

Original Article

Standards for practical allergen-specific immunotherapy

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Foreword

The paper was drafted by Emilio Alvarez-Cuesta (chairman), *Spain*, Jean Bousquet, *France*, G Walter Canonica, *Italy*, Stephen Durham, *England*, Hans-Jørgen Malling, *Denmark* and Erka Valovirta, *Finland*. The paper was revised and input added by a European Reference Group, endorsed by National Societies associated EAACI and approved by the Executive Committee of EAACI.

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Introduction

This paper was produced to establish a common European Standard for Practical Allergen-Specific Immunotherapy that could serve as an overall 'gold standard' to ensure optimum quality for this form of treatment. WHO defines quality of health care as a 'high professional standard', 'effective use of resources', 'minimal patient risk', 'high patient satisfaction' and 'continuity in patient care'. These Standards are minimum requirements for Best Clinical Practice and form the basis for a Quality Assurance Programme. It is intended that the Standards should be an inspiration for local Clinical Guidelines (more comprehensive local guidelines for immunotherapy) that are adapted to National regulations, local conditions and related to the service and the patients. The Clinical Guidelines should be available, known and understood by all staff dealing with allergen-specific immunotherapy.

The greatest problem encountered in trying to provide standards related to practical immunotherapy is the lack of evidence-based information. Consequently, the present standards are based on scientific information as far as possible. The statements of evidence follows the rules of WHO based on Shekelle PG, Woolf SH, Eccles M, Grimshaw J. Clinical guidelines: developing guidelines. *BMJ* 1999;318:593–596. Dosing adjustments and safety procedures are based on evidence (when existing) combined with the authors' long-term experience and system-

atic attempts to make the treatment as rational as possible, to identify risk-factors and to improve safety balancing time consumption and patient inconvenience and the risk of inducing systemic reactions.

Immunotherapy glossary

Allergen denotes a protein or glycoprotein capable of binding IgE. Most allergens are derived from naturally occurring substances like pollens, animal hair and dander, insects, moulds, foodstuffs etc. Allergenicity is related to the conformational structure of the folded protein recognized by the Fab part of the IgE molecule.

Allergen product means a biologic product including allergens or allergen components administered to man for diagnosis, prevention and treatment of allergy and allergic diseases. *Allergen extracts* are solutions of allergens extracted from source materials. *Allergen vaccines* is a term used for therapeutic products in some publications.

Allergen-specific immunotherapy is the practice of administering gradually increasing quantities of an allergen product to an individual with IgE-mediated allergic disease in order to ameliorate the symptoms associated with subsequent exposure to the causative allergen. Other terms used in the past include *desensitization*, *hyposensitization*, and *allergy vaccination*.

Allergic anaphylaxis is a severe immediate systemic reaction occurring in IgE-sensitized individuals after exposure to an allergen. It is caused by the rapid release of vasoactive mediators from mast cells and basophils. *Anaphylactic shock* implies a drop in blood pressure.

Cluster immunotherapy the term for the administration of two or more injections per visit with the aim to achieve the maintenance dose more rapidly than by the conventional 'one-injection-per-week' schedule. Cluster immunotherapy saves time with the cost of a slightly increased frequency of side effects.

Desensitization is a previously used term for allergen-specific immunotherapy. Now mostly used in relation to making effector cells less responsive or nonreactive by the (continuous) administration of incremental doses of an allergen or allergenic substance. Desensitization is most often used for the treatment of allergic reactions to

penicillins in patients with an urgent need for penicillin. Desensitization does not induce a long-lasting immunological tolerance as the effect is related to occupying reactive IgE-molecules rather than changing the immune response.

Immunomodulation relates to altered immune responses induced by a variety of interventions. Includes changes in specific T and B cells, immune deviation, anergy or tolerance, modification of inflammatory pathways like adhesion, chemotaxis, or signalling within or between immunocompetent cells.

Immunotherapy is a general term for the treatment of immunologic diseases. It includes both active and passive immunization for improving a host's defences against microorganisms. A number of diseases are treated by immunotherapy now involving clonal deletion, tolerance and immune deviation. Except for immunotherapy in allergic diseases, the use in other immunologic diseases is immunologically nonspecific (not applying a specific antigen).

Major allergen refers to an antigenic determinant (epitope) from a complex allergen binding IgE in > 50% of patients sensitive to the allergen, as detected by immunoblot or electrophoresis. For the individual patient a minor allergen (binding < 50% of IgE) might clinically represent a 'major' allergen in inducing clinically symptoms.

Rush immunotherapy is a form of immunotherapy in which injections are administered at 30- to 60-min intervals implying that the maintenance dose might be reached within hours or days. The technique might be advantageous if rapid protection is needed (like in Hymenoptera venom allergy), or when geographic conditions make the use of conventional or cluster immunotherapy problematic. The risk of systemic side effects is increased and rush immunotherapy should only be performed in hospital in a specialist setting.

Aim

- To create a quality assured practical daily routine for allergen-specific immunotherapy ensuring a high professional standard and an effective use of resources.
- To ensure that patients and staff are confident and feel secure at initiation and during treatment by describing safety procedures and practical methods to obtain a minimal patient risk, high patient satisfaction and continuity in the course of treatment.
- To supply directions for documentation and follow up of the result of treatment.

Background

Allergen-specific immunotherapy is a well-documented treatment in allergic diseases (1–3). An important issue is

the need for optimal technical performance of immunotherapy. At present this is a limitation for more widespread dissemination of the treatment. Especially for subcutaneous allergen-specific immunotherapy, the clinical outcome and the safety of the treatment necessitate a detailed knowledge of the principles and execution of the treatment. The practical performance of allergen-specific immunotherapy is to a large extent based on empirical experience. These guidelines are based on evidence insofar as this is available (4). The Standards for Practical Allergen-Specific Immunotherapy relate mainly to subcutaneous immunotherapy as this type of treatment involves the greatest risk of anaphylaxis. Noninjective immunotherapy has a better safety profile than subcutaneous treatment and is normally self-administered outside the physician's office.

Definition of allergen-specific immunotherapy

Allergen-specific immunotherapy is the practice of administering gradually increasing quantities of an allergen product to an allergic subject to ameliorate the symptoms associated with the subsequent exposure to the causative allergen. Allergen-specific immunotherapy induces clinical and immunologic tolerance, has long-term efficacy and may prevent the progression of allergic disease. Allergen-specific immunotherapy also improves the quality of life of allergic patients.

This definition is based on category I evidence.

Treatment strategy

Available treatments for allergic diseases include allergen avoidance, pharmacotherapy, allergen-specific immunotherapy, and patient education. There are few studies that directly compare the relative advantage of these interventions. However, their optimal combination for each individual patient should improve the clinical outcome. Allergen-avoidance should be considered as a first-line intervention and even when not completely effective, may reduce the need for additional treatment (5). Drug treatment is the next step to reduce disease severity. In patients who need regular pharmacotherapy, it is advantageous to start immunotherapy early while disease remains plastic and when it remains possible to prevent progression of disease (1, 2). Although many drugs are effective and without significant side-effects, drugs represent a symptomatic treatment, while immunotherapy represents the only treatment that might alter the natural course of the disease (6–8). Using an appropriate allergen product and a correct indication, immunotherapy can significantly reduce the severity of the allergic disease, reduce the need for anti-allergic drugs, and improve the quality of life for allergic patients (9).

Since allergen-specific immunotherapy is a disease modifying treatment, it should be initiated early in the course of the disease in order to prevent irreversible damage in mucous membranes of the shock organ.

In summary an optimal strategy for the treatment of allergic patients includes:

- Control of symptoms using an optimal pharmacologic treatment.
- Performing allergy diagnostic procedures (to evaluate the possibilities to institute disease modifying specific treatment).

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Allergen products

Allergen product 'means a biologic product, including allergenic extracts and others, that is administered to man for diagnosis, prevention and treatment of allergy and allergic diseases' (1). The quality of allergen products is a key issue for both diagnosis and therapy. The heterogeneity of allergen extracts and the unknown properties of many of the components of each preparation have made it necessary to develop methodologies to assess their potency and ensure their consistency. In addition, the variable response of each patient to the different allergen components (mainly proteins) may influence the potential clinical outcome and has led to different approaches to allergen standardization.

Standardization

In a joint effort, authorities, basic researchers, clinical groups and manufactures are trying to define a common platform for the standardization of allergy vaccines (2–8).

In vivo standardization methodologies using a representative patient population and dose response studies, based on skin tests, were performed to assign biological activities to reference extracts that were later used as yardsticks to compare production batches (9).

- Disease modifying treatment.
 - Allergen avoidance (-reduction).
 - Allergen-specific immunotherapy.
- Stepping down the pharmacologic treatment to the lowest possible dose keeping the patient adequately controlled.
- Patients should be followed-up with education and adjustment of the pharmacological treatment until a stable situation is obtained.

As in-house reference standards (IHRs) are to be developed, European regulations (10) now define specific requirements for the starting materials, production processes and quality control of IHRs. IHRs have to be fully characterized and potency must be assigned by immunoassays and/or skin prick test in units of biological activity. The references will be used in routine production to assess antigen and allergen composition and thus ensure the consistent quality of each production batch.

In addition, potency should be measured in the last feasible step of the manufacturing process (for modified extracts, this implies just prior to the modification procedure). Guidelines on 'stability tests on active ingredients and finished products' should be followed.

It is likely that recombinant allergens, in the near future, will provide standards for allergen analysis and in consequence, new diagnostic and therapeutic products will be developed.

Units of biological potency

Skin prick testing provides basic *in vivo* standardization in Europe and units are assigned by comparison to a reference substance such as histamine (usually 10 mg/ml histamine hydrochloride) or by expressing mean wheal areas in a selected population (6).