A first-in-human phase 2 dose-finding trial with grass pollen allergoids coupled to mannan in subcutaneous and sublingual immunotherapy. 1. Evaluation of safety.

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Introduction

Allergoids conjugated to non-oxidized mannan are novel vaccines for allergen-specific immunotherapy with reduced allergenic activity. These preparations have at least a 95% reduction in specific-IgE binding capacity, providing the chance for administering high doses with a decreased risk of systemic reactions.

We have evaluated the safety of mannan-allergoid conjugates of grass pollen (mixture of *Phleum pratense* and *Dactylis glomerata*) in a dose-finding study conducted to evaluate safety and to find the optimal dose for subcutaneous (SC) and sublingual (SL) routes of administration.

Methods

The study (EudraCT: 2014-005471-88) was multicentre, randomized, double-blind, double-dummy and placebo-controlled. The duration was 4 months per subject. Four concentrations (500, 1,000, 3,000 and 5,000 mTU/mL) of these mannan-allergoid conjugates (Inmunotek, Spain) were used for SL and SC administration.

The SL administration was 2 puffs (100 µL/puff) of spray daily and the SC administration was 0.2mL+0.3mL for the first day followed by 0.5 mL monthly for 4 months (Figure 1).

Subjects sensitized to grass pollens were randomly allocated into 9 groups. Four groups received different concentrations of SL active preparation and SC placebo. The other 4 groups received different SC active preparations and SL placebo. One group received SL and SC placebo (Figure 1). Subjects who received at least one dose of treatment were eligible for safety evaluation were 162. Safety was assessed by recording all side reactions related to immunotherapy. These reactions were graded according to the criteria of the EAACI [1]:

- Grade 0: No symptoms or nonspecific symptoms. Symptoms: Localized urticaria, rhinitis or mild asthma (PF < 20% decrease from baseline).
- Grade I: Mild systemic reactions. Symptoms: Localized urticaria, rhinitis or mild asthma.
- Grade II: Moderate systemic reactions. Symptoms: Slow onset (>15 min) of generalized urticaria and/or moderate asthma.
- Grade III: Severe (non-life-threatening) systemic reactions. Symptoms: Rapid onset (<15 min) of generalized urticaria, angioedema, or severe asthma
- Grade IV: Anaphylactic shock.

Local reactions were graded as:

- Mild: No interfere with the patient´s daily activities and was not clinically relevant.
- Moderate: Discomfort but was tolerable.
- Severe: Affected usual daily activities and was clinically relevant.

Results

No systemic reactions of Grade III and IV were reported.

Sublingual administration of active (Table I):

- Local reactions: One subject receiving 3,000 mTU/mL experienced 1 mild immediate.
- Systemic reactions: One grade 0 and one of grade I in two subjects receiving 5,000 mTU/mL.

Subcutaneous administration of active (Table II):

- Local immediate reactions: 1 in one subject receiving 500 mTU/mL, 3 in subjects receiving 5,000 mTU/mL. Local delayed reactions: 2 in subjects receiving 500 mTU/mL, 2 in 1,000 mTU/mL, 14 in 3,000 and 16 in 5,000 mTU/mL.
- Systemic reactions (all delayed): 1 in one subject receiving 500 mTU/mL (grade 0) and 3 in subjects receiving 5,000 mTU/mL (1 of grade 0 and 2 of grade I).

All reactions resolved spontaneously without the need of medication.

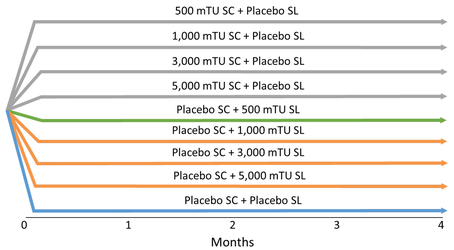

Figure 1. Subject's allocation groups

Table I. Adverse reactions reported with the active sublingual route

mTU/mL	n	Reaction	Onset	Evaluation
3,000	1	Local	Immediate	Mild
5,000	1*	Systemic	Delayed	Grade 1
5,000	1**	Systemic	Delayed	Grade 0

*: mild rhinitis

**: discomfort

Table II. Adverse reactions reported with the active subcutaneous route

		Local				Systemic			
		Mild		Moderate		Grade 0		Grade I	
mTU/mL	Onset	n	%*	n*	%	n	%*	n*	%
500	Immediate	1	0.79%	0	0.00%	0	0.00%	0	0.00%
	Delayed	2	1.59%	0	0.00%	1**	0.79%	0	0.00%
1,000	Immediate	0	0.00%	0	0.00%	0	0.00%	0	0.00%
	Delayed	2	1.59%	0	0.00%	0	0.00%	0	0.00%
3,000	Immediate	0	0.00%	0	0.00%	0	0.00%	0	0.00%
	Delayed	10	7.94%	3	2.38%	0	0.00%	0	0.00%
5,000	Immediate	3	2.38%	0	0.00%	0	0.00%	0	0.00%
	Delayed	11	8.73%	5	3.97%	1**	0.79%	2***	1.59%

*: related to the total number of injections of the corresponding group

**: discomfort

***: one reaction was mild dyspnoea and the other was oral pruritus (this reaction may be attributed to sublingual placebo)

Conclusions

These results indicate excellent tolerability of the sublingual route and a high safety profile of the subcutaneous route of administration.

References

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