

Expert Opinion

Risks and benefits of allergen immunotherapy

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Specific allergen immunotherapy is an effective method of causative treatment of IgE-dependent allergic disorders. Its safety is still a matter of concern especially because of the risk of life-threatening reactions. The side effects of immunotherapy may be divided into IgE- and non-IgE-dependent, early and late, mild or severe, local or systemic. In this article some aspects of side effects of immunotherapy, risk factors of their occurrence and the way of their management are discussed. Long-term consequences of immunotherapy, such as immune complexes disease and future trends in immunotherapy, are also covered.

Specific allergen immunotherapy is the only, beside avoidance of the offending allergens, causative treatment of IgE-mediated allergic disorders. The efficacy and safety of this mode of treatment has been well established in many well-controlled, well-designed studies. Allergen immunotherapy has been successfully used worldwide since near the beginning of the previous century; nevertheless, its safety is still a matter of concern.

Every medical procedure involves risk and burden. It is also the case with regard to allergen immunotherapy. One should remember this kind of treatment consists of the administration of gradually increasing doses of allergens to human beings hypersensitive to them aimed at inducing immune tolerance to the offending agents and consequently suppress the symptoms of the diseases. It constitutes the risk of anaphylaxis induction.

Apart from the undoubted advantages of allergen immunotherapy as the ability of significant suppression or even total remission of allergic symptoms and alteration of the natural evolution of allergic rhinitis with regard to diseases progression and onset of new sensitisations, this mode of treatment can produce life-threatening reactions [1-4].

Additionally, in spite of the great progress in the field, it remains to be further explained which of the changes in immune function occurring following immunotherapy are directly responsible for clinical improvement and may be used to monitor continuing the treatment. The awareness of this risk among the physicians dealing with allergen immunotherapy is essential for assuring the optimal safety of the patients undergoing this mode of treatment.

From the pathophysiological point of view, adverse reactions to the treatment are classified as IgE- and non-IgE-dependent, and with regard to the time of onset as early and late. Considering the extensiveness and intensity of the reactions, the division as mild and severe ones has been proposed [5].

The injection of allergen vaccine can induce:

1. *Local reaction (e.g., oedema, reddening, pain and itching).* Such reactions are usually not the herald of systemic reaction development and most of them can be managed without any treatment. Nevertheless, depending on the size of these reactions, the reduction of the following dose of allergen vaccine should be taken under consideration.

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Most allergists are used to reducing the following dose of injection in patients with local side effects depending on the size of this response, although it is not a standard of management. The results of some studies indicate the frequency of the systemic side and the effects of immunotherapy in the group of patients with and without dose reduction owing to the large local response to allergen vaccine, which is comparable. Nevertheless there are data giving the proof of the fourfold increase in the frequency of severe systemic reactions occurrence in patients with local side effects in the course of treatment in comparison with those with no adverse events to immunotherapy [6-9]. The results of these studies substantiate the American Academy of Allergy Asthma Immunology recommendations that caution should be exercised in the patients demonstrating extensive and repeatable local reaction to allergen vaccination [10].

2. *Systemic reactions: i) mild or moderate (e.g., rhinitis, urticaria, angioedema, asthma exacerbation).* Such reactions occur usually in one-third of patients (~ 2.5% of injections). Approximately 50% of them happen in 30 min and nearly all in 24 h after injecting the allergen vaccine. The management analogical to the above mentioned disorders is recommended. *ii) life-threatening reactions (e.g., larynx oedema, severe, nonresponsive to treatment asthma exacerbation and anaphylactic shock).* Such reactions happen in 0.8% of patients (~ 1/3000 injections) and nearly all occur in 30 min after allergen vaccine administration. Nevertheless, these reactions can occasionally occur in time longer than 30 min after the injection. It is important inasmuch as such dangerous reactions can happen in time exceeding the current recommended waiting time for allergen immunotherapy administrations.

There is general agreement that in comparison with local side effects the systemic allergic reactions to allergen vaccines are substantially less frequent but more severe [11,12].

Adverse reactions to allergen immunotherapy could be fatal, although it happens very rarely. It is worth noting that systemic but not life-threatening reactions happen comparably frequently in the group of patients with allergic rhinitis and concomitant asthma but those suffering only from asthma constitute the group of the highest risk of severe/fatal adverse events development. As the results of Bousquet [13] prospective study indicate, FEV1 (forced expiratory volume at 1 sec) value is a considerable enough predictive marker of that risk. The cutoff FEV1 measure is 80% of the predicted value. The more severe asthma the greater risk of fatal reactions to immunotherapy is proved. Thus, the spirometric evaluation at least of the PEF (peak expiratory flow) before every allergen vaccine application is highly recommended to be performed.

The frequency of the fatal reaction occurrence in the US in the years 1990 – 2001, based on questionnaire data obtained from practicing allergists, is rare: 3.4 deaths a year (1/2.5 million of injections) [14]. In Germany, in the

same time frame, an analysis of data gathered by central registration system indicated 3 deaths a year owing to specific immunotherapy [15]. Although the direct comparison of the results is difficult to perform because of the different evaluation methods applied, these data give evidence of the rare frequency of fatalities in the course of treatment.

According to the results of the above mentioned studies, non-fatal severe anaphylactic reactions happen more frequently, both in the US and in Germany, 23 and 7.7 events a year, respectively. Taking into account the German study was based on central registration of data one could assume that the results are at least to some extent underestimated.

It should be emphasised that frequency of non-fatal although severe anaphylactic reactions was comparable both in patients with allergic rhinitis and those with allergic rhinitis and concomitant asthma. But fatalities owing to the allergen vaccination were more frequent in patients suffering only from bronchial asthma.

It is worth bearing in mind that even mild allergic skin symptoms in the beginning can develop into anaphylactic shock. Moreover serious reactions can also develop in patients without prodromal symptoms as pruritus and urticaria. They are characterised by sudden onset of respiratory and cardiac disturbances. The time of onset of these reactions is irreversibly correlated with the degree of life hazard.

This is why physicians involved in the practice of immunotherapy have to constantly assess the medical status of their patients independently on the phase of treatment to avoid the severe adverse events, which can be fatal. The appropriate and timely treatment is essential. What is particularly important to note is that in the vast majority of fatalities owing to anaphylactic shock, there was either a substantial delay in adrenaline administration or even adrenaline was not administered.

What are the risk factors associated with adverse reactions to immunotherapy?

1. Dosage errors: too high dose of allergen/allergens or too short time frame between subsequent vaccine administration
2. Build-up period phase of the treatment particularly with regard to rush regime
3. Change of a vial or improper vial used
4. Extremely high sensitivity to allergen
5. Environmental exposure to the offending allergens
6. Inadvertent intravenous injection of allergen vaccine
7. Febrile diseases
8. Severe and/or uncontrolled asthma [16,17].

There are data allowing the belief that pretreatment with antihistamines can prevent the occurrence of side effects of immunotherapy. It can reduce the frequency and severity of adverse reactions to immunotherapy but it should be kept in mind that antihistamines do not prevent from the anaphylactic shock. It is worth mentioning the results from experimental studies that indicate the ability of antihistaminics to facilitate specific immune tolerance development in the

course of immunotherapy. Clinical observations published by Muller [18] confirm these preliminary experimental results. Further research aimed at answering the question about the role of histamine receptors in immune tolerance induction is highly warranted. Furthermore, antihistaminics can conceal the prodromal signs and symptoms of anaphylaxis. In this context the administration of these drugs in course of immunotherapy could even be perceived as being dangerous [19,20].

The combinations of anti-IgE monoclonal antibody with allergen immunotherapy has proved beneficial for the treatment of allergic disorders in terms of the ability to potentate immunomodifying effects of immunotherapy and limiting adverse effects of this treatment. The administration of anti-IgE during the induction phase of immunotherapy might reduce the risk of IgE-mediated anaphylaxis. These results encourage further investigations [21,22].

Allergen immunotherapy being perceived as immunostimulating treatment may induce, at least from a theoretical point of view, a synthesis of circulating immune complexes composed of allergen and blocking activity of IgG. However, this hypothesis can hardly be validated. First, the manifestation of allergic diseases is a consequence of exposure to a vestigial amount of allergen. Second, during conventional immunotherapy, very small amounts of allergen may get into the circulation.

Thus, it can be assumed that those complexes that constitute the combination of an allergen with an antibody are small. They undergo phagocytosis and are eliminated from circulation. As indicated the results of our study complexes isolated from sera of the patients who underwent specific immunotherapy by precipitation with solution of polyethylene glycol are presumably the combination of IgE with its antibody (IgE/anti-IgE). Hitherto, no data have been available to determine whether allergen immunotherapy induces the immune-complex diseases, in either the immunologic or the clinical sense [23,24].

The awareness of the risk of anaphylaxis being developed by injection immunotherapy stimulates the looking forward to new methods of allergen immunotherapy and contains the rationale for the sublingual route of allergen vaccination. The efficacy of this mode of treatment is close to the effect of subcutaneous immunotherapy. Safety profile according to the available data seems to be higher than injection vaccination

although not free from the risk of the severe anaphylaxis induction. The most frequently reported side effect is oral–sublingual itching, which in vast majority of cases is mild and self-resolving [25–29].

It is commonly known that specific allergen immunotherapy is the treatment of choice of hymenoptera venom hypersensitivity. Safety profile of this type of treatment is also a relevant issue. It is worth emphasising that the frequency of severe adverse events of this treatment modality is lower than those observed in the course of immunotherapy of inhalant allergy. Most of them were reported in build-up doses phase and only one-third required treatment. Severe systemic reactions mainly occur during ultra-rush regimen. Risk has also been proved to be higher in female and in bee-venom sensitised subjects. It raises interest that severity of the insect sting allergic reaction is not related to the risk of severe adverse events.

Apart from the efficacy, safety of specific allergen immunotherapy has been the subject of many well-designed, well-controlled studies since it was introduced at the turn of the previous century. Nevertheless, when the management is optimal (adequately selected patients, correct allergen vaccines administered under the supervision of highly qualified physicians), the risk of adverse reactions is low and fatal reactions are extremely rare. Such stance is commonly accepted by international experts and supported by the results of many recently published studies.

Our knowledge of complex cellular/molecular network of IgE-dependent reactions has been constantly advancing. Thus, other attractive approaches to specific treatment of allergic disorders have been proposed. They consist of the application of recombinant allergens, immunisation with DNA-encoding allergen proteins and peptides derived from immunodominant domains of the major allergens. These methods do not constitute any risk of anaphylaxis; they offer promise in reducing the risk of adverse events and optimal benefit of the treatment.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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