

The LOCAL Study: Local reactions do not predict local reactions in allergen immunotherapy

Christopher W. Calabria, MD, Christopher A. Coop, MD, and Michael S. Tankersley, MD *San Antonio, Tex*

Background: Although previous immunotherapy studies have demonstrated that a local reaction does not predict a systemic reaction, no study has investigated whether a local reaction predicts a local reaction.

Objective: To determine whether a local reaction predicts a local reaction at the next immunotherapy injection.

Methods: A retrospective analysis of an electronic immunotherapy database over a 12-month period was performed at a single site that did not dose-adjust for local reactions. Total injections, small local reactions (less than or equal to the size of patient's palm), large local reactions (LLRs; larger than the patient's palm), systemic reactions, and whether a local reaction was followed by a local reaction were recorded. **Results:** Between August 2005 and July 2006, 360 patients received a total of 9678 injections. Of all patients, 78.3% had at least 1 local reaction, and 7.5% had an LLR. The total local reaction rate was 16.3% (1574/9678), the small local reaction rate was 15.9% (1536/9678), and the LLR rate was 0.4% (38/9678). Of all local reactions followed by another injection, 27.2% were followed by a local reaction. The sensitivity and positive predictive value for a local reaction predicting a local reaction at the next injection were 26.2% and 27.2%, respectively. In contrast, the specificity for the absence of a local reaction predicting the absence of a subsequent local reaction was 85.5%. For LLRs, only 6.0% were followed by another LLR; the sensitivity, positive predictive value, and specificity were 5.2%, 6.0%, and 99.6%, respectively.

Conclusion: In a clinic that does not dose-adjust for local reactions, local reactions do not predict local reactions at the next immunotherapy injection. (*J Allergy Clin Immunol* 2009;■■■:■■■-■■■.)

Key words: Local reaction, large local reaction, systemic reaction, subcutaneous immunotherapy, safety

A responsible subcutaneous immunotherapy (SCIT) program includes investigation of adverse events to include local and systemic reactions. Previous studies have demonstrated that local reactions are common, ranging from 26% to 82% of patients and 0.7% to 16% of injections¹⁻⁵ over a course of SCIT. Allergists

Abbreviations used

IFA: Imported fire ant

SCIT: Subcutaneous immunotherapy

use a variety of approaches for management of local reactions, as demonstrated by a recent local reaction survey.⁶ One common approach is routinely to dose-adjust for local reactions, reported by 91.9% of respondents. The reasons given for dose adjustments include that local reactions cause noncompliance (88.9%), local reactions predict local reactions (45.7%), and local reactions predict systemic reactions (29.2%). Previous studies have demonstrated that local reactions do not predict a systemic reaction at the next injection,^{3,5,7-9} and local reactions are not a common reason for patient noncompliance.¹⁰ The majority of allergists are dose-adjusting for local reactions and doing so with the assumption that their dose adjustment will influence the size of any local reaction at the next injection. However, no previous study has examined whether a local reaction predicts a local reaction at the next injection, and that is the primary purpose of this study.

METHODS

A retrospective analysis of an electronic SCIT database (Rosch Immunotherapy, Altoona, Pa) over a 12-month period at a single site was performed. All SCIT vials were 10-mL vials, and each patient's SCIT kit consisted of 4 vials (1:1000 vol/vol, green; 1:100 vol/vol, blue; 1:10 vol/vol, yellow; 1:1 vol/vol, red). We used the color system recommended by the current immunotherapy practice parameter.¹¹ For aeroallergen and imported fire ant (IFA) SCIT, a maintenance vial (1:1 vol/vol) consisted of 0.5 to 1 mL of each allergen taken from the manufacturer's stock bottle. Flying *Hymenoptera* extracts were received from the manufacturer in a lyophilized form and were reconstituted with diluent in our clinic. The diluent used when filling the 10-mL vials and when mixing down to less concentrated vials was 0.9% sodium chloride, 0.03% albumin (human), and 0.4% phenol for all types of SCIT.

The build-up phase of IFA and aeroallergen SCIT was 4 to 6 months and consisted of 1 to 2 injections per week, starting at 0.05 mL of the 1:1000 vol/vol (green) vial and advancing in dose increases of 0.05 to 0.1 mL with each subsequent injection until reaching a maintenance dose of 0.5 mL of the 1:1 vol/vol (red) vial. For flying *Hymenoptera*, the maintenance dose was 1.0 mL of the 100 µg/mL vial (or 300 µg/mL for mixed vespid).

Small local, large local, and systemic reactions were documented in the electronic SCIT database for each patient at each visit as they occurred by the nurse or technician who administered the injection. The number of consecutive local reactions was also documented for each patient (ie, whether a local reaction followed a local reaction at the next injection). Local reactions not followed by another injection could inherently not be analyzed for the presence of a subsequent local reaction. There were no dose adjustments for small or large local reactions in this patient population. Patients on more than 2 vials were excluded from analysis because more than 1 injection was delivered in the same arm (n = 17). Approval for the study was obtained from the Wilford Hall Medical Center Institutional Review Board.

The primary endpoint of the study was to investigate whether a local reaction predicted a local reaction at the next injection. We also investigated

From the Department of Allergy and Immunology, Wilford Hall Medical Center, Lackland Air Force Base.

Disclosure of potential conflict of interest: The authors have declared that they have no conflict of interest.

Received for publication February 28, 2009; revised July 20, 2009; accepted for publication July 27, 2009.

Available online September xx, 2009.

Reprint requests: Christopher W. Calabria, MD, Department of Allergy and Immunology, Wilford Hall Medical Center, 2200 Bergquist Drive Suite 1, Lackland Air Force Base, San Antonio, TX 78236. E-mail: christopher.calabria@lackland.af.mil.

0091-6749/\$00.00

© 2009 by Elsevier, Inc. on behalf of the American Academy of Allergy, Asthma & Immunology

doi:10.1016/j.jaci.2009.07.048

whether frequent small local reactions (whether consecutive or recurrent) were risk factors for large local reactions.

Reaction definitions

A small local reaction was defined as erythema and/or swelling ≥ 5 mm and less than or equal to the size of the patient's palm measured at 30 minutes. A large local reaction was defined as erythema and/or swelling greater than the size of the patient's palm (average adult, 80–100 mm) measured at 30 minutes. These definitions are customary at our institution. A delayed large local reaction was defined as the presence of erythema and/or swelling larger than the patient's palm and was reported by the patient at the next SCIT visit as occurring after the patient left the clinic (ie, after 30 minutes). To maximize reporting and identification of delayed reactions and as an added safety measure, patients filled out a prescreening questionnaire before each SCIT injection.

A consecutive local reaction patient was defined as a patient who had ≥ 2 local reactions in a row during the SCIT course. A recurrent local reaction patient was defined as a patient who experienced ≥ 2 local reactions at any point during the SCIT course. Patients encountering consecutive or recurrent small local reactions were investigated to determine whether they were experiencing more frequent large local reactions (than patients with isolated small local reactions). Next, data were analyzed to determine the frequency of patients with high numbers of consecutive local reactions, and whether consecutive local reactions increased a patient's chance of having additional local reactions (ie, the likelihood of a third local reaction after experiencing 2 small local reactions in a row). Finally, we queried whether patients with high individual rates of small local reactions (taking into consideration the number of total injections) were having higher large local reaction rates.

Statistics

See Table I for definitions in graphic form. Sensitivity was defined as the percentage of all local reactions that were preceded by a local reaction (true positives [a]/all local reactions [a + c]). Specificity was defined as the percentage of all injections not resulting in a local reaction that were not preceded by a local reaction (true negatives [d]/all injections without local reactions [b + d]). Positive predictive value was defined as the presence of a local reaction predicting the presence of a local reaction at the next injection (true positives [a]/true positives plus false positives [a + b]). Negative predictive value was defined as the absence of a local reaction predicting the absence of a local reaction at the next injection (true negatives [d]/true negatives plus false negatives [c + d]). *P* values were calculated using the Fisher exact test (GraphPrism Software, San Diego, Calif).

RESULTS

Overview

Between August 2005 and July 2006, 360 patients received a total of 9678 injections. There were 185 patients who received single injections and 175 patients who received 2 injections at each clinic visit. Seventeen patients receiving 3 or more injections at each clinic visit were excluded from the analysis. In all, 84% (302/360) of patients were treated with aeroallergen SCIT, 7% (25/360) with IFA, 3% (11/360) with flying *Hymenoptera*, and 6% (22/360) with combinations of these types. Aeroallergen SCIT vials (all 10 mL) contained an average of 11 allergens and 7.9 mL allergen. A total of 78.3% (282/360) of patients had at least 1 local reaction, whereas 7.5% (27/360) of patients had at least 1 large local reaction. For all injections, the total local reaction rate was 16.3% (1574/9678), the small local reaction rate was 15.9% (1536/9678), and the large local reaction rate was 0.4% (38/9678). The systemic reaction rate was 0.5% (51/9678) of injections. Thirty-seven percent (14/38) of large local reactions were delayed. There were no differences in small or large local reaction rates between the various types of SCIT.

Predictive value of a local reaction

Overall, 27.2% of all local (small and large) reactions were followed by another local reaction at the next injection. Six percent (2/33) of all large local reactions were followed by another large local reaction. The sensitivity and positive predictive values were low for all analyses, ranging from 0.7% to 31.2% for sensitivity and 0.8% to 33.3% for positive predictive value. In contrast, the specificity (83.9% to 99.7%) and negative predictive value (83.2% to 99.7%) were high for all analyses (Table II).

Consecutive small local reactions

Of the 278 patients who experienced a local reaction, 51% (143/278) experienced consecutive (2 or more in a row) small local reactions at some point during their SCIT course. As shown in Table III, although the small local reaction rate increased as patients experienced an increase in consecutive small local reactions, the large local reaction rate stayed the same. In addition, patients with consecutive small local reactions experienced additional small local reactions at the next injection as much as 32.9% to 48.0% of the time depending on the scenario (ie, the likelihood of a third local reaction after experiencing 2 small local reactions in a row; Table IV). For example, the chance that patients with 2 small local reactions in a row had a third small local reaction was 32.9%. No patients experienced more than 5 local reactions in a row.

Recurrent small local reactions

Eighty-six percent (240/278) of the local reaction patients experienced recurrent (2 or more local reactions at any point during their SCIT course) small local reactions. As shown in Table V, the large local reaction rate increased in the group with >10 small local reactions (0.99%), which is significantly higher than the group with 0 to 4 small local reactions, but not statistically higher than the group with 5 to 10 small local reactions.

High individual rates of small local reactions

As shown in Table VI, most patients experienced individual small local reaction rates of $<20\%$ of injections. The large local reaction rate increased significantly in patients with small local reaction rates of $\geq 20\%$ compared with patients with rates of $<20\%$. However, the large local reaction rate plateaued in the 30% to 39% group and actually decreased (although not significantly) in the group with small local reaction rates of $\geq 40\%$.

DISCUSSION

This is the first study to investigate whether a local reaction predicts a local reaction at the next injection in allergen immunotherapy. Our data suggest that local reactions are followed by local reactions at the next injection 27.2% of the time (Table II). However, the majority (almost three fourths) of patients will not have a local reaction at the next injection, and the sensitivity and positive predictive value remain low for the ability of a local reaction to predict a local reaction at the next injection. The specificity and negative predictive values were much higher in the absence of a local reaction.

Consecutive large local reactions (larger than the patient's palm) were infrequent, because only 6% of large local reactions were followed by a subsequent large local reaction at the next injection. There were no instances of 3 large local reactions in a

TABLE I. Definitions of sensitivity, specificity, and positive and negative predictive values as applied to the current study

		Local reaction at next injection (gold standard in this example)		
		Yes	No	
Local reaction at this injection	Yes	A (true positive)	B (false positive)	→ Positive predictive value = $a/a + b$
	No	C (false negative)	D (true negative)	→ Negative predictive value = $d/c + d$
		↓ Sensitivity = $a/a + c$	↓ Specificity = $d/b + d$	

TABLE II. Demonstration of whether a local reaction (small or large) predicts a local reaction (small or large) at the next injection

Statistical measure	Local reaction predicts a local reaction	Small local reaction predicts a small local reaction	Small local reaction predicts a large local reaction	Large local reaction predicts a small local reaction	Large local reaction predicts a large local reaction
Sensitivity (%)	26.2	26.0	31.2	0.7	5.2
PPV (%)	27.2	27.0	0.8	33.3	6.0
Specificity (%)	85.5	85.8	83.9	99.7	99.6
NPV (%)	84.8	85.2	99.7	83.2	99.7

NPV, Negative predictive value; PPV, positive predictive value.

The sensitivity and positive predictive values are low for the ability of a local reaction to predict a local reaction at the next injection. Conversely, the absence of a local reaction is better at predicting the absence of a local reaction, evidenced by higher NPVs.

TABLE III. Consecutive small local reactions

Small local reactions in a row (n)	No. of patients	Total no. of injections among these patients	Small local reaction rate, % (n/N)	Large local reaction rate, % (n/N)
2	82	2638	20.0 (82/2638)	0.57 (15/2638)
3	43	1605	25.4 (408/1605)	0.75 (12/1605)
4	10	420	34.3 (144/420)	0.71 (3/420)
5	8	273	42.9 (117/273)	0.37 (1/273)
>5	None	NA	NA	NA

A consecutive local reaction is defined as when a patient experiences 2 or more local reactions in a row. Higher numbers of consecutive small local reactions were not associated with a higher rate of large local reactions. No patients encountered more than 5 small local reactions in a row.

row. Similarly, the sensitivity and positive predictive values were low for the ability of a large local reaction to predict a subsequent small local or large local reaction at the next injection.

We performed various analyses to determine whether a higher number or frequency of small local reactions was associated with a higher frequency of large local reactions. We discovered that large local reactions were more common in patients with small local reaction rates of 20% to 29% (0.89%) compared with those with rates of <20% (0.09%; Table VI). However, this increase was not linear, and it was at its highest in the 30% to 39% small local reaction group and actually decreased slightly in the ≥40% small local reaction group. Large local reactions were also more common in patients with more than 10 small local reactions (0.99%) compared with those with 4 or fewer (Tables III and IV). One could argue that these mild increases, although statistically significant, are not clinically significant.¹² In addition, there were no increases in large local reactions in patients with higher numbers of consecutive small local reactions. Therefore, patients with even 5 small local reactions in a row did not experience higher large local reaction rates.

Notably, these findings were seen within a no dose adjustment population. Previous studies have demonstrated that local reactions do not predict systemic reactions and that dose adjustments for local reactions do not influence systemic reaction rates.^{5,7} Consistent with our department's previous study,⁵ this current

study also demonstrates that within a no dose adjustment population, local reactions also do not predict local reactions. In fact, our local reaction criteria, defined as the presence of any swelling and/or erythema measured at 30 minutes, may overestimate the local reaction rate, and thus may overestimate the ability of a local reaction to predict a local reaction.

Although local reactions do not predict systemic reactions at the next injection,^{3,5,7-9} a recent retrospective (case-control) study within a large multicenter allergy group demonstrated that patients experiencing systemic reactions had an increased frequency of large local reactions (defined as ≥25 mm measured at 20-30 minutes) compared with patients not experiencing systemic reactions.¹³ This association occurred among practices that performed routine dose adjustments for local reactions of ≥25 mm.¹³ However, no conclusions can be made about the influence of dose adjustments because there was no control group in this study in which no dose adjustments were made. Interestingly, our department has also noted that patients with systemic reactions have a higher frequency of large local reactions within a no dose adjustment population (unpublished data, C. W. Calabria and M. S. Tankersley, July 2009). Therefore, systemic reactors may experience more frequent local reactions, but this association occurs irrespective of whether dose adjustments are made. A prospective study design would be necessary to confirm this association and determine whether frequent large local reactions are a risk factor for systemic reactions. In

TABLE IV. Consecutive small local reactions

If a patient had "x" small local reactions in a row (number in this column is "x")	The chance that the patient with "x" consecutive small local reactions in a row will have "x + 1" consecutive small local reactions in a row (number in this column is "x + 1")	Frequency of injections with which a patient who had "x" small local reactions in a row went on to have "x + 1" small local reactions in a row,* % (n/N)
1	2 small local reactions in a row	27.0 (411/1512)
2 in a row	3 small local reactions in a row	32.9 (83/252)
3 in a row	4 small local reactions in a row	35.1 (26/74)
4 in a row	5 small local reactions in a row	48.0 (12/25)
5 in a row	6 small local reactions in a row	0 (0/10)

This table evaluates the frequency of having additional consecutive local reactions. If a patient has "x" small local reactions (where "x" = the number of small local reactions experienced in a row), it evaluates the frequency with which patients experienced "x + 1" small local reactions in a row.

*The denominator in this column is the number of injections that were evaluated during the period of the study. There were injections at the end of the study period that were followed by additional injections given after the study period that could not be evaluated. The numerator in this column is the number of injections that resulted in another local reaction.

TABLE V. Recurrent small local reaction patients

No. of small local reactions	No. of patients	No. of injections among these patients	Small local reaction rate, % (n/N)	Large local reaction rate, % (n/N)
0	77	1068	0	0
1	44	855	5.1 (44/855)	0.23 (2/855)
2	41	919	8.9 (82/919)	0 (0/919)
3-4	68	1853	12.6 (234/1853)	0.16 (3/1853)
5-7	58	1934	17.4 (337/1934)	0.41 (8/1934)
8-10	36	1440	22.5 (324/1440)	0.42 (6/1440)
>10	36	1917	30.8 (591/1917)	0.99 (19/1917)*

Recurrent small local patients were those patients who experienced 2 or more small local reactions during the study period. This table examines whether patients with higher numbers of small local reactions also experienced a higher large local reaction rate.

* $P = .001$ for patients with 10 or more small local reactions having a higher large local reaction rate compared with patients with 4 or fewer small local reactions (but not compared with patients with 5-10 small local reactions).

TABLE VI. High individual rates of small local reactions

Small local reaction rate (%)	No. of patients	No. of injections received by these patients	Small local reaction rate, % (n/N)	Large local reaction rate, % (n/N)
<20	238	6407	8.5 (548/6407)	0.09 (6/6407)
20-29	69	2257	24.3 (548/2257)	0.89* (20/2257)
30-39	34	867	34.0 (295/867)	1.04* (9/867)
≥40	19	455	48.6 (221/455)	0.66* (3/455)

Patients with individual small local reaction rates of $\geq 20\%$ had significantly higher large local reaction rates than patients with individual small local reaction rates of $< 20\%$. However, this increase in large local reaction rates was not linear, because it was highest in the group of patients with a 30% to 39% small local reaction rate and then actually decreased in the group with a $\geq 40\%$ small local reaction rate. The large local reaction rate in both the 30% to 39% and the $> 40\%$ groups was not significantly higher than the 20% to 29% small local reaction rate group.

* $P < .01$. These 3 groups had a significantly higher large local reaction rate than the group with a small local reaction rate of $< 20\%$.

addition, the percentage of all patients with large local reactions who go on to have a systemic reaction is unknown (ie, vs what percentage of all systemic reactors experienced large local reactions).

Local reactions are common, occurring in 77% of patients overall. Eighty-six percent of local reaction patients experienced recurrent local reactions, whereas 51% experienced consecutive local reactions of 2 or more. Therefore, education for local reactions is paramount before initiation of SCIT. Clinicians must explain to patients that they are likely to experience a local reaction at some point during the SCIT course and must emphasize that clinicians can provide symptomatic care to alleviate discomfort. This is analogous to anticipatory guidance at well child checks or risk communication when starting a new medication.

In a recent survey among patients on immunotherapy,¹⁴ 82% of patients reported their local reactions were not or were only

slightly bothersome, with only 5% of patients reporting their local reactions to be very bothersome. Ninety-six percent said they would not stop their SCIT because of local reactions, and 97% of patients reporting large local reactions (larger than the patient's palm) would not stop their SCIT. In a recent local reaction survey of allergists,⁶ the most common reason given for local reaction dose adjustments was concern for patient noncompliance. However, in a recent SCIT compliance study conducted within an immunotherapy population that did not dose-adjust for local reactions,¹⁰ inconvenience was the most common reason for discontinuing SCIT, and local reactions were an uncommon reason for SCIT discontinuation, with only 5% of patients discontinuing as a result of local reactions.

Because dose adjustments for local reactions increase patient visits and increase inconvenience, it can be argued that a dose

TABLE VII. Previous local reaction studies demonstrating the various criteria for defining a local reaction and their findings

Conventional or standard schedules		
	LR rate (per injection, %)	Minimum size of LR
Nelson et al ³	4.0	5 mm Dose adjusted for >15 mm
Tankersley et al ⁵	4.7-7.3	15 mm
Prigal ¹	0.1-2.8 depending on allergen	Not mentioned
Ramirez et al ²	4.2	15 mm
Roy et al ¹³	19.3 systemic reactors; 5.3 nonsystemic reactors	25 mm
Current study	16.0 (small LR) 0.4 (large LR)	Small LR: 5 mm Large LR: > patient's palm (average adult, 8-10 cm)
Rush schedules		
	Findings	Local reaction criteria
Berchtold et al ¹⁷ <i>Hymenoptera</i>	Antihistamine pretreatment decreased LR size vs placebo during first 4 wk of treatment but not thereafter	4-point scale for each of erythema, edema, and pruritus
Nielsen et al ⁸ Birch or grass*	No early LRs were >5 cm Late LR >8 cm: Placebo group: 9.5% Loratadine group: 6.5%	No specified minimum; measured early (30 min) and late LR (31 min to 48 h)
Reimers et al ¹⁵ Honeybee	Terfenadine reduced severe LR	4-point scale: 0, no LR; 1, <5 cm; 2, 5-10 cm; 3, over elbow; 4, middle of forearm
Portnoy et al ⁹ Inhalant	LR rate (per patient): 73% (8/11) of placebo group vs 27% (3/11) of treatment group	Larger than half dollar
Brockow et al ¹⁶ Honeybee	Premedication with fexofenadine reduced frequency of LR >6 cm vs placebo during rush but not during subsequent injections	4-point scale: 0, no LR; 1, 1-6 cm; 2, 6.1-12 cm; 3, 12.1-18 cm; 4, >18 cm
Wohrl et al ¹⁹ <i>Hymenoptera</i>	Premedication with montelukast delayed onset and size of LR	>3 cm
Heijaoui et al ²⁰ Inhalant	Dose adjustments for large LR during rush decreased systemic reaction incidence	>1.5 cm induration and >5 cm erythema

LR, Local reaction.

*Cluster, not rush.

adjustment policy for local reactions to immunotherapy will actually decrease patient compliance with this therapy. Regardless, dose adjustments will delay attainment of a maintenance dose and thus delay the onset of optimum dosing and efficacy. In addition, dose adjustments do not prevent systemic reactions at the next injection.^{5,7} Instead of routine dose adjustments for local reactions, we recommend that allergists consider focusing on interventions that will not increase inconvenience for our patients, such as pretreatment with an antihistamine, acetaminophen, non-steroidal anti-inflammatory drug, or montelukast; application of a cold compress during their 30 minute wait; or split dosing of their injection (ie, in patients on 1 injection, give half the dose in one arm and half the dose in the other arm), to name a few possibilities. For those patients reporting difficulty with local reactions, we find these interventions to be most effective.¹⁴

Although many interventions have been used by the allergy community to decrease the size and/or frequency of local reactions,⁶ only 3 interventions have been studied. First, pretreatment with antihistamines has not been shown to be efficacious in decreasing local reactions with conventional maintenance venom SCIT injections (given subsequent to an initial rush),^{15,16} and its effect on local reactions during conventional build-up schedules has not been reported, but it has been effective in decreasing local reactions during cluster⁸ and rush protocols.^{9,15-17} Pretreatment with antihistamines taken 2 hours before the injection also reduced the occurrence of severe systemic reactions in a single

study using a conventional build-up schedule.¹⁸ Second, discontinuation of a dose adjustment protocol for local reactions did not result in an increase in local reactions but, of interest, did result in a decrease in local reactions, although not statistically significant.⁵ Finally, a recent pilot study demonstrated that premedication with montelukast delayed the onset and decreased the size of local reactions during venom rush immunotherapy.¹⁹ Although we do not recommend dose adjustments for local reactions, we do use other comfort measures for the minority of patients who report bothersome local reactions. Further study is needed to assess the efficacy of the commonly used interventions.

Limitation of the current study include its retrospective design; however, use of an electronic SCIT database improved documentation and optimized data collection and analysis. In addition, with no universal definition for a local reaction, most allergists likely use different cut-off values. Despite these limitations, we feel the current study is pertinent to most practices. Our high cut-off for defining a large local reaction should reassure those clinicians using smaller classifications. Using the current definitions, only 6% of large local reactions were followed by a subsequent large local reaction. In addition, the ability of these large local reactions to predict a small local reaction was only 33%; two thirds of these large local reactions were not even followed by a local reaction. If one presumes that a larger local reaction can better predict a local reaction, then those practices using smaller large local reaction definitions (ie, 25 mm vs 80-100

mm) should see lower rates of consecutive large or small local reactions than the current study. Similarly, for small local reactions in the current study, with our criteria of ≥ 5 mm of erythema and/or swelling classified a local reaction, we may actually be overestimating the ability of a local reaction to predict a local reaction. However, future studies measuring the ability of local reactions of a specific size (ie, 50 mm, and so forth) to predict local reactions would further add to the local reaction and immunotherapy literature. To put this study into perspective, the current results and findings are presented with previous local reaction studies in Table VII.

In conclusion, 27% of local reactions are followed by a local reaction at the next injection. This occurred within a practice that did not dose-adjust for local reactions. The majority of patients will not experience a local reaction at the next injection, and the sensitivity and positive predictive value remain low for the ability of a local reaction to predict a local reaction.

Clinical implications: Local reactions do not predict local reactions at the next immunotherapy injection within a clinic that does not dose-adjust for local reactions and should not be used to make immunotherapy dose adjustments.

REFERENCES

1. Prigal SA. Ten-year study of repository injections of allergens: local reactions and their management. *Ann Allergy* 1972;30:529-35.
2. Ramirez D, Londono S, Evans R. Adverse reactions to venom immunotherapy. *Ann Allergy Asthma Immunol* 1981;47:435-9.
3. Nelson BL, Dupont LA, Reid MJ. Prospective survey of local and systemic reactions to immunotherapy with pollen extracts. *Ann Allergy* 1986;56:331-4.
4. Calabria C, Coop C, Tankersley M. The GILL study: glycerin induced local reactions in immunotherapy. *J Allergy Clin Immunol* 2008;121:222-6.
5. Tankersley MS, Butler KK, Butler WK, Goetz DW. Local reactions during allergen immunotherapy do not require dose adjustment. *J Allergy Clin Immunol* 2000;106:840-3.
6. Coop CA, Tankersley MS. Dose adjustments among allergists for local reactions from immunotherapy. *Ann Allergy Asthma Immunol* 2007;99:77-81.
7. 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;92:225-7.
8. Nielsen L, Johnsen C, Mosbech H, Poulsen L, Malling HJ. Antihistamine pre-medication in specific cluster immunotherapy: a double-blind, placebo-controlled study. *J Allergy Clin Immunol* 1996;97:1207-13.
9. Portnoy J, Bagstad K, Kanarek H, Pacheco F, Hall B, Barnes C. Premedication reduces the incidence of systemic reactions during inhalant rush immunotherapy with mixtures of allergenic extracts. *Ann Allergy Asthma Immunol* 1994;73:409-18.
10. More D, Hagan L. Factors affecting compliance with allergen immunotherapy at a military medical center. *Ann Allergy Asthma Immunol* 2002;88:391-4.
11. Allergen immunotherapy: a practice parameter second update. Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma and Immunology, the American College of Allergy, Asthma and Immunology, and the Joint Council of Allergy, Asthma and Immunology. *J Allergy Clin Immunol* 2007;120:S25-85.
12. Kain ZN, MacLaren J. *P* less than .05: what does it really mean? *Pediatrics* 2007;119:608-10.
13. Roy S, Sigmon J, Olivier J, Moffitt J, Brown D, Marshall D. Increased frequency of large local reactions among systemic reactors during subcutaneous allergen immunotherapy. *Ann Allergy Asthma Immunol* 2007;99:82-6.
14. Coop CA, Tankersley MS. Patient perceptions regarding local reactions from allergen immunotherapy injections. *Ann Allergy Asthma Immunol* 2008;101:96-100.
15. 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;55:484-8.
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;100:458-63.
17. 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.
18. Ohashi Y, Nakai Y, Murata K. Effect of pretreatment with fexofenadine on the safety of immunotherapy in patients with allergic rhinitis. *Ann Allergy Asthma Immunol* 2006;96:600-5.
19. Wohrl S, Gamper S, Hemmer W, Heinze G, Stingl G, Kinaciyan T. Premedication with montelukast reduces local reactions of allergen immunotherapy. *Int Arch Allergy Immunol* 2007;144:137-42.
20. Heijaoui A, Ferrando R, Dhivert H, Michel FB, Bousquet J. Systemic reactions occurring during immunotherapy with standardized pollen extracts. *J Allergy Clin Immunol* 1992;89:925-33.