placebo updosing (T1), placebo maintenance (T2), initiated active treatment (maintenance) at T3, and continued active treatment until the end of the study (T4). Adverse events (AEs) were assessed at T1–T4. 66 grass- and 69 mite-allergic patients were evenly distributed between groups. **Results:** 229 AEs were reported, 157 AEs were related to treatment. The most frequently reported AEs (>5% of patients in any

group) related to treatment were oral itching, ocular itching, rhinitis, and sublingual edema. For group 1 at T2, the rate of all AEs related to treatment per dose administered was 1.79%, and for group 2 at T3 the rate was 1.33% (p = 0.37). For the most frequently reported AE, oral itching, the rate per dose administered was 1.01% for group 1 at T2, and 0.74% for group 2 at T3 (p = 0.53). **Conclusions:** Once daily SLIT was well tolerated and can be safely initiated without updosing.

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Introduction

During the last years, several clinical studies on sublingual immunotherapy (SLIT) have been performed, and efficacy of this treatment has been evidenced in patients with allergic rhinoconjunctivitis in addition to a favorable safety profile [1]. To achieve a superior effect of a self-administered treatment like once-daily SLIT, patient compliance must be high [2], and given that one of the cornerstones for compliance is convenience [2, 3], it is relevant to improve this particular feature of a product, if possible. Current treatment regimens with specific immunotherapy including sublingual immunotherapy comprise an updosing phase. Due to the excellent tolerance of SLIT, the possibility of eliminating the updosing phase has been

Table 1. Patient characteristics (total n = 135)

	Group 1 (n = 69)	Group 2 (n = 66)
Sex		
Male	38 (55%)	31 (47%)
Female	31 (45%)	35 (53%)
Mean age $\pm$ SD, years	22.6 $\pm$ 11.2	22.1 $\pm$ 9.7
Patients		
$\leq$ 14 years	21 (30%)	19 (29%)
>14 years	48 (70%)	47 (71%)
Diagnosis		
Rhinitis	33 (48%)	32 (48%)
Rhinitis + asthma	36 (52%)	34 (52%)
Withdrawals		
Total	6	6
Related to AEs	3	2
Allergen		
Grasses	33	33
Mites	36	33

taken into consideration. This would improve patient convenience, and may thereby increase compliance. The purpose of this study was to evaluate the tolerability of once-daily SLIT without updosing in patients with allergy to mites or grasses.

Patients and Methods

Patients

A total of 135 patients were included (66 grass- and 69 mite-allergic patients), aged between 7 and 55 years, all diagnosed with moderate-severe rhinitis or rhinoconjunctivitis with/without asthma symptoms, due to sensitivity to either mites or grasses. The diagnosis was made by a positive skin prick test (prick test, ALK-Abelló, S.A., 100 BU/ml) and/or positive IgE (CAP $\geq$ IgE class 2). In accordance with WHO recommendations [4], the trial excluded patients where treatment with immunotherapy was contraindicated, those sensitive to allergens other than those evaluated in the trial, and those who had received immunotherapy previously.

Study Design

The study was a randomized, multicenter, double-blind, placebo-controlled, parallel-group study. The total duration was 100 days. Patients were randomly allocated to two groups. Group 1 (n = 69) received active treatment throughout the study. This included 10 days updosing (T1), 20 days maintenance treatment (T2), and two consecutive periods of 1 month duration each (T3 and T4) on maintenance treatment. Group 2 (n = 66) received placebo updosing during T1, placebo maintenance during T2, and active treatment (at maintenance dose) at the beginning of T3 and continued active treatment until the end of the study (T4). Data

were collected at baseline and at T1–T4. Each patient received a card where any clinical incidents related to each treatment dose were noted. The investigator noted the adverse events on the case report forms.

The study was double-blind, and the blinding was not broken at any time until completion of the study. All patients signed an informed consent form before commencing their participation in the trial. The study was approved by all the ethics committees of the participating centers, as well as the health authorities, and was conducted in accordance with the principles expressed in the Declaration of Helsinki.

Treatment

Once-daily SLIT (SLITone®; ALK-Abelló, Madrid, Spain) was administered sublingually and composed of either mite extract (*Dermatophagoides pteronyssinus* or *Dermatophagoides pteronyssinus* + *Dermatophagoides farinae*) or an extract of a grass mixture (*Dactylis glomerata*, *Festuca pratensis*, *Lolium perenne*, *Phleum pratense*, *Poa pratensis* or *Secale cereale*). Treatment consisted of 10 days updosing with a multidose vial (beginning with 1 drop and increasing to 10 drops) and a maintenance phase with monodose containers. Administration was once daily. The dose of the major allergens administered in each monodose container was 2 μ g of major allergen 5 (for grasses) and 0.8/0.4 μ g of Der 1/Der 2 (for mites).

The appearance, smell, and taste of the placebo treatment were similar to the active treatment.

Statistics

Descriptive statistics was used for the number of patients reporting AEs, the percentage of patients experiencing AEs, and the number of AEs. The difference between groups in the rate of AEs (%) as well as in the rate of oral itching (%) per dose administered were evaluated by testing the null hypothesis $\text{Rate}_{\text{Group1}} = \text{Rate}_{\text{Group2}}$ by a Pearson χ^2 test with continuity correction. Analysis were performed using S-PLUS 6.2.

Results

Of the 135 patients included, 123 completed the study. Patient characteristics are shown in table 1. The age of the patients ranged from 7 to 55 years, with a mean age of 22 in both treatment groups. In group 1, 36 patients received grass extract and 33 received mite extract compared to 33 receiving grass extract and 33 receiving mite extract in group 2.

A schematic overview of the study design is shown in table 2. A total of 229 AEs were reported, and 157 AEs (69 and 88, in group 1 and 2, respectively) were related to treatment by the investigator and included in the analysis. The most frequently reported AEs (>5% of patients in any group) related to treatment were oral itching, ocular itching, rhinitis, and sublingual edema (table 3), totally accounting for 57.3% of all related AEs. Oral itching was the most frequently reported AE related to treatment: 16 pa-

Table 2. Schematic overview of the study design

	T1 10 days	T2 20 days	T3 1 month	T4 1 month
Group 1 n = 69	SLIT updosing	SLIT maintenance	SLIT maintenance	SLIT maintenance
Group 2 n = 66	Placebo updosing	Placebo maintenance	SLIT maintenance	SLIT maintenance

Data were collected at baseline and after T1, T2, T3, and T4.

tients (23.2%) reported 28 events of oral itching in group 1 compared to 21 patients (31.8%) reporting 39 events of oral itching in group 2. Oral itching was the only AE that was reported by >10% of patients in any group and as a total accounted for 42.7% of all events.

The total number of SLIT doses administered was 6,258 and 6,081 in group 1 and 2, respectively. The treatment intervals T1–T4 had different durations. In order to compare the number of AEs between groups and across time intervals, a relative expression of how frequent AEs occur was calculated, i.e. the rate (%) of adverse events per dose administered. This allows a comparison across time intervals between groups, in spite of time intervals being different in duration.

The rate of all AEs related to treatment per dose administered by time (T1–T4) is shown in table 4. For group 1 at T2, the rate was 1.79% and for group 2 at T3, the rate was 1.33% ($p = 0.37$). The rate of oral itching per dose administered by time (T1–T4) is shown in table 5. For group 1 at T2, the rate was 1.01% and for group 2 at T3, the rate was 0.74% ($p = 0.53$).

The breakdown of the most frequently reported AEs related to treatment indicates that more patients suffering from grass allergy experienced oral itching and sublingual edema than patients suffering from mite allergy (table 6), whereas the opposite was the case with ocular itching and rhinitis.

The most frequently reported AEs related to treatment for patients ≤ 14 years (children) and for patients >14 years (adolescents and adults) are shown in table 7.

A total of 5 patients withdrew due to AEs. In group 1, 3 subjects withdrew due to headache at T1; asthma, rhinitis and pruritus at T1, and sublingual edema at T4, respectively. In group 2, 2 subjects withdrew due to dyspnea and cough at T2, and tongue and mouth edema at T4, respectively.

Table 3. Most frequently reported AEs (>5% in any group) related to treatment (total n = 135)

	Group 1, n = 69			Group 2, n = 66		
	n	%	E	n	%	E
Oral itching						
T1	4	5.9	5	8	12.1	8
T2	12	18.2	13	5	7.6	6
T3	5	7.7	5	13	20.6	15
T4	5	7.8	5	9	14.8	10
Total	16	23.2	28	21	31.8	39
Ocular itching						
T1	4	5.9	4	1	1.5	1
T2	1	1.5	1	0	0.0	0
T3	0	0.0	0	1	1.6	1
T4	0	0.0	0	0	0.0	0
Total	5	7.2	5	1	1.5	2
Rhinitis						
T1	1	1.5	1	1	1.5	1
T2	0	0.0	0	1	1.5	3
T3	1	1.5	1	0	0.0	0
T4	0	0.0	0	1	1.6	1
Total	2	2.9	2	4	6.1	5
Sublingual edema						
T1	0	0.0	0	0	0.0	0
T2	0	0.0	0	0	0.0	0
T3	1	1.5	1	3	4.8	3
T4	1	1.7	1	4	6.6	4
Total	1	1.4	2	4	6.1	7

The number of patients (n) reporting the most frequently reported AEs (>5% of patients in any group), the percentage of the group population (%), the number of events (E), and the time of reporting in both treatment groups. Group 1 received active treatment from T1–T4, group 2 received placebo during T1 and T2. Total number of patients is corrected for patients repeatedly reporting the same type of AEs.

Discussion

The purpose of this randomized, double-blind, placebo-controlled, parallel-group study was to investigate the tolerability of once-daily SLIT administered without an initial updosing phase. The results presented here indicate that once-daily SLIT (grasses and mites) is well tolerated, and that tolerance is not influenced by omission of the updosing phase. Overall the number of patients reporting AEs was slightly higher in group 2 (receiving placebo updosing) compared to group 1 (receiving active updosing), and so was the number of events. However, in this study,

Table 4. Rate of all treatment-related AEs (%) per dose administered by time of reporting

Time	Group 1			Group 2			Pearson χ^2 test T2, group 1 vs. T3, group 2
	E	doses administered	rate %	E	doses administered	rate %	
T1	27	875	3.09	20	811	2.47	0.37
T2	23	1,288	1.79	22	1,238	1.78	
T3	11	2,039	0.54	27	2,027	1.33	
T4	7	2,056	0.34	19	2,005	0.95	
Total	69	6,258	1.10	88	6,081	1.45	

E = Number of AEs related to treatment.

Table 5. Rate of oral itching (%) per dose administered by time of reporting

Time	Group 1			Group 2			Pearson χ^2 test T2, group 1 vs. T3, group 2
	E	doses administered	rate %	E	doses administered	rate %	
T1	5	875	0.57	8	811	0.99	0.53
T2	13	1,288	1.01	6	1,238	0.48	
T3	5	2,039	0.25	15	2,027	0.74	
T4	5	2,056	0.24	10	2,005	0.50	
Total	28	6,258	0.45	39	6,081	0.64	

E = Number of events of oral itching.

Table 6. Most frequently reported AEs (>5% in any group) by allergen

Total, n = 135	Mites						Grasses					
	group 1, n = 36			group 2, n = 33			group 1, n = 33			group 2, n = 33		
	n	%	E	n	%	E	n	%	E	n	%	E
Oral itching	2	5.6	2	5	15.2	6	14	42.4	26	16	48.5	33
Ocular itching	3	8.3	3	0	0.0	0	2	6.1	2	1	3.0	2
Rhinitis	1	2.8	1	3	9.1	4	1	3.0	1	1	3.0	1
Sublingual edema	0	0.0	0	1	3.0	1	1	3.0	2	3	9.1	6

The number of patients (n) reporting the most frequently reported AEs (>5% of patients in any group), the percentage of the group population of mite- or grass-allergic patients (%), and the number of events (E) by allergen in group 1 and 2, respectively.

the higher absolute number of AEs in group 2 compared to group 1 does not appear to lead to an increased number of withdrawals, nor were more serious AEs reported in group 2 compared to group 1. A substantial number of events were reported during the placebo treatment (T1

and T2). The most frequently reported AE was oral itching. Oral itching is an expected and well-known side effect of sublingual immunotherapy, and has been reported to the same extent or more frequently by other authors [5–8].

Table 7. Number of patients with the most frequently reported AEs related to treatment by age

	Group 1			Group 2		
	n	%	E	n	%	E
≤ 14 years	21					
Oral itching	8	38.1	15	8	42.1	17
Ocular itching	1	4.8	1	1	5.3	2
Rhinitis	2	9.5	2	3	15.8	3
Sublingual edema	0	0.0	0	2	10.5	4
>14 years	48			47		
Oral itching	8	16.7	13	13	27.7	22
Ocular itching	4	8.3	4	0	0.0	0
Rhinitis	0	0.0	0	1	2.1	2
Sublingual edema	1	2.1	2	2	4.3	3

Number of patients, the percentage of the group population (%), and the number of events (E) with the most frequently reported AE in total related to treatment by age.

The use of updosing in SLIT is empirical, based on tradition, and is probably adapted from the necessary step-wise dose increase used in subcutaneous immunotherapy. Data from previous clinical trials [5, 7] and pharmacovigilance studies [8] indicate excellent tolerance of SLIT, but it was not until recently that the impact of the updosing phase on tolerability was put up for discussion. The possible impact of updosing in SLIT is speculative. Assuming that the effect of updosing in SLIT is for the patient to be able to administer the maintenance dose safely after updosing, the data presented here prove this hypothesis to be wrong. The number of patients in group 2 reporting oral itching at T3 (when active treatment was initiated as maintenance dose) was higher than in group 1 at T1, but it was similar to the number of patients in group 1 reporting oral itching at T2, at which time the hypothesized effect of the updosing phase on the patient's tolerability warranted a lower number. Thus, when comparing the rate of all AEs related to treatment per administered dose (T2, group 1 vs. T3, group 2), there was no difference between groups. This result was confirmed when the most frequently reported AE related to treatment (oral itching) was tested statistically. Due to the short duration of this study, any firm conclusions cannot be drawn on whether or not reporting of oral itching will decline over time. However, the relatively few withdrawals observed indicate that the patients did not consider the intensity and duration of oral itching bothersome.

Sublingual edema was reported more frequently in group 2 than in group 1. In group 2, this type of event was reported when active treatment was administered (T3 and T4), and resolved within 1 h to 3 days. One patient withdrew from the study due to this AE at T4 after a minimum of 30 days active treatment. Sublingual edema was also reported in group 1 at T4.

When comparing oral itching in children to that in adolescents and adults, it appears from the data that oral itching is reported more frequently in children than in adolescents and adults. The reasons for this are not apparent, but it remains a topic for further investigation. However, the number of withdrawals among children was not different from that of adolescents and adults. Furthermore, the withdrawals among children (n = 2) were not related to oral itching.

Among grass-allergic patients, the number of treatment-related AEs reported was higher compared to patients being allergic to mites. In particular oral itching occurred more often in grass-allergic patients compared to mite-allergic patients. Smaller differences between allergen subgroups were also found for rhinitis and sublingual edema, which were more common with grasses. All the four most frequently reported AEs (>5% in any group) were represented in both allergen subgroups.

In conclusion, these study results indicate that once-daily SLIT (mites and grasses) is well tolerated. The clinical implication of these results is that once-daily SLIT treatment can be initiated safely without an updosing phase.

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References

- 1 Wilson DR, Torres LM, Durham SR: Sublingual immunotherapy for allergic rhinitis: systematic review and meta-analysis. *Allergy* 2005;60:4–12.
- 2 Osterberg L, Blaschke T: Adherence to medication. *N Engl J Med* 2005;353:487–497.
- 3 Blaiss M: Current concepts and therapeutic strategies for allergic rhinitis in school-age children. *Clin Ther* 2004;26:1876–1889.
- 4 Bousquet J, Lockey RF, Malling HJ: WHO Position Paper. Allergen immunotherapy: therapeutic vaccines for allergic diseases. *Allergy* 1998;53:1–42.
- 5 Pajno GB, Morabito L, Barberio G, Parmiani S: Clinical and immunologic effects of long-term sublingual immunotherapy in asthmatic children sensitized to mites: a double-blind, placebo-controlled study. *Allergy* 2000;55:842–849.
- 6 Canonica GW, Passalacqua G: Noninjection routes for immunotherapy. *J Allergy Clin Immunol* 2003;111:437–448.
- 7 Quirino T, Iemoli E, Siciliani E, Parmiani S, Milazzo F: Sublingual versus injective immunotherapy in grass pollen allergic patients: a double blind (double dummy) study. *Clin Exp Allergy* 1996;26:1253–1261.
- 8 Di Rienzo V, Pagani A, Parmiani S, Passalacqua G, Canonica GW: Post-marketing surveillance study on the safety of sublingual immunotherapy in pediatric patients. *Allergy* 1999;54:1110–1113.