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# Subcutaneous allergen specific immunotherapy: best clinical practice as cornerstone for future development

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## KEY WORDS

*Allergen immunotherapy, allergic asthma, allergic rhinitis, side effects, adherence*

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## SUMMARY

*Allergen subcutaneous immunotherapy is a long lasting treatment which can modify the natural history of allergic respiratory diseases. Recommended administration is required for a minimum of three years. During this long term therapy the daily management is based on two crucial points, discussed in this review, such as the prevention and the treatment of side effects and the improvement and follow-up of patient adherence. This review specifically focuses on subcutaneous immunotherapy*

## Introduction

Allergen specific immunotherapy (SIT) is a long-lasting treatment, which can modify the natural history of allergic respiratory diseases by reducing the risk of asthma and the development of new sensitizations (1). Recommended administration is required for a minimum of 3 years. However in common with all chronic treatments poor adherence to immunotherapy can hamper its positive outcome (2). Many reasons account for low adherence, including perceived lack of efficacy, cost, side effects and need for regular follow-up (3). Therefore, allergist should be aware that successful immunotherapy requires not only appropriate initiation of treatment but also long term follow-up to limit the risk of withdrawal. Although allergists are not responsible for costs

or other practical problems (e.g. concomitant diseases, moving out of area), the daily management of this treatment is based on two crucial points, discussed in this review:

1. The management and prevention of side effects.
2. Improvement and follow-up of patient adherence.

We will specifically focus on subcutaneous immunotherapy in this review.

## The prevention and the management of side effects

In the assessment of the side effects of subcutaneous immunotherapy, it is mandatory to separate the systemic side effects related to the safety of the treatment from the local reactions, which can affect its tolerability.

Systemic reactions (SR) are the main drawback, being one of the reasons for a decreased use in Europe (4). However, it has to be noted that according to the most recent papers published, the current rate of systemic reactions during immunotherapy remains very low. Furthermore, it has to be stressed that rates of systemic reactions are mainly reported from American studies (5) and these data may not be directly applicable to the European reality, where different protocols, extracts and schedules are used (6). A further decrease of systemic reactions can be also expected with the use of allergoid extracts, which seem to have lower allergenicity while still maintaining immunogenicity (7,8). Even more important is to keep in mind that severe allergic systemic reactions can occur following use of other drugs, such as NSAIDs, antibiotics as well as herbal remedies (9,10). Nevertheless allergists need to be prepared to identify risk factors for reactions and promptly and appropriately treat systemic side effects if they occur.

#### *Identification of risk factors*

##### *a. Asthma*

Asthma patients have an increased risk of systemic reactions (11). Therefore, regular evaluation regarding recent exacerbations has to be performed in every patient with asthma and in case of positive history a functional evaluation is necessary. Routine assessment of respiratory function (Peak expiratory flow or FEV1) in asthmatic patients before and after every vaccine administration should be at the physician's discretion.

##### *b. Concomitant treatment*

The concomitant use of some antihypertensive drugs (beta-blockers and ACE-inhibitors) can be another risk factor for patients on SIT (12). It is important that clinicians enquire about recent changes of concomitant medications. However, the role of ACE inhibitors as a risk factor for systemic reactions has been recently disputed (13).

##### *c. Recommended equipment and medication*

Appropriate facilities and regularly updated medical supplies for the emergency treatment of potential reactions are mandatory for allergists performing SIT (14). Among these epinephrine and oxygen supply are essential as a delay or even the lack of their use can lead to very severe consequences of adverse reactions (15). Surprisingly in a recent Italian survey just seven out of 10 allergists had epinephrine available and six out of ten had oxygen supply in their clinic (16).

##### *d. Allergen reactivity*

Subjects with intense skin or serum positivity have to be carefully monitored as high skin reactivity has recently been shown to be a risk factor for systemic reactions (17). Increased levels of serum tryptase also seem to increase the risk of systemic reactions and should be assessed in every patient with severe SRs (18).

##### *e. Local reactions*

Local reactions are fairly common during subcutaneous immunotherapy, ranging from 26 to 82% of patients and 0.7-16% of injections (19,20). This raises three questions:

1. Patient's discomfort and reduced compliance;

A recent survey addressed this issue by asking 249 patients undergoing immunotherapy about the incidence of local reactions, the size of their local reactions and how bothersome these reactions were. Among patients with local reactions, 84.7% reported reactions smaller than the palm of the hand and 81.9 % deemed local reactions not to be bothersome at all or slightly bothersome. Only 4% stopped the treatment for this reason (21).

2. Local reactions (LR) as risk factor for future LRs or large local reactions (LLR).

A recent study performed on 360 patients who received a total of 9,678 injections reported a total reaction rate of 16.3% per injection. The rate for small reactions was 15.9% whereas the large local reaction rate was 0.4%. The sensitivity and positive predictive value of local reactions in predicting local reaction at the following dose was (26%), whereas the specificity of absence of local reactions in predicting the absence of local reactions at the following injection was high (85.5%). For LLR only 6% were followed by a LLR (20). Though these results suggested to avoid schedule modifications, it is common among American allergists to change the schedule (94.7%), with dosage adjustment (79.1%) and adding an anti-histamine pre-treatment (70.1%) (22). High concentration of glycerine in the extract (even > 50%) is not associated with significantly higher small or large local reactions (19). However, an incorrect intradermal administration can lead to granuloma formation (23), which may be long-lasting (24). Contact sensitization to aluminium can be a risk factor for nodule development (25).

3. Large local reactions (LLR) as risk factor for future systemic reactions.

The role of LLR in predicting systemic reactions is still controversial. Several studies have demonstrated the lack of sensitivity and specificity of LLRs in predicting

SRs to the subsequent dose and therefore recommend ignoring them to reduce errors from dose adjustment, as well time wasting (26,27). However more recently Roy et al. observed a significantly increased number of LLRs among patients developing SRs (28) and accordingly a retrospective survey observed that a subgroup of patients (41.7%) LLR can be at risk of subsequent SRs. However, in this study no distinctive features of these patients have been identified. Furthermore, occurrence of systemic reactions was independent from dosage adjustment (29).

A standardized dose-adjustment was shown to significantly reduce the risk of subsequent SRs after LLR (30);

#### *f. Previous systemic reactions to immunotherapy*

Previous systemic reactions to immunotherapy seem to be a risk factor for following subsequent systemic reactions (31).

#### *g. Medical errors*

Human errors are unfortunately not uncommon and may be related to the administration of the extract to the wrong patient or the incorrect dose. Most of them lead to local reactions however some severe systemic reactions have been reported (32). Helpful suggestions to reduce this risk of mistakes are available in the American Practice Parameters on Immunotherapy (14).

### **Observation time**

The recent American Practice Parameter states that the observation time after every extract administration has to be of 30 minutes (14). This statement is shared by the common practice in Europe, with the exception of the United Kingdom where the observation time is one hour. However delayed systemic reactions account for up 50% of SRs, occurring without any preceding symptoms as well as being part of a biphasic reaction (11,14). As several large studies have demonstrated that they are hardly ever life-threatening the suggested length of the waiting period could remain of 30 minutes but patients have to be counselled of the possibility of immediate and delayed reactions and an action plan has to be discussed with each patient. The decision of prescribing epinephrine should be at the physician's discretion (14).

Biphasic anaphylaxis is not uncommon but generally is mild and self limiting. Patients experiencing biphasic anaphylaxis are more likely to be female and treated with

more than a dose of epinephrine (33). Late reactions generally do not require additional epinephrine. Low baseline peak expiratory flow rate values and co-existing asthma have been suggested as further risk factors (34).

In case of biphasic anaphylaxis a prolonged observation period (up to 24 hours) before ED discharge has to be carried out.

### **Improvement and follow-up of patient adherence.**

Many reasons have been reported as responsible for patient's stopping treatment. These will be discussed below, focusing on the possible role of allergist's intervention (35).

### **Time consumption**

Classical schedules of subcutaneous immunotherapy are time consuming, with the up dosing phase lasting 12-14 weeks. To shorten this period, cluster immunotherapy protocols have been proposed and are used in some centres. This entails administering several injections at increasing dosages (2/3 per visit) sequentially in a single session of treatment on non consecutive days. The maintenance dose is achieved in 4-8 weeks. Optimal tolerance is associated with use of depot preparations, no more than four administrations per cluster, one or two cluster per week and the use of the premedication (36,37).

The efficacy of different anti-histamines as premedication has been mainly shown in hymenoptera venom allergy (38) whereas a single report suggests the efficacy of montelukast in reducing local reactions (39).

The concomitant use of omalizumab significantly reduces but doesn't abolish the risk of severe systemic reactions. However the associated costs of this approach are quite high so it could be indicated in only very selected cases (40).

In order to reduce the build up period, another strategy is the use of allergoid vaccines or adjuvanted extracts. Recently, the clinical efficacy and steroid sparing effects have been demonstrated after a 5 months treatment with allergoid in mite allergic children (41). Moreover an ultra-short course of allergoids adjuvanted by monophosphoryl Lipid A has shown some degree of efficacy and a good safety profile (42).

A recent German market analysis performed to evaluate the persistence of the use of different extracts of SCIT demonstrated a significantly higher renewal of maintenance vials for shortened therapy regimen during the 2nd

and 3rd year of therapy in comparison with extract administered according to the classical schedule, confirming a better adherence to short course of SCIT (43).

Of note, a significantly higher compliance has been also observed in patients receiving the injection in the allergist's office compared to those receiving the injections in facilities outside the clinic (44).

### Costs

Immunotherapy is a pricey treatment considering not only direct (allergen extract) but also indirect (e.g. transport, loss of working days) costs. For this reason many people are unable to afford this therapy. American studies confirm that the cost is one of the main reasons for stopping SIT, although private patients were more compliant than publicly funded ones (45). An indirect evidence of the role of costs on SIT drop outs comes from recently published data from the Italian market of sublingual immunotherapy. A significant lower number of maintenance extracts were renewed in regions where patients have to pay themselves for immunotherapy in comparison to other regions where the costs of the treatment are totally or partially reimbursed (46).

Moreover, inadequate health insurance coverage has been shown as a risk factor for premature discontinuation as recently demonstrated in a group of 155 patients with allergic rhinitis (47).

However a Danish study performed to evaluate the role of socio-economic factors in the choice and use of SIT showed that the use of SIT is related to both severity of disease and level of education, but not to income level (48).

Unfortunately, allergists in most countries do not have a strong role in the decision making regarding reimbursement. The long term favourable cost/benefit ratio of immunotherapy as well as the positive results of recent pharmaco-economical studies have to be stressed and considered (49).

However the choice of the extract and the schedule used concerns the allergist. The use of shorter schedule can be cost/effective, mainly reducing indirect costs (50).

### Patient information

Patient information before and throughout the length of treatment is vital for successful immunotherapy. Interestingly, the only survey performed so far in the United States assessing patient's knowledge about the aims and risks of immunotherapy found that this was surprisingly poor. In fact, a

complete recovery of their allergy was expected by 37% of patients and 18% were convinced that the improvement should be expected within days. Of note, only 32% of patients receiving immunotherapy were aware of the risks of the treatment. Furthermore, patients who were interviewed during the first six months of treatment were more informed about it than those who were on treatment for longer, confirming the key role of regular information refreshers (51).

On the other hand, in a recent Italian study patients who received a short education course before starting sublingual immunotherapy showed a better adherence to the treatment after one year and a lower number of drop outs in comparison with the control group, which was only instructed about the use and the administration of the therapy (52).

A regular follow-up is also necessary to ensure better compliance. In a recent paper Vita et al. demonstrated a relationship between the follow-up visits for SLIT per year and adherence to the treatment, more compliant patients having asked to attend for more visits during the year (53).

### Conclusion

SCIT remains a fundamental treatment for allergic respiratory diseases, its efficacy having been shown in meta-analyses and controlled trials. Of note, the subcutaneous route is still used for the study of future new developments of allergen immunotherapy (54). The use of new adjuvants promises to improve the immunogenicity of the treatment as well as reduce the number of administrations (55) whereas the utilization of recombinant allergens could offer better patient tailored treatment in the future (56). The introduction of more convenient and shorter schedules may also increase adherence to this treatment and perhaps expand its use in daily practice. For these reasons, the best clinical practice includes also a regular update of the new developments in the practice of SCIT as well as the use in daily practice of shorter schedules or new standardized extracts, whose efficacy and safety has been shown in controlled trials.

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