
Increased frequency of large local reactions among systemic reactors during subcutaneous allergen immunotherapy

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Background: Large local reactions are not uncommon during allergen immunotherapy (AIT). Dosage adjustments after large local reactions are commonly instituted despite literature that suggests individual large local reactions do not seem to predict subsequent systemic reactions.

Objective: To investigate the relationship between large local reactions and the risk of systemic reactions to AIT.

Methods: Retrospective review of the AIT database of a large, multicenter allergy practice group was conducted between June 1, 2003, and May 31, 2005. Numbers of large local reactions in 258 patients who experienced systemic reactions to AIT were compared with 299 age-, sex-, and sensitivity-matched control patients who did not experience systemic reactions during AIT.

Results: A total of 283 systemic reactions occurred in 258 patients during the surveillance period, which included 661,123 patient visits for 1,108,621 allergy injections. The systemic reaction rate was 0.043% of visits and 0.025% of injections. The large local reaction rate was 35.2% of visits and 19.5% of injections among systemic reactors compared with 8.9% of visits and 5.3% of injections in the controls ($P < .001$ each). Thus, the odds of experiencing large local reactions were significantly increased among systemic reactors.

Conclusions: Although AIT is a safe and effective immunomodulatory therapeutic option for the treatment of allergic diseases, patients with increased frequency of large local reactions may have increased risk for future systemic reactions. Identifying additional risk factors remains viable. Recognizing the relevance of frequent large local reactions is important for designing safer protocols for successful AIT in these patients.

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INTRODUCTION

Subcutaneous allergen immunotherapy (AIT) has been used as a treatment modality for more than 100 years.¹ It remains one of the most effective tools for managing allergic rhinoconjunctivitis, asthma, or venom hypersensitivity in the armamentarium of a trained allergist-immunologist.² By inducing immune tolerance and anergy to offending allergens, as well as immune deviation from T_H2 to T_H1 responses and clonal deletion of sensitized cells, the hyperreactivity of the recipient is reduced.³ As a consequence of several such mechanisms, AIT is one of the only therapeutic modalities that can alter the natural history of an allergic disorder. Understanding effective doses, effective duration, and safe administration of AIT has been evolving during the past century. Venom immunotherapy is highly effective when administered in care-

fully selected patients following published guidelines.⁴ AIT can also be highly effective in reducing morbidity from diseases such as allergic rhinitis and asthma. Administration of immunotherapy to sensitized children at an early age can reduce their risk of future sensitization to other allergens and decrease their risk of progressing to asthma, further demonstrating the powerful immunomodulatory properties of AIT.⁵

From the time of its first description by Leonard Noon and John Freeman in the early 20th century, the risk of local and systemic reactions to AIT has been well recognized by both patients and physicians.^{6,7} Administering allergens to a sensitized individual can sometimes result in large local reactions (LLRs) characterized by redness, swelling, and pruritus at the site of the injection. On rare occasions, AIT can cause systemic reactions and anaphylaxis, which can be fatal as first reported by Lamson in 1924.⁸ Fatalities due to anaphylactic reactions after AIT remain extremely rare and have been estimated to occur in 1 in every 1.5 million injections administered.⁹ Nonfatal systemic reactions with conventional immunotherapy occur at a rate ranging from 0.093% to 0.14% of injections administered and can be upsetting to both the patient and the physician.^{10,11} Studies of rush immunotherapy (rapid administration of multiple doses of AIT over several hours to days) have described much higher rates of systemic reactions in up to 36% of patients on this form of AIT.¹² Systemic reactions have been reported to occur up to 6 hours

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after an allergy vaccination but usually occur within 20 to 30 minutes.¹²

Several practice parameters have been published within the last decade to provide principles of safe and effective administration of AIT.¹³⁻¹⁵ These parameters have helped physicians standardize several aspects of AIT and provided guidelines to improve safety and reduce adverse effects. However, several areas remain ill-defined. One such area of ambiguity pertains to the clinical relevance of LLRs that occur after injection during AIT. Several studies have demonstrated the lack of sensitivity and specificity of LLRs in predicting systemic reactions to the subsequent dose of AIT and hence recommend ignoring them to reduce errors from dose adjustments.¹⁶⁻¹⁸ However, many practicing allergists seem uncomfortable doing so. Indeed, the most recent practice parameters on AIT state, "Published studies do not indicate that large local reactions are always predictive of subsequent reactions. Nevertheless, in the experience of some experts, a correlation between large local reactions and subsequent systemic reactions can be made in some patients."¹³ Besides reducing the discomfort that patients experience from LLRs, clearly this practice of dose adjustment after LLRs may be relevant. To the best of our knowledge, none of the larger studies published so far have looked at the frequency of LLRs as a risk factor for systemic reactions during AIT. We sought to answer precisely this question.

METHODS

A retrospective review of a database was conducted from a large, multicenter, single-subspecialty private group practice (Allergy Partners, PA) with 41 allergists in 11 states distributed throughout the Midwestern, Southern, and Eastern United States (hereafter referred to as the Allergy Partners Study Group [APSG]). A unique attribute of this group practice is the centralization of their immunotherapy mixing and distribution from a central laboratory located in Asheville, North Carolina. This laboratory uses Greer Laboratories aeroallergen extracts (Greer Laboratories, Lenoir, North Carolina) and ALK-Abelló venom extracts (ALK-Abelló Inc, Round Rock, Texas). Individual physicians select patients who would benefit from AIT and write prescriptions for their AIT mix(es). The mix(es) are prepared at the central laboratory and shipped overnight to the respective offices for administration.

Data Collection and Transmission

During AIT, any reactions that occur, whether local or systemic, are carefully documented for every patient at the respective offices. Mandatory reporting of all systemic reactions for quality control, safety, and regulatory purposes is made to the central extract laboratory in Asheville. All details regarding the systemic reactors, such as demographics, allergen skin test reactivity, allergen mix(es), doses administered, type of reaction, patient symptoms, treatment received, and outcomes, are reported on a form by the individual offices to be entered into a database at the central extract laboratory.

The recommended guidelines within the Allergy Partners, PA practices are "to repeat the same dose if a LLR between 25 to 30 mm size occurred after the preceding AIT dose. In the event of a LLR between 30 to 50 mm, it is recommended to reduce the dose by 2 steps and proceed to build-up per protocol if no further significant LLR occurs." Data were deidentified and made available to offsite research collaborators for independent analysis.

Study Groups

For the present study, data were gathered on systemic reactions that occurred during AIT between June 1, 2003, and May 31, 2005. Retrospective review of this database was conducted by us (S.R., G.D.M.) in a blinded fashion. A systemic reaction was defined as "any reaction occurring distant from the site of administration of the AIT dose including, but not limited to cutaneous reactions with pruritus and hives, upper and lower respiratory symptoms, hypotension and other well-described symptoms of anaphylaxis."¹⁹ An LLR was defined as "redness and swelling measuring 25 mm or greater around the site of injection occurring within 20 to 30 minutes of administration of the AIT dose that day." Data on total number of visits and injections received by the systemic reactors and number of LLRs to AIT doses before the systemic reaction were gathered from the respective offices where these patients were receiving their AIT. A group of 299 control patients receiving AIT who had not experienced systemic reactions were selected from several different practice locations. The control group was selected by requesting retrospective data from several of the larger practices in the APSG. Each control was carefully selected so that the overall sample of controls had a similar age and sex distribution when compared with the cases. To avoid selection bias, LLR information was unknown at the time of selection. After cases and controls were determined, practices were requested to provide LLR data on patients with significant allergen sensitization (4+ reaction on skin prick testing to 1 or more allergens). The total number of visits and injections per patient was also requested at the same time. This control group was chosen to have similar age distribution, sex distribution, and allergy sensitivity as the cases. The frequency of LLRs in the control group was then gathered from their immunotherapy office records.

Data and Statistical Analysis

The APSG collaborated with the University of Mississippi Medical Center (UMMC) for the design of this study and analysis of the data gathered during this surveillance. All data shared with researchers at UMMC were blinded by APSG investigators. The study was approved by the institutional review board at UMMC and was self-funded by the APSG and UMMC.

The Fisher exact test was used to compare the LLR rates between systemic reactors and the control group. Further, the risk of systemic reaction for frequency of LLRs was evaluated. Often it is beneficial to categorize continuous variables

such as frequency to assist in making clinical decisions. Frequency of LLRs was categorized by either low or high frequency using cut points of 10%, 20%, 30%, 40%, and 50%. This approach allowed us to evaluate the level of risk of systemic reaction associated with LLRs for various frequencies of occurrence using odds ratios (ORs) and 95% confidence intervals (CIs) for each cut point. $P < .05$ was considered statistically significant.

RESULTS

Between June 1, 2003, and May 31, 2005, 661,123 patient visits for AIT took place at the various practice sites of the ASPG. A total of 1,108,621 allergen vaccine injections were administered. The database included all patients regardless of whether they received venom or aeroallergen immunotherapy. Only 2 systemic reactions were recorded after Hymenoptera venom immunotherapy and 5 systemic reactions to imported fire ant immunotherapy in this database. We do not know the total number of patients receiving Hymenoptera venom immunotherapy in the APSG practices for the 2003 to 2005 study period. Only 5 patients were receiving single-aeroallergen extract immunotherapy. The rest received 2 or more aeroallergens in their immunotherapy extract(s).

A total of 283 systemic reactions were recorded in 258 patients, giving a systemic reaction rate of 0.043% of all AIT visits and 0.025% of all AIT injections administered during that period. Of these systemic reactors, 61.5% were female and 38.5% were male. Forty-five percent of the reactions occurred in those younger than 18 years, 41.5% in those 18 to 50 years, and 13.5% in those older than 50 years (Table 1).

Since, we did not know the exact number of patients who received AIT during this retrospective database review, a crude estimate of the total number of patients receiving AIT was derived by dividing the total number of AIT visits per year by the average number of AIT visits per year for any given patient, taking into consideration differences in buildup and maintenance injection frequency for the APSG injection protocol. Thus, we reached a rough estimate of 12,963 patients receiving AIT during this study, giving a systemic reaction rate of 2.2 per 100 patients during the 2-year study period.

Table 1. Demographics of Systemic Reactors and Controls

Demographics	Systemic reactors, No. (%) (n = 258)	Controls, No. (%) (n = 299)
Age, y		
<18	116 (45)	128 (43)
18–50	106 (41)	114 (38)
>50	36 (14)	57 (19)
Sex		
Male	98 (38)	120 (40)
Female	160 (62)	179 (60)
Patients with 4+ SPT reactivity to at least 1 aeroallergen	222 (86)	275 (92)

Abbreviation: SPT, skin prick test (4+ defined by wheal >3 mm with pseudopods and surrounding erythema greater than 21 mm).

Thirty-three percent of the systemic reactions were preceded by an LLR to the immediately preceding dose of allergen vaccine. Most of these systemic reactions (84%) occurred during the buildup phase either in the maintenance or pre-maintenance vials. No fatalities were recorded from any of the systemic reactions. Seventy percent of the systemic reactors had experienced LLRs before their systemic reactions compared with 46% of the control patients who had ever experienced LLRs (OR, 2.7; 95% CI, 1.9–3.9; $P < .001$). Among the systemic reactors (n = 258), 1,573 LLRs occurred during 4,460 AIT visits before the systemic reaction (reaction rate, 35.2% of all visits). Hence, their LLR rate was significantly higher compared with the control group (n = 299) in which 1,388 LLRs occurred during 15,540 visits (reaction rate, 8.9% of all visits; $P < .001$). This represents a 5.56-fold greater chance of having had an LLR at any visit for the systemic reactors compared with the controls (OR, 5.6; 95% CI, 5.1–6.0). In the systemic reactors, these 1,573 LLRs were attributable to the 8,081 allergen vaccine injections they received (reaction rate, 19.5% of all injections). This rate was significantly higher than that observed in the control group in which 1,388 LLRs were noted for 26,259 allergen vaccine injections (reaction rate, 5.3% of all injections; OR, 4.3; 95% CI, 4.0–4.7; $P < .001$).

The frequency of LLRs was significantly associated with systemic reactions using LLR rate cut points of 10%, 20%, 30%, 40%, and 50%. The ORs and corresponding 95% CIs are presented in Table 2 and Figure 1 for each cut point. The vertical axis was truncated to allow more graphic detail. As a reference, the horizontal dotted line represents the value where the level of risk is the same in both groups. The CIs that do not cross this line are equivalent to statistical significance. Notice that each interval does not cross the line. Further, the point estimates of the ORs appear to increase as the cut points increase. The implication is that patients with high frequency of LLRs are more at risk for systemic reactions than those with few or no LLRs.

DISCUSSION

This is the first report, to our knowledge, that shows that patients who have systemic reactions to AIT experience significantly higher LLR rates compared with those who never had a systemic reaction. It also suggests that patients who are experiencing frequent LLRs to AIT may be at an increased risk of developing systemic reactions to future allergen vaccine doses.

The rate of LLRs was almost 4 times higher (35.2% vs 8.9% of all visits and 19.5% vs 5.3% of all injections; $P < .001$ for each) among patients who subsequently experienced a systemic reaction compared with those who had never experienced a systemic reaction. These data would suggest that patients with higher rates of LLRs during conventional AIT are at an increased risk of experiencing systemic reactions. This finding lends credibility to the common practice of carefully documenting all LLRs. It also raises questions about what the safest practice might be for such patients with

Table 2. Frequency of Large Local Reactions Among Systemic Reactors vs Controls

Large local reaction rate	Systemic reactors, % (n = 258)	Controls, % (n = 299)	OR (95% CI)
10%	127	36	7.08 (4.63–10.84)
20%	82	17	7.73 (4.44–13.47)
30%	63	10	9.73 (4.68–18.64)
40%	47	5	13.10 (5.12–33.49)
50% of the injections received	34	2	22.54 (5.36–94.81)

Abbreviations: CI, confidence interval; OR, odds ratio.

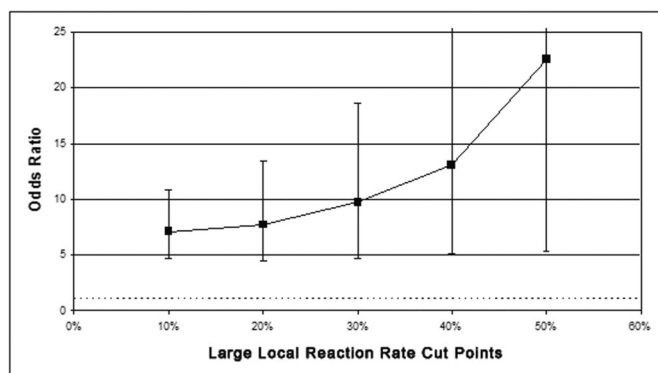


Figure 1. Odds ratios for the large local reaction cut points.

multiple LLRs. Open dialogue with these patients about risks and benefits of continued immunotherapy vs discontinuation of immunotherapy seems intuitive and appropriate. Those patients who experience increased rates of LLRs might benefit from modifications to their current AIT protocol as deemed appropriate by the prescribing physicians. Potential modifications that require further studies to prove efficacy could especially include attentive monitoring, slowing down the buildup schedule, repeating doses after an LLR before advancing, reducing the interval between injections (if already receiving maintenance and extended therapy), or choosing a lower maintenance dose as the final goal. Although pretreatment with oral antihistamines, corticosteroids, and antileukotriene agents has been beneficial in reducing systemic reactions during rush and cluster immunotherapy, it has generally been discouraged with conventional immunotherapy because of fear of masking early signs of systemic reactions.¹³ Every one of these suggestions has pros and cons; therefore, careful studies are necessary to validate a specific approach.

An LLR occurred with the injection immediately preceding the one that caused a systemic reaction in approximately one third of the study group patients. Previously, a retrospective study by Tankersley et al¹⁷ reported that 16% and 18% of their systemic reactions were immediately preceded by an LLR during the dose adjustment and no adjustment after LLR phases, respectively, of their 18-month study period. The

positive predictive value of a single LLR for a subsequent systemic reaction was only 17% in that study and 12% in a similar study repeated by Nelson et al.¹⁶ These studies support the notion that individual LLRs cannot reliably predict systemic reactions to the subsequent dose of AIT. Interestingly, 30% of the systemic reactors in our study had never experienced LLRs before their systemic reaction. Similarly, in their study of 416 patients who received 26,645 injections during the 18 months of monitoring in an academic allergy-immunology practice, Nelson et al¹⁶ reported that 36% of their patients had systemic reactions without a preceding LLR. This finding would imply that relying only on presence or frequency of LLRs to predict systemic reactors is inadequate. Clearly, some patients can experience a systemic reaction without ever having had an LLR, and some patients with recurrent LLRs (in this case the control group) would not subsequently develop systemic reactions. Multiple other risk factors, such as patient's degree of allergen sensitivity, uncontrolled asthma, pharmacotherapy with β -blockers, formulation and standardization of allergen vaccines, injections given during increased seasonal allergen exposure, dosing errors, and injections from new vials, may play a role in inciting systemic reactions or altering their severity during AIT.

One of the major strengths of this study is that the observations are derived from the largest reported AIT database in the United States, which has a wide patient base that represents several different regions of the country. Thus, these findings may be more applicable to other practices and settings. Allergy vaccine preparation was centralized, improving consistency and standardization of therapy in the study and control groups. The systemic reaction rate of 0.025% of injections is lower than those reported in some previously mentioned studies^{12,17,18} but similar to 0.06% to 0.01% of the 435,854 injections reported by Ragusa and Massolo²⁰ and 0.061% of the 300,086 injections reported by Luigi et al.²¹ The other findings from this study that are supported by previous studies include the 84% of systemic reactions that occurred during buildup compared with maintenance²² and female preponderance among systemic reactors.¹⁶

Limitations of this study include its retrospective nature. Certainly, the question of whether frequent LLR signals increase the risk for systemic reactions would be best answered in a prospective study design. A second group was randomly selected from the Allergy Partners, PA practices in an attempt to control the most obvious variables of age, sex, and degree of allergen sensitivity. The lower than usual systemic reaction rates in such a large practice database raises the question of whether lower (and perhaps suboptimal) concentrations of allergens were used in vaccine preparation. If so, both the control and study groups should have been affected uniformly by such a practice. In the study group of 258 systemic reactors, 475 allergen vials were mixed with a mean allergen content of 2.21 mL per 5-mL vial. Indeed, if the lower systemic reaction rates can be accounted for by a suboptimal allergen concentration, those physicians who use allergen

vaccines at the higher end of the recommended dosage spectrum should heed the findings of this study even more.

Making conventional subcutaneous AIT safer than it already is for our patients has been the shared goal of all allergists-immunologists since the inception of this effective treatment. With increasing interest in sublingual immunotherapy and the use of immunostimulatory sequence (such as CpG) or monophosphoryl lipid A–modified vaccines (which cause relatively fewer systemic reactions compared with conventional subcutaneous immunotherapy), these modalities hold future promise for improving AIT.^{23–25} In the meantime, recognizing that patients receiving AIT, who have frequent LLRs, may be at increased risk for systemic reactions may provide a more sensitive and specific method of identifying these currently unpredictable at-risk patients for appropriate intervention.

In summary, although AIT is a safe and effective immunomodulatory therapeutic option for the treatment of allergic diseases, our retrospective data suggest that, for some patients, an increased frequency of LLRs might be associated with an increased risk for systemic reactions. Recognizing the relevance of frequent LLRs may be important for designing safer protocols for successful AIT in these patients.

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