
Patient perceptions regarding local reactions from allergen immunotherapy injections

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Background: Although most allergists agree that local reactions to immunotherapy are not predictive of future systemic reactions, the 2 main reasons for dose adjustments are the concern that local reactions cause discomfort that may lead to patient noncompliance and the concern that local reactions are predictive of future local reactions.

Objectives: To determine patient perceptions regarding local reactions from immunotherapy.

Methods: A survey on allergen immunotherapy was provided to patients. Participants were asked about the presence of local reactions, the size of their local reactions, and how bothersome these local reactions were. Patients were also asked if they had considered stopping immunotherapy because of these local reactions.

Results: All 249 patients undergoing immunotherapy completed the survey. Seventy-one percent of the patients reported that they had experienced a local reaction during allergen immunotherapy. Of those patients who reported local reactions, 84.7% reported local reactions smaller than the palm of the hand and 81.9% deemed local reactions not to be bothersome at all or only slightly bothersome. Of those who experienced local reactions, 96.0% stated they would not stop immunotherapy because of these local reactions.

Conclusions: Although most patients reported local reactions, these local reactions were usually small and not very bothersome. Most patients would not stop allergen immunotherapy because of local reactions.

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INTRODUCTION

Local cutaneous reactions are a frequent occurrence during allergen immunotherapy.^{1–6} To prevent future local and systemic reactions, dose adjustments of immunotherapy have been suggested and used by allergists.⁷ Several studies^{2,4,8} have demonstrated that a local reaction from immunotherapy is not predictive of a future systemic reaction and does not require dose adjustment. However, some authors have proposed that local reactions are a major reason for noncompliance with immunotherapy regimens, and they continue to make dose adjustments for local reactions.⁹ Compliance studies^{10,11} of immunotherapy have not supported this proposal. A recent survey¹² revealed that 92% of allergists continue to dose adjust for local reactions from immunotherapy because of local and systemic reaction concerns, fear of patient discontinuation, or both. The goal of the present study was to determine patient perceptions regarding local reactions from immunotherapy.

METHODS

A survey on allergen immunotherapy was provided to patients at the Wilford Hall Medical Center Allergy Clinic. This immunotherapy population consists of 84% aeroallergen, 7%

imported fire ant, 3% flying Hymenoptera, and 6% combinations of these types of immunotherapy.⁶ All immunotherapy was administered using safety needles. Patients were given the survey when they presented for an immunotherapy injection, and they completed the survey during their 30-minute obligatory waiting period. The survey consisted of 8 questions (Table 1). A Likert scale was used for question 4. The survey and study protocol were approved by the Wilford Hall Medical Center institutional review board.

RESULTS

A total of 249 patients (100% of patients undergoing immunotherapy) completed the survey, and their responses were anonymous. The mean patient age was 40.7 years (range, 13–76 years). There were 120 males (48.2%) and 129 females (51.8%). The patients included active-duty and retired military personnel and their spouses and children. The patients were educated regarding the risks and benefits of immunotherapy, and each patient signed an informed consent document. A total of 37.5% of patients had been undergoing allergen immunotherapy for less than 1 year, 27.4% for 1 to 3 years, 15.7% for 4 to 5 years, and 19.4% for greater than 5 years. Patients undergoing aeroallergen, imported fire ant whole-body extract, or flying Hymenoptera venom immunotherapy were included in the survey. Seventy-one percent (177 of 249) of the patients reported local reactions from allergen immunotherapy. Most of these reactions (84.7%, 150 of 177) were smaller than the palm of the hand, 20.3% (36 of 177) were larger than the palm, and 2.8% (5 of 177) extended beyond the elbow. Most patients (81.4%, 144 of 177) deemed

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Table 1. Questionnaire Given to Patients for Local Reactions From Immunotherapy

1. How long have you been receiving allergy injections?
 - A) <1 y
 - B) 1–3 y
 - C) 4–5 y
 - D) >5 y
2. Have you ever had a local reaction from your allergy injections? A local reaction is defined as swelling, redness, or itching at the injection site.
 - A) Yes
 - B) No (go to question 6)
3. How large was this local reaction? (circle all that apply)
 - A) Smaller than the palm of your hand
 - B) Larger than the palm of your hand
 - C) The reaction extended beyond the elbow
4. How bothersome are the local reactions to you?
 - A) Not at all bothersome
 - B) Slightly bothersome
 - C) Moderately bothersome
 - D) Very bothersome
 - E) Extremely bothersome
5. Have you considered stopping your allergy injections because of local reactions?
 - A) Yes
 - B) No
6. To your knowledge, which of the following has been used by you or your allergist to prevent/decrease local reactions to your allergy injections? (circle all that apply)
 - A) Taking an antihistamine (Claritin, Zyrtec, Allegra, Benadryl, etc) before your allergy injection
 - B) Taking Tylenol, Motrin, or Naprosyn before your allergy injection
 - C) Using of a dry needle (ie, injecting the dose using a different needle than was used to draw up the dose)
 - D) Split dosing (ie, half the dose in each arm rather than the full dose from 1 vial in the same arm)
 - E) Stretching the skin before the injection and maintaining light pressure afterwards at the injection site for 1 min
 - F) Cold compress at the site during the 20- to 30-min waiting time after the injection
 - G) Reformulating the extract using lower doses in the extract prescription
 - H) Coating the needle with epinephrine before 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 local reaction after the previous injection
 - K) Using a "rush" schedule. A rush schedule involves receiving injections every hour for 6 to 8 h in 1–2 d to get to a maintenance dose quickly rather than the usual 1 injection per visit that achieves maintenance in 3–6 mo.
 - L) Using separate injection sites other than the arm (eg, leg or abdomen)
 - M) Alternating injection sites (right arm, left arm, right arm, left arm, etc)
 - N) Other (please list):
7. Do you feel that a local reaction(s) from your allergy injections will make it more likely that you have another local reaction?
 - A) Yes
 - B) No
8. Do you feel that a local reaction(s) from your allergy injections will make it more likely that you have a systemic anaphylactic/allergic reaction? A systemic reaction is defined as symptoms distant from the injection site that might require the use of epinephrine. Examples of a systemic reaction include difficulty breathing, hives all over your body, swelling of your face or throat, and lightheadedness.
 - A) Yes
 - B) No

their local reactions not to be bothersome at all or only slightly bothersome. Although 13.6% (24 of 177) of the patients found their local reactions to be moderately bothersome, only 5.1% (9 of 177) of the local reactions were very bothersome or extremely bothersome. Of the 177 patients who had local reactions, 170 (96.0%) stated that they would not stop immunotherapy because of the local reactions.

Of the 36 patients who reported local reactions larger than the palm of the hand, most (58.3%, 21 of 36) deemed their local reactions not to be bothersome at all or only slightly

bothersome, 27.8% (10 of 36) reported their local reactions to be moderately bothersome, and 13.9% (5 of 36) reported their local reactions to be very or extremely bothersome. Of these 36 patients, 35 (97.2%) would not stop immunotherapy because of local reactions that were larger than the palm of the hand. Of the 5 patients who had local reactions that extended beyond the elbow, 60% (3 of 5) deemed their local reactions to be not at all bothersome or only slightly bothersome (0 of 5 were moderately bothersome, 1 of 5 were very bothersome, and 1 of 5 were extremely bothersome). None of these 5

patients would stop their immunotherapy because of local reactions.

Many strategies were used by patients and their allergists to prevent or minimize local reactions from allergen immunotherapy (Table 2). The most common strategies were taking an antihistamine before the allergy injection (59.0%, 147 of 249), using a dry needle (45.0%, 112 of 249), and alternating injection sites (28.9%, 72 of 249). A dry needle was defined as injecting the dose using a different needle than was used to draw up the dose. Other less common strategies reported by patients to prevent local reactions included taking acetaminophen or a nonsteroidal anti-inflammatory drug before the allergy injection (12.9%, 32 of 249) and a dose adjustment based on the local reaction from the previous injection (7.6%, 19 of 249). An equal number of responders (5.2%, 13 of 249) reported split dosing of the allergy injection (ie, half the dose in each arm rather than the full dose from 1 vial in the same arm), stretching the skin and maintaining pressure at the injection site for 1 minute, and using a cold compress at the site during the 30-minute waiting time. Patients were also allowed to write in responses regarding the prevention of local reactions, and of 11 write-in responses, 6 patients stated that they used a topical corticosteroid (spray or cream) applied to the site of injection to prevent or minimize local reactions. Most patients did not believe that a local reaction from their allergy injections would make it more likely that they would have another local reaction (74.8%) or a systemic anaphylactic reaction (86.3%).

DISCUSSION

The main reason we conducted this study was to evaluate how bothersome local reactions were to patients undergoing immunotherapy and to evaluate whether local reactions were a reason they would want to stop immunotherapy. These concerns were foremost in our minds because of a recent survey¹² that showed that allergists dose adjust immunotherapy because of local and systemic reaction concerns. In fact,

the number one reason given by allergists (89% of allergists) for dose adjustment for local reactions was the concern that local reactions cause discomfort that may lead to patient noncompliance. We show that most local reactions are small and not bothersome to patients. Most patients (96.6%) would not stop allergen immunotherapy because of local reactions. This is a significant finding because the patients participating in this study receive their immunotherapy in a clinic that does not routinely dose adjust for local reactions. In addition, most of these patients did not believe that a local reaction predicted another local reaction or a future systemic reaction. It is assumed that these responses reflect the education we provide to patients about immunotherapy as it relates to local reactions.

Other studies have explored the rationale for immunotherapy noncompliance. In a study¹⁰ in which 381 immunotherapy charts were analyzed and patients who had stopped allergen immunotherapy were contacted, the authors found that inconvenience (34.5% of patient responses) was the single most important reason for discontinuation of immunotherapy. Local reactions from immunotherapy were an uncommon reason for discontinuation and were reported as a reason in only 5.5% of those who stopped. It is significant that this was a patient population that received immunotherapy where routine dose adjustments were not made for local reactions. This was reinforced in a study by Cohn and Pizzi,¹¹ who evaluated 217 medical records of patients who had discontinued allergen immunotherapy and contacted these patients to determine their reasons for stopping immunotherapy. They also found that inconvenience was the major contributing factor to noncompliance with subcutaneous allergen immunotherapy and that local reactions were not a reported reason for discontinuation.

In the present survey, which focused on local reactions, we found that local reactions occur commonly in patients undergoing immunotherapy. Most patients (71.1%) had experienced at least 1 local reaction during immunotherapy. These

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

Strategy	Patients, No. (%) (N = 249)
Pretreatment with an antihistamine	147 (59.0)
Use of a dry needle ^a	112 (45.0)
Alternating injection sites	72 (28.9)
Pretreatment with an NSAID	32 (12.9)
Dose adjustment (repeat or decrease) based on a large local reaction after previous injection	19 (7.6)
Split dosing (half the dose in each arm)	13 (5.2)
Stretching skin before injection and maintaining light pressure at site for 1 min	13 (5.2)
Cold compress at the site during the 30-min waiting time after the injection	13 (5.2)
Reformulate the extract using lower doses in the extract prescription	6 (2.4)
Coating the needle with epinephrine before pulling the allergen extract out of the vial	3 (1.2)
Rush immunotherapy protocol	3 (1.2)
Mixing epinephrine with the allergen at the time of injection	2 (0.8)
Use separate injection sites other than the arm	0

Abbreviation: NSAID, nonsteroidal anti-inflammatory drug.

^a Defined as injecting the dose using a different needle than was used to draw up the dose.

data agree with previous studies^{2-4,13,14} reporting that local reactions occur in 5% to 82% of patients undergoing immunotherapy depending on the criteria used to define a local reactions. Although this study consisted primarily of patients undergoing aeroallergen immunotherapy, we previously reported that local reaction rates were similar for aeroallergen, flying Hymenoptera, and imported fire ant.⁶ This recent study⁶ also found that local reactions larger than the palm of the hand were uncommon (0.4% reaction rate, and only 2.4% of all local reactions were larger than the patient's palm).

When looking at ways to prevent and minimize local reactions from immunotherapy, 59.0% of the patients took an antihistamine before their allergen immunotherapy injection. We do not routinely recommend antihistamine pretreatment, but we do offer it as an option for patients who have recurrent local reactions that are bothersome. Several studies¹⁵⁻¹⁷ evaluating the use of antihistamines in venom rush immunotherapy have found that pretreatment with antihistamines is helpful in preventing and decreasing the rate and size of local reactions. Note that this preventive effect was noted only during the rush immunotherapy phase and was not seen in the maintenance phase. Late local reactions were evaluated only in 1 of these studies during the rush phase,¹⁷ but none of the 3 studies evaluated late local reactions during the maintenance phase. There have been no studies, to our knowledge, evaluating the utility of local reaction prevention with traditional buildup schedules.

The dry needle technique was also cited by 45.0% of the patients as a way to prevent and decrease local reactions. The technique is accomplished by discarding the needle that is used to draw the extract into the syringe and replacing it with a needle that has not come into contact with the allergen. The theoretical rationale for the use of the dry needle is to avoid allergen contact with the patient's skin and tissue as the needle is injected. There is no literature to support the dry needle technique; however, anecdotally, these patients find the dry needle technique to be effective in decreasing local reactions.

A recent study¹⁸ in the immunization literature showed that local reactions to intramuscular vaccinations decreased significantly with the use of wide, long needles (23 gauge, 0.6 mm in diameter, 25 mm long) compared with narrow, short needles (25 gauge, 0.5 mm in diameter, 16 mm long). Because needle length could not be changed because immunotherapy is delivered subcutaneously, one potential area of study is to compare various bore sizes and the incidence of local reactions. Of note, none of the strategies commonly used by allergists to prevent or minimize local reactions have been evaluated (Table 2). This is an area that should be explored in future studies because a significant amount of time and energy is invested by the patient and the allergist to combat local reactions.

Because most of these patients undergoing immunotherapy are not active-duty military members but rather dependents and retirees, we believe that the findings from this study translate to the general population. Because we had a cap-

tured population given the regular visits and mandatory 30-minute waiting time for patients undergoing immunotherapy, we achieved 100% contact and completion. Given that patients were required to wait in the clinic for 30 minutes, none refused to complete the brief survey. Because we have been practicing under a policy of no dose adjustment for local reactions for the past 10 years and educating patients about local reactions before immunotherapy initiation and again when they have local reactions, we were not surprised that there was little in the way of complaint of the local reactions. Our experience has shown us that when patients are properly educated and interventions are offered to attempt to minimize or prevent local reactions, the result is a cooperative patient who desires to attain an effective, therapeutic immunotherapy dose with few interruptions in their dosing schedule. One standard of practice regarding strategies to reduce local reactions in our clinic is that we do not use a routine dose adjustment policy. Each allergist, however, has the liberty to use various strategies other than dose adjustments for local reactions (eg, pretreatment with an antihistamine or a non-steroidal anti-inflammatory drug, cool compress during the waiting time, and split dosing).

In conclusion, most patients report local reactions; however, these local reactions are usually small and not bothersome to patients. Most patients would not stop allergen immunotherapy because of these local reactions. In addition, no profound association was seen between the size of the local reactions and the discontinuation of immunotherapy. Allergist concerns about patient noncompliance should not be a motivating factor for routine dose adjustments for local reactions. Because the primary reason for immunotherapy noncompliance is inconvenience, routine dose adjustments may actually increase immunotherapy noncompliance because it delays advancement to maintenance dosages and introduces additional visits for the patient.

REFERENCES

1. Bousquet J, Lockey RF, Malling H-J. Allergen immunotherapy: therapeutic vaccines for allergic diseases. *Allergy*. 1998;53:1-42.
2. Nelson BL, Dupont LA, Reid MJ. Prospective survey of local and systemic reactions to immunotherapy with pollen extracts. *Ann Allergy*. 1986;56:331-334.
3. Prigal SJ. A ten-year study of repository injections of allergens: local reactions and their management. *Ann Allergy*. 1972;30:529-535.
4. Tankersley MS, Butler KK, Butler WK, Goetz DW. Local reactions during allergen immunotherapy do not require dose adjustment. *J Allergy Clin Immunol*. 2000;106:840-843.
5. Roy SR, Sigmon JR, Olivier J, Moffitt JE, Brown DA, Marshall GD. Increased frequency of large local reactions among systemic reactors during subcutaneous allergen immunotherapy. *Ann Allergy Asthma Immunol*. 2007;99:82-86.
6. Calabria CW, Coop CA, Tankersley MS. The GILL study: glycerin-induced local reactions in immunotherapy. *J Allergy Clin Immunol*. 2008;121:222-226.
7. Ramirez DA, Londono S, Evans R III. Adverse reactions to venom immunotherapy. *Ann Allergy*. 1981;47:435-439.
8. Kelso JM. The rate of systemic reactions to immunotherapy injections is the same whether or not the dose is reduced after a local reaction. *Ann Allergy Asthma Immunol*. 2004;92:225-227.
9. Alessandrini AE, Berra D, Rizzini FL, et al. Flexible approaches in the

-
- design of subcutaneous immunotherapy protocols for Hymenoptera venom allergy. *Ann Allergy Asthma Immunol.* 2006;97:92–97.
10. More DR, Hagan LL. Factors affecting compliance with allergen immunotherapy at a military medical center. *Ann Allergy Asthma Immunol.* 2002;88:391–394.
 11. Cohn JR, Pizzi A. Determinants of patient compliance with allergen immunotherapy. *J Allergy Clin Immunol.* 1993;91:734–737.
 12. Coop CA, Tankersley MS. Dose adjustment practices among allergists for local reactions from immunotherapy. *Ann Allergy Asthma Immunol.* 2007;99:77–81.
 13. Golden DB, Valentine MD, Kagey-Sobotka A, Lichtenstein LM. Regimens of Hymenoptera venom immunotherapy. *Ann Intern Med.* 1980;92:620–624.
 14. Can D, Demir E, Tanac R, Gulen F, Yenigun A. Immediate adverse reactions to immunotherapy. *J Invest Allergol Clin Immunol.* 2003;13:177–180.
 15. Berchtold E, Maibach R, Muller U. Reduction of side effects from rush-immunotherapy with honey bee venom by pretreatment with terfenadine. *Clin Exp Allergy.* 1992;22:59–65.
 16. Brockow K, Kiehn M, Riethmuller C, Vieluf D, Berger J, Ring J. Efficacy of antihistamine pretreatment in the prevention of adverse reactions to Hymenoptera immunotherapy: a prospective, randomized, placebo-controlled trial. *J Allergy Clin Immunol.* 1997;100:458–463.
 17. Reimers A, Hari Y, Muller U. Reduction of side-effects from ultrarush immunotherapy with honeybee venom by pretreatment with fexofenadine: a double-blind, placebo-controlled trial. *Allergy.* 2000;55:484–488.
 18. Diggle L, Deeks JJ, Pollard AJ. Effect of needle size on immunogenicity and reactogenicity of vaccines in infants: randomised controlled trial. *BMJ.* 2006;16:333:571–577.
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