POSITION PAPER

GA²LEN/EAACI pocket guide for allergen-specific immunotherapy for allergic rhinitis and asthma

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Abstract

This pocket guide is the result of a consensus reached during several GA²LEN and EAACI meetings. The aim of the current pocket guide is to offer a comprehensive set of recommendations on the use of immunotherapy in allergic rhinoconjunctivitis and asthma in daily practice. This pocket guide is meant to give simple answers to the most frequent questions of practitioners in Europe, including 'practising allergists', general practitioners and any other physicians with special interest in allergen-specific immunotherapy (SIT). It is not a long or detailed scientific review of the topic. However, the recommendations in this pocket guide were compiled following an in-depth review of existing guidelines and publications, including the 1998 EAACI position paper, the 1998 WHO Position Paper on SIT and the 2001 Allergic Rhinitis and its Impact on Asthma (ARIA). It is also based on the ARIA update 2008 (prepared in collaboration with GA²LEN), the 'Sub-lingual Immunotherapy: WAO Position Paper 2009' (from the World Allergy Organisation) and the Methodology paper of ARIA. The recommendations cover patient selection, allergen extract to be used, route of administration of SIT (in particular, sublingual and subcutaneous immunotherapy), and necessary precautions to be followed in using SIT.

Allergen-specific immunotherapy (SIT) is defined as a method to administer increasing amounts of specific allergens to subjects with clinical symptoms, caused by those allergens based on a specific IgE-mediated sensitization to modulate the immune system to tolerate this specific allergen again.

Allergen-specific immunotherapy has been in use for almost 100 years and studied for the past few decades. In recent years, highly standardized extracts have been available, as well as the results of randomized controlled trials performed according to modern standards. These trials have established SIT as part of the evidence-based state of the art management of inhalant allergy.

In principle, immunotherapy can be administered via different routes (subcutaneous, sublingual, oral, nasal, bronchial and lymphatic) but currently only subcutaneous immunotherapy (SCIT), with s.c. injections in the arms, and sublingual immunotherapy (SLIT), with the allergen kept under the tongue for 1–2 min and then swallowed, are widely used.

The aim of the current pocket guide is to offer a comprehensive set of recommendations on the use of immunotherapy in allergic rhinoconjunctivitis and asthma in daily practice. We include the most common questions regularly asked about SIT by those 'practising allergists', general practitioners and any other physicians with special interest in SIT.

Methods

This pocket guide was prepared by a GA²LEN taskforce during two consensus meetings and finally presented to all GA²LEN partners for comments.

The guide follows in the history the 1998 EAACI position paper (1), the 1998 WHO Position Paper on SIT (2) and the

2001 Allergic Rhinitis and its Impact on Asthma (ARIA) (3). It is also based on the ARIA update 2008 (prepared in collaboration with GA²LEN) (4), the 'Sub-lingual Immunotherapy: WAO Position Paper 2009' (5) and the Methodology paper of ARIA (6). In addition, the taskforce performed a new evaluation of the available trials in SCIT, and SLIT checking them for the adherence to the CONSORT statements (7–11; Bousquet P. J. et al., submitted). The recommendations are compiled from the exhaustive overview of these guidelines. Finally, the paper was reviewed by an EAACI working group consisting of members from the EAACI Executive Committee and the Interest Group of Immunotherapy.

This pocket guide is not intended to address in detail evidence-based medicine (EBM) issues regarding SIT. It will use EBM information, but it is written to give clear-cut answers to the most frequent questions raised by practitioners and patients. Some other papers with stronger and deeper clinical and scientific EBM background will follow this pocket guide as part of a large educational program supported by GA²LEN and EAACI.

The classification of rhinitis will follow, in most instances, the ARIA classification (3, 4).

Recommendations for practical use

The WHO constitution proposes that absence of symptoms of disease is the primary goal of the work of a physician. In addition, in the ARIA guideline, it is stated that in allergic rhinitis a combination of treatment options on individual basis should be chosen, ensuring best possible symptom relief for patients. Thus, the following recommendations deal with immunotherapy but need to be seen as part of the global treatment as outlined in ARIA (3). Box 1 at the end of this document summarizes the recommendations.

Which patients are eligible for allergen-specific immunotherapy?

In principle, immunotherapy can be of benefit in all patients with proven IgE sensitization to inhalant allergens with clinical significance.

Evidence for efficacy is found for the following allergens relevant in Europe: Birch; Alder; Hazel; Olive; Ash; Grass; Cypress; *Parietaria*; *Ambrosia*; *Dermatophagoides pteronyssinus* and *farinae*; Cat. For other less frequently studied allergens, the clinical efficacy has not been proven. Thus, immunotherapy for other allergens can be useful in individual patients but cannot be generally recommended. The physician may decide to start immunotherapy, but he or she should weight up the pros and cons, especially when there is little knowledge about the quality of the allergen preparation.

Taking the direct and indirect costs of allergen-specific immunotherapy into account, we suggest to consider SIT in patients with moderate-severe intermittent or persistent allergic rhinitis and rhinoconjuctivitis, in particular in those who do not respond sufficiently to current pharmacological treatment (9) or those who wish to reduce or avoid long-term pharmacotherapy and its potential adverse effects. In addition, SIT can be used in mild allergic asthma proven to be caused by a well-defined allergen, if asthma is under control and FEV_1 is above 70%. Table 1 summarizes indications and contra-indications.

Table 1 Indications and contra-indications for immunotherapy

Indications
IgE-mediated disease
Sensitization is relevant for the symptoms
Symptoms are of sufficient severity and duration
Availability of a standardized high-quality (best as technically possible) allergen extract of the specific allergen intended to be used for immunotherapy.
Contraindications
Malignant diseases
Autoimmune diseases
Current therapy with beta blockers
Asthma patients with FEV_1 below 70% under treatment, or uncontrolled asthma
Pregnancy at the start of immunotherapy
Acute infections e.g. common cold with fever.

During treatment with SIT, the algorithm (Fig. 1) is recommended to ensure that eligibility remains.

Which patients are NOT eligible for immunotherapy?

General contraindications are serious immunological diseases, serious cardiovascular diseases, malignancies, chronic infections and use of beta blockers (even beta blocker eye drops). Uncontrolled and severe asthma (FEV_1 under treatment $< 70\%$) is the most important absolute contraindication (see Table 1). In addition, SIT should not be started in pregnant women. Pregnancy is a contra-indication during the building-up phase, but not during the maintenance phase.

Considering the direct and indirect costs of allergen-SIT and the major effort required from patients undergoing this treatment, it should therefore be clearly discussed with the patient whether she or he is willing or able to be compliant with the therapy for the full treatment period of at least 3 years. Patients noncompliant to medication, noncooperative or not being able to understand the pros and cons of the treatment should not undergo SIT.

Which age group is eligible for immunotherapy?

In general, it has been established that the immune system can be modulated from infancy to old age, as demonstrated by vaccinations.

For immunotherapy these principles may hold true as well, but efficacy studies (and some safety studies) have been mostly limited to children above the age of 5.

For practical purposes, it can be proposed that immunotherapy should in general not be offered to patients below the age of 5, while for older ages there is no upper limit.

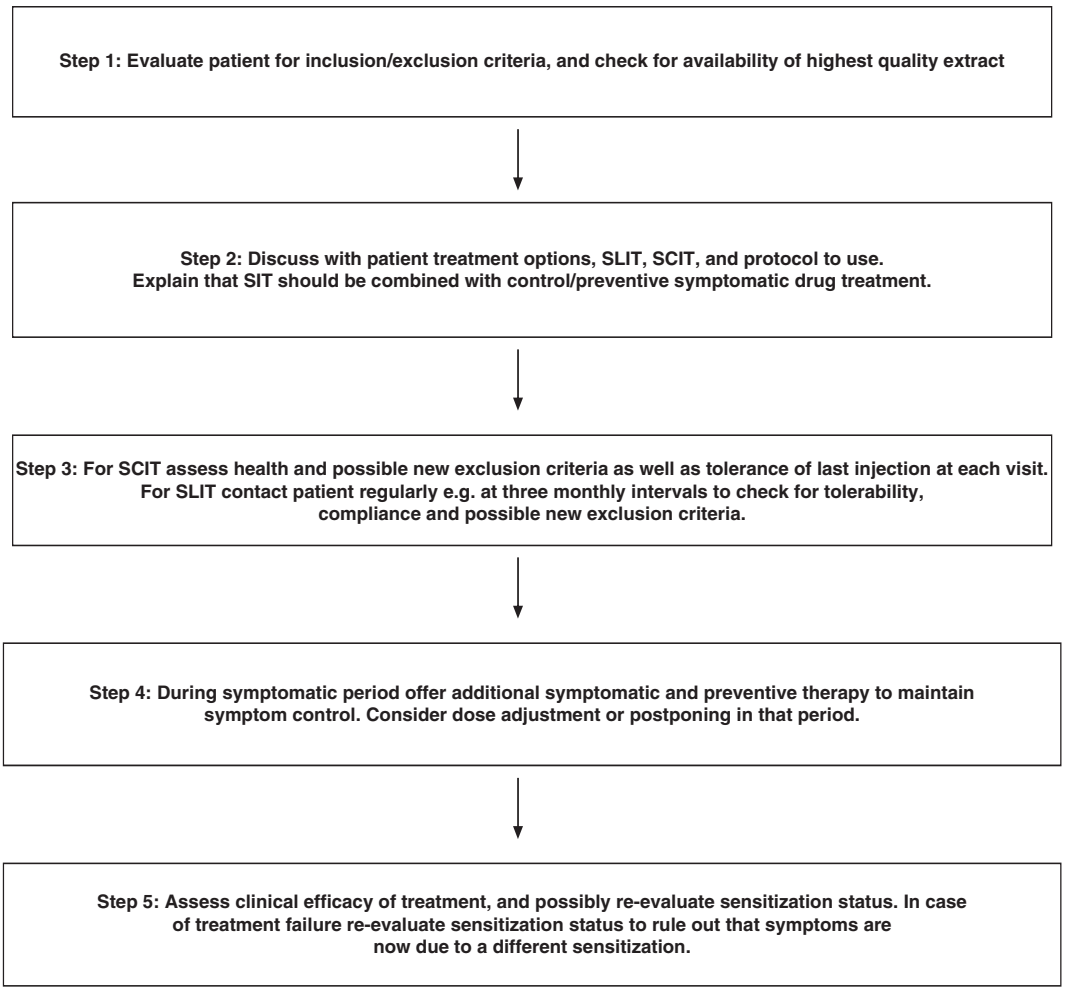

Figure 1 Algorithm for immunotherapy.

Should immunotherapy be reserved to patients being sensitized to one allergen?

Only a few studies address this question.

Most clinical trials are performed with monosensitized patients or in polysensitized patients with symptoms for single allergens (12). One study demonstrated that asthmatics allergic to house dust mites did not benefit from immunotherapy if other concomitant perennial allergies were present. Seasonal allergies and the effects on rhinitis were not taken into account (13). Another study in patients sensitized to grass- and birch pollen demonstrated that immunotherapy with two allergens was feasible and more effective than treatment with one (14). One study with SLIT showed similar efficacy in mono- and polysensitized subjects with symptoms only during the grass pollen season (12).

Thus, from the few published studies, it cannot be concluded that immunotherapy should be restricted to monosensitized patients.

How many different sensitizations can patients have to allow a successful immunotherapy?

There are no controlled randomized trials to answer this question. For a practical approach, it can be suggested that the number of sensitizations itself is less important than the clinical relevance of each unrelated allergen. Thus, for instance, the closely related tree pollen birch/hazel/alder do not necessarily count as different sensitizations; the same holds for different grasses.

An individual approach is always recommended. For example, in a patient with four clinically relevant sensitizations e.g. cat, dog, olive pollen and grass pollen, the decision must be based on the allergen which causes

1 the longest duration of symptoms per year
2 the most severe symptoms
3 a major impact on quality of life
4 which is more difficult to avoid

In the previous example, the pet allergens could be avoided, whereas grass pollen is the allergen that has the longest

duration of pollen season, however, in some regions like the South of Spain, olive pollen causes the more severe symptoms during a shorter pollen season.

How many allergens can be used in immunotherapy simultaneously?

There are no randomized controlled trials available to answer this question, but a number of studies show that the cumulative dose is relevant and that diluting the allergen contents by mixing different unrelated allergens is not beneficial. In the past, recommendations have been set up that mixtures of unrelated allergens should not exceed three different allergens, preferably less. Currently, we do not recommend to use mixtures. In some EU countries, it is a common clinical practice to give injections of different vaccines containing unrelated allergens, which can be administered on alternative days or during the same visit in the left and the right arm with at least 30 min interval. Some clinicians also combine SCIT and SLIT. These protocols, however, have never been tested in clinical trials.

Which route of administration is preferable SLIT or SCIT?

Unfortunately, there is only one double-blinded placebo-controlled head-to-head study where SLIT and SCIT have been compared (15). The study was not sufficiently powered to draw a firm conclusion. Therefore, the study results under similar experimental conditions need to be taken into consideration as indirect evidence.

Independent studies show that both forms of immunotherapy are effective in allergic rhinitis and asthma if optimally used. Side-effects of SLIT and SCIT differ. No fatal and only a few severe adverse events have been reported with SLIT. Moreover, SCIT induces more frequently systemic adverse events, while SLIT appears to have a higher rate of local side-effects that are frequently short-lasting. While with SLIT, it is advisable that patients have the first dose at the doctor's office, with SCIT it is recommended that all injections are given by a trained doctor, in an office environment with the essential resuscitation facilities available. It must be noticed that the occurrence of adverse events with SCIT largely depends on the allergen type and preparation. Higher frequency is seen with native allergens compared to allergoids (16) and animal dander compared to pollen and mite.

Regarding the final choice between SLIT and SCIT, the decision needs to be made individually with each patient after careful considerations of factors such as home-based treatment *vs* doctor visits, fear of injections, costs and compliance.

Which products and which brands are to be chosen?

As comparative head-to-head trials between the different products and brands are missing, it can only be suggested to choose a brand product depending on the available level of scientific information for a specific allergen. Whenever possible, only products with a sufficient level of evidence should be used. This should be documented according to modern standards in clinical trials. Recommendations for requirement of high-quality clinical trials have been published (17, 18).

Manufacturers should be able to provide a good scientific documentation of efficacy and safety, adhere to the modern standards of good manufacturing practice, which include high-quality allergen materials, standardized quantities of allergen contents and a sufficient cumulative dose. The latter is of highest importance, as studies have shown that SIT efficacy is, at a certain extent, dose-dependent. Furthermore, there may be an effect of the total cumulative dose on the efficacy after over 3- years period of treatment.

How to choose between licensed products and individual mixtures?

In some European Union countries, immunotherapy products can be bought both as licensed products or individualized products containing either an allergen from one source or individual mixtures of allergens specially prepared according to the individual patient's sensitivities and physician prescription. While licensed products undergo in principle the same procedures as other licensed drugs and can be directly purchased via the pharmacy, individual mixtures are prepared by the manufacturer according to the wishes and the needs of the prescribing doctors.

It is recommended to base the choice of the immunotherapy on the individual patients' needs and the scientific data – as stated in the previous paragraph – provided by the companies only for the time being. Products licensed recently have been tested according to Good Clinical Practice and thus provide the highest level of evidence for clinical efficacy.

How often and how long should immunotherapy be administered?

It is recommended to adhere to the manufacturer's instructions regarding the administration intervals and also regarding the possible adjustment of doses depending on e.g. side-effects. Although SIT is usually effective within 2–4 months of treatment, a treatment period of at least 3 years is recommended to obtain long-lasting effects after cessation of treatment. Efficacy and possible contraindications need to be regularly re-evaluated (see Fig. 1).

Which precautions are needed to perform immunotherapy?

It is mandatory that SCIT is only given by trained healthcare professionals with experience in the field of immunotherapy in a practice setting allowing resuscitation, if needed. According to the EAACI Standards for practical allergen-SIT (17), it is recommended that SCIT should be initiated by a specialist in allergy or under the responsibility of that specialist. The staff of the clinic should consist of physicians and nurses trained in SCIT, including the observation and rescue treatment of systemic anaphylactic reactions ('minimal patient risk'). A competent physician should always be present in the clinic when SCIT is carried out and be responsible for the treatment.

Table 2 Example of essential items for a checklist for documenting immunotherapy in an individual patient

Date:	Name of patient:	
	Itching and swelling at the injection site after previous visit or new drugs since then Y / N	
	Occurrence of respiratory symptoms in close temporal association to the last injection Y / N	
	Any allergy symptoms in last days, e.g. conjunctivitis, sneezing, nasal congestion Y / N	
	Any infection, e.g. common cold with fever today Y / N	
Solution administered:	/ amount: ml	
Batch number:		
Name of doctor:	signature:	

Patients and caregivers should be informed of the possible side-effects and educated how to control them before the start of immunotherapy.

For SLIT, it is suggested that the first dose is administered at a physician's office. This is based on one report of anaphylaxis following the first dose of SLIT. The patients should be instructed on the possible side-effects of SLIT (mainly local) and on how to manage them (13).

In general, each patient should always be asked for new drugs possibly interfering with immunotherapy, e.g. beta blockers, newly detected diseases, which could be a contraindication and active infection, e.g. common cold with fever. Good documentation is suggested (e.g. Table 2). For SLIT, it is important to inform patients about the possible aggravating factors for adverse events, especially wounds in the mouth and tooth extraction.

How to monitor patients after ending immunotherapy?

It is recommended that the specialist who initiated SIT re-evaluates the clinical symptoms for efficacy of immunotherapy every year. There is no biologic marker that can help.

In case of good clinical response, it is not required to re-assess sensitization.

However, in case of insufficient clinical response, it is recommended to re-assess sensitization of patients, diagnosis and co-morbidities, as it is possible that the symptoms are not related to the originally desensitized allergen but to new sensitizations.

What are the long-term benefits of immunotherapy?

As SIT is recommended for a limited period, it is relevant to consider the potential on-going benefits. Some studies have shown long-term efficacy of SCIT even after discontinuing the treatment, for periods as long as 10 years (19–21). Recent publications also point to a persistent effect after SLIT immunotherapy (22). The prevention of the evolution from rhinitis to asthma has also been a significant outcome in some of these studies.

Although the evidence is not so robust, there seems to be a preventive effect in the development of new sensitizations in individuals who have received single allergen SCIT (23–27).

Box 1 Allergen-specific immunotherapy (SIT) for allergic rhinoconjunctivitis and asthma

Summary points

- SIT can be of benefit in all patients with proven IgE sensitization to inhalant allergens with clinical significance.
- Consider SIT in patients with moderate/severe intermittent or persistent allergic rhinitis, in particular in those who do not respond sufficiently to current pharmacological treatment. In addition, SIT can be used in mild allergic asthma proven to be caused by a well-defined allergen, if asthma is under control and FEV1 is above 70%
- Uncontrolled and severe asthma (FEV_1 under treatment <70%) is the most important absolute contraindication for SIT. Patients noncompliant to medication, noncooperative or not being able to understand the pros and cons of the treatment should not undergo SIT.
- Independent studies show that both forms of immunotherapy (SLIT, SCIT) are effective in allergic rhinitis, if optimally used.
- While with SLIT, it is advisable that patients have the first dose at the doctor's office, with SCIT it is mandatory that all injections are given by a trained doctor, in an office environment with the essential resuscitation facilities available. Adverse events with SCIT largely depend on the allergen type and preparation (e.g. higher frequency with native allergens than allergoids and with animal dander than pollen or mite).
- Although SIT is usually effective within 2–4 months of treatment, a treatment period of at least 3 years is recommended to obtain long-lasting effects after cessation of treatment.
- It is recommended re-evaluating the clinical symptoms for efficacy of SIT every year, as there is no biologic marker that can help to assess efficacy or the decision to end the treatment. In case of insufficient clinical response, it is recommended to re-assess patient's sensitization, diagnosis and co-morbidities.

Review board

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