



Reducing and managing systemic reactions to immunotherapy

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Purpose of review

To identify and discuss recent articles pertaining to the reduction and management of systemic reactions to allergen immunotherapy (AIT).

Recent findings

Fatal reactions to AIT may be declining. Screening asthma patients before AIT and dose adjustment during pollen season may contribute to lower systemic reaction rates. Cluster build-up protocols with multi-allergen subcutaneous immunotherapy (SCIT) may lead to an increased risk of systemic reactions compared with cluster build-up protocols with single-allergen SCIT. Sublingual immunotherapy (SLIT) studies confirm the low rates of systemic reactions using this method, including for rapid build-up schedules. Studies of newer forms of AIT (intralymphatic, epicutaneous, recombinant allergens) have too few patients to form confident systemic reaction risk estimates. High-grade delayed systemic reactions to AIT may be less frequent than previously reported.

Summary

Recent studies increase confidence in risk estimates for systemic reactions to AIT, suggest useful strategies to predict systemic reactions to AIT, and offer strategies to prevent systemic reactions.

Keywords

desensitization, hypersensitivity, immunologic, immunotherapy

INTRODUCTION

Allergen immunotherapy (AIT) is an effective treatment option for allergic rhinitis, asthma, venom hypersensitivity, and atopic dermatitis [1]. Given the variability in the practice of AIT worldwide, estimates of safety and effectiveness may vary [2]. New approaches are needed to understand and manage the risks associated with AIT [3]. Having a systemic reaction is an important risk associated with administering AIT. In this review, we [1] identify studies that describe the risk of systemic reactions with AIT, including venom immunotherapy (VIT) [2], consider AIT given via different routes and schedules [3], consider studies that identify strategies to predict or prevent systemic reactions to AIT, such as tests or clinical characteristics and pretreatment regimens, and [4^{***}] review studies that pertain to management of systemic reactions to AIT.

UPDATE ON RISK ESTIMATES OF SYSTEMIC REACTIONS TO AEROALLERGEN ALLERGEN IMMUNOTHERAPY

A recent summary document of the efficacy and safety of AIT was published in 2011 [1]. The risk

of systemic reactions to AIT based on conventional build-up protocols is approximately 0.2% per injection (1 in 500) [1]. Additional risk estimates from recent studies do not substantially differ, except possibly the estimated fatality rate.

Monitoring of subcutaneous immunotherapy (SCIT) in the US has been ongoing since 2008 by survey of the American Academy of Allergy, Asthma, and Immunology and American College of Allergy, Asthma, and Immunology membership [4^{***}]. No fatal SCIT reactions from 2008 to 2011 occurred, likely representing a decline from previous estimates of fatal reactions of 1 in 2.5 million injections. The systemic reaction rates (0.1% of injection visits) and severity were similar for all 3 years. Screening for worsening asthma symptoms was performed in nearly all of the practices surveyed

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KEY POINTS

- Dose adjustment during pollen season may decrease systemic reaction rates.
- Cluster build-up protocols with multiallergen SCIT may lead to an increased risk of systemic reactions compared with cluster build-up protocols with single-allergen SCIT.
- SLIT studies confirm the low rates of systemic reactions using this method, including for rapid build-up schedules.
- Studies of newer forms of AIT (intralymphatic, epicutaneous, recombinant allergens) have too few patients to form confident systemic reaction risk estimates.
- High-grade delayed systemic reactions to AIT may be less frequent than previously reported.

(86% always screened). Practices that always reduced doses during peak pollen season were significantly less likely to report grade 2 or 3 systemic reactions ($P=0.04$). Limitations of this study include low response rate, risk of under-reporting, and generalizability to other providers. This study suggests that fatal reactions to SCIT appear to be declining, possibly related to near-universal screening of asthmatic patients. Also, dose adjustment during pollen season may be associated with decreased risk for severe systemic reactions.

Other recently reported AIT studies report updated risk estimates. Tabar *et al.* [5] performed a randomized trial comparing 3 and 5-year house dust mite SCIT courses and found that five systemic reactions occurred in the 5-year group ($n=41$) compared with four in the 3-year group ($n=52$). This study adds to the previous data of a low risk of systemic reactions to SCIT. Also it suggests risks are unlikely to be significantly different between a 3 and 5-year treatment course. In a retrospective review of 575 patients with dust mite ultra-rush immunotherapy, 8 patients experienced eight systemic reactions (systemic reactions/injections 0.1%) [6]. In a multicenter, randomized controlled trial, 400 patients with grass pollen allergy received a five-step up-dosing protocol using an extract with an optimized allergen-to-aluminum hydroxide ratio either once or twice weekly [7]. Systemic reactions were reported in 20% of once-weekly up-dosing versus 32% of twice-weekly up-dosing (none had hypotensive episodes). The authors report that the once-weekly up-dosing schedule appears safer than the twice-weekly one. The overall systemic reaction rates for this approach with this particular extract

product are similar to those for rush immunotherapy schedules and far higher than previous reported systemic reaction rates for standard build-up protocols. These single-allergen SCIT cluster protocols likely have similar risks to standard build-up protocols, although a five-step up-dosing protocol appears to have a substantially higher systemic reaction risk than standardized build-up protocols.

A recent article that considered cluster build-up of SCIT using multiallergen treatment vials, however, found a higher risk of systemic reactions than would be expected for standard build-up schedules. Copenhaver *et al.* [8] performed a retrospective review of a multicenter allergy practice in the US and identified 441 patients that received cluster SCIT using a previously published cluster schedule. Of patients receiving cluster SCIT, 10.9% reported a systemic reaction. Notably, only 10.6% of these were grade 3 systemic reactions, 2.1% were grade 4, and no grade 5 was reported. In a risk factor analysis, the authors suggest that female sex, physician-diagnosed asthma, age 21–40 years, and inclusion of grasses, weeds, cat, or dog in the SCIT were associated with an increase for systemic reactions using a cluster build-up protocol. The authors conclude that cluster SCIT may lead to a higher rate of systemic reaction than conventional SCIT build-up protocols. Authors of the most recent practice parameter guidelines note that most studies examining the rate of systemic reactions in single-allergen cluster SCIT find similar rates to conventional build-up. This US study of primarily multiallergen SCIT found an increased risk, and therefore those who are prescribing multiallergen SCIT may find these risk estimates more appropriate for their patient population.

UPDATE ON RISK ESTIMATES OF SYSTEMIC REACTIONS TO VENOM IMMUNOTHERAPY

In a study that randomly assigned individuals to a semi-rush or ultra-rush jack jumper ant VIT build-up schedule, Brown *et al.* [9^{*}] found that systemic reactions were significantly higher in the ultra-rush group (65 versus 29%; $P < 0.001$). All the individuals were regularly pretreated with antihistamine. The authors further compared those who received 50 or 100 μg maintenance doses. Those on 50 μg maintenance dose were less likely to have a systemic reaction. Therefore, the safest protocol of those tested was semi-rush with 50 μg maintenance dose. Limitations of this study include generalizability to other venoms and uncertainty about long-term comparative efficacy between maintenance doses.

Konstantinou *et al.* [10] retrospectively studied 54 children with history of at least one anaphylactic reaction to hymenoptera sting who underwent a modified cluster VIT protocol with a maintenance dose of 50 µg lasting 5 years. Most (40 out of 54) were pretreated with antihistamine prior to the injection. Only two children had a systemic reaction to the VIT during the course of the 5-year treatment period (4% of children). This study suggests that a cluster VIT course using a 50 µg dose may have similar or lower risk than standardized build-up protocols using 100 µg.

These two recent studies offer additional data on the safety of different VIT protocols. Additional trials comparing build-up protocols and maintenance dosing are needed, specifically for other VIT types.

UPDATE ON RISK ESTIMATES OF SYSTEMIC REACTIONS TO SUBLINGUAL IMMUNOTHERAPY

Recently published sublingual immunotherapy (SLIT) trials have confirmed that systemic reactions are extremely rare. First, Creticos *et al.* [11] reported on 784 adults who received either ragweed SLIT or placebo for 52 weeks. No systemic reaction occurred during this study. Second, Nayak *et al.* [12[■]] reported a dose-escalation study for ragweed SLIT, reporting three patients in dose groups at least 24 Amb a 1-U who had symptoms suggestive of a systemic reaction. The dose escalation to 50 and 100 Amb a 1-U was discontinued and stopped, respectively, due to these studies. This study suggests that SLIT, if used at higher doses, may lead to a higher risk of systemic reactions than previously reported. Third, Roger *et al.* [13] reported on an observational study of individuals who had undergone an ultra-rush dust mite SLIT protocol. Eight of the 218 individuals had possible systemic reactions (3.7%), none of which was a serious adverse event.

UPDATE ON RISK ESTIMATE OF SYSTEMIC REACTIONS TO ROUTES OTHER THAN SUBCUTANEOUS OR SUBLINGUAL

Intralymphatic immunotherapy (ILIT) involves allergen delivery to T and B cells through routing the allergen to the lymph node and major histocompatibility complex (MHC) class II pathway. Relatively few individuals have been treated with ILIT and therefore risk estimates for systemic reactions remain less certain than those estimates for SCIT and SLIT. Hylander *et al.* [14] report on six individuals who received a total of 21 pollen

allergen injections via the intralymphatic route, none of whom had a serious adverse event (no systemic reactions). In another study [15] of ILIT, 12 individuals were treated with a recombinant cat dander allergen and no severe adverse reactions (no systemic reactions) were reported. These two preliminary studies on ILIT suggest that it may be a well tolerated route to administer AIT; however, confidence in risk estimates for this type of therapy will only be increased by larger studies.

The potential advantages of epicutaneous immunotherapy (EPIT) include a needle-free, self-administrable therapy which may increase its utilization and adherence. Senti *et al.* [16[■]] performed a randomized controlled trial of grass pollen EPIT before and during grass pollen season (six total patches were applied) in 132 patients. A systemic reaction was reported in 11 patients (10 from the treatment arm), for a rate of 8.3% per patient. All 11 reported pruritus at sites distant from the patch application site and 4 reported both rhinitis and cough, or either of the two; none required treatment with epinephrine or hospitalization. This study suggests systemic reaction rates for EPIT may be similar to those for SCIT.

Recombinant fusion proteins consisting of nonallergenic allergen-derived peptides fused to allergen-unrelated carrier molecules are designed to reduce systemic reactions. In a safety dose-ranging study [17] for a mixture of five recombinant grass pollen allergen SLIT, no systemic reaction was reported in the 50 enrolled individuals who received doses up to 120 µg via the sublingual route. Similarly, in a randomized controlled trial, 66 patients who underwent SCIT with a modified house dust mite extract had no systemic reactions over a 1-year study period [18]. These studies highlight the exciting potential of modified allergens to decreased systemic reaction risk.

Studies of ILIT, EPIT, and use of modified allergens have generated early evidence of efficacy. It remains unclear how the risk of systemic reactions with these immunotherapy methods will compare with the established risk rates of SCIT and SLIT.

PREDICTING SYSTEMIC REACTIONS TO ALLERGEN IMMUNOTHERAPY

Knowing which individuals have a higher than typical systemic reaction risk when receiving AIT may lead to choosing other treatments, more aggressive pretreatment regimens, additional monitoring periods, or adjustment in administration schedules.

In a retrospective review by DaVeiga *et al.* [19], of 1675 SCIT injections, 20 patients experienced 46 systemic reactions. Compared with matched

controls, patients with greater than 33% 3 or 4+ graded aeroallergen skin tests had a six-fold higher odds for systemic reactions, with an increase by 17% for each additional 4+ skin tests. Skin test patterns demonstrating a greater number of larger skin test responses to inhalant skin testing are associated with significantly elevated risk for systemic reactions in patients. Patients with larger and high numbers of positive skin tests may require additional caution when administering AIT.

It remains unclear whether large local reactions (LLRs) to SCIT predict future systemic reactions. Calabria *et al.* [20] studied individuals who have had both LLRs and systemic reactions, and compared them to a control group who had a systemic reaction but no LLR. They found the rate of systemic reaction was 1.3% for those with a previous LLR and 0.4% for those without a LLR. They further were able to identify a subgroup of individuals who had frequent LLRs and an increased systemic reaction risk. Despite this large and well designed study, there is ongoing uncertainty of how to intervene when individuals have LLRs. Prospective controlled studies are needed to provide further clarification.

In VIT, the predictive value for systemic reactions by an elevation of baseline serum tryptase has recently been described. In a prospective study of 19 children who developed systemic reactions during VIT, Cichocka-Jarosz *et al.* [21] showed that serum tryptase was higher both before and after desensitization and increased significantly following VIT in those who had systemic reactions. A controlled study reported by Asero *et al.* [22], however, was unable to show that an elevated serum tryptase poses excess risk in 15 SCIT patients who had previously experienced a systemic reaction. Rank *et al.* [23] were unable to demonstrate a predictive effect for three different mast cell mediators (urinary 11-beta prostaglandin, urinary N-methylhistamine, or serum tryptase) in a small controlled study.

In summary, baseline tryptase may be useful for prediction of systemic reactions to VIT (and undiagnosed systemic mastocytosis), but has not yet been proven to be predictive in aeroallergen SCIT (not yet been studied on a large scale). LLRs may be associated with an increased risk, but a rather a poor predictor, for systemic reactions. Size and number of positive skin tests may predict systemic reactions.

PREVENTING SYSTEMIC REACTIONS TO ALLERGEN IMMUNOTHERAPY

Pretreatment regimens such as antihistamines and monoclonal anti-IgE antibody have been

previously shown in prospective trials to reduce systemic reactions to AIT, at least in certain populations using specific build-up protocols. A recent trial of anti-IgE treatment in 221 children undergoing grass or birch pollen SCIT found four severe adverse events in the placebo group compared with no such events in the anti-IgE group, suggesting a protective effect against systemic reactions [24]. Massanari *et al.* [25] examined omalizumab's effect on cluster SCIT in 248 patients with allergic rhinitis and persistent asthma. Patients receiving omalizumab experienced significantly fewer systemic reactions, including respiratory-related, and more were able to reach maintenance than those receiving placebo ($P=0.017$ and 0.004 , respectively) [25]. Also, 35% of patients also received pretreatment with antihistamines which had no effect on the number of systemic reactions. We were unable to identify any recent study examining the risk of systemic reactions if antihistamines or antileukotrienes were used. Therefore, we report that recent studies in summary provide additional support for the use of anti-IgE as a preventive measure against systemic reactions to AIT. Anti-IgE treatment may be particularly useful for preventing lower respiratory reactions that can be part of systemic reactions to AIT.

TREATMENT OF SYSTEMIC REACTIONS TO ALLERGEN IMMUNOTHERAPY

Recognition and prompt management of anaphylaxis are important to prevent fatalities. In a retrospective study by Phillips *et al.* [26], 773 patients representing 14 707 SCIT visits received approximately 28 000 injections over 1 year and 32 systemic reactions occurred in 31 (4%) patients. Systemic reactions were classified by the World Allergy Organization grading system: 14 as grade 1, 13 as grade 2, 3 as grade 4, and 0 as grade 5. No late-phase systemic reactions were reported in this study. Twenty-nine (90.6%) reactions were treated with epinephrine, 27 (84.4%) with systemic corticosteroids, and 30 (93.8%) with H1 antihistamine. Epinephrine administration resulted in a successful response in all those who received the early intervention.

In a study by Epstein *et al.* [27], 289 (14%) had delayed-onset systemic reactions compared with 1816 early-onset systemic reactions (86%). Fifteen percentage (226/1519) of grade 1, 10% (54/538) of grade 2, and 12.5% (9/72) of grade 3 systemic reactions were delayed-onset systemic reactions. This survey study suggests that delayed systemic reactions to AIT may be less frequent than previously reported. Also, high-grade delayed systemic

reactions to AIT are rare. These studies should be taken in consideration when deciding about which AIT patients should be instructed to carry epipen with them after they leave the office.

CONCLUSION

Recent studies offer updated estimates for the risk of systemic reactions to AIT. Screening for worsening asthma may be a key factor contributing to a decline in systemic reactions; reducing AIT dose during pollen season was also recently found to be associated with a decrease in systemic reactions. Cluster AIT with multiple allergens may confer a higher risk for systemic reactions than single-allergen cluster AIT. Recent data continue to support a low risk of systemic reactions for SLIT, whereas intralymphatic, epicutaneous, and recombinant allergens have not been used in a sufficient number of patients to form confident risk estimates. Pretreatment with omalizumab decreases systemic reaction risk, especially lower respiratory reactions. High-grade delayed systemic reactions to AIT may be less frequent than previously reported. In a recent large study of systemic reactions, all patients with systemic reactions responded to early administration of epinephrine.

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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
- of outstanding interest

1. Cox L, Nelson H, Lockey R, *et al.* Allergen immunotherapy: a practice parameter third update. *J Allergy Clin Immunol* 2011; 127 (Suppl 1):S1eS55.
 2. Larenas-Linnemann DE, Gupta P, Mithani S, Ponda P. Survey on immunotherapy practice patterns: dose, dose adjustments, and duration. *Ann Allergy Asthma Immunol* 2012; 108:373–378.
 3. Burks AW, Calderon MA, Casale T, *et al.* Update on allergy immunotherapy: American Academy of Allergy, Asthma, & Immunology/European Academy of Allergy and Clinical Immunology/PRACTALL consensus report. *J Allergy Clin Immunol* 2013; 131:1288–1296.
 4. Epstein TG, Liss GM, Murphy-Berends K, Bernstein DI. AAAAI and ACAAI surveillance study of subcutaneous immunotherapy, year 3: what practices modify the risk of systemic reactions? *Ann Allergy Asthma Immunol* 2013; 110:274–278; 278.e1.
- This survey of practicing allergists has provided insight into risk estimates for systemic reactions to allergen immunotherapy as well as potential factors that may mitigate these risks.
5. Tabar AI, Arrobarren E, Echechipia S, *et al.* Three years of specific immunotherapy may be sufficient in house dust mite respiratory allergy. *J Allergy Clin Immunol* 2011; 127:57–63.

6. Cardona R, Lopez E, Beltrán J, *et al.* Safety of immunotherapy in patients with rhinitis, asthma or atopic dermatitis using an ultra-rush buildup: a retrospective study. *Allergol Immunopathol (Madr)* 2012. [Epub ahead of print]
 7. Jung K. Safety and tolerability of immunotherapy using various up dosing schedules of a new SCIT product with an optimised allergen/aluminium hydroxide ratio. *Allergy* 2011; 66 (Suppl 95):41–43.
 8. Copenhaver CC, Parker A, Patch S. Systemic reactions with aeroallergen cluster immunotherapy in a clinical practice. *Ann Allergy Asthma Immunol* 2011; 107:441–447.
 9. Brown SG, Wiese MD, van Eeden P, *et al.* Ultrarush versus semirush initiation of insect venom immunotherapy: a randomized controlled trial. *J Allergy Clin Immunol* 2012; 130:162–168.
- This randomized trial of jack jumper ant found lower rates of systemic reactions for semi-rush build-up versus ultra-rush build-up and for a 50 µg maintenance dose versus a 100 µg maintenance dose.
10. Konstantinou GN, Manoussakis E, Douladiris N, *et al.* A 5-year venom immunotherapy protocol with 50 µg maintenance dose: safety and efficacy in school children. *Pediatr Allergy Immunol* 2011; 22:393–397.
 11. Creticos PS, Maloney J, Bernstein DI, *et al.* Randomized controlled trial of a ragweed allergy immunotherapy tablet in North American and European adults. *J Allergy Clin Immunol* 2013; 131:1342–1349.
 12. Nayak AS, Atiee GJ, Dige E, *et al.* Safety of ragweed sublingual allergy immunotherapy tablets in adults with allergic rhinoconjunctivitis. Safety of ragweed sublingual allergy immunotherapy tablets in adults with allergic rhinoconjunctivitis. *Allergy Asthma Proc* 2012; 33:404–410.
- This dose-escalation study of ragweed SLIT found that at higher SLIT doses, systemic reaction risk increases. Findings from this article highlight the importance of the allergen dose, which if high enough, can cause an increased systemic reaction even using routes previously reported to have extremely low risk of systemic reactions.
13. Roger A, Justicia JL, Navarro LA, *et al.* Observational study of the safety of an ultra-rush sublingual immunotherapy regimen to treat rhinitis due to house dust mites. *Int Arch Allergy Immunol* 2011; 154:69–75.
 14. Hylander T, Latif L, Petersson-Westin U, *et al.* Intralymphatic allergen-specific immunotherapy: an effective and safe alternative treatment route for pollen-induced allergic rhinitis. *J Allergy Clin Immunol* 2013; 131:412–420.
 15. Senti G, Cramer R, Kuster D, *et al.* Intralymphatic immunotherapy for cat allergy induces tolerance after only 3 injections. *J Allergy Clin Immunol* 2012; 129:1290–1296.
 16. Senti G, von Moos S, Tay F, *et al.* Epicutaneous allergen-specific immunotherapy ameliorates grass pollen-induced rhinoconjunctivitis: a double-blind, placebo-controlled dose escalation study. *J Allergy Clin Immunol* 2012; 129:128–135.
- This randomized controlled trial of epicutaneous immunotherapy suggests a systemic reaction rate similar to that for subcutaneous immunotherapy.
17. Klimek L, Schendzielorz P, Pinol R, *et al.* Specific subcutaneous immunotherapy with recombinant grass pollen allergens: first randomized dose-ranging safety study. *Clin Exp Allergy* 2012; 42:936–945.
 18. Riechelmann H, Schmutzhard J, van der Werf JF, *et al.* Efficacy and safety of a glutaraldehyde-modified house dust mite extract in allergic rhinitis. *Am J Rhinol Allergy* 2010; 24:e104–e109.
 19. DaVeiga SP, Liu X, Caruso K, *et al.* Systemic reactions associated with subcutaneous allergen immunotherapy: timing and risk assessment. *Ann Allergy Asthma Immunol* 2011; 106:533–537.
 20. Calabria CW, Stolfi A, Tankersley MS. The REPEAT study: recognizing and evaluating periodic local reactions in allergen immunotherapy and associated systemic reactions. *Ann Allergy Asthma Immunol* 2011; 106:49–53.
 21. Cichocka-Jarosz E, Sanak M, Szczeklik A, *et al.* Serum tryptase level is a better predictor of systemic side effects than prostaglandin D2 metabolites during venom immunotherapy in children. *J Investig Allergol Clin Immunol* 2011; 21:260–269.
 22. Asero R, Farioli L, Pastorello EA. Baseline serum tryptase levels and adverse reactions to injection specific immunotherapy with airborne allergens: is there a relationship? *Int Arch Allergy Immunol* 2012; 158:276–280.
 23. Rank MA, Kita H, Li JT, Butterfield JH. Systemic reactions to allergen immunotherapy: a role for measuring a PGD2 metabolite? *Ann Allergy Asthma Immunol* 2013; 110:57–58.
 24. Kamin W, Kopp MV, Erdnuess F, *et al.* Safety of anti-IgE treatment with omalizumab in children with seasonal allergic rhinitis undergoing specific immunotherapy simultaneously. *Pediatr Allergy Immunol* 2010; 21 (1 Pt 2):e160–e165.
 25. Massanari M, Nelson H, Casale T, *et al.* Effect of pretreatment with omalizumab on the tolerability of specific immunotherapy in allergic asthma. *J Allergy Clin Immunol* 2010; 125:383–389.
 26. Phillips JF, Lockey RF, Fox RW, *et al.* Systemic reactions to subcutaneous allergen immunotherapy and the response to epinephrine. *Allergy Asthma Proc* 2011; 32:288–294.
 27. Epstein TG, Liss GM, Murphy-Berends K, Bernstein DI. Immediate and delayed-onset reactions after subcutaneous immunotherapy injections: ACAAI/AAAAI surveillance study of subcutaneous immunotherapy year 2. *Ann Allergy Asthma Immunol* 2011; 107:426–431.