

E. Toubi
A. Kessel
A. Blant
T.D. Golan

Follow-up after systemic adverse reactions of immunotherapy

Authors' affiliations:

E. Toubi, A. Kessel, A. Blant, T.D. Golan,
Division of Clinical Immunology, Bnai Zion
Medical Center, Haifa, Israel

Correspondence to:

Elias Toubi, MD
Director, Division of Clinical Immunology
Bnai Zion Medical Center
47 Golomb Street
PO Box 4940
Haifa 31048
Israel

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Out of 280 immunotherapy (IT)-treated patients in our allergy clinic, 37 (13%) developed systemic adverse reactions. *Parietaria judaica* (Pj) extract, a highly allergenic pollen in northern Israel, was part of the IT regimen in 46% of treated patients who developed systemic adverse reactions. Twenty-six (70%) of systemic adverse reactions occurred during the buildup phase, whereas 11 (30%) occurred in the maintenance phase of treatment. Mild systemic reactions developed in 15/37 (40%), moderate in 20/37 (54%), and severe in 2/37 (5%) of patients. In 22/37 (59% of our IT-treated patients, adverse reactions developed within 30 min after injection. Among these were the two patients with severe systemic reactions. In 19%, moderate adverse reactions appeared at 30–60 min; in 22%, mild to moderate reactions appeared after 1–2 h. Our study concludes that severe systemic reactions to IT usually appear within 30 min after injection. In Israel, IT with highly allergenic pollens such as Pj frequently causes systemic reactions, even during the maintenance phase of treatment. In such cases, the reduction of IT dosage should be more than 50% during the pollen season, and a waiting period of 1 h should also be considered.

During the last decade, many well-controlled studies have proven the efficacy of immunotherapy (IT) in patients suffering from hypersensitivity to Hymenoptera, allergic rhinitis, and asthma, when properly selected (1, 2). Following a few reported cases of sudden death after IT, the Committee on the Safety of Medicine in the UK issued a report in 1986, describing 26 fatal cases after allergen IT, two of which occurred over 30 min after the injection (3). This committee recommended that the observation period after

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injection should be at least 2 h. This led to the virtual abandonment of allergen IT in the UK. Soon after this recommendation, a working-group report by the World Health Organization concluded that a 30-min waiting period is adequate, because most deaths had occurred during this period, and only among patients who were in the increased-risk group, such as moderate asthmatics (4).

In 1990, the executive committee of the American Academy of Allergy and Immunology issued a position statement entitled "The waiting period after allergen skin testing and immunotherapy" (5). This states that patients should be under medical supervision for at least 20 min after the administration of allergenic extract.

The position statement issued in 1994 (6) suggested that the patient should be kept under observation for an appropriate period of time after the injection, which will ordinarily be 20 min. This period can be extended to 30 min or more for high-risk patients, such as those with asthma or those with a clinical history of systemic reactions to allergenic extract injection.

A recent fact sheet, "The efficacy and safety of immunotherapy", was published in 1997 (7). It stated that severe systemic reactions and deaths following the injection of allergen extracts include dose errors, seasonal exacerbation of allergenic disease, symptomatic asthma, and a high degree of allergen sensitivity.

In this prospective multicenter study, we investigated whether the frequency and the severity of systemic adverse reactions following allergen IT in Israel are similar to those reported in other countries. In addition, we asked whether the observation period after injection may differ in relation to the country where this mode of therapy is introduced, the severity of the pollen season, and pollen allergenicity.

Material and methods

We followed, prospectively, 280 patients treated with allergen IT in three outpatient allergic clinics. All three clinics are in northern Israel, where house-dust concentration is high, and the pollenosis season is prolonged.

Table 1. Distribution of adverse reactions that developed after IT in 37 patients

Hymenoptera	Pj	Mixture pollens	Mixture mites and pollens	Mites
4 (11%)	10 (27%)	11 (30%) (4 also with Pj)	9 (24%) (3 also with Pj)	3 (8%)

Parietaria judaica (Pj) in this part of the country is the most frequently implicated pollen; it is highly allergenic and frequently a selective one (8).

Out of 280 patients, 60 were treated with pure Hymenoptera venom, 70 with a Pj extract, 80 with mixed different pollens, 50 with mites and pollens, and 20 with mites only. All extracts were obtained from Center Laboratories, Port Washington, NY, USA.

The follow-up period was 1996–8, during which 160 patients reached a maintenance dose of IT. The maintenance dose of all allergens was the maximal tolerated one generally accepted in the literature. Accordingly, the Hymenoptera maintenance dose was 50–100 µg/injection and the mite dosage was in the range 300–600 AU/injection. All pollens were given in 0.5 ml of 1:100 or 1:200 w/v dilution. Pj was an exception due to its high allergenicity, and its maintenance dose ranged between 0.5 ml of 1:20 000 w/v and 0.5 ml of 1:2000 w/v. The other 120 were in the buildup phase of treatment, in an attempt to approach gradually the above mentioned doses. During this period, we recorded all the systemic adverse reactions in relation to the following factors.

Severity

The severity of the adverse reactions was divided into three grades:

- 1) generalized skin reaction and rhinoconjunctivitis
- 2) the above, together with mild to moderate asthma
- 3) severe urticaria and asthma associated with hypotension.

Time of onset

All systemic adverse reactions were divided as follows:

- 1) those which were reported within 30 min
- 2) those reported at 30–60 min
- 3) late-phase adverse reactions, which appeared after 60 min.

Maintenance dosage

In all the clinics, our policy was to decrease the allergen IT dose during the relevant season by 30–50% of the maintenance dose, as in many centers (6, 9). Therefore, all systemic reactions recorded during the maintenance phase of therapy were in relation to that decrease.

Results and Discussion

Out of 280 IT-treated patients, 37 (13%) developed systemic adverse reactions. Twenty-six (70%) of these adverse reactions occurred in the buildup phase, whereas 11 (30%) occurred during the maintenance phase of treatment. All systemic adverse reactions were divided as in Table 1.

Severity of systemic reactions

Mild systemic reactions (grade 1) occurred in 15/37 (40%) patients. All required antihistamine treatment only. They occurred with no relation to any specific allergen, pollen season, or allergy activity. Moderate (grade 2) systemic reactions were recorded in 20/37 (54%) patients. In 17/20 patients, they were observed during spring or autumn, when mite and pollen concentrations were increased. During this period, both rhinitis and asthma required an increase of antiallergic treatment. In the remaining 3/20, systemic reactions developed without any relation to the pollen season or allergy activity. Severe (grade 3) adverse reactions developed in only 2/37 (5%) patients. Both needed s.c. epinephrine, responded well, and were discharged to their homes within 2 h. Both were recorded in the buildup phase of treatment and within 30 min after injection. The first was treated with Pj extract at the dose of 0.2 ml of 1:20 000 w/v, and the second with a mixture of mite and olive extract, at the doses of 100 IU and 0.3 of 1:2000 w/v, respectively.

Time of onset

In 22/37 (59%) of subjects, the adverse reactions occurred within 30 min after injection, when all patients were still in the clinic. This group included the two patients with severe systemic reactions. In 7/37 (19%), the adverse reactions appeared at 30–60 min, all with grade 2 severity. In the remaining 8/37 (22%), the adverse reactions developed at 1–2 h (3 with grade 1 severity and 5 with grade 2). It is of interest to note that in 7/11 patients on maintenance dose of IT, the adverse reactions occurred during the active pollen season, all with grade 2 severity. In four of them, the injected allergen was Pj.

Systemic adverse reactions, in their incidence, time of onset, and the needed waiting time after the allergen injection, may differ in different countries. This difference is probably due to the severity of the pollen season, its

duration, and the allergenicity of many pollens in that country. Another reason may be differences in injection schedules and dosages. Therefore, we believe that it is highly important to establish individual criteria for IT schedules and dosages, and follow-up time after IT injection in each country. In northern Israel, Pj is an important pollen, a frequent cause of allergy, for which IT was found to be highly effective. Our study shows that at least 27% of our systemic adverse reactions were caused by this pollen, probably due to its high allergenicity. (In another seven [19%], Pj was included in the mixed injections [Table 1]). Therefore, we think that special caution is required when patients are treated with this pollen.

Systemic reactions occurred frequently during the maintenance phase of therapy. In this regard, 7/11 (64%) of them occurred during the active flowering season and when patients were clinically unstable. This is an important consideration, especially when the pollen season is long, as it is in Israel.

Although 59% of our systemic reactions occurred within 30 min during the buildup phase of the treatment, 41% of our adverse reactions occurred after 30 min, and 8/37 (23%) more than 1 h later.

We believe that these results, namely, the frequency of adverse reactions during the maintenance phase of therapy, and their frequent late time of onset after some pollen injections, may be specific to this region, and cannot be explained only by the possible differences in injection schedules and dosages.

Based on the above findings, the following conclusions may be specific to Israel, and perhaps also to other, similar Mediterranean countries:

- 1) The severe systemic reactions occurred with a frequency similar to all the reported cases, and within 30 min after injection.
- 2) Pj is a highly allergenic pollen; therefore, systemic reactions after IT with this allergen are more frequent.
- 3) In Israel, where the active pollen season is long and severe, and highly allergenic pollens are included in IT, the reduction of the IT dosage of some allergens should be more than 50% during the pollen season.
- 4) In this study, 41% of the adverse reactions developed after more than 30 min. Therefore, a waiting period of 1 h should be considered, mainly when IT allergens are the highly allergenic ones.

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