

Risk factors for systemic reactions to allergen immunotherapy

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Purpose of review

To update safety information regarding allergen-specific immunotherapy (ASIT) in clinical practice and highlight the risk factors associated with the adverse reactions, product and each dose.

Recent findings

Efforts in recent years have focused on increasing our understanding of the efficacy and safety of ASIT, especially the sublingual variety (SLIT), in multicenter studies. Moreover, new Clinical Practice Guidelines (CPGs) and an international consensus concerning ASIT have been published recently. Although no deaths as a result of subcutaneous immunotherapy or SLIT have been reported in the last 2 years, systemic reactions mainly arising from administration errors still appear. Recent studies support the safety of new forms of specific immunotherapy.

Summary

An understanding of the risk factors for each patient, product and dose, and the implementation of CPGs are the main factors that could improve the safety of ASIT. The standardization of all procedures for prescribing and administering ASIT, and the systematic collection of standardized safety data in a multicenter database (postmarketing surveillance), may be required to generate new information on the safety of ASIT.

Keywords

adverse effects, allergen and sublingual immunotherapy, risk factors, subcutaneous immunotherapy, systemic reactions

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Introduction

Allergen-specific immunotherapy (ASIT), both subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT), has been shown to be effective for the treatment of allergic respiratory disease in randomized controlled trials and meta-analyses [1[•],2[•]] with the highest degree of scientific proof [3[•],4^{••}]. Indeed, SCIT is the treatment of choice for preventing anaphylaxis in patients with systemic reactions to hymenoptera [5].

The greatest drawback to the more widespread use of ASIT is the associated risk of severe side-effects, as the dose which has been shown to be well tolerated and effective in a group of patients may not be so for a specific patient [5,6].

Systemic reactions are those which produce symptoms and signs far from the administration site. They may be immediate systemic reaction (ISR), appearing in the first 30 min postadministration, or delayed systemic reaction (DSR), occurring after the first 30 min, with the former tending to be more severe [5,7].

The incidence of systemic reactions has been estimated at between 1 and 34% of patients and around 0.2–0.3% of doses, depending on the type of study, patient, diagnosis, extract or treatment scheme [4^{••},8]. There are very few risk factors that could allow the incidence of potentially serious reactions to be reduced outside of controlled trials.

Historical reviews of ASIT-related mortality [9,10] highlighted severe or poorly controlled asthma and administration errors as the main causes of fatal systemic reactions. These findings led to the drafting of Clinical Practice Guidelines (CPGs) for ASIT treatment [6,11–13], and their subsequent updates [4^{••},14,15[•]], in the 1990s. Adherence to such guidelines is the main reason behind the reduced frequency and severity of systemic reactions in the past 20 years. The statistics regarding mortality and systemic reactions prior to these CPGs are no longer applicable [16]. Likewise, new insights into the mechanisms underlying ASIT [17] and biotechnological advances are resulting in the development of new forms of ASIT that require new information regarding their safety to be generated.

Although SLIT has become the most widely used technique in the past few years, especially in Europe [18], as a result of its lower incidence of systemic reactions, further studies are still required to compare its cost/efficacy and preventive ability. New SLIT products in tablet form, which have been registered in Europe following the ‘mutual recognition’ procedure and for which controlled dose–response studies have been performed in large numbers of patients [19*,20*], have appeared recently. These new dosage forms have a similar efficacy to SCIT.

This review describes the main risk factors for ASIT-related systemic reactions and classifies them on the basis of whether they are related to the patient, the allergen extract or the dose, in order to facilitate the implementation of preventive measures.

Patient-related risk factors

An understanding of the risk factors for systemic reactions associated with patient-related variables allows us to analyze the risk/benefit balance appropriately before prescribing a treatment. Thus, for a specific patient with a certain risk, we can choose how and where to administer allergen-specific immunotherapy (AIT) *a priori*.

Sex–age

The systemic reactions provoked by SCIT with standardized extracts were analyzed in a single-centre, prospective, two-phase study [21*] of 568 consecutive patients with rhinoconjunctivitis and/or asthma or hymenoptera-related anaphylaxis. The multivariate analysis found a higher risk of ISR in women (odds ratio, OR 2.29; 95% confidence interval, CI 1.23–4.27; $P=0.009$), those patients sensitized to fungi (OR 2.34; 95% CI 1.19–4.59; $P=0.013$) and in patients with unstable asthma (OR 2.31; 95% CI 1.28–4.17; $P=0.005$). The main risk factor for DSR was occupational exposure (cleaners with respiratory allergy exposed to animals or dust). In the second phase of this study, stabilization of the asthma (the only modifiable risk factor) at least 1 week prior to a dose reduced the risk of ISR and DSR significantly ($P<0.001$).

No review of fatal reactions has found any increased risk of death linked to the patient’s sex. In the case of nonfatal reactions, some studies have reported a higher incidence of systemic reaction in women [22,23], although others found no such difference [24,25].

Other patient-related variables, such as age, are rarely cited as risk factors for systemic reactions [26,27]. Tabar *et al.* [28] found a higher risk of systemic reaction in children allergic to *Alternaria*.

Key points

- Although the safety of allergen-specific immunotherapy (ASIT) has improved in the past years, systemic adverse reactions are the main limitation for use of this treatment.
- The standardization of all the procedures for the prescription and administration of ASIT as well as the implementation of the GPCs are the main factors to reduce the risk of systemic reactions.
- The new models and formulations of ASIT require giving new information about its safety by means of the systematic and standardized collection of different variables involved in the safety of the treatment and with the participation of all the staff responsible for it.

In a case–control study [29] based on retrospective chart reviews of patients who had received SCIT for respiratory or hymenoptera allergy, 29 systemic reactions were reported in 25 patients, with a frequency of 0.28% per injection-visit and 7.4% per patient. Around 48% of these systemic reactions were delayed, and 13 were grade 4. The variables studied (sex, phase, asthma, beta-blocker or ACE inhibitor use and allergen composition of the SCIT) were not significant risk factors.

Asthma

Asthma is a risk factor for the development of a systemic reaction and its severity. The majority of fatal specific immunotherapy (SIT)-related systemic reactions reported in the literature occurred in asthmatic patients [10,13]; therefore severe or poorly controlled asthma is a contraindication for SIT administration [4*,15*].

Some guidelines [12,30] recommend that a peak flow (PEF) (or spirometry) be performed both before and after a dose, although all stress the need to avoid administering SIT to patients with poorly controlled asthma.

High hypersensitivity

Although not well defined, ‘high hypersensitivity’ is known to be a risk factor for fatal systemic reactions [12,31].

A prospective observational study [32] performed in the south of Spain (where olive pollen predominates) analyzed the risk factors of the systemic reactions in 611 patients who received SIT following a cluster regimen. Around 10.6% of patients developed a systemic reaction. Age older than 14 years (OR 2.6; 95% CI 1.2–5.6; $P=0.016$), prior use of another SIT (OR 0.3; 95% CI 0.2–0.8; $P=0.01$), sensitization to *Chenopodium* (OR 3.0; 95% CI 1.6–5.6; $P=0.001$), IgE to olive pollen greater than 20% of total IgE (OR 4.1; 95% CI 2.1–7.9; $P=0.001$) and IgE to grass pollen greater than 20% of

total IgE (OR 2.3; 95% CI 1.0–5.4; $P=0.042$) were identified as risk factors. Systemic reactions were also more frequent in those patients vaccinated with 100% Olea extract (OR 2.6; 95% CI 1.1–5.9; $P=0.021$) than those vaccinated with a mixture of grass and olive and in those who received the two-visit initiation cluster (OR 7.1; 95% CI 2.5–20.0; $P<0.001$).

Polysensitization has also been related to a higher incidence of systemic reactions [26]. In a retrospective study [33] with SCIT, 46 systemic reactions were recorded in 20 patients, with a frequency of 0.28 per injection-visit. Some 13% of these systemic reactions were classed as serious (using the EAACI 2006 criteria), and all were immediate. An almost six-fold higher risk (OR 5.83; 95% CI 1.23–7.59; $P=0.026$) was found for those patients classed as ‘highly allergic’ (‘patients with SPT of 3+ or 4+ in more than 33% of allergens tested’).

Allergen extract-related risk factors

The allergen-related variables that could be risk factors for systemic reaction are the allergen composition (including chemical, physical and molecular modifications and adjuvants) and the administration route. The improved standardization and consistency of allergen extracts, especially as regards quantification of the majority allergens, have probably contributed to reducing the incidence of adverse reactions, although similar products from different manufacturers are not yet comparable.

Casale and Stokes [34] have recently reviewed the new ASIT formulae that could improve efficacy and safety.

Composition

No specific allergen is currently thought to produce higher mortality. In contrast, some authors, in retrospective and prospective studies of nonfatal systemic reactions, have found a higher frequency with pollen vaccines [35,36], although no such effect was found in a different study with children [37]. Further studies have reported a higher systemic reaction incidence with mite extracts [22]. The supposedly worse tolerance to fungal extracts remains controversial [28,38].

Very few fatal reactions to pure hymenoptera venom immunotherapy (VIT) have been reported. Indeed, several studies [22,35,36] have found a lower incidence of systemic reactions with hymenoptera vaccines, with bee vaccines being tolerated worse than wasp vaccines [23,39].

Systemic reactions appear to be more frequent when aqueous extracts are used, and some guidelines [12,30] recommend the use of adsorbed vaccines (depot).

Polymerized extracts pose a lower systemic reaction risk because of their lower ability to bind to specific IgE (allergenicity) whilst conserving T-cell epitopes (immunogenicity) [40], although other factors, such as the dose administered, could also have an effect.

A German study [41•] in which 768 patients with respiratory allergy received SCIT for mites and pollen with a depigmented glutaraldehyde-modified polymerized allergen extract has been reported. A total of 27 systemic reactions (from a total of 5923 doses), 20 of which were grade 1 and 7 grade 2, were recorded in 10 patients, thus suggesting a better safety profile than conventional SCIT.

A double-blind, randomized, multicentre study [42•] evaluated the efficacy and safety of an ultrashort course (four doses) of the immunotherapy grass-modified allergen tyrosine adsorbate monophosphoryl lipid A (a Toll-like receptor 4 agonist) in 1028 adult patients with grass-induced rhinitis. Only one patient in the active group had a systemic reaction (generalized erythema).

Route

Although SLIT has been the most widely studied form of ASIT over the past few years, it is most commonly used only in Europe. Its safety profile is better than that of SCIT [43,44•], even at high doses and with no initiation phase, thus allowing it to be administered at the patient’s home. This has also allowed it to be formulated as a fixed-dose tablet [19•,20•,45]. Despite this, however, systemic reactions have been reported [46•,47], even for the first dose [48]. This has meant that the patient must be informed about how to manage a possible systemic reaction, and it is recommended that the first dose be administered in a health centre [1•].

A recent Cochrane systematic review [2•] of SLIT trials contains information regarding systemic reactions in 18 of the 60 studies evaluated, with a similar incidence to that of placebo and no case of anaphylaxis, although a lack of standardization when recording the adverse effects was noted.

Lesions to the oral mucosa have been suggested to be a risk factor for a SLIT-related systemic reaction [49].

Dose-related risk factors

Administration errors are the main identifiable and avoidable cause of ASIT-related systemic reactions, including SLIT [50]. Any delay in the treatment of a systemic reaction increases its severity [4••,7]. Although CPGs provide recommendations to avoid such errors [4••,5,14,15•,43], they continue to occur with a greater than expected frequency [51].

An awareness of the risk factors associated with a specific dose allows specific preventive measures to be established upon administration, such as modifying the scheme or dose, premedication or deciding where to administer the treatment.

In a prospective study [12] that used dose as the statistical unit and followed the EAACI guidelines, a total of 277 patients received 5768 doses of SCIT and 78 ISR (grade 2 and 3) were recorded in 48 patients and 67 DSR in 55 patients [26,27]. The multivariate analysis found age (>10 years; OR 2.3; 95% CI 1.2–4.6; $P=0.01$), sensitization to fungi (OR 4.3; 95% CI 2.6–7.4; $P<0.001$), persistent asthma (OR 2.0; 95% CI 1.3–3.3; $P<0.001$), a higher dose concentration (OR 2.1; 95% CI 1.1–3.8; $P=0.016$), presence of an ISR with the previous dose (OR 5.4; 95% CI 2.4–12.3; $P<0.001$) and an asymptomatic decrease of the PEF greater than 15% with the previous dose (OR 3.2; 95% CI 1.4–7.6; $P=0.007$) to be risk factors for an ISR. A delayed local reaction (DLR) with the previous dose (OR 4.1; 95% CI 1.2–13.5; $P<0.019$) and a lower dose concentration (OR 2.4; 95% CI 1.5–4.0; $P=0.001$) were found to be risk factors for a DSR. A second phase of the same study [21•] showed that a dose reduction subsequent to an asymptomatic decrease of the PEF greater than 15% reduced the ISR frequency (from 6.5 to 0%; $P=0.039$). However, reduction of the dose subsequent to that which produced a DLR did not affect the systemic reaction frequency.

Dosing scheme

In the case of SCIT with airborne allergens, the use of fast regimens (rush and cluster) has been associated with a higher number of systemic reactions [4•,52•], although more recent studies have shown their safety to be similar to that of conventional schemes [53]. There appears to be a lower risk with depot and polymerized extracts [54•] on reducing the number of clusters and, above all, the number of doses per cluster [55].

Some studies involving fast VIT regimens have found a lower incidence of systemic reaction than with conventional treatments [23], whereas the systemic reaction incidence was higher with other protocols [56].

Omalizumab has been used to reduce the systemic reaction incidence in patients receiving SCIT with inhaled allergens [57•] and VIT [58], with good results.

Ultrarush initiations or even regimens with no SLIT initiation phase have proven to be well tolerated. A randomized, double-blind, placebo-controlled, multicentre study [59•] evaluated the safety of an ultrarush regimen that reached the maintenance dose (300 IR) in 90 min using SLIT with *Betula* extract in 116 children aged between 6 and 14 years with rhinoconjunctivitis

with or without asthma. No adverse systemic effect was reported.

Various studies with SCIT found a higher incidence of systemic reaction in the dose-increase phase with both inhaled [24,25] and hymenoptera allergens [23,39], although a similar effect was not found in other prospective studies [37].

The seasonal administration of pollen-containing SCIT doses has been associated with higher mortality [10,60], although it has been shown that more reactions are not produced upon reducing the coseasonal dose [8,24].

In an SCIT-based study [25] using standardized extracts, 12 of the 35 systemic reactions occurred upon changing the vial, although a similar effect was not observed in a different study [26].

Prior reactions

ISRs and DSRs tend to recur in the same patient. Together with poorly controlled asthma, the presence of a prior systemic reaction during AIT is the main risk factor associated with a new systemic reaction [52•]. There is currently no evidence that the dose adjustments recommended in clinical guidelines reduce recurrent systemic reaction in a patient [21•]. Premedication with antihistamines [61] or omalizumab [58] has been shown to be useful in some studies, although such treatment is not recommended as standard [4•]. SLIT may be tolerated in patients who presented a SCIT-related systemic reaction [62], although not in all cases [63].

Local reactions do not predict the appearance of a systemic reaction, although some studies have suggested them to be a risk factor [64]. The dose adjustments subsequent to major local reactions recommended in the clinical guidelines do not reduce the frequency of future systemic reactions [21•,65•,66].

Conclusion

The main interest in determining risk factors is to be able to inform patients of their personal risk/benefit balance and to take preventive measures.

The incidence and, above all, severity of systemic reactions have decreased significantly since the publication of CPGs [16]. However, despite having accumulated almost 100 years' worth of information regarding the safety of ASIT, we still do not understand why some patients have a systemic reaction and why they tend to recur.

A significant amount of progress has been made as regards the standardization of all procedures involved in the administration of ASIT, including recommendations

for its indication and administration that minimize errors [4[•],14,51,52[•]]. However, progress is also being made in the use of a common terminology when it comes to designing ASIT studies [67[•]], standardizing allergen extracts [14,68] or defining the adverse reactions [69].

Although the structured and prospective collection of postmarketing pharmacovigilance data [70^{••},71^{••},72] will undoubtedly prove to be a vital tool for generating new understanding of safety aspects, ASIT prescribers and administrators will need to be motivated to collect this information in order for it to be truly useful in determining the risk factors (and finally causes) for systemic reactions [1[•],71^{••}].

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Conflicts of interest

There are no conflicts of interest.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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