PRACTICAL DRUG SAFETY

Drug Safety 2000 Oct; 23 (4): 323-332
0114-5916/00/0010-0323/$20.00/0

Minimising the Risks of Allergen-Specific Injection Immunotherapy

Hans-Jørgen Malling

Allergy Unit, National University Hospital, Copenhagen, Denmark

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Abstract

The clinical advantages of allergen-specific immunotherapy are counterbalanced by the risk of inducing systemic adverse effects. Although the frequency of life-threatening systemic reactions is low, the treatment carries a risk of inducing anaphylactic reactions. A fundamental point in risk assessment is to use a clinically meaningful and internationally accepted grading system for reactions. Of importance in minimising the risk of systemic adverse effects is the identification of at-risk patients and factors, the institution of procedures for monitoring patients before injections, and the adjustment of dosages in accordance with defined rules. Asthma, especially uncontrolled asthma, is a significant risk factor for the induction of systemic reactions. Likewise, dose escalation during allergen exposure, i.e. during pollen seasons, increases the risk of adverse effects. It is recommended that standardised extracts with a documented potency and consistency between production batches are used in order to prevent overdose when changing to a new vial.

The intensity of the induction regimen is a balance between the risk of inducing

systemic reactions and the time required to administer the regimen. Single injections once a week are generally well tolerated, in contrast to rush immunotherapy which may carry an increased frequency of adverse effects. A clustered induction regimen (2 to 4 injections per visit) represents a compromise of a patient-friendly fast regimen without an unacceptably high frequency of systemic reactions.

A major issue in improving the safety of allergen injections is minimising the human factor, e.g. mistakes of patient identification, allergen extracts and dosages. Meticulous care in monitoring every patient before the injection, which requires education and training of the staff in the dosage decision process, is the cornerstone in reducing adverse effects. Involving the patient actively in the safety monitoring process might be helpful and improves patient compliance by allowing the patient to be an active partner in the treatment. Finally, if anaphylactic reactions are induced, a successful outcome is related to the staff being able to identify the early signs and to institute immediate rescue treatment. A quality assurance programme is the optimal way to minimise the risk of immunotherapy-associated systemic reactions.

1. Risks of Allergen-Specific Injection Immunotherapy

The clinical efficacy of allergen-specific injection immunotherapy in the treatment of allergies is well documented.[1-3] A major limitation which has restricted its use is systemic adverse effects, as injection of allergens into an immunoglobulin (Ig) E-sensitised individual always carries a risk of inducing anaphylactic adverse effects.[1-3] Systemic adverse effects are caused by exceeding the patient's tolerance, i.e. by injecting a dose of allergen that triggers an extensive release of histamine and other mediators from mast cells and basophils.

The frequency and severity of systemic reactions vary between studies, depending on patient selection, disease, allergen extract and formulation, and induction regimens. Evidence suggests that the patients most likely to have anaphylactic reactions are highly allergic patients, based on skin test or specific IgE-tests, and patients with more severe disease, e.g. with asthma.[4] Systemic adverse effects occur more frequently during induction than during maintenance treatment.[2,5-8] Some studies report a lower frequency of systemic adverse effects with the use of standardised aluminium extracts compared with aqueous extracts and a reduction in the number of injections required to reach the maintenance dose.[2,6]

Some practical guidelines to reduce the risk of inducing systemic adverse effects may be valuable for the practising allergist. A problem is that limited scientific documentation exists and most guidelines are based on empiric observations. This paper attempts to summarise guidelines based on position papers,[2,3] but many of the recommendations herein are solely the author's experience from many years' use of the treatment.

1.1 Grading of Systemic Adverse Effects

When discussing the frequency of systemic adverse effects a grading system is essential. Systemic adverse effects may vary from a few sneezes to fulminant anaphylactic shock and even death.[2,3] Systemic reactions can be categorised into immediate systemic reactions (occurring within 30 minutes) and late systemic reactions (arising >30 minutes after injection). A useful grading system has been proposed in the European Academy of Allergology and Clinical Immunology (EAACI) Immunotherapy Position Paper[2]:

- Grade 0: No symptoms
- Grade 1: Nonspecific symptoms probably not IgE-mediated, i.e. discomfort, headache, arthralgia, etc
- Grade 2: Mild systemic reactions, e.g. mild rhi-

nitis or asthma responding adequately to antihistamines or inhaled β_2-agonist
- Grade 3: Non–life-threatening systemic reactions, e.g. urticaria, angioedema, or severe asthma, responding well to treatment
- Grade 4: Anaphylactic shock, e.g. rapidly evoked reaction of itching, flushing, erythema, bronchial obstruction, etc. requiring intensive treatment.

1.2 Frequency of Systemic Adverse Effects

The frequency of systemic adverse effects varies substantially in various studies, and comparisons may be difficult because of differences in allergen sensitivity in treated groups and the concentration of allergen extract used as the therapeutic dose. Looking at controlled studies published since 1980,[1] 15% of 68 papers did not provide any information on adverse effects (this may be attributable to either no adverse effects occurring or the authors not considering it important enough to report). Immunotherapy does not always induce systemic reactions as no immunotherapy-related adverse effects were observed in 26% of the studies. In the remaining studies, a mean of 24% of the patients experienced various degrees of adverse effects, mostly mild. In only a few cases did life-threatening reactions require the administration of epinephrine (adrenaline). Generally, but not consistently, aqueous extracts elicited more systemic adverse effects than depot preparations.[1,4,5,7,9]

In daily practice based on a rather large population of patients (>2000) and a high number of injections (almost 200 000), systemic adverse effects were observed in 115 patients, corresponding to 5.2% of the patients or 0.06% of the injections.[9] Data from the author's clinic using various clustered induction regimens in 657 adult patients (10 369 injections) with rhinitis, asthma, and *Hymenoptera* venom allergy showed important systemic adverse effects (EAACI[2] grade 3 and 4) in 4.3% of the patients.

2. Risk Factors

2.1 Patients

Patients allergic to Hymenoptera venom are often considered to have a greater risk of immunotherapy-induced systemic adverse effects, as these patients have previously experienced anaphylactic reactions. Depending on the dosage regimen and allergen extract formulation, the frequencies of serious adverse effects have been reported to be 5 to 10%.[10] Based on our own data using a clustered induction regimen and a depot insect venom extract, results in 117 such patients showed a lower general risk of adverse effects compared with 540 patients treated with inhalant allergens using an identical induction regimen (total frequency of adverse effects grade 2 to 4 was 9.4% in patients treated with *Hymenoptera* venom and 27.6% in patients treated with inhalant allergens). The frequency of more severe reactions in patients allergic to *Hymenoptera* venom was, however, comparable with inhalation allergy (3.4 *vs* 4.4%). This suggests that these patients as a group experience a low incidence of adverse effects, but when they do have a reaction, it is more likely to be of the life-threatening anaphylactic type.

Several studies have documented that patients with asthma are at a higher risk of adverse effects.[4,5,11] Furthermore, uncontrolled asthma further increases the risk of adverse effects,[4] which also is the problem with severe asthma with persistently reduced lung function <70% of predicted.[12] The higher frequency of adverse effects in patients with asthma is most likely related to the size of the shock organ (lungs *vs* upper airways in patients with rhinitis). This suggests the possibility that in patients with asthma a higher number of mast cells may be activated, and also that these patients have a higher degree of hyper-reactivity.

It might be of importance that the allergen extracts used most often in asthma are perennial allergens, i.e., house dust mites and domestic pets like cats and dogs. These are allergens to which the patient might have been exposed close to the time of injection. A recent exposure to a cat, for exam-

ple, might induce subclinical asthma not detected by the monitoring of the patient before the injection, but which will increase the susceptibility of the patient and consequently the risk of systemic adverse effects. In mite allergy, persistent minimal inflammation caused by low grade exposure to the allergen might also increase the susceptibility of the patient.[13]

Patients with the lowest degree of adverse effects, and consequently the easiest to treat outside specialised units, are those with hay fever treated outide the pollen season. When considering the higher risk of patients with asthma a genuine effect of the allergen source cannot be ruled out, but mostly this is a matter related to the potency of the extract. The severity of the disease is mainly of importance when dealing with asthma.

It is generally recommended that immunotherapy (induction treatment) is not started during allergen season.[2] In many parts of the world this is not problematic when using pollens in patients with seasonal hay fever. However, when using perennial allergens the induction phase is performed in patients exposed to the allergen in question. Furthermore, it includes a high proportion of patients with asthma and consequently more severe disease and a higher risk of inducing adverse effects. The age of the patient might also influence the frequency of adverse effects, as some studies have shown a higher frequency of adverse effects in children below the age of 5 years compared with adults.[14]

2.2 Allergen Extracts

Most controlled studies documenting clinical efficacy of immunotherapy have been performed with aqueous extracts.[1,3] The advantage of aqueous extracts is that life-threatening systemic adverse effects evolve rapidly, i.e., within 30 minutes (and usually within 2 to 10 minutes). This means that anaphylactic reactions appear while the patient still is under observation in the physician's office.[2] The use of aqueous extracts suggests that immediate access to mast cell-bound-IgE may be the reason for the high frequency of systemic adverse effects.

Over the last 20 to 30 years, new formulations of allergen extracts for immunotherapy have been developed with the aim of reducing the IgE-binding capacity and, consequently, the risk of inducing systemic reactions. One approach is the use of depot extracts (slow release) to prevent the extensive exposure of mast cells to allergens.[2,3] Several 'depots' have been used: oil, aluminium, polyethylene glycol, calcium, liposomes, etc. The slow release formulations prevent a massive degranulation of mast cells and consequently an anaphylactic reaction. Their success is related to the capacity to reduce the risk of adverse effects and retain the clinically active allergen in a form that may interact with and stimulate the immune system to ensure clinically effective extracts.

Another approach is to reduce the allergenicity of the extract, i.e., the capacity to induce mast cell degranulation, by physical or chemical modulation of the IgE-binding allergenic determinants (epitopes).[2,3] The fundamental success of this modification depends on whether it is possible to modify the IgE-binding epitopes of the allergen, i.e. to reduce allergenicity, without destroying allergen sites important for the immune response essential for clinical efficacy. Most of the studies employing modified extracts have documented a reduction in the frequency of adverse effects, mostly without a loss of efficacy.[1-3,15]

The potency of the extracts is related to the risk of inducing adverse effects.[16] Use of high potency extracts increases the frequency of adverse effects. The individual susceptibility to allergen administration varies according to sensitisation, indicating a varying tolerance in individual patients. This may be a problem when applying standard doses to all patients. In discussions of allergen standardisation and calibration, it is often claimed that the use of standardised extracts improves their safety.[17] This is only correct when changing batches (using a new vial), as standardisation reduces the risk of important differences in potency between different batches. Standardisation ensures that different production batches do have a potency (total biologic activity) within predefined limits.[3,17] However, if only 1

batch is used for immunotherapy, the standardised extracts are not better tolerated than unstandardised extracts. Occasionally the opposite is the case, as some standardised extracts are more potent than unstandardised extracts.

2.3 Dosage Regimens

The intensity of the induction regimen is also related to the risk of inducing adverse effects. A regular 'one injection per week' regimen is the most common. Induction regimens using a gradual increase of appropriate doses over 10 to 15 weeks are well tolerated in most patients.[1,2] The problem with extensive induction regimens is that there is a risk of low patient compliance, since many visits to the doctor's office may be required and consequently much time may be spent travelling and waiting.

It should also be noted that, to a certain degree, the risk of adverse effects is related to the number of injections needed to reach the maintenance dose. Simply extending the induction phase does not necessarily improve the safety of the regimen.

To speed up the induction phase, and thereby make the treatment more user-friendly, more rapid induction regimens have been investigated. The fastest is rush allergen-specific immunotherapy, in which injections are given every 30 to 60 minutes and the highest dose reached in 2 to 3 days. The risk of adverse events with rush allergen-specific immunotherapy is, however, substantially higher compared with conventional allergen-specific immunotherapy.[1-3] On the other hand, using some ultra-fast regimens, in which a maximum dose of 100μg venom was reached in 3.5 hours in patients allergic to *Hymenoptera* venom, no adverse effects were observed.[18] For practical purposes, this treatment necessitates hospitalisation of the patient.

A compromise approach that hastens the induction phase without increasing the frequency of adverse effects to an unacceptably high level is to use clustered induction regimens. This involves administering 2 to 4 injections in a series and then continuing with another series 1 to 2 weeks later.[19] Maintenance dosages may be reached in 6 to 8 weeks at the expense of only a slight increase in adverse effects.

2.4 The Human Factor

The most important risk factor for inducing systemic adverse effects is the human factor. Mistakes of patient identification, allergen extracts, concentrations and volumes constitute a substantial proportion of errors resulting in systemic reactions.[20] Likewise, the severity may progress from mild to life-threatening anaphylactic reactions because of insufficient observation and identification of emerging systemic reactions and inadequate treatment.[2]

3. Procedures to Minimise the Risk

The greatest problem when suggesting guidelines for practical allergen-specific immunotherapy is the lack of evidence-based information. Often, authors of controlled studies do not give useful practical information or refer to international position papers.[2,3] Consequently, the present recommendations are based on scientific information as far as possible. Nevertheless, several safety procedures are exclusively based on the authors' long term experience. These observations attempt to identify risk factors systematically and to improve safety, by balancing time consumption and patient inconvenience against the risk of inducing systemic reactions.

3.1 Selection of Patients

Careful evaluation of the patient and adhering to accepted guidelines for the indication[2,3] will ensure that only patients suitable for allergen-specific immunotherapy will be offered this kind of treatment. In patients with asthma, careful exclusion of patients with chronic irreversibly reduced lung function is important as these patients have a higher risk of systemic adverse effects and a poor response to treatment.[21] Exclusion of patients with other risk factors,[2,3] especially patients that *per se* have an increased probability of developing systemic reactions, is part of the patient evaluation procedure by experienced allergists.

Regarding age, most paediatricians only recommend allergen-specific immunotherapy after the age of 5 years.[2,3] When allergen-specific immunotherapy is prescribed before 5 years of age, it is critical that the physician responsible for the injections is able to identify emerging signs of anaphylaxis and to treat this critical emergency adequately, including mastering the administration of an intravenous line.

3.2 Organisation of Allergen-Specific Immunotherapy Office Facilities

The practical organisation of office facilities may improve the safety of allergen-specific immunotherapy. In particular, the postinjection observation and supervision of patients are important. To recognise the early signs of an impending anaphylactic reaction it is important that the staff are able to have both visual and audible contact with the patients (sneezing may be an early warning sign). Isolating patients receiving allergen-specific immunotherapy from other patients in 1 room where they can be watched collectively may help identify emerging anaphylactic reactions, and can minimise 'noise' from patients present in the office for other reasons. Open waiting facilities in direct proximity with the injection office will improve the observation.

Likewise, emergency facilities should be in direct proximity to the waiting room to avoid transportation of patients with anaphylaxis and to allow emergency treatment to be instituted immediately. The emergency room should be equipped with resuscitation equipment for treating anaphylactic reactions. According to the World Health Organization Immunotherapy Position Paper[3] this should include: (i) stethoscope and sphygmanometer; (ii) tourniquets, syringes and needles; (iii) epinephrine for injection [1 mg/ml for intramuscular and subcutaneous administration and 0.1 mg/ml for intravenous injection]; (iv) equipment for administering oxygen; (v) equipment for administering intravenous fluids; (vi) oral airway; (vii) antihistamine for injection (and oral administration); (viii) corticosteroids for intravenous injection and; (ix) a vasopressor.

In settings carrying a high risk of anaphylactic reactions and where the facility is distant from intensive care units, equipment for direct laryngoscopy, DC cardioversion, tracheotomy and intracardiac injections may be optional. However, the rare situation in which these procedures might be essential does not demand that these procedures and equipment are immediately available in facilities where allergen-specific immunotherapy is performed.[3]

3.3 Education of Staff and Patients

Education of responsible staff in the principles of allergen-specific immunotherapy is essential for the correct monitoring and treatment of patients. Nurses and technicians may be taught to manage most patients given allergen-specific immunotherapy using a training programme and close direct observation during the training process. It is essential that the indication for allergen-specific immunotherapy is established by an experienced specialist and that injections are given under the auspices and responsibility of an experienced physician.[3]

When nonphysicians perform allergen-specific immunotherapy, it is critical that a well-trained physician is immediately available in the office for decision-making in case of doubt and for the treatment of anaphylactic reactions. If injections (and the decision on allergen dose) are made by nonphysicians, clear delegation of responsibility and competence should exist (optimally in written form). The staff should be regularly trained in the treatment and recognition of anaphylactic reactions.

In Europe it is recommended that the induction phase be carried out by an allergist, as the risk of systemic reactions is highest during this phase.[2] The patient may continue maintenance allergen-specific immunotherapy by a general practitioner (GP) in close collaboration with the specialist (under condition that the GP has sufficient training and experience).[2] In some parts of the world, the induction phase might be undertaken by GPs with instructions provided by an allergist, for practical reasons such as lack of proximity to a specialist.

Training of the patient in practical aspects such as preinjection monitoring and decisions on actual allergen dose and self-observation of early warning signs of anaphylaxis may improve safety (and com-

pliance). Based on the authors' experience, incorporating the patient in the checking of the allergen extract, batch number, concentration, dose, and expiry date will ensure a greater understanding of the principle of immunotherapy, and will give the patient the feeling of being an active partner in his/her treatment. Furthermore, the gained knowledge may be helpful in immunotherapy settings under less ideal circumstances (e.g. when GPs need to administer the treatment).

3.4 Standards (Clinical Guidelines) for Treatment

It is recommended that detailed written clinical guidelines for the practical treatment should be formulated based on international standards, including the organisation and delegation of competence and responsibility. These guidelines should, whenever possible, be evidence-based and regularly updated. The guidelines should give clear and unequivocal information on:

- how to handle allergen extracts
- the technique of deep subcutaneous injection, including aspiration and how to handle the occurrence of aspirated blood
- different induction regimens
- safety procedures including procedures for checking of rescue equipment
- defining actual allergen dose based on the preinjection monitoring of the patient
- deciding when to postpone an injection, when to administer a reduced dose or whether not to give increments of the dose
- how to administer extracts and calculate doses during exacerbations, during allergen season and in case of intercurrent infections and other diseases
- how to diagnose and treat local and systemic reactions.

From a legal point of view, sticking to the standards will place the responsibility for emergencies in the hands of the head of the office, while on the other hand, breaking the rules places the responsibility on the person performing the injections. The use of recording forms is recommended for the documentation of the safety procedures and to document dosages and possible adverse effects.[2] Table 1 outlines some recommendations for minimising the risk of adverse systemic reactions.

3.5 Preinjection Monitoring of Patients

Before deciding on the dose of allergen, a careful evaluation of the patients' suitability to receive the scheduled dose represents a crucial step to avoid systemic adverse effects.[2] Recent infections, especially in the airways, within the last 3 days suggest the injection should be postponed until the patient is recovered.[2] Likewise, recent exposure to allergens (allergen season or accidental exposure, e.g. to pets) also can mean postponing the injection if the patient has clinical symptoms.[2,3]

The planned allergen dose should be reduced in the case of a systemic reaction at the preceding visit. The magnitude of reduction depends on the severity of the reaction. In the case of anaphylactic and other life-threatening reactions, the continuation of immunotherapy should be carefully evaluated (except in case of *Hymenoptera* venom allergy, in which it actually reinforces the indication for immunotherapy).

Traditionally, the late local reaction at the injection site has been used to adjust the allergen dose at the next allergen administration. Several studies have indicated that the late local reaction at the preceding injection is not related to a risk of developing a systemic reaction at the next injection.[19,22]

During allergen season, injections should not be given if the patient has clinical symptoms.[2] As a general safety precaution, a routine reduction in allergen dose during allergen season is commonly used,[2,3] but if the patient is symptom-free, experiences from the authors' clinic indicate that the dose does not need to be reduced. In patients with symptoms, the injection should be postponed, symptomatic treatment instituted (or intensified), and the allergen dose reduced when the patient is asymptomatic. In patients with asthma, subclinical bronchial obstruction should be detected before giving the injection[2,3] and measuring lung function before each injection is mandatory (peak flow is sufficient).[2]

Table I. Recommendations to minimise the risk of inducing systemic reactions

Evaluation of the patient for suitability to receive injections
Postpone injections in patients with airway infections or other important diseases within the last 3 days
Postpone injections in patients with deterioration of allergy symptoms or increased need for antiallergic drugs due to recent allergen exposure within the last 3 days
Postpone injections in patients with decreased lung function (peak flow or FEV_1 <80% of personal best)
Reduce the scheduled dose if the interval between injection sessions has been exceeded
Reduce the scheduled dose in patients with systemic reactions after the preceding injection
(Optional) Reduce the scheduled dose during allergen season in symptom-free patients (in symptomatic patients the injection should be postponed)
(Optional) Reduce the dose when changing to a new vial
Safety procedures
Control of patient identification, changes in drug treatment and correct allergen extract, concentration, dose, and expiry date
Inform the patient of the early signs of anaphylaxis, and instruct them to notify the staff
Ensure a responsible physician is present
Resuscitation equipment and postinjection observation
Ensure the presence and optimal function of resuscitation equipment
Constant observation of patients for 30 minutes after injections
Education of staff and patients
Regular training of staff in preinjection monitoring of patients, decisions on dose, and identification and treatment of systemic reactions
Written guidelines on practical aspects of the treatment
Make the patient an active partner to the treatment by including them in the safety procedures

FEV_1 = forced expiratory volume in 1 second.

The preinjection monitoring of the patient also includes a check of drug intake that may either increase the risk of systemic adverse effects or render the treatment of anaphylactic reactions more difficult; of these, β-blockers are the most important.[2,3] Heavy beer drinking may similarly increase the risk because of the inhibition of the histamine-converting enzyme diamine oxidase.[23]

3.6 Pretreatment with Antihistamines

In several reviews, the routine use of antihistamines as pretreatment has not been recommended because of the potential risk of masking mild systemic reactions and, by continuing to escalate the dose, inducing a severe anaphylactic reaction.[2,3] Some controlled studies have not supported this assumption, and have, on the contrary, shown a significant reduction in both the frequency and the severity of systemic reactions.[24] Before a general recommendation can be made for intervention with antihistamine pretreatment, more large-scale controlled studies need to be performed.

3.7 Identification and Treatment of Systemic Adverse Effects

The most important safety aspect in immunotherapy is of course to avoid inducing systemic adverse effects. However, after parenteral administration of the causative allergen to an IgE-sensitised person, systemic reactions will unavoidably occur.[2,3] An important aspect of safety procedures relates to the observing staff and their ability to identify the early signs of an impending systemic reaction and to start rescue treatment promptly.[2] The earlier in the course of a developing systemic reaction treatment is instituted, the milder the reaction, and the less risk that it will progress to a life-threatening anaphylactic reaction.

The severity of the reaction is mostly directly related to the interval between injection and the development of clinical symptoms. Symptoms starting within the first 5 minutes after the injection are likely to be more severe, requiring intensive treatment, and increase the risk of progressing to anaphylactic shock.[25,26]

On the other hand, symptoms developing 20 to 30 minutes after injection often progress more slowly and do not require the same intensive emergency treatment. Of course, late symptom onset does not exclude progression to anaphylactic shock, especially when using slow release depot extracts, and the severity of the reaction in progress should never be underestimated or insufficiently treated.

The treatment of choice, and the only drug that can reverse all the pathophysiological events involved in the anaphylactic reaction, is epinephrine.[2,3] Epinephrine should be administered in sufficient dosages (depending on the size and age of the patient and, to a lesser extent, on the severity of symptoms), and by the appropriate parenteral route. In most patients intramuscular injection is preferred. Subcutaneous injection may be acceptable for patients with mild reactions but, as the subcutaneous circulation may be compromised without other signs of shock, the intramuscular route circumvents this problem. In patients with more severe anaphylactic shock intravenous injection may be needed. In that case the use of 10-fold diluted epinephrine is recommended.[27] In more severe cases general guidelines for shock treatment must be followed.

4. Conclusion

Allergen-specific immunotherapy is, based on the documented clinical efficacy in selected patients, a useful tool in allergy disease management and potentially can positively modify the natural course of the disease. The advantages of combining symptomatic drug treatment with a disease-modifying intervention should be seriously considered in all patients with clinical symptoms induced predominantly by allergens. Some major problems in the widespread use of immunotherapy are related to the risk of inducing systemic adverse effects. The very principle of immunotherapy (involving injections of allergen extracts into IgE-sensitised persons) carries a risk of anaphylactic reactions. The risk is substantially increased when such immunotherapy is undertaken by inexperienced physicians. The immunotherapy principle requires a high degree of skill and experience to identify risk factors and, based on the interpretations of these, to adjust allergen doses and consequently reduce the risk of adverse events associated with the treatment. As immunotherapy is no longer a routine procedure in many parts of the medical community, its use in untrained hands may increase the frequency of systemic adverse effects or reduce the clinical efficacy (by use of insufficient allergen doses in an effort to avoid systemic reactions).

The only way to bypass this problem is to centralise allergen-specific immunotherapy to centres with sufficient practical experience, and to educate the staff dealing with patients receiving immunotherapy continuously. A quality assurance programme dealing with safety procedures, patient selection and monitoring, and practical administration of this therapy is the only way to minimise the risk of systemic reactions associated with allergen-specific immunotherapy.

References

1. Malling H-J. Immunotherapy as an effective tool in allergy treatment. Allergy 1998; 53: 461-72
2. Malling HJ, Weeke B. EAACI Immunotherapy position papers. Allergy 1993; 48 Suppl. 14: 9-35
3. Bousquet J, Lockey RF, Malling H-J, editors. WHO Position Paper. Allergen immunotherapy: therapeutic vaccines for allergic diseases. Allergy 1998; 53 Suppl. 44: 1-42
4. Bousquet J, Hejjaoui A, Dhivert H, et al. Immunotherapy with a standardized Dermatophagoides pteronyssinus extract. III. Systemic reactions during the rush protocol in patients suffering from asthma. J Allergy Clin Immunol 1989; 83: 797-802
5. Tabar AI, Garcia BE, Rodriguez A, et al. A prospective safety-monitoring study of immunotherapy with biologically standardized extracts. Allergy 1993; 48: 450-3
6. Østerballe O. Side effects during immunotherapy with purified grass pollen extracts. Allergy 1982; 37: 553-62
7. Greenberg MA, Kaufman CR, Gonzalez GE, et al. Late and immediate systemic allergic reactions to inhalant allergen immunotherapy. J Allergy Clin Immunol 1986; 77: 865-70
8. Wells JH. Systemic reactions to immunotherapy: comparisons between two large allergy practices. J Allergy Clin Immunol 1996; 97: 1030-2
9. Ragusa FV, Passalacqua G, Gambardella R, et al. Nonfatal systemic reactions to subcutaneous immunotherapy: a 10-year experience. Invest Allergol Clin Immunol 1997; 7: 151-4
10. Müller U, Mosbech H, editors. Immunotherapy with Hymenoptera venom, Position Paper. Allergy 1993; 48 Suppl. 14: 37-46
11. Reid MJ, Lockey RF, Turkeltaub PC, et al. Survey of fatalities from skin testing and immunotherapy 1985-1989. J Allergy Clin Immunol 1993; 92: 6-15
12. Global strategy for asthma management and prevention. WHO/NHLBI workshop report. In: National Institutes of Health, National Heart, Lung and Blood Institutes, Publication no. 95-3659, Bethesda (MD): 1995

13. Ciprandi G, Buscaglia S, Pesce G, et al. Minimal persistent inflammation is present at mucosal level in patients with asymptomatic rhinitis and mite allergy. J Allergy Clin Immunol 1995; 96: 971-9
14. Hejjaoui A, Dhivert H, Michel FB, et al. Immunotherapy with standardized *Dermatophagoides pteronyssinus* extract. IV. Systemic reactions according to the immunotherapy schedule. J Allergy Clin Immunol 1990; 85: 473-79
15. Bousquet J, Michel FB. Safety considerations in assessing the role of immunotherapy in allergic disorders. Drug Saf 1994; 10: 5-17
16. Haugaard L, Dahl R, Jacobsen L. A controlled dose-response study of immunotherapy with standardized, partially purified extract of house dust mite: clinical efficacy and side effects. J Allergy Clin Immunol 1993; 91: 709-22
17. Dreborg S, Frew A, editors. EAACI allergen standardization and skin test position paper. Allergy 1993; 48: 49-83
18. Birnbaum J, Charpin D, Vervloet D. Rapid Hymenoptera venom immunotherapy: comparative safety of three protocols. Clin Exp Allergy 1993; 23: 226-30
19. Malling H-J, Dreborg S, Weeke B. Diagnosis and immunotherapy of mould allergy. V. Clinical efficacy and side effects of immunotherapy with *Cladosporium herbarum*. Allergy 1986; 41: 507-19
20. Vervloet D, Khairallah E, Arnaud A, et al. A prospective national study of the safety of immunotherapy. Clin Allergy 1980; 10: 59-64
21. Bousquet J, Hejjaoui A, Clauzel AM, et al. Specific immunotherapy with a standardized Dermatophagoides pteronyssinus extract. II. Prediction of efficacy of immunotherapy. J Allergy Clin Immunol 1988; 82: 971-7
22. Mosbech H, Dirksen A, Dreborg S, et al. Hyposensitization in asthmatics with mPEG-modified and unmodified house dust mite extract. IV. Occurrence and prediction of side effects. Allergy 1990; 45: 142-50
23. Wantke F, Demmer CM, Götz M, et al. Inhibition of diamine oxidase is a risk in specific immunotherapy. Allergy 1993; 48: 552
24. Nielsen L, Johnsen ER, Mosbech H, et al. Antihistamine premedication in specific cluster immunotherapy: a double-blind, placebo-controlled study. J Allergy Clin Immunol 1996; 97: 1207-13
25. Lockey RF, Benedict LM, Turkeltaub PC, et al. Fatalities from immunotherapy (IT) and skin testing (ST). J Allergy Clin Immunol 1987; 79: 660-77
26. Hejjaoui A, Ferrando R, Dhivert H, et al. Systemic reactions occuring during immunotherapy with standardized pollen extracts. J Allergy Clin Immunol 1992; 89: 925-33
27. AAAI Board of directors. Guidelines to minimize the risk from systemic reactions caused by immunotherapy with allergenic extracts. J Allergy Clin Immunol 1994; 93: 811-2

Correspondence and offprints: Dr *Hans-Jørgen Malling*, Allergy Unit 7551, National University Hospital, Blegdamsvej 9, DK-2100 Copenhagen, Denmark.
E-mail: all-unit@rh.dk