
Dose adjustment practices among allergists for local reactions to immunotherapy

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Background: Dose adjustments for local reactions to immunotherapy have been previously proposed. Several studies have shown that systemic reactions from immunotherapy injections are not predicted by previous local reactions. However, no previous reports have evaluated the prevalence and rationale of dose adjustment protocols within allergists' practices.

Objective: To examine allergists' response after patients' local reaction to immunotherapy.

Methods: On behalf of the American College of Allergy, Asthma and Immunology (ACAAI) Immunotherapy and Diagnostics Committee, an electronic survey was sent to all practicing allergists of the ACAAI. Participants were asked whether they make dose adjustments for local reactions to immunotherapy and the rationale behind this decision. Strategies to prevent and minimize local reactions were also queried.

Results: A total of 2,797 electronic letters were successfully sent, and 761 allergists (27.2%) responded to the survey, with 94.7% of the participants having completed a fellowship in allergy and immunology. Common strategies used by allergists to prevent and minimize local reactions included a dose adjustment based on the local reaction from the previous injection (79.1%) and pretreatment with an antihistamine (70.1%). Most allergists (91.9%) dose adjusted for local reactions. Most of these dose adjustments were based on protocols that included criteria for both repeating and decreasing the dose of immunotherapy based on the size of the local reaction. Rationales used by allergists for local reaction dose adjustment protocols included beliefs that local reactions cause discomfort that leads to patient noncompliance (88.9%), local reactions are predictive of future local reactions (45.7%), and local reactions are predictive of future systemic reactions (29.2%).

Conclusions: Our survey results indicate that most allergists dose adjust for local reactions to allergen immunotherapy. Although most allergists agree that local reactions are not predictive of future systemic reactions, the 2 main reasons for dose adjustments include the concern that local reactions cause discomfort that may lead to patient noncompliance with immunotherapy and the concern that local reactions are predictive of future local reactions.

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INTRODUCTION

Local reactions at the site of the injection are a frequent occurrence during allergen immunotherapy.¹ The frequency of local reactions reported in studies of allergen immunotherapy has ranged from 26% to 82%.^{2,3} Dose adjustments for local reactions to immunotherapy have been previously suggested as a method to prevent future local reactions and systemic reactions. Several studies have shown that a local reaction to immunotherapy is not predictive of a future systemic reaction, and local reactions do not require dose adjustments.^{2,4,5} Nevertheless, many allergists continue to recommend immunotherapy dose adjustments in response to local reactions. In addition, some authors⁶ have proposed local reactions to be a major reason for noncompliance with immunotherapy treatment regimens, although compliance studies have not supported this proposal.^{7,8} No previous reports

have analyzed the prevalence and rationale of dose adjustment protocols within allergists' practices. The goal of this study was to evaluate allergists' practices with regard to local reactions to immunotherapy.

METHODS

On behalf of the American College of Allergy, Asthma and Immunology (ACAAI) Immunotherapy and Diagnostics Committee, an electronic survey was sent to practicing allergists of the ACAAI. The survey was again sent to the same allergists 2 weeks later. The survey was approved by the Wilford Hall Medical Center Institutional Review Board. The survey consisted of 9 questions, which are listed in Table 1.

RESULTS

A total of 2,797 electronic letters were successfully sent, and 761 allergists (27.2%) responded to the survey. Almost all (99.3%) of the participants prescribed aeroallergen and/or venom immunotherapy in their practice. Most allergists (77.6%) described their practice as clinical, with the remaining practices split between academic (8%) and mixed (14%). Most allergists (94.7%) had completed a fellowship in allergy and immunology, and there was an even distribution among the Northeast (24%), Southeast (22%), Southwest (20%), and Midwest (22%) regions. Five percent of responders were

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Table 1. Questionnaire Sent to Allergists Regarding Local Reactions

1. Do you prescribe aeroallergen and/or venom immunotherapy in your practice?
 - A) Yes
 - B) No
2. How would you describe your current practice?
 - A) Clinical
 - B) Academic
 - C) Mixed clinical and academic
3. Have you completed a fellowship in allergy and immunology?
 - A) Yes
 - B) No
4. Where is your practice located?
 - A) Northeast United States
 - B) Northwest United States
 - C) Southeast United States
 - D) Southwest United States
 - E) Midwest United States
 - F) Outside the United States
5. Which of the following do you use to prevent/minimize large local reactions to immunotherapy? (check all that apply)
 - A) Pretreatment with an antihistamine
 - B) Pretreatment with a NSAID
 - C) Use of a “dry” needle (ie, injecting dose with different needle than was used to draw up dose)
 - D) Split dosing (ie, half dose in each arm)
 - E) Stretching the skin before the injection and maintaining light pressure afterwards at the injection for 1 minute
 - F) Cold compress at the site during the 20–30 minute wait time following the injection
 - G) Reformulate the extract using lower doses in the extract prescription
 - H) Coating the needle with epinephrine prior to pulling the allergen extract out of the vial
 - I) Mixing epinephrine with the allergen extract at the time of injection
 - J) Dose adjustment (ie, repeat or decrease) based on a large local reaction after the previous injection
 - K) Rush immunotherapy protocol
 - L) Utilize separate injection sites other than the arm (eg, leg or abdomen)
 - M) Alternating injection sites
 - N) Other (please list):
6. Do you dose adjust (ie, repeat or decrease) for local reactions when giving allergen immunotherapy?
 - A) Yes
 - B) No
7. Do you have a written protocol for dose adjustments for local reactions to immunotherapy?
 - A) Yes
 - B) No
8. Which of the following describes your protocol for dose adjustments for large local reactions? (check all that apply)
 - A) May repeat the dose but never decrease the dose
 - B) Dose adjustment protocol includes criteria for both repeating and decreasing dose
 - C) May decrease the dose but never repeat the dose
 - D) Dose adjustment amount is based on the size of the local reaction
 - E) Dose adjustment amount is always the same regardless of the size of the local reaction
9. Which of the following describes the rationale for your dose adjustment protocol? (check all that apply)
 - A) Local reactions are predictive of future systemic reactions
 - B) Local reactions are predictive of future local reactions
 - C) Local reactions cause discomfort that may lead to patient noncompliance

Abbreviation: NSAID, nonsteroidal anti-inflammatory drug.

from the Northwest, and 8% were from outside the United States. In general, responses did not differ by practice or region, except for a few exceptions.

Allergists used many strategies to prevent and minimize local reactions to allergen immunotherapy. The most common strategies were a dose adjustment based on the local reaction from the previous injection (79.1%) and pretreatment with an antihistamine (70.1%). Other less common strategies advocated by

allergists to prevent local reactions included alternating injection sites (44.6%), applying a cold compress at the injection site during the 30-minute postinjection wait time (38.9%), reformulating the extract using lower doses in the extract prescription (34.7%), and splitting the dose into each arm (32.5%) (Table 2). Allergists from the Northwest region were more likely to pretreat with an antihistamine rather than make a dose adjustment for local reactions.

Table 2. Strategies to Prevent or Minimize Large Local Reactions to Immunotherapy

Strategy	Responses, %
Pretreatment with an antihistamine	70.1
Pretreatment with a NSAID	5.2
Use of a "dry" needle (injecting dose with different needle than was used to draw up dose)	13.0
Split dosing (half dose in each arm)	32.5
Stretching skin before injection and maintaining light pressure at site for 1 minute	11.9
Cold compress at the site during the 30-minute wait time after the injection	38.9
Reformulate the extract using lower doses in the extract prescription	34.7
Coating the needle with epinephrine before pulling the allergen extract out of the vial	4.1
Mixing epinephrine with the allergen at the time of injection	2.0
Dose adjustment (repeat or decrease) based on large local reaction after previous injection	79.1
Rush immunotherapy protocol	8.1
Use separate injection sites other than the arm	5.4
Alternating injection sites	44.6

Abbreviation: NSAID, nonsteroidal anti-inflammatory drug.

Allergists were also allowed to write in responses regarding the prevention of local reactions. Of 111 write-in responses, 35 allergists (31.5%) stated that they used a leukotriene modifier, 13 allergists (11.7%) recommended a topical steroid applied to the site of injection, 6 allergists (5.4%) reported that they used a steroid mixed in the extract injection, and 3 allergists (2.7%) used aluminum precipitated extracts to prevent and minimize large local reaction.

Most allergists (91.9%) dose adjust for local reactions. Most of these dose adjustments were based on written protocols that included criteria for both repeating and decreasing the dose of immunotherapy (70.6%) and basing the dose adjustment on the size of the local reaction (58.2%). Rationales used by allergists for local reaction dose adjustment protocols included the idea that local reactions cause discomfort that lead to patient noncompliance (88.9%), local reactions are predictive of future local reactions (45.7%), and local reactions are predictive of future systemic reactions (29.2%). A higher percentage of clinical allergists compared with academic allergists (91.7% vs 81.8%) believed that large local reactions cause discomfort and may lead to patient noncompliance as a rationale for dose adjustment.

DISCUSSION

Several key points can be taken from this dose adjustment for local reactions survey. First, most allergists (91.9%) dose adjust for local reactions when giving allergen immunother-

apy. The main reason that allergists dose adjust for local reactions is the belief that large local reactions cause discomfort that may lead to patient noncompliance. This notion was identified in 645 (88.9%) of 726 allergists (88.9%).

When looking at the literature regarding compliance with allergen immunotherapy, the most common reason cited for patient noncompliance with immunotherapy is inconvenience. More and Hagan⁷ analyzed 381 active immunotherapy records and contacted patients who had stopped allergen immunotherapy. They found that inconvenience (34.5% of patient responses) was the most important reason for discontinuation of immunotherapy. Other factors found for noncompliance with immunotherapy were a precluding medical condition (18.2%) and an adverse systemic reaction (16.4%). Local reactions from immunotherapy were a minor and uncommon reason for noncompliance with immunotherapy and were a reported factor in only 5.5% of patient responses. Cohn and Pizzi⁸ evaluated 217 medical records of patients who had discontinued allergen immunotherapy. These patients were contacted to determine their reasons for stopping immunotherapy. The authors also found that inconvenience was the major contributing factor for noncompliance with subcutaneous allergen immunotherapy.

The next most common response given by allergists of why they dose adjust immunotherapy for local reactions is the idea that large local reactions are predictive of future large local reactions. This belief was found among 332 (46%) of the allergists surveyed. Tankersley et al⁴ evaluated the rate of local reactions with a dose adjustment policy vs a no dose adjustment policy. They found that the local reaction rates during the 2 periods studied (7.3% vs 4.7%) were not statistically different, implying that local reactions do not predict subsequent local reactions. Further studies are needed to determine whether a local reaction is predictive of another local reaction at the next visit.

The final reason chosen by allergists for dose adjusting local reactions is the belief that large local reactions are predictive of future systemic reactions. This belief was found in almost one third of the allergists surveyed and may stem from an article published in 1981 by Ramirez et al.⁹ In this study, 22 Hymenoptera-sensitive patients were treated with venom immunotherapy. Large local reactions occurred in 50% of these patients, and a subsequent dose adjustment was made proportionately to the local reaction. Using this approach, the investigators observed no systemic reactions to venom immunotherapy. They concluded that systemic reactions to venom immunotherapy may be decreased by a dose adjustment after a local reaction. However, there was no control group in this study.

Several additional articles have examined the relationship of local reactions to systemic reactions. Nelson et al² published a prospective study in 1986 that evaluated local and systemic reactions of 416 immunotherapy patients receiving 25,508 pollen extract injections. They concluded that most reactions were local and that the presence of local reactions was not helpful in predicting which patients would develop

systemic reactions. Portnoy et al,¹⁰ in a double-blind, placebo-controlled study of 22 children receiving rush immunotherapy, noted that local reactions were not associated with subsequent systemic reactions.

In 2000, Tankersley et al⁴ also analyzed local reactions in relationship to systemic reactions, comparing a 9-month period of dose adjustments for local reactions with a 9-month period of no dose adjustments for local reactions. During the 18-month period, 12,926 immunotherapy injections were given and 114 systemic reactions occurred. The systemic reaction rates were not statistically different between the 2 periods. The authors concluded that a local reaction is an insensitive predictor of a subsequent systemic reaction at the next allergen vaccine dose. In addition, they stated that dose adjustment for most local reactions is unnecessary and may delay therapy, increase costs, and put the patient at increased risk of dose administration errors.

In 2004, Kelso⁵ compared 2 treatment periods to examine the rate of systemic reactions to immunotherapy injections. During the first period (3,250 visits), dose adjustments were made for local reactions, but during the second period (4,692 visits) no dose adjustments were made. The systemic reaction rate during the 2 periods was not statistically different. Kelso concluded that the rate of systemic reactions to immunotherapy injections is the same whether or not the dose is adjusted after a local reaction.

When considering therapies that prevent or minimize local reactions from immunotherapy, several published studies have evaluated the use of antihistamines in venom rush immunotherapy. Berchtold et al¹¹ demonstrated in a double-blind, placebo-controlled trial of 52 bee venom allergic patients undergoing rush immunotherapy that large local reactions were significantly reduced by pretreatment terfenadine, 120 mg twice daily, during the rush portion of the protocol. Brockow et al¹² conducted a double-blind, placebo-controlled study of 121 Hymenoptera venom allergic patients who participated in rush immunotherapy who were pretreated with either terfenadine, 120 mg, plus ranitidine, 300 mg, terfenadine alone, 120 mg, or placebo. The authors concluded that pretreatment with histamine₁-antihistamines with or without histamine₂-antihistamines significantly reduced local and systemic adverse reactions to Hymenoptera venom immunotherapy. The therapeutic benefit was limited to the first 4 weeks of treatment. Finally, Reimers et al¹³ performed a double-blind, placebo-controlled trial of 57 patients undergoing bee venom ultrarush immunotherapy. The patients were treated with fexofenadine, 180 mg, or placebo on days 1, 8, 22, and 50 of the protocol. The authors noted that pretreatment with fexofenadine during venom immunotherapy reduced local reactions only on day 1, but no statistical difference in local reaction size was seen on days 8, 22, and 50.

In addition to using antihistamines to prevent local reactions, a recent article from Italy demonstrated that depot immunotherapy with aluminum hydroxide reduced local reactions during the induction phase for Hymenoptera venom allergy.⁶ In this study of 43 patients, depot venom immuno-

therapy was better tolerated because of a lower frequency of local adverse effects (5.9% vs 42.5%) when compared with venom immunotherapy with aqueous extracts. Of interest, the article noted that most European inhalant subcutaneous immunotherapy is performed almost exclusively with depot extracts.

Local reactions are a result of both IgE and non-IgE cutaneous responses. In addition, glycerin, which is used as a preservative^{14,15} for allergenic extracts, can cause pain and local dermal reactions. Van Metre et al¹⁶ injected 15 healthy subjects subcutaneously with various doses and concentrations of glycerin. The authors observed that the glycerin produced pain that was proportional to the total dose injected, although a significant variance was found in perceived discomfort among individuals. However, total glycerin doses (ie, volume $\times$ concentration) less than 0.05 mL rarely produced clinically important pain.

Although this large local reaction survey produced only a 27.2% response rate, the absolute number of 761 responses is significant and was geographically representative. Additionally, a higher response rate was achieved from the survey when compared with the response rate of a recent electronic survey of skin testing techniques performed by Oppenheimer and Nelson¹⁷ (27.2% vs 18% response rate). This higher response rate can be attributed to electronically mailing the survey a second time 2 weeks after the initial mailing. This second mailer is recommended for future electronic mail surveys as a means of increasing the response rate.

In conclusion, our survey results indicate that most allergists dose adjust for local reactions to allergen immunotherapy. Most allergists agree that local reactions are not predictive of future systemic reactions. The main reasons for dose adjustment include the concern that local reactions are predictive of future local reactions and the concern that local reactions cause discomfort that may lead to patient noncompliance with immunotherapy. These concerns may not be valid as evidenced by data from published trials; nevertheless, more studies should be conducted to further evaluate these concerns.

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