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Local reactions from subcutaneous allergen immunotherapy

Local reactions from subcutaneous allergen immunotherapy are very common during the course of immunotherapy. These local reactions are not bothersome to patients. Local reactions from immunotherapy also do not predict future local or systemic reactions. This review discusses the studies that show that local reactions are not predictive of future reactions and that dose adjustments for local reactions from allergen immunotherapy are unnecessary. The article also focuses on factors that lead to patient noncompliance with immunotherapy and evaluates methods to prevent local reactions from subcutaneous allergen immunotherapy.

KEYWORDS: allergen immunotherapy ■ local reactions ■ systemic reactions

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Local cutaneous reactions from allergen immunotherapy are an important and common occurrence [1]. Studies of local reactions from allergen immunotherapy have shown the frequency of local reactions to range from 26 to 82% with a local reaction rate from 0.7 to 4% per 100 immunotherapy injections [2,3].

Local reactions are defined as swelling and redness that occur in the immediate vicinity of the injection site. They are classified as immediate or delayed reactions, depending on whether they occur within, or after, a 30-min time period [4]. Local reactions may persist for 24 h or longer [5]. These reactions usually cause pain associated with swelling and erythema. Local reactions can also be classified according to their size. Some authors grade a large local reaction as greater than 20 mm [6], whereas others consider a large local reaction to be larger than the palm of the patient's hand or even greater than 10 cm [7]. At our institution, we consider a small local reaction to be less than the size of the patient's palm and a large local reaction to be larger than the patient's palm.

There have been studies evaluating delayed reactions, both local and systemic, after allergen immunotherapy. In general, delayed systemic reactions after allergen immunotherapy are not as common as immediate reactions [8]. Additionally, delayed reactions tend not to be as severe as immediate reactions [9]. Local mucosal reactions can also occur after sublingual immunotherapy [10,11].

The objective of this article is to provide a review of studies evaluating local reactions from subcutaneous allergen immunotherapy. A literature search using PubMed was conducted

for articles on local reactions from immunotherapy using the keywords 'local reactions' and 'immunotherapy'.

Mechanisms of local reactions

Local reactions are a result of both IgE and non-IgE cutaneous responses [12]. These non-IgE responses include IgG antibodies [13] and delayed-type hypersensitivity mediated by T lymphocytes [14]. There is also the possibility of having immune complexes that can result in local reactions from immunotherapy. An injection of proteins to which the patient will develop antibodies could cause the formation of antigen–antibody complexes. Some authors have suggested that immune complex-mediated disease may result from allergen immunotherapy [15]. However, no evidence of immune complex-mediated disease was found in several studies on patients who received immunotherapy for many years [16,17].

Additional causes of local cutaneous reactions include an irritant mechanism [18] and a hygroscopic mechanism [19]. These phenomena were observed in studies of patients receiving subcutaneous injections of immunotherapy solutions containing glycerin. Glycerin, which is used as a preservative in allergen immunotherapy extracts, acts via a hygroscopic and an irritant-type mechanism as a cause of local reactions. The hygroscopic effect of glycerin pulls water out of subcutaneous tissues and causes induration after an allergen immunotherapy injection. As an irritant, glycerin produces pain and inflammation when injected into the skin or subcutaneous tissue.

Alum is used as an adjuvant to help boost the immunological response to a variety of antigens.

Alum has also been shown to cause local reactions when given with allergen immunotherapy and with vaccines [20,21]. Specifically, alum has been shown to cause subcutaneous nodules [22,23]. Monophosphoryl lipid A is also an adjuvant used with vaccines that can be associated with local cutaneous reactions [24]. Local cutaneous reactions are seen when patients are given allergen immunotherapy, whether it is with one allergen or multiple allergens [25,26].

Local reactions are common, but are not bothersome to patients

Local reactions to immunotherapy are common and they develop in 5–82% of immunotherapy patients depending on the criteria used to define a local reaction [2,3,27,28]. A recent survey demonstrated that local reactions occurred in 71.1% of patients in one allergy practice [29]. The majority (81.9%) of these local reactions were smaller than the palm of the hand, and were not at all bothersome or only slightly bothersome to the patients that answered the survey. Furthermore, most of the patients (96.6%) responding to the survey would not stop allergen immunotherapy because of local reactions from their immunotherapy.

Local reactions do not predict future systemic reactions

Dose adjustment for local reactions from immunotherapy has been suggested as a method to prevent future systemic reactions. This idea was postulated by Ramirez *et al.* in a study of 22 Hymenoptera-sensitive patients treated with venom immunotherapy who developed large local reactions [30]. Dose adjustments were made for these local reactions and there were no systemic reactions. Therefore, the authors concluded that systemic reactions to venom immunotherapy may be decreased by a dose adjustment after a local reaction; however, there was not a control group in this study. Many allergists continue to recommend immunotherapy dose adjustments in response to local reactions. In a recent survey of 761 allergists, 92% of the participants stated that they dose adjust for local reactions to immunotherapy [31].

There have been several articles focusing on the relationship of local reactions to systemic reactions. In 1986, Nelson *et al.* evaluated local and systemic reactions of 416 immunotherapy patients receiving 25,508 pollen extract injections [2]. The authors noted that the majority of immunotherapy reactions, were local reactions and that these local reactions were not helpful

in predicting which patients would develop systemic reactions. In 1987, Hepner *et al.* presented an abstract evaluating the safety of conventional immunotherapy (2989 patients). There were 27 systemic reactions analyzed with a systemic reaction rate of 0.05% per injection. Most of the systemic reactions occurred within 30 min (24 out of 27), and large local reactions did not precede systemic reactions [32]. Portnoy *et al.* conducted a double-blind, placebo-controlled trial of 22 children who received inhalant rush immunotherapy in 1994. Their results showed that local reactions were not associated with subsequent systemic reactions [33].

In 2000, Tankersley *et al.* evaluated local reactions in relation to systemic reactions [25]. A 9-month period of dose adjustments for local reactions was compared with a 9-month period of no dose adjustments for local reactions. Over 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 two periods of time; therefore, the authors concluded that a local reaction is a very insensitive predictor of a subsequent systemic reaction at the next allergen vaccine dose. In addition, the authors 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. Tankersley also analyzed systemic reactions using a no dose adjustment policy over a 3-year period while being a solo allergy practitioner. He evaluated 10,636 immunotherapy injections with 89 systemic reactions, and concluded that local reactions did not increase systemic reaction rates and that patients did not discontinue immunotherapy due to local reactions [34]. In another study of satellite Air Force allergy clinics, Tankersley also demonstrated that a no dose adjustment policy for local reactions did not increase systemic reaction rates and that local reactions do not require routine dose adjustments [35].

In 2004, Kelso compared two treatment periods looking at the rate of systemic reactions to immunotherapy injections [36]. Each treatment period was 2 years. During the first period (3250 visits), dose adjustments were made for local reactions, but during the second period (4692 visits) no dose adjustments were made. The systemic reaction rate was not statistically different during the two periods. 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 (TABLE 1).

Table 1. Studies of local reactions of immunotherapy not predicting future reactions.

Study (year)	Details of reactions	Ref.
Local reactions do not predict future systemic reactions		
Ramirez <i>et al.</i> (1981)	22 patients on venom immunotherapy No systemic reactions Dose adjustments prevent systemic reactions	[30]
Nelson <i>et al.</i> (1986)	416 immunotherapy patients 25,508 pollen immunotherapy injections Local reactions do not predict systemic reactions	[2]
Hepner <i>et al.</i> (1987)	2989 immunotherapy patients 27 systemic reactions Large local reactions did not precede systemic reactions	[32]
Portnoy <i>et al.</i> (1994)	22 children on inhalant rush immunotherapy Local reactions were not associated with subsequent systemic reactions	[33]
Tankersley <i>et al.</i> (2000)	12,926 immunotherapy injections 114 systemic reactions Local reaction is an insensitive predictor of a subsequent systemic reaction at next allergen vaccine dose	[25]
Tankersley (2003)	10,636 immunotherapy injections 89 systemic reactions Local reactions did not increase systemic reaction rates	[34]
Kelso (2004)	Dose adjustment for local reactions (3250 visits) versus no dose adjustment (4692 visits) Systemic reaction rate were not statistically different	[36]
Local reactions do not predict future local reactions		
Tankersley <i>et al.</i> (2000)	Dose adjustment for local reactions versus no dose adjustment Local reaction rates were not statistically different (7.3 vs 4.7%)	[25]
Calabria <i>et al.</i> (2009)	Only 27.2% of local reactions were followed by a local reaction at the next immunotherapy injection	[37]

Local reactions do not predict future local reactions

In addition to not predicting future systemic reactions, local reactions also do not predict future local reactions. In their paper published in 2000, Tankersley *et al.* also analyzed the rate of local reactions with a dose adjustment policy versus a no dose adjustment policy [25]. The local reaction rates during the two periods studied (7.3 vs 4.7%) were not statistically different implying that local reactions do not predict subsequent local reactions. Another paper was published demonstrating that local reactions do not predict local reactions [37]. The authors noted that of all the local reactions followed by another injection at their allergy clinic, only 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. The conclusion was that local reactions do not predict subsequent local reactions.

Local reactions are not associated with immunotherapy noncompliance

Local reactions from immunotherapy do not lead to patient noncompliance. Studies evaluating adherence with allergen immunotherapy have concluded that the most common reason for patient noncompliance with immunotherapy is inconvenience. In 2002, a compliance study analyzed 381 active immunotherapy charts and contacted patients who had stopped allergen immunotherapy [38]. The single most important reason for discontinuation of immunotherapy was inconvenience (34.5% of patient responses). 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. Another study evaluated 217 charts of patients who had discontinued allergen immunotherapy and patients were contacted to determine their reasons

for stopping immunotherapy [39]. Again, inconvenience was the major factor for noncompliance with subcutaneous allergen immunotherapy. Inconvenience was also a major factor for patient dropout in a study conducted by Rhodes over a 4-year period, which evaluated 207 patients who had discontinued multiple allergen immunotherapy [40]. Additional studies have also shown that local reactions do not lead to patient noncompliance with immunotherapy [29,35].

Prevention of local reactions

When looking at therapies to prevent or minimize local reactions from immunotherapy, antihistamines have been used successfully in patients. There have been several studies published evaluating the use of antihistamines in venom rush immunotherapy. A double-blind, placebo-controlled trial of 52 bee venom allergic patients undergoing rush immunotherapy demonstrated that large local reactions were significantly reduced by terfenadine 120 mg twice-daily pretreatment during the rush portion of the protocol [41]. Another double-blind, placebo-controlled study of 121 Hymenoptera venom allergic patients participating in rush immunotherapy were pretreated with either terfenadine 120 mg plus ranitidine 300 mg, terfenadine 120 mg alone or placebo [42]. Pretreatment with H1-antihistamines with or without H2-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 al.* accomplished a double-blind, placebo-controlled trial of 57 patients undergoing bee venom ultrarush immunotherapy [43]. The patients were treated with fexofenadine 180 mg or placebo on days 1, 8, 22 and 50 of the protocol. 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. These studies have found pretreatment with antihistamines to be helpful in preventing and decreasing the rate and size of local reactions. It is important to note that this preventive effect was only noted during the rush immunotherapy phase and was not seen in the maintenance phase. Only one of these studies analyzed late local reactions during the rush phase [43] and none of the three evaluated late local reactions during the maintenance phase.

In addition to using antihistamines to prevent local reactions, depot immunotherapy with aluminum hydroxide has been shown to reduce local reactions during the induction phase for Hymenoptera venom allergy [44]. A study of 43 patients demonstrated that depot venom immunotherapy 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, it was noted in the article that the majority of European inhalant subcutaneous immunotherapy is performed almost exclusively with depot extracts.

Other methods to prevent and minimize local reactions have been suggested. These include pretreating the patient with a NSAID, such as ibuprofen or acetaminophen, using a cold compress at the site of injection during the 30-min wait time, splitting the dose into two injections (half the dose in each arm), alternating injection sites and using a dry needle to inject the allergen (using a different needle to inject the extract than was used to draw up the extract). Many allergists feel that dose adjustments also prevent local reactions; however, as with the aforementioned methods, there have not been clinical studies evaluating this method.

In the immunization literature, there has been a randomized controlled trial of 372 children that showed no clinical benefit with acetaminophen or ibuprofen prophylaxis prior to the diphtheria–tetanus toxoids–acellular pertussis vaccination [45]. Another study involving immunizations demonstrated that local reactions to intramuscular vaccinations decreased significantly with wide, long needles (23 gauge/0.6-mm diameter, 25 mm length) when compared with narrow, short needles (25 gauge/0.5-mm diameter, 16 mm length) [46]. Since needle length could not be changed as immunotherapy is delivered subcutaneously, one potential area of study would be to compare various bore sizes and the incidence of local reactions (Box 1).

Box 1. Therapies to prevent local reactions from immunotherapy.

- Terfenadine 120 mg twice-daily pretreatment
- Terfenadine 120 mg plus ranitidine 300 mg pretreatment
- Fexofenadine 180 mg pretreatment
- Depot immunotherapy with aluminum hydroxide
- Ibuprofen or acetaminophen pretreatment
- Cold compress at the site of injection for 30 min
- Splitting immunotherapy dose into two injections (one in each arm)
- Alternating sites of immunotherapy injections
- Dry needle technique (using a different needle to inject the extract than was used to draw up the extract)

Conclusion & future perspective

Local reactions at the site of injection are common during the course of allergen immunotherapy. These reactions, which are caused mainly by IgE antibody, are associated with localized erythema, edema and pain. However, the majority of the local reactions experienced by patients are small and not worrisome.

There have been several research studies focusing on the relationship between local reactions and systemic reactions. The conclusion of these studies is that local reactions do not predict future systemic reactions. Another conclusion from these studies is that there is no need to make dose adjustments for local reactions because they may delay effective dosages of immunotherapy and place the patient at increased risk of dose administration errors.

Local reactions are also not associated with patient noncompliance. Nevertheless, because most patients experience local reactions and some patients have frequent large local reactions, allergists must be knowledgeable in methods

to prevent and decrease local reactions. These methods include pretreatment with antihistamines, depot allergen administration and possibly wider injection needles. Other methods to prevent local reactions have been employed by allergists, but they have not been fully evaluated by randomized controlled trials. This is an area where future research could be conducted.

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Executive summary

Background

- Local cutaneous reactions from allergen immunotherapy are an important and common occurrence.
- Local reactions are defined as swelling and redness that occur in the immediate vicinity of the injection site.

Mechanisms of local reactions

- Local reactions are a result of both IgE and non-IgE cutaneous responses.
- Additional causes of local cutaneous reactions include an irritant mechanism and a hygroscopic mechanism associated with glycerin.
- Alum has also been shown to cause local reactions when given with allergen immunotherapy and vaccines.

Local reactions do not predict future systemic or local reactions

- Multiple studies have shown that local reactions do not predict future systemic or local reactions.
- In a recent study, 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.

Local reactions are not associated with immunotherapy noncompliance

- Inconvenience is the main reason for discontinuation of immunotherapy.
- Other factors associated with noncompliance with immunotherapy are a precluding medical condition and an adverse systemic reaction.
- Local reactions are a minor factor associated with noncompliance with immunotherapy.

Prevention of local reactions

- Antihistamines have been used successfully in patients to prevent and minimize local reactions from allergen immunotherapy.
- Depot immunotherapy with aluminum hydroxide have been shown to reduce local reactions.
- Other methods to prevent local reactions are pretreating the patient with a NSAID, using a cold compress at the site of injection during the 30-min wait time, splitting the dose into two injections (half the dose in each arm), alternating injection sites and using a dry needle to inject the allergen.

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