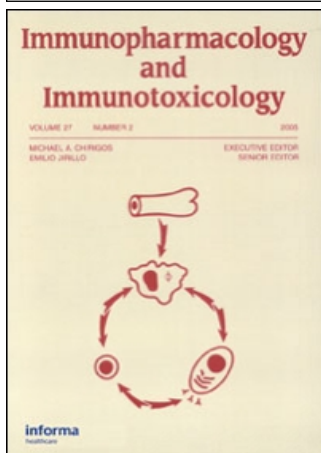


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Immunopharmacology and Immunotoxicology

Publication details, including instructions for authors and subscription information:
<http://www.informaworld.com/smpp/title-content=t713597257>

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Online Publication Date: 01 March 2008

To cite this Article: Ventura, M. T., Giuliano, G., Buquicchio, R., Accettura, F. and Carbonara, M. (2008) 'Local and Systemic Reactions Occurring During

Immunotherapy: An Epidemiological Evaluation and a Prospective Safety-Monitoring Study', Immunopharmacology and Immunotoxicology, 30:1, 153 - 161

To link to this article: DOI: 10.1080/08923970701620008

URL: <http://dx.doi.org/10.1080/08923970701620008>

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Local and Systemic Reactions Occurring During Immunotherapy: An Epidemiological Evaluation and a Prospective Safety-Monitoring Study

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The efficacy of specific immunotherapy in allergic patients with IgE-mediated rhinoconjunctivitis, asthma and allergic reaction for stinging insects suggests the opportunity of improving technical procedures to minimize risk and optimise the safety of immunotherapy. This study investigated both local and systemic reactions, occurring in a population of 218 patients undergoing immunotherapy, in an attempt to correlate them with some parameters as well as age, sex and allergenic extracts. The epidemiological evaluation was based on the administration of a questionnaire to 218 patients in order to assess possible reactions to immunotherapy. The following data were evaluated: personal data, diagnosis, specific allergens, adverse reactions undergone during treatment, number of reactions and symptoms. The patients were followed-up by the medical staff of the Section of Allergological and Immunological Disease (SAID), University of Bari (Bari-Italy) for compilation of questionnaires. We found a correlation between female sex and adverse reactions. Among 107 patients referring reactions to the immunotherapy, 71 patients (66.3%) presented only local reactions; 11 patients (10.3%) systemic reactions and 25 patients (23.4%) systemic reactions associated with local reactions. *Parietaria* was mostly involved in patients with local reactions, instead, in patients with systemic reactions the prevalent allergens seem to be *Dermatophagoides* and grass-pollen. Rhinitis was the most frequent diagnosis for patients who have presented both local and systemic reactions. In our study, we had frequently mild systemic reactions and some cases of respiratory difficulties, while it is evident that in our group

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of patients no cases of anaphylaxis occurred. In addition, we considered some events before the administration of immunotherapy, such as assumption of drugs, meals, exposure to sun, stress or physical activity and the percentage of adverse reactions. On the light of a small number of fatality, immunotherapy represents a safer therapy for allergic diseases; nevertheless, our data suggest that safety is strictly correlated with prescriptions by specialists, administration by trained physicians and accurate follow-up of patients. In particular it is recommended to avoid some events before the administration of immunotherapy, above all the assumption of drugs and physical exercise.

Keywords Specific Immunotherapy, Local Reactions, Systemic Reactions, Risk Factors.

INTRODUCTION

It is well known that specific immunotherapy (STI) represents the most appropriate approach for allergic patients with IgE-mediated rhino-conjunctivitis, asthma and allergic reaction for stinging insects.^(1–5) The efficacy is specific for the antigen administered and capable of inducing a stable modification of the natural real cause of the disease. Anyway, systemic as well local reactions may occur during the treatment, suggesting a strict correlation to risk factors during management. In particular, the reported deaths from the British Committee of Safety of Medicines⁽⁶⁾ suggest some precautions in these procedures. In this respect, guidelines have been proposed to avoid systemic reactions, identifying some risk factor that include the use of beta-blockers, symptomatic asthma, high hypersensitivity and rush STI.^(7,8) Despite some retrospective studies which have indicated fatalities, the efficacy of such a treatment suggests the opportunity of improving technical procedures to minimize risk and optimise the safety of STI.

In these lights, we have considered both local and systemic reactions occurring in a population of 218 patients treated with STI at the Section of Allergological and Immunological Disease (SAID) of Bari University and have correlated them with some parameters as well as age, sex and allergenic extracts.

MATERIALS AND METHODS

Two hundred and eighteen patients who had undergone STI were examined in our study at the SAID of Bari University over a period of 8 months. They were 108 males and 110 females, mean age 29 years (range 6–70 years). In order to consider the age effects, we analysed patients subdivided in groups by intervals of 5 years.

All patients had a history of allergic rhinitis, rhino-conjunctivitis or asthma, positive skin prick test (SPT) and Radio Allergo Sorbent Test (RAST) for specific allergens. At the moment of recruitment, the majority of the patients were in maintenance phase and the other were in induction phase.

To assess possible reactions to STI, we collected data through 218 questionnaires with a sequence of questions designed to elicit the following information: personal data, diagnosis, specific allergens, possible reactions undergone during treatment, number of reactions, symptoms and period from the beginning of therapy. Each patient completed his own questionnaire, sometimes under the supervision of the SAID specialized medical staff.

STATISTICAL ANALYSIS

We used some descriptive statistics, such as mean, proportions and histogram to handle data and to summarize the relevant features of our set of values. The possible relationships between significant variables (sex, age, reaction to STI, number of sensitisations) were performed by correlation analysis ($p < 0.05$).

RESULTS

Among 218 patients studied, 110 were female and 108 were male, thus confirming the significance of the considered population. In fact there is an equal representation of both genders with a percentage of Adverse Drug Reaction (ADR) to STI equal to 49.1% (107 patients). In these patients we supposed the existence of a positive correlation with female sex, in fact the percentage of women reached 60.8% with mean age of 29 years, that coincided with the fertile age.

To represent graphically the course of the phenomenon in the different ages for both sexes, we considered as representation the histogram based on classes of amplexness of 5 years. The mean age of the 218 patients who underwent STI was 29 years; this value is included in the class of age 25–29 years that, in this case, is superior to the modal class (20–24 years). As far as the number of allergens to which every patient resulted sensitive, we observed a large percentage of polysensitized patients, above all among subjects that manifested ADR to STI (Table 1). In addition, when we calculated Spearman

Table 1: Features of 218 patients.

	Sex		Number of sensitization		Mean age (years)	
	Male	Female	Monosensitized patients	Polysensitized patients	Male	Female
Patients with ADR to STI	39.2%	60.8%	29.9%	70.1%	29.6	29.5
Patients without ADR to STI	59.5%	40.5%	38.7%	61.3%	28.5	29.4

indexes of correlation¹ to verify possible correlations between the features of the 218 patients and the presence of ADR to STI, we found that the correlation index “*r*” between the presence of ADR and the age is next to zero; instead, a correlation exists between female sex and ADR (Table 2).

By examining the frequency of the diagnosis in the 218 patients with or without reactions to the STI, we found in both cases a great percentage of patients with diagnosis of allergic rhinitis. In the group of patients with ADR to STI 18.7% cases of rhinitis were associated to asthma and only 11.2% suffered from asthma. These percentages are shown in Table 3.

Looking at the questionnaires of 107 patients who have referred reactions to the STI: 71 patients (66.3%) presented local reactions alone; 11 patients (10.3%) systemic reactions and 25 patients (23.4%) systemic reactions associated with local reactions. These results are shown in Table 4 and indicate that local reactions are more frequent, even if they disappear after a short time without any therapy and do not discourage the regular administration of STI.

Table 2: Correlation indexes between features of 218 patients and STI.

Features	STI
Sex	0.2
Age	0.04
Number of sensitisation	0.09

Table 3: Frequencies of diagnoses in 218 patients.

Diagnosis	Patients with ADR to STI	Patients without ADR to STI
Asthma	11.2%	13.5%
Oculorhinitis	20.6%	15.3%
Rhinitis	33.6%	48.6%
Asthma+Rhinitis	18.7%	10.8%
Asthma+Oculorhinitis	11.2%	7.2%

Table 4: Type of reaction in 107 patients with ADR to STI.

	Sex		Total
	Male	Female	
Local reactions	28.0%	38.3%	66.3%
Systemic reactions	4.7%	5.6%	10.3%
Systemic and local reactions	6.6%	16.8%	23.4%
Total	39.3%	60.7%	100%

In Table 5 it is shown that, among patients who have presented ADR to STI, the greatest percentage (22.9%) is represented by subjects treated with *Parietaria* antigen. Patients with *Dermatophagoides* and the grass-pollen antigens, respectively, underwent ADR with less frequency. In Table 6 are reported the frequencies of antigens responsible for local and/or systemic reactions. We have noticed that in the patients with local reactions, *Parietaria* is mostly involved. In the patients with systemic reactions, the greatest percentages of administered antigens were *Dermatophagoides* and grass-pollen. Mixed reactions occurred, instead, especially after administration of grass-pollen antigens.

When we take into account the frequencies of the allergological diagnoses in the 107 patients enrolled, it is evident that rhinitis, isolated or in association to other symptoms it is still the most frequent diagnosis either for subjects who presented local reactions or for those with systemic reactions (Table 7). In addition, in our study we subdivided systemic reactions in: nonspecific reactions; mild systemic reactions; non-life-threatening systemic reactions and anaphylactic shock, according to the Grading established from Malling and Weeke in the position paper of the EAACI.⁽⁹⁾

The analysis of the questionnaires of all patients with systemic reactions permitted us to divide these reactions in immediate and delayed. Immediate reactions appeared within 30 minutes from the administration of the STI, while delayed reactions occurred after 30 minutes. Since the systemic immediate reactions occurred within the observation time, they have been diagnosed and

Table 5: Frequencies of antigens in 218 patients studied.

Antigens	Patients with ADR to STI	Patients without ADR to STI
Grass-pollen	18.3%	15.6%
Parietaria	22.9%	17.4%
Olive	11.0%	10.1%
Cypressus	0.9%	2.3%
Dermatophagoides	20.2%	18.8%
Compositae	0.4%	0.9%

Table 6: Frequencies of antigens in 107 patients with ADR to STI.

Antigens	Patients with local reactions	Patients with systemic reactions	Patients with local systemic reactions
Grass-pollen	20.6%	3.7%	12.1%
Parietaria	32.7%	3.7%	9.3%
Olive	13.1%	1.9%	7.5%
Cypressus	0.9%	0.9%	0.0%
Dermatophagoides	29.9%	6.5%	4.7%
Compositae	0.0%	0.0%	0.9%

Table 7: Frequencies of diagnoses in 107 patients with ADR to STI.

Diagnosis	Patients with local reactions	Patients with systemic reactions	Patients with local systemic reactions
Asthma	7.5%	0.9%	2.8%
Oculorhinitis	17.7%	1.9%	2.8%
Rhinitis	21.5%	3.7%	8.4%
Asthma+Oculorhinitis	6.5%	1.9%	3.7%
Asthma+Rhinitis	13.1%	2.8%	3.7%

treated with appropriate therapy. In the following times, patients have recorded other systemic delayed reactions and pharmacological treatment.

The gravity of immediate reactions was higher in comparison to the delayed ones. In relevance to the safety of STI, it is important to notice that the immediate reactions represents the 39.6% versus the 60.4% of delayed reactions (Table 8).

Table 8 shows the relatively more frequent systemic reactions. The reactions that are verified more frequently are the mild systemic reactions, 47.1% of all systemic reactions. Among them, respiratory difficulties are the most frequent, while it is evident that no cases of anaphylaxis occurred.

Finally, we have studied the relationship between some events before the administration of STI, such as assumption of some drugs, meals, exposure to

Table 8: Frequencies percentage and reaction time of systemic reactions.

Type of systemic reactions	Reaction time		Total
	Immediate reactions	Delayed reactions	
Nonspecific reactions			
Headache	1.9	9.4	11.3
Asthenia	1.9	0	1.9
Fever	7.5	1.9	9.4
Scalp itch	0	1.9	1.9
Hand and foot itch	5.7	1.9	7.6
Total	17	15.1	32.1
Mild systemic reactions			
Rhinitis	0	9.4	9.4
Asthma	0	1.9	1.9
Respiratory difficulties	9.4	11.3	20.7
General itching	9.4	5.7	15.1
Total	18.8	28.3	47.1
Non-life-threatening systemic reactions			
Urticaria	3.8	11.3	15.1
Throat constriction	0	5.7	5.7
Total	3.8	17	20.8
Anaphylactic shock	0	0	0
Total	39.6	60.4	100

Table 9: Events before the administration in 107 patients with ADR to STI.

Events before the administration	Type of reaction							
	Local reactions		Systemic reactions		Local and systemic reactions		Total	
	%	Pz	%	Pz	%	Pz	%	Pz
Drugs	8.3	1	8.3	1	8.3	1	25	3
Meal	0.0	0	0.0	0	8.3	1	8.3	1
Physical exercise	8.3	1	16.7	2	0.0	0	25	3
Stress	0.0	0	0.0	0	16.7	2	16.7	2
Shower	8.3	1	0.0	0	8.3	1	16.7	2
Exposure to sun	0.0	0	8.3	1	0.0	0	8.3	1
Total	25	3	33.3	4	41.6	5	100	12

sun, stress or physical activity (Table 9). In fact, it is however advisable not to practise these actions before the administration, above all the assumption of drugs or physical exercise.^(10,11)

DISCUSSION

From our data it emerges that patients who have undergone STI mainly belong to the interval of age between 15 and 40 years without any distinction of sex. In particular the modal class belongs to the 20–24 year age range. These data are in accordance with current literature according to which an increase of allergic diseases falls in this period of age. In addition, in the female sex such pathology occurs more frequently, thus representing a significant risk factor for reactions to STI, likely in correlation with hormone production in the period of fertile age.

Nevertheless, from the entire statistical evaluation of data it results that STI represents a more safe and efficacious treatment for allergic diseases.⁽¹²⁾ On the other hand, STI represents, at the moment, the only specific therapy capable of inducing modifications in the immunological pattern of allergic patients.^(13–15) In the view of these considerations, it is essential to pay strict attention to risk factors and to techniques of management during STI to minimize risks of reaction. The development and use of standardized vaccines are encouraged, even if some risk factors should be considered such as errors in dosage, symptoms of asthma, use of beta-blockers, injections from new vials (oromucosal) and injections made during periods of exacerbation of symptoms.^(16–19)

The percentage of subjects who had a systemic reaction, in our evaluation, is small, but in the literature⁽²⁰⁾ appears to increase as the STI schedule is

accelerated, such as rush STI with venoms, and high-dose regimens are used in hypersensitivity subjects. Maintenance STI appears to be associated with fewer systemic reactions than the build-up period of rush and accelerated schedules of STI. A period of 20–30 minutes is recommended for conventional STI. However, a longer waiting period is necessary for high risk subjects or in situations such as rush STI, unstable asthma, use of beta-blockers and high-degree of hypersensitivity.⁽²¹⁾ At the same time, it is recommended, in view of the fact that benefits if STI start after at least 6 months–1 year, to give, an additional pharmacological treatment during the first year of STI. The prompt recognition of systemic reaction and the immediate use of epinephrine are the mainstays of therapy.^(22,23)

In the last few years it seems that the elevated costs of vaccines discouraged people from this therapy. Nevertheless, in consideration of the social economic charge of a disease like asthma,⁽²⁴⁾ it should be outlined to recommend STI as the most appropriate approach for allergic diseases. In conclusion, our data confirm that the risk of fatality from STI is extremely small also in consideration of a low percentage of systemic reactions during the clinical practice.

NOTE

1. The coefficient of correlation “*r*”, given by the relationship among the codeviance among the two considered characters and the square root of the product of the respective deviances, it assumes values among –1 and 1, which correspond respectively to the maximum discordance and the maximum agreement between the characters. For *r* = 0 there is not agreement neither discordance between two considered characters.

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