Original Article

The safety of allergen immunotherapy (IT) in Turkey

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Abstract. Allergen immunotherapy (IT) has encouraging therapeutic outcomes but its safety is still being questioned because of possible severe systemic reactions. The aim of this study was to determine the frequency of systemic reactions (SR), and to identify their correlation with the characteristics of therapy, such as allergen composition and IT schedule, and diagnosis. We analyzed the data of 126 patients who received IT between 2000-2003, and suffered from respiratory allergy or hymenoptera venom anaphylaxis. IT was given by rush, clustered or conventional schedules. The standardized allergen extracts used were grass pollen, house dust mite and hymenoptera venom in 88, 18 and 20 patients, respectively. None of the patients received premedication. A total 4705 injections were administered. One hundred and twenty-three adverse events (AE) (2.6% per injection) were documented in 46 patients. Sixty-one of them were SRs (1.3% SRs per injection) and they were seen in 28 patients. Asthmatics had more tendency to SRs (p=0.05). Rush (1.8%) and clustered (2.8%) IT protocols were associated with a higher rate of SRs (per injection) when compared to conventional schedule (0.9%) (rush vs conventional; p=0.013, clustered vs conventional; p=0.001). The majority of SRs corresponded to grade 3 (49%). Forty-nine (80%) of the 61 SRs were observed during the build-up phase, and mostly with pollen extracts (75.5%). Patients showed more severe SRs during the build-up phase (p<0.05). Twenty-six (42.6%) of the SRs were immediate, whereas 35 (57.4%) SRs appeared within 2 hours. Delayed SRs were significantly more frequent in polysensitized patients when compared to monosensitized subjects (p=0.018). Our data indicate that rapid IT regimens and the presence of asthma represent a greater risk for SR development. Since the late SRs occur as frequently as the early ones, we suggest a longer waiting period beyond 30 minutes, especially in polysensitized and asthmatic patients.

Key words: Immunotherapy, systemic reactions, safety, asthma.

Resumen. Los resultados terapéuticos de la inmunoterapia (IT) con alérgenos son alentadores, pero se sigue cuestionando su seguridad debido a posibles reacciones sistémicas graves. El objetivo de este estudio fue determinar la frecuencia de las reacciones sistémicas (RS) e identificar su correlación con las características del tratamiento, tales como composición de los alérgenos y pauta de IT, y el diagnóstico. Se analizaron los datos de 126 pacientes que recibieron IT entre 2000–2003 y que padecían alergia respiratoria o anafilaxis al veneno de himenópteros. La IT se administró mediante pautas rápidas, cluster o convencionales. Los extractos de alérgeno estandarizados utilizados fueron polen de gramíneas, ácaros del polvo doméstico y veneno de himenópteros en 88, 18 y 20 pacientes, respectivamente. Ninguno de los pacientes recibió medicación previa. Se inyectaron un total de 4.705 vacunas y se documentaron 123 acontecimientos adversos (AA) (2,6% por inyección) en 46 pacientes. Sesenta y uno de los AA fueron RS (1,3% de RS por inyección) y se observaron en 28 pacientes. Los asmáticos presentaron una mayor tendencia a experimentar RS (p = 0,05). Los protocolos rápidos (1,8%) y cluster (2,8%) de IT se asociaron con una tasa más elevada de RS (por inyección) en comparación con la pauta convencional (0,9%) (rápida frente a convencional; p = 0,013, cluster frente a convencional; p = 0,001). La mayoría de RS fueron de grado 3 (49%). Cuarenta y nueve (80%) de las 61 RS se observaron durante la fase de iniciación, principalmente con extractos de polen (75,5%). Los pacientes mostraron RS más graves durante la fase de iniciación (p < 0,05). Veintiséis (42,6%) de las RS fueron inmediatas, mientras que 35 RS (57,4%) aparecieron al cabo de 2 horas. Las RS retardadas fueron significativamente más frecuentes en los pacientes polisensibilizados que en los monosensibilizados (p = 0,018). Nuestros datos indican que las pautas rápidas de IT y la presencia de asma representan un mayor riesgo para el desarrollo de RS. Dado que las RS tardías ocurren con la misma frecuencia que las tempranas, se propone un período de espera más largo, superior a los 30 minutos, especialmente en pacientes polisensibilizados y asmáticos.

Palabras clave: inmunoterapia, reacciones sistémicas, seguridad, asma.

Introduction

Allergen immunotherapy (IT) has been used in the management of allergic diseases for nearly 100 years. It is the only specific treatment for allergic rhinitis and asthma, and hymenoptera venom anaphylaxis [1-6]. In consensus reports and meta-analyses, allergen IT has been reported to be effective in reducing allergic symptoms and drug consumption in cases of respiratory allergy due to pollens, mites, animal dander and moulds [7]. However, some concerns still exist about the relative safety of this form of therapy. Allergen IT has potential risks of serious systemic reactions, as it involves subcutaneous injection of allergen extracts to which the patient is sensitive [8]. Despite clear advances in the prevention of such reactions over the last years, varying rates of severe reactions have been reported since the introduction of standardized and more potent extracts. There are several studies in the literature about the safety of this treatment, that attempt to identify patients who are at risk for development of systemic reactions [9-12].

The aim of this study was to evaluate the frequency of local and systemic reactions due to allergen immunotherapy in our country, and to determine whether these reactions were correlated to risk factors such as age, gender, diagnosis, IT regimen and type of allergen extract.

Material and methods

Patients

The adverse reactions observed, during the administration of specific immunotherapy within a period of 4 years (2000-2003), were analyzed in this study. A total of 126 patients were included, with the indications in accordance with the WHO position paper [13]. Written informed consents were obtained from all patients before the initiation of immunotherapy, and the guidelines were followed to monitor patients during allergen extract injection. The patients were diagnosed as having only rhinitis (n=56), rhinitis and/or mild to moderate asthma (n=50), and only hymenoptera venom anapylaxis (n=20). Diagnosis of asthma and rhinitis was based on the international guidelines [14,15]. Allergy to mites, grass pollen and hymenoptera venom was defined by means of a typical history, positive skin prick test, and presence of specific IgE antibodies. Patients with respiratory allergy received standardized extracts of grass pollen or house dust mite (*Dermatophagoides pteronyssinus* or *Dermatophagoides farinae*). Inclusion criteria for venom immunotherapy were based on the EAACI's position paper [16].

Allergen extracts

Biologically standardized extracts in depot (adsorbed in aluminum hydroxide or calcium phosphate) and aqueous formulations, commercially available in Turkey, were used. Allergen extracts in the conventional schedule were supplied by three different laboratories; ALK-Abellò (Madrid, Spain), Allergopharma (Reinbeck, Germany) and Stallergenes (Antony Cedex, France). Hymenoptera venom (*Apis mellifera* and *Vespula*) extracts were supplied only by ALK-Abellò. Allergen extracts used in rush and clustered protocols were also purchased from the same manufacturer (ALK-Abellò).

Administration schedule

Immunotherapy was given in terms of conventional, clustered and rush schedules. Conventional IT build-up was typically given as an injection per week until the maintenance dose was reached. Once a weekly cluster regimen of 2 or more injections per visit was applied during the updosing phase for a period of 7 weeks, followed by monthly maintenance injections of 100 000 SQ-U/ml. Rush regimen was completed within 6 days, while the patients were hospitalized. It was started without premedication, with an initial dose of 10 SQ-U/ml of aqueous extract. The dose was then increased gradually with intervals of 60 minutes up to 100 000 SQ-U/ml and completed with the depot form. Vital signs of all patients were obtained at the beginning of the protocol, then before each injection and hourly thereafter. Baseline spirometry was performed in asthmatic patients. Full emergency resuscitation equipment was readily available. The maintenance dose of all allergens was the maximal tolerated dose of the highest antigen concentration. Generally, the maintenance doses for ALK-Abellò, Allergopharma and Stallergenes extracts were 1 ml of 100 000 SQ-U, 1 ml of 5000 TU and 0.75 ml of 10 IR, respectively. Maintenance therapy was administered once a month.

Clustered and conventional regimens were applied at the out-patient clinic. The injections were administered by the trained nurses, and the subcutaneous route was used. Patients were questioned before each immunotherapy dose about their disease stability compared to their previous visit and post-injection problems. If the patient had experienced exacerbation of his/her disease, a decision about modification of the treatment was made. Full emergency resuscitation facilities were available at all time. All the patients stayed at the immunotherapy unit for at least 30 minutes after application of the dose. Allergen extract dosage, local and systemic reactions, and treatment of adverse reactions, were recorded.

The dose was reduced in the case of systemic reactions, immediate local reactions larger than 5 cm, unpleasant large delayed local reactions or exceeding intervals between two consecutive injections.

Classification of adverse reactions

Adverse reactions were classified by their type and severity. Indurations larger than 5 cm were described as local reactions. Systemic reactions were divided into 4 grades [17]; grade 1: generalized cutaneous reactions; flushing, pruritis, urticaria, grade 2: grade 1 plus mucosal

involvement such as rhinoconjunctivitis, pruritus of the oral mucosa, and angioedema, grade 3: grade 2 plus mild to moderate asthma, grade 4: severe urticaria and asthma associated with hypotension, weakness, dizziness, abdominal pain, nausea, vomiting. The onset time of any reaction was recorded. If the reaction developed during the first 30 minutes following IT injection, it was accepted as immediate, and as delayed after 30 minutes.

Results

During the study period, a total of 4705 injections were administered to 126 patients (77 female/ 49 male, mean age: 30 ± 7.1 years, range: 15-51 yrs) diagnosed with respiratory allergy or hymenoptera venom anaphylaxis. The patients with respiratory allergy were diagnosed as having only asthma (n=5), allergic rhinitis without asthma (n=56) and allergic rhinitis with asthma (n=45). The injection schedules were categorized as rush in 1117 doses, as clustered in 504 doses, and conventional in 3084 doses. Numbers of patients according to IT schedules and type of allergen are presented in Table 1.

Of the 126 patients, 28 (22.22%) had systemic reactions (SR) with or without local reaction (LR), and 18 (14.3%) had only large local reactions. A total of 123 adverse events (2.6 % AE/injection) have been recorded in 46 patients. The mean age of these patients was 29±7 years (ranged from 15 to 49 yrs (9 male/37 female)). Sixty-one of them were SRs, and the rate per number of injections was 1.3 % (61/4705), and per patients treated (28/126) 22.2%. Of the systemic reactions, 43 (70%) occurred with pollen extracts, 9 (15%) with mite extracts, and 9 (15%) with hymenoptera venom extract. The majority of SRs were categorized as grade 3 (49.18%).

The 61 SRs occurred in 28 patients, of whom 10 had allergic rhinitis and 16 allergic rhinitis with asthma. Two suffered from hymenoptera venom allergy.

Forty-eight of 61 SRs (80%) developed in the build-up phase, versus 13 (20%) in the maintenance phase ($p<0.05$). Five systemic reactions seen in the maintenance phase were due to grass pollen allergen, and three of them occurred in the season.

With respect to reaction time, 26 (42.6%) of the SRs were immediate, and 35 (57.4%) were delayed. Although occurrence of delayed SRs was not related to allergen type and IT schedule, polysensitized patients (to more than one antigen) significantly experienced more frequently delayed SRs ($p=0.018$). As an interesting fact, a significantly lower rate of delayed SRs was found in the presence of local reaction ($p=0.009$). There was no relationship between development of immediate and delayed SRs.

Factors affecting development of AEs and SRs

When the analysis was based on the numbers of patients, we did not find significant influences of age, gender, IT regimen and type of allergen on the development of either AEs or SRs ($p>0.05$). However, with respect to the total number of injections, comparison of the three allergen groups revealed different rates of SRs ($p=0.057$, CI: 90%). The frequency of SRs per injection was significantly higher with the grass pollen than with venom extracts (1.6 % vs 0.7%) ($p=0.027$, CI: 95%). There was no difference in SRs between mite and pollen, or mite and venom vaccine groups (1.0% vs 1.6%, and 1.0% vs 0.7%, respectively). In addition, asthmatic patients had a greater tendency to have SRs ($p=0.05$). They showed higher frequency of both immediate and delayed SRs than patients with only rhinitis.

There was a significant difference between IT schedules in which high levels of reactions were induced by rush and clustered protocols when compared to conventional regimen ($p<0.001$). Conventional protocol caused significantly lower rates of SRs than both clustered and rush regimens ($p=0.001$ and $p=0.013$, respectively, CI: 95%). However, no difference was detected between rush and clustered protocols ($p>0.05$ %). Rates of systemic reactions with respect to type of allergen and IT schedule are shown in Table 2.

Factors affecting severity of SRs

There was no significant effect of age and gender upon the severity of SRs. However, both schedule type and phase of IT was significantly correlated with the severity of SRs. The severity of SR was worse in rush protocol ($p<0.001$). A higher rate of severe SRs was detected in the build-up period compared to maintenance period ($p<0.05$). During the build-up phase, the rate of grade 3 SRs was 54.2%. All grade 4 SRs were observed in rush schedule only ($p<0.001$). Of the 8 grade 4 SRs, seven occurred with venom extract in the same patient, and another with a pollen extract at the last doses of highest concentration during the build-up phase. SR rates are detailed in Table 3.

When we compared the severity of immediate and

Table 1. Numbers of patients treated with different immunotherapy schedules and allergen type.

	Rush (n)	Clustered (n)	Conventional (n)	Total (n)
Grass pollen	4	23	61	88
House dust mite	4	2	12	18
Hymenoptera venom	16	1	3	20
Total	24	26	76	126

Table 2. Systemic reaction rates according to allergen extracts and immunotherapy schedules.

	Injections		Patients	
	Nº	SR Nº (%)	Nº	SR Nº (%)
Pollen	2626	43 (1.6)	88	22 (25)
Mite	875	9 (1.0) *	18	4 (22.2)
Hymenoptera venom	1204	9 (0.7)	20	2 (10.0)
Total	4705	61 (1.3)	126	28 (22.2)
Rush	1117	20 (1.8)	24	6 (25)
Clustered	504	*** 14 (2.8) **	26	8 (30.8)
Conventional	3084	27 (0.9)	76	14 (18.4)
Total	4705	61 (1.3)	126	28 (22.2)

* pollen versus hymenoptera venom, p = 0.027; ** conventional versus clustered, p < 0.001; *** conventional versus rush, p = 0.01.

Table 3. Severity of systemic reactions according to allergens, the phase and schedule of immunotherapy.

	Injection	Allergen type*			Schedule of IT**			Phase of IT***	
	Nº (%)	Pollen	Mite	Venom	Rush	Clustered	Conventional	Build-up	Maintenance
Grade 1	10 (20%)	6	2	2	3	5	2	8	2
Grade 2	13 (26%)	12	1	0	2	1	10	11	2
Grade 3	30 (49%)	24	6	0	7	8	15	26	4
Grade 4	8 (5%)	1	0	7	8**	0	0	3	5
Total	61	43* (70%)	9 (15%)	9 (15%)	20 (33%)	14 (23%)	27 (44%)	48** (80%)	13 (20%)

* Comparison between pollen, mite and venom extracts (p = 0.057); ** Rush protocol caused significantly most severe SRs than the others (p< 0.001); *** Difference between build-up and maintenance periods (p< 0.05).

delayed SRs, immediate SRs were significantly more severe than delayed ones (p=0.003). Comparison of grades of immediate and delayed SRs are given in Figure 1. Only 40% of the Grade 3 SRs were early; while all of grade 4 SRs occurred immediately within 30 minutes. The majority of grade 1 SRs (90%) were also of the delayed type. All of the SRs responded well to treatment with epinephrine, antihistamine and bronchodilator, etc. None of them was life-threatening or fatal.

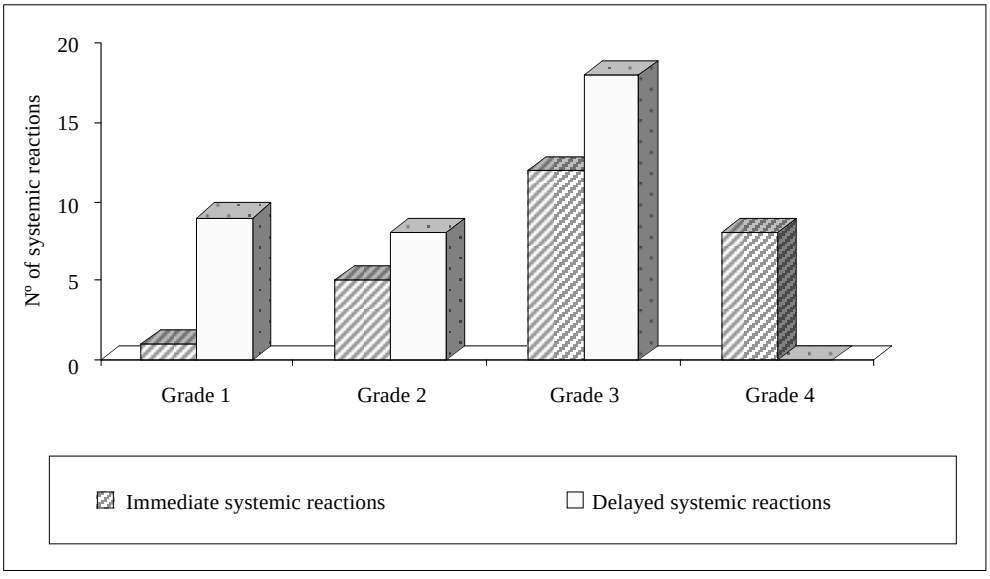

Figure 1. Severity of systemic reactions according to time of onset (Severity of immediate versus delayed systemic reactions, p = 0.003).

Discussion

The occurrence of adverse systemic reactions due to allergen IT remains a major problem for both patients and clinicians. It can sometimes be severe and even life-threatening. Despite many preventive measures against such reactions (premedications, etc.), there is no proven predictive factor for the appearance, type and severity of reactions. There are some confounding factors that need to be clarified in the anticipation and prevention of these reactions. In this study, we could not find any influence

of age and gender either upon the development of adverse reactions (including systemic and local), or on the severity of SRs.

When we overviewed the other factors associated with SRs, the most important one was the presence of asthma. Asthma has been previously described as a critical risk factor in the development of systemic and fatal reactions in IT [10, 18]. During our study, all asthmatic patients were stable and under treatment. However, asthmatics had a significantly higher rate of both immediate and delayed type systemic reactions than those with rhinitis alone. Our results are consistent with the literature, in terms of increased incidence of SRs in asthmatics [19-21]. In a recent study, it was reported that most of the fatalities occurred in asthmatics with poor optimal control [11], which was also in accordance with a previous report by Reid et al [22]. This author determined that 76% of the patients who died from SR due to IT had severe asthma. Contrary to these reports, Tinkelman et al. found no increase in the rate or severity of reactions in asthmatic patients [23]. According to our results, it should be noted that even stable, well-controlled asthmatic patients are prone to higher risk for SRs.

Regarding the type of allergen extracts, grass pollen allergic patients, while on maintenance therapy and in the pollen season, experienced SRs more frequently compared to those with venom allergy. The maintenance dose of pollen extracts was reduced during the pollen season in these subjects. Our finding was again similar to those obtained in other studies [10, 20, 24]. Hejjaoui et al. also found that bronchial adverse reactions developed more often in asthmatic patients treated with pollen extracts [25]. In another study, it was shown that a lower frequency of SRs occurred with mite extracts than with pollens and venoms [26]. In contrast, Moreno et al. found higher ratios of SRs in mite allergic patients and among asthmatics [19]. Nevertheless, no difference between the rates of adverse reactions in the venom and inhalant therapy group was shown by Tamir *et al* [27].

In the present study, the appearance of SRs was higher during the dose-escalation phase of IT. Additionally, the reactions in this period were more severe and mostly of grade 3 type. These observations also confirm previous reports indicating that most SRs occurred during the dose build-up phase of IT [20-23]. However, Moreno et al. found similar rates of SRs in both up-dosing and maintenance phases of IT (19). However, in a recent survey, it was reported that most fatal reactions (59%) had developed with maintenance allergen doses [11].

An important aspect of our results was the frequency of late-onset (up to 2 hours) SRs. Concerning the time of occurrence, 42.6% of the SRs were immediate (within 30 minutes), whereas 57.4 % were delayed. This particular finding is in contrast to the results of the other studies [7, 21, 24]. In one study, it was reported that grass pollen vaccines caused mostly delayed (after 30 minutes) SRs [26]. It was also reported that the onset of 3 fatal reactions began more than 30 minutes after injections [11]. We found a higher frequency of delayed SRs in polysensitized patients than in monosensitized subjects - in contrast to the results of Iglesias-Cadarso *et al* [28]. The most recent IT guidelines recommend a waiting period of 20-30 minutes after injections [7, 21]. Although severe SRs usually appear within 30 minutes after injection, as we have found in our study, a subgroup of patients, such as polysensitized and asthmatic individuals, can experience late-onset SRs. Therefore, we suggest that the observation period should be extended beyond 30 minutes.

Three different IT schedules were used in this study. Apparently, rush schedules are more rapid than cluster schedules and are designed to accelerate the build-up phase of IT. However, it has been shown that rush and clustered schedules are associated with a greater possibility of SRs than conventional protocols [7, 21, 25, 29, 30]. We found a significant difference of influence of IT schedules on the development of SRs. Most severe SRs of grade 4 type were seen only during rush IT. Conventional IT regimen was the safest modality compared to both rush and clustered schedules. Although some authors reported that rapid IT regimens might be an appropriate therapeutic alternative to conventional ones [31], our results suggest that rush and clustered schedules have an increasing incidence of severe SRs.

The reported rate of systemic reactions per injection has been variable from 0.06% to < 1% [7, 10, 18, 19, 21, 26]. Our frequency of SRs was 1.3 % and similar to the proportion found in several studies. The treatment conditions were convenient for the patients even without premedication in this study.

Finally, the present study showed that SIT was a safe treatment with a low risk to elicit severe SRs, in which no fatality was observed. We can conclude that rapid IT regimens and asthma represent two main risk factors contributing to serious side effects. Moreover, our data clearly support the idea that the number of SRs can be minimized with appropriate use of IT, and at least an hour of waiting is required, especially in polysensitized patients with asthma.

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