A first-in-human phase 2 dose-finding trial with grass pollen allergoids coupled to mannan in subcutaneous and sublingual immunotherapy. 2. Evaluation of efficacy using titrated nasal provocation test.

J. Subiza[1], P. Ojeda[2], C. Barjau[1], I. Ojeda[2], A. Moreno[3], E. Solano[4], A. Alonso[5], A. Orovitg[6], M. Donado[6], J. Ruiz[7], I. Sánchez[8], P. Guardia[9], V. De Luque[9], C. Diéguez[10], A. Caso[11], A. Conde[12], M. Lluch[13], R. Caballero[14], M. Casanovas[14]

[1]Clínica Subiza, Madrid, Spain, [2]Clínica de Asma y Alergia Dres. Ojeda, Madrid, Spain, [3]Clínica Atlas, Aranjuez, Spain, [4]Hospital Universitario Ramón y Cajal, Madrid, Spain, [5]Clínica Alianza Médica, Valladolid, Spain, [6]Hospital Viamed, Sevilla, Spain, [7]Hospital Universitario Infanta Elena, Valdemoro, Spain, [8]Clínica Dermatología y Alergia, Badajoz, Spain, [9]Hospital Universitario Virgen Macarena, Sevilla, Spain, [10]Hospital Universitario 12 de Octubre, Madrid, Spain, [11]Hospital San Agustín, Dos Hermanas, Spain, [12]Hospital Nisa, Sevilla, Spain, [13]Hospital Universitario La Paz, Madrid, Spain, [14]Inmunotek, Alcalá de Henares, Spain.

Introduction

Polymerized allergoids conjugated with non-oxidized mannan (PM) are novel vaccines for allergen immunotherapy (AIT). PM are readily up taken by dendritic cells and promote T-reg cell-induction, which may improve AIT. [1, 2]

A first-in-human dose-finding study was conducted with PM derived from grass pollen (mixture of *Phleum pratense* and *Dactylis glomerata*) (PM grasses) to find the optimal dose for both sublingual (SL) and subcutaneous (SC) routes (EudraCT: 2014-005471-88). The primary outcome was the titrated allergen-specific nasal provocation-test (NPT).

Methods

The study was randomized, multicentre, double-blind, double-dummy and placebo-controlled. The duration was 4 months/subject. Four concentrations (500, 1,000, 3,000 and 5,000 mTU/mL) of PM grasses (Inmunotek, Spain) were evaluated. Subjects randomized who received at least one dose were 162 (mean age: 33 years, range: 14-58). All were sensitized to grass pollen and were randomly allocated in 9 groups (Table I). One group received SC and SL placebo, 4 groups received SC-active and SL-placebo. The remaining groups received SL-active and SC-placebo. SL administration was 2 spray-puffs daily; SC was 0.2mL+0.3mL first day, followed by 0.5 mL/monthly for 4 months.

Titrated NPT with native extract of *Phleum pratense* pollen was assessed by acoustic rhinometry at baseline and at the end of the study. Nasal challenges were initiated with saline as negative control, followed by increasing concentrations (0.3, 1.0 and 3.0 HEP/mL) until a positive response was obtained. Subjects who had NPT at baseline and at the end of the study were 150. Improvement was scored as positive when the allergen concentration needed at the end of the study to achieve a positive NPT was higher, i.e., at least three times, than at baseline.

The Chi-square test was used to compare the number of subjects who experienced improvement in each group with those who experienced improvement in the placebo group.

Results

Subjects experiencing improvement in titrated NPT were: placebo 12%; 500 mTU/mL, 33% SC, 33% SL; 1,000 mTU/mL, 36% SC, 33% SL; 3,000 mTU/mL, 50% SC, 47% SL; 5,000 mTU/mL, 50% SC and 47% SL. (Table I and Figure 1).

Conclusions

PM grasses produced a significant clinical improvement, measured by NPT, after 4 months of treatment, using concentrations of 3,000 and 5,000 mTU/mL, by both SC and SL routes.

References

1.- Sirvent S, Soria I, Cirauqui C, Cases B, Manzano AI, Diez-Rivero CM, et al. Novel vaccines targeting dendritic cells by coupling allergoids to nonoxidized mannan enhance allergen uptake and induce functional regulatory T cells through programmed death ligand 1. J Allergy Clin Immunol 2016; 138:558-567

2.- Benito-Villalvilla C, Soria I, Subiza JL, Palomares O. Novel vaccines targeting dendritic cells by coupling allergoids to mannan. Allergo J Int 2018; 27:256-262

Table I. Group allocation and results of the NPT.

Group	Subjects with improvement	Subjects without improvement	% of subjects with improvement	P (Chi square)
Placebo SC + Placebo SL	2	15	12%	
500 mTU/mL active SC + placebo SL	6	12	33%	0.129
1,000 mTU/mL active SC + placebo SL	5	9	36%	0.113
3,000 mTU/mL active SC + placebo SL	**9**	**9**	**50%**	**0.015**
5,000 mTU/mL active SC + placebo SL	**9**	**9**	**50%**	**0.015**
500 mTU/mL active SL + placebo SC	5	10	33%	0.141
1,000 mTU/mL active SL + placebo SC	6	12	33%	0.129
3,000 mTU/mL active SL + placebo SC	**7**	**8**	**47%**	**0.028**
5,000 mTU/mL active SL + placebo SC	**8**	**9**	**47%**	**0.010**

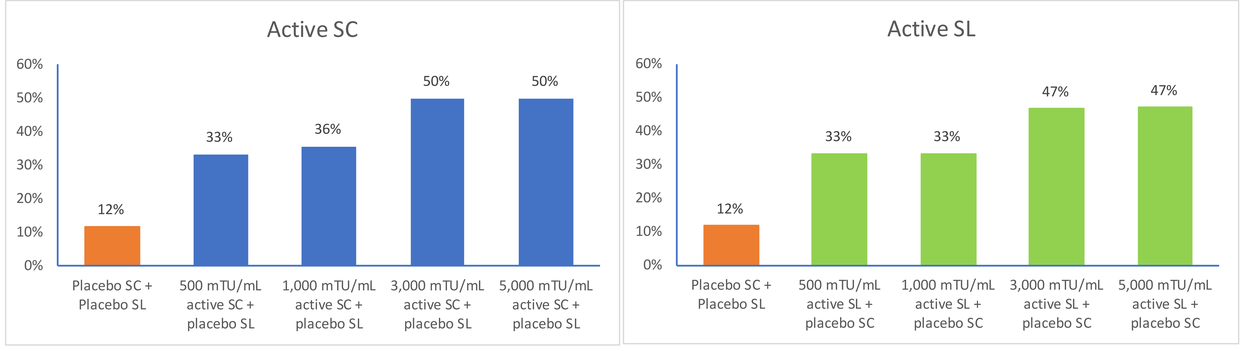

Figure 1. Percentage of subjects who experienced improvement receving placebo (SC and SL), active SC+Placebo SL and Active SL+Placebo SC