

Immunotherapy safety: a prospective multi-centric monitoring study of biologically standardized therapeutic vaccines for allergic diseases

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Summary

Background The fear of side-effects has led to strict regulations preventing a more widespread use of specific immunotherapy (SIT) in some countries, in spite of the low risk of systemic reactions (SRs) reported in well-controlled studies. The goal of the study was to carry out a prospective and multi-centric trial to evaluate the safety, risk factors and compliance degree of commercially available SIT.

Materials and methods The study was carried out in 14 allergy departments from Spain. Four-hundred and eighty-eight patients with rhinitis and/or asthma were submitted to treatment with biologically standardized allergen extracts commercially available. They were administered following the European Academy of Allergy and Clinical Immunology guidelines.

Results Four hundred and twenty-three patients (86.7%) completed the treatment and remained under control at the end of the trial. Out of 17 526 administered doses, 17 368 doses (99.1%) were not associated with a reaction. Eighteen patients (3.7%) experienced 53 (0.3% of the doses) SRs. All immediate SRs were mild or moderate and responded well to ordinary treatment measures. There were no fatal reactions, anaphylactic shock or life-threatening reactions. A higher ratio of SRs was found among asthmatic and dust mite allergic patients, although multi-variable logistic analysis did not demonstrate any risk factor associated with SRs. There was also a subgroup of patients at risk for recurrent reactions, and therefore 40% of SRs had been avoided if the maximal number of SRs had been previously limited to only three SRs.

Conclusions This multi-centric study showed that SIT was a safe treatment with a very good compliance. Future guidelines of SIT should limit the maximal number of SRs.

Keywords asthma, compliance, immunotherapy, mite, pollen, rhinitis, safety, side-effects

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Introduction

Specific immunotherapy (SIT) is an aetiological treatment for allergic diseases, whose clinical efficacy is well documented [1–5]. Nowadays, the most important problem concerning practical SIT is safety [6]. A fatal reaction associated with allergen extracts was first reported by Lamson [7] in 1924 after skin testing in a 5-month-old child with chronic eczema. The risk associated with SIT was not fully appreciated until 1985, when Lockey et al. [8] made a preliminary report and, 2 years later, reported the completed analysis of this study,

comprising 46 fatalities. The fear of side-effects of SIT, mainly fatal reactions, has led to strict regulations preventing a more widespread use of this treatment in some countries (i.e. England). Notwithstanding this, the controlled studies carried out evaluating the SIT safety to date have reported a low risk of systemic side-effects [1, 2]. We believe that it is very important to clarify this point because elucidating the risk of, and possible risk factors for, systemic reactions (SRs) would have a profound effect on the decision of how to manage allergic diseases. Based on these arguments, the aim of the study was to carry out a prospective and multi-centric study to evaluate the safety, risk factors and compliance degree of commercially available SIT.

Materials and methods

Patients

A total of 488 patients (220 females and 268 males) from 14 allergy departments in Spain (Fig. 1) were included in the study. The inclusion period was from April 1996 to April

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Fig 1. Allergy units from Spain taking part in a specific immunotherapy safety multi-centric trial.

1997. The distribution of allergic disease involved rhinitis without asthma in 152 cases (32%) and asthma with or without rhinitis in 336 cases (68%). Mild or moderate bronchial asthma was diagnosed according to Global Initiative for Asthma (GINA) guidelines [9], and allergy to mites or pollen was defined by means of a typical case history and positive skin prick tests and/or specific IgE antibodies in serum samples. The mean age of patients was 20.9 ± 11.2 years, ranging from 5 to 54 years and a median of 18 years.

Immunotherapy

All patients received written information concerning allergen avoidance. The indication and contraindication for SIT followed the recommendations of the European Academy of Allergy and Clinical Immunology (EAACI) guidelines [1]. EAACI guidelines were also followed to monitor patients during allergen extract injection [1]. After each injection, patients were observed by nurses and physicians in the clinic for at least 30 min. Allergen extract dosages, local and SRs, and the treatment of such reactions were registered in a patient record form. The dose was reduced in the case of SRs, unpleasant large delayed local reactions or exceeding intervals between two series of injections. Doses were repeated when immediate local reaction was larger than 5 cm in diameter. Patients presenting with SR were observed and rescue treatment was instituted by a responsible physician, who also graded the SR based on symptoms and the patient's response to rescue treatment.

Biologically standardized allergen extracts commercially available in Europe with depot formulation (adsorbed in aluminium hydroxide or calcium phosphate) were used for SIT. Patients were treated with mite or pollen vaccines, but they were never mixed in the same vaccine. The prescribed allergen extracts are shown in Fig. 2. Biological units used by the manufacturer to standardize allergenic vaccines have been

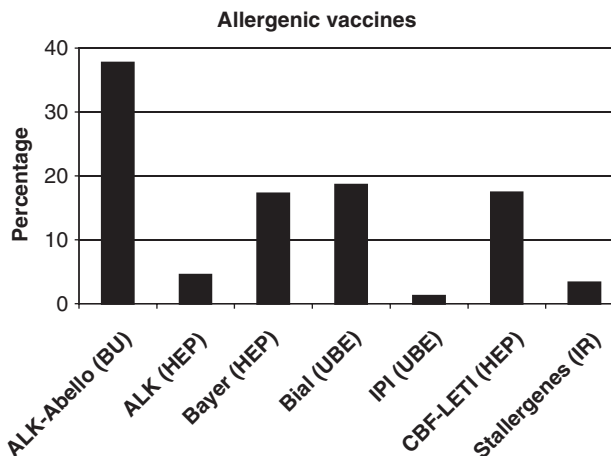


Fig 2. Allergen vaccines and manufacturers. Biological units are expressed in brackets.

previously reported [10]. The buildup phase of SIT was carried out according to conventional schedules provided by the manufacturer. Weekly injections were administered to reach the recommended optimal dose. After that, every patient followed a trial of monthly maintenance injections for 2 years of SIT (a total of 27 months). In the case of the pollen vaccines, a reduction of 50% of maintenance dose was applied during the pollination season. The entire programme of SIT was administered under controlled conditions in clinical settings where experienced nurses injected vaccines, physicians evaluated patients, and safety measures were available.

Side-effect monitoring

SRs were categorized into immediate SRs (occurring within 30 min) and late SRs (debut > 30 min after injection). They were graded according to the EAACI Immunotherapy Position Paper (1):

Grade 0: No symptoms.

Grade I: Non-specific symptoms probably not IgE-mediated, i.e. discomfort, headache, arthralgia, etc.

Grade II: Mild SRs, e.g. mild rhinitis or asthma responding adequately to antihistamines or inhaled β_2 -agonist.

Grade III: Non-life-threatening SRs, e.g. urticaria, angioedema or severe asthma, responding well to treatment.

Grade IV: Anaphylactic shock, e.g. rapidly evoked reaction of itching, flushing, erythema, bronchial obstruction, etc. requiring intensive treatment.

Recording of data

For each of the 488 patients, the following data were recorded: patient's identification number, gender, year of birth, date of treatment start, season, pollination season, disease (rhinitis or asthma), phase of treatment (buildup or maintenance) and whether or not the patients terminated the treatment before reaching the maintenance dose. Only data related to local and SRs were reported in this study.

Adverse reactions were recorded on a form by considering three topics: (a) *quality and severity of reaction* (previously

described); (b) *aggravating circumstances*: current infectious disease, current asthma, recent exposure to responsible allergen, cardiac disease, active treatments with β -blockers or angiotensin-converting enzyme inhibitor drugs, new batches of vaccines and others; and (c) *rescue treatment*: epinephrine, inhaled β -agonists, antihistamines, systemic steroids, oxygen and invasive measures (endotracheal intubation, mechanic ventilation and intensive haemodynamic cares) as well as the further decision about the continuity of the immunotherapy programme: (a) to go on without changes, (b) to introduce mild changes for safety (e.g. to repeat a dose or to inject two hemidoses in both arms to prevent local reactions) before going on, (c) to reduce the planned dose below lower than those recommended by the manufacturer and (d) to withdraw the vaccination.

Statistical analysis

Descriptive parameters (mean, standard deviation, absolute frequency and percentage) were estimated. Student's *t*, Mann-Whitney's or one-way Kruskal-Wallis's tests were applied for continuous variables, and χ^2 (Yates corrected χ^2 if necessary) or exact Fisher's tests, where appropriate, for categorical data. A probability value of less than 0.05 was considered to be significant.

Age, sex, asthma, manufacturer, clinical observer and allergen extract were tested as possible risk factors for the predictive model of the dependent variable, SR, in the multi-variable logistic regression analysis. The likelihood ratio test (*G* statistic) was subsequently used to assess the significance of the variables and to obtain the final model with the usual significance level of 0.05. The scales of the quantitative variables were assessed using the Box-Tidwell test. The presence of confounding and interaction was tested prior to assessing the model's goodness-of-fit. Finally, model validity was assessed first by estimating its goodness-of-fit (the extent

to which the model reflects the data) using the Hosmer-Lemeshow *C* statistic. STATA 5.0 (© Stata Corporation, TX, USA) was used for these analyses.

Results

Four hundred and twenty-three patients (86.7%) who participated in the multi-centric study, completed the treatment and followed to the end of the trial. Vaccination was withdrawn by physicians in four patients after reactions. In three cases due to recidivate reactions and in one, a single reaction occurred. Four more patients left the trial by their own decision, after local reactions during the buildup phase, a fact that indeed differed from their allergists' opinion. Up to 65 patients were excluded due to personal reasons not related to SIT.

A total number of 17 526 injections were administered, 7325 corresponding to the buildup phase and 10 141 to maintenance doses. Fifty-eight patients (11.9%) developed a total of 105 local adverse reactions, which correspond to 0.6% of the administered doses. Most of the buildup local reactions disappeared after optimal dose ($P = 0.002$). There was a higher rate of local reaction among female than male patients which was statistically associated (males 8.95%; females 15.5%; $P < 0.05$), and although local reactions were also more frequent during the buildup phase of pollen treatments, no statistical significance was found.

Eighteen patients (3.7%) experienced 53 SRs (0.3% of administered doses): 30 grade II reactions, 21 grade III reactions and two exacerbations of a previous atopic dermatitis. After the administration of 17 526 doses, no anaphylactic shock, life-threatening or fatal reaction were registered.

An individual description of these reactions can be seen in Table 1. All SRs were immediate –except for two late atopic

Table 1. Main features of patients with systemic reactions (SRs)

N	Sex	Age (years)	Clinical syndrome	Extract	Local reactions (buildup)	SRs (buildup)	SRs (maintenance)	Continuity
1	M	15	R+A	P	–	–	II	N Ch
2	M	7	R+A	P	–	–	III/II	M Ch
3	F	29	R+A	M	–	II	–	N Ch
4	F	26	R+A	P	+	II $\times$ 2	–	M Ch
5	M	9	R+A	M	+	II	–	D
6	F	28	R+A	P	–	II	–	D
7	M	6	R+A	M	–	–	II $\times$ 4	R
8	F	24	R	P	–	II	–	N Ch
9	M	15	R+A	M	–	–	II $\times$ 3	R
10	M	13	R+A	M	–	–	III $\times$ 8	W
11	M	5	R+A	M	–	II $\times$ 3	II $\times$ 7	W
12	M	7	R+A	M	–	–	III $\times$ 6	W
13	M	13	R+A	M	–	III $\times$ 4/II $\times$ 2	II/III	R
14	F	17	R+A	M	+	AD	–	M Ch
15	M	18	R	P	–	II	–	D
16	M	10	R+A	P	–	–	AD	W
17	M	19	R+A	M	–	–	II	N Ch
18	M	26	R+A	P	–	II	–	D

M, male; F, female; R, rhinitis; A, asthma; P, pollen; M, mite; Severity degree, I–III – see text/number of reactions; AD, atopic dermatitis; N Ch, no changes; M Ch, mild changes; R, reduction of maintenance dose; D, drop-out; W, withdrawal.

Table 2. Administered rescue medication

	Epinephrine	β -agonists	Antihistamines	Steroids
Number	7	39	18	3
Percentage (51 reactions)	14	76	35	6
Grade	7 grade III	27 grade II 12 grade III	10 grade II 28 grade III	3 grade III

dermatitis – and they could be treated during the 30 min waiting period. Only ordinary cares were administered (see Table 2) and no invasive measure was required. All patients had a satisfactory response to treatment.

An interesting fact was the number of reactions by patients. Thus, 11 patients had only one and seven patients experienced several reactions. Five patients experienced more than three SRs in a total of 36 reactions, most of them happening during the maintenance doses. About 40% of SRs (21 reactions) would have been avoided if patients experiencing the third SR had been withdrawn.

The absolute frequency of local and SRs in several subgroups is shown in Table 3. From the point of view of number of patients, SRs were not associated with sex, clinical syndrome, vaccine composition, phase of the treatment, age of the patients, manufacturers or new batches of the extracts, pollination season and other circumstances considered as aggravating. When focusing on the number of doses, χ^2 (Yates corrected χ^2 if necessary) or exact Fisher's tests (where appropriate) revealed a higher percentage of SRs among male than female patients which was statistically associated. A higher frequency of systemic side-effects among asthmatic compared with non-asthmatic patients (0.41%–0.06%; $P < 0.001$) as well as among patients receiving mite compared with those those receiving pollen extracts (0.40–0.15%; $P < 0.01$) was also found. Nonetheless, multi-variable logistic analysis did not demonstrate that any of these facts were a risk factor associated with SRs during SIT treatment.

Discussion

The fear of side-effects associated with SIT treatment has led to the restricted use of allergenic vaccines in some countries,

in spite of the low risk of SRs reported in well-controlled studies. The results of this prospective and multi-centric study with commercially available therapeutic vaccines for allergic diseases in Europe showed that SIT was a safe treatment with a very good compliance [11–13]. It was based on the low frequency and severity of SRs, which responded well to rescue treatment. Although we did not find statistical differences among manufacturers of vaccines, it would be desirable to reach a wide consensus on allergen extract standardization methods.

The importance of the results reported in this article is based on the characteristics of the study, and three main aspects should be emphasized: study design, patients/disease and allergen extracts. The design of the study was prospective and multi-centric. Among the characteristics of multi-centric studies, we must highlight the fact of evaluating the experience of several physicians along with a high diversity among the patients (i.e. several geographical areas as well as differences in environmental exposure to allergens) [14], while following the same criteria for SIT administration (EAACI guidelines). This study was focused on both rhinitis and asthma, which are areas of SIT. Allergen extracts were limited to dust mites and pollens because both of them constituted the most frequent cause of allergic respiratory diseases and they are well standardized. Additionally, the fact that allergen extracts used along the study were commercially available and that the treatment schedule and optimal doses were those provided by the manufacturer gives a clinical sense in the day-to-day practice of the results of this study. Finally, the protocol for administration and monitoring of adverse reactions were EAACI guidelines [1], which are known worldwide.

Asthma has been described as a critical risk factor in the development of systemic and fatal reactions [2], and it is well established that allergen extracts should not be administered to patients with unstable asthma or forced expiratory volume in 1 s (FEV₁) under 70% of the predicted value. This parameter was well controlled during the study and checked previously to administration of all doses. Interestingly, asthmatic patients had a higher ratio of side-effects than rhinitic patients. This fact has also been described in other reports [15, 16] and should be kept in mind on prescribing SIT, although reactions were not severe and responded well to treatment. Asthma and dust mite allergy were statistically associated and, consequently, dust mite allergic patients (perennial allergen exposure) also experienced SRs more

Table 3. Side-effects of specific immunotherapy in several subgroups

	Sex		Syndrome		Phase			Extract	
	M	F	Rhin	Asth	B-up	Maint	Both	Mite	Pol
Patients	268	220	152	336	488	476	–	296	192
Doses	9671	7855	5375	12 151	7385	10 141	17 526	10 872	6654
Local R _(patients)	24	34	18	40	33	12	13	32	26
Systemic R _(patients)	13*	5	3	15	8	8	2	10	8
Local _(n reactions)	54	51	36	69	64	41	–	63	42
Systemic _(n reactions)	47†	6	3‡	50	18	35	–	43§	10

M: male; F: female; Rhin: rhinitis; B-up: buildup; Maint: maintenance; Pol: pollen. * $\chi^2 = 6.7$; $P = 0.035$. † $\chi^2 = 19.6$; $P = 0.0001 \times 10^{-3}$. ‡ $\chi^2 = 14$; $P = 0.00014$. § $\chi^2 = 6.2$; $P = 0.013$.

frequently than pollen allergic patients (seasonal allergen exposure). The maintenance dose of pollen extract was reduced during the pollen season and the patient's symptoms were checked; a higher ratio of SRs was not found during the pollen season although the allergen concentrations had significantly increased. So, we believe that co-seasonal administration of SIT is not associated with a higher frequency of adverse reactions when SIT is well controlled and doses reduced to half.

The results of this study revealed that our knowledge of factors contributing to side-effects is not complete. No additional risk factor was discovered during the treatment because, according to the EAACI guidelines, classical risk factors were systematically checked before administration of each dose. Curiously, patients suddenly developed immediate SR after several months on maintenance therapy and following previously tolerable maintenance doses, making clear that the cause of SRs is unclear and our knowledge about factors contributing to side-effects is not sufficient [17]. Besides, there was a subgroup of patients who were prone to experience recurrent SRs. It was found that a considerable number of SRs (about 40%) would have been prevented if the number of SRs had been previously limited, especially during the maintenance treatment. Evaluating these data, it was discussed if this group, due to too many reactions, should be excluded from the final analysis. Finally, these data were not removed because, as EAACI guidelines do not express any criteria in this sense [1], they represent a fact which can happen even when EAACI guidelines are strictly followed. These data clearly support the idea that the number of SRs should be limited and SIT withdrawn, at least in patients experiencing three SRs.

An overview of the safety data of SIT shows the low risk of SRs with mild or moderate severity and good response to treatment when the recommendations of EAACI or WHO guidelines are followed [1, 18, 19]. It is worth stressing that fatalities have been exceptional and, when thoroughly analysed, one or several mistakes could be confirmed [8, 20, 21]. Among them, inadequate treatment of the reaction, mistakes in doses, lack of equipment for emergency treatment or contraindications of the dose, such as unstable asthma, β -blocker treatment, exacerbations of allergic symptoms, etc., were the most frequent errors. We should not forget that other drugs such as penicillin [22] or aspirin [23], commonly used in the general practice of medicine, are not free of risk to elicit anaphylactic or fatal reactions.

In summary, SIT was a safe treatment with a very good compliance (>80%) and a low risk to elicit SRs when EAACI guidelines are strictly followed, and none of the SRs were fatal or life-threatening reactions. Future guidelines of SIT should limit the maximal number of SRs.

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