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Safety of allergen immunotherapy: a review of premedication and dose adjustment

From the first allergen immunotherapy proposed in the early 1900s to the present day, numerous studies have proven the efficacy of allergen immunotherapy for the treatment of allergic rhinitis, allergic conjunctivitis, allergic asthma and stinging insect hypersensitivity. The major risk, however small, with allergen immunotherapy is anaphylaxis. There has been considerable interest and debate regarding risk factors for immunotherapy reactions (local and systemic) and interventions to reduce the occurrence of these reactions. One of these interventions that is especially debated regards dose adjustment for various reasons, but in particular for local reactions. In this review, we discuss the safety of immunotherapy and provide a comprehensive review of the literature regarding immunotherapy schedules and doses.

KEYWORDS: dose adjustment ■ immunotherapy ■ inhalant allergen ■ subcutaneous immunotherapy ■ venom immunotherapy

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From the first allergen injections proposed in the early 1900s to the present day, numerous studies have proven the efficacy of allergen immunotherapy (AIT) for the treatment of allergic rhinitis, allergic conjunctivitis, allergic asthma and stinging insect hypersensitivity. This treatment modality should be considered for patients who have symptoms of allergic rhinitis, conjunctivitis or asthma with natural exposure to allergens, and who demonstrate specific IgE antibodies to a relevant allergen or allergens. Immunotherapy is also recommended for patients with a history of systemic reaction to Hymenoptera stings who demonstrate the presence of Hymenoptera-specific IgE antibodies *in vivo* (skin test) or *in vitro* [1].

AIT is the only antigen-specific immunomodulatory treatment in routine clinical use that alters the natural history of allergic disease [2]. It results in immunologic tolerance, which is manifested by a relative decrease in antigen-specific responsiveness that might be accompanied by immune deviation, T-cell anergy and/or T-cell apoptosis [1]. There exists an allergen-specific immune deviation from Th2 to Th1 responses and a clonal deletion of sensitized cells that reduces the hyper-reactivity of the recipient to those allergens [2]. When immunotherapy is initiated in children with sensitivity to a single allergen, the number of new sensitivities that subsequently develop over time is reduced [3]. It has also been shown to be effective in reducing the development of asthma in children with pre-existing allergic rhinitis [3].

Venom immunotherapy is highly effective in reducing the risk of anaphylaxis when administered to adults and children with a history of systemic reaction(s) to Hymenoptera stings, including both flying insects and imported fire ants [1].

A patient receiving subcutaneous AIT would ideally receive increasing doses during build-up, without interruption, until reaching and continuing the maintenance dose in order to achieve the earliest maximum clinical benefit. The ultimate duration of AIT injections is largely related to preservation of the clinical improvement gained in the first 1–2 years of treatment. Although the majority of patients receive a full course of AIT without any serious clinical complications, there are several scenarios where practicing allergists will recommend dose adjustment for immediate or delayed local reactions at the injection site, missed injections, newly mixed vials and after systemic reactions. In each case, the concern is that administration of nondose-adjusted injections may deliver an allergen concentration greater than that which the patient can safely tolerate. The main intention of dose adjustment, although not proven in previous studies, is to reduce the risk of systemic reactions [4]. There may also be other perceived benefits, such as reducing patient discomfort and increasing patient adherence to the immunotherapy treatment. However, the practice of dose adjustment is largely anecdotal with elements of tradition and is not evidence based [4].

Safety of AIT: role of local reactions

■ Do local reactions predict local reactions with the next injection?

Local reactions from immunotherapy are fairly common. They occur with a frequency of 26–82% among patients receiving AIT and in 0.7–16% of injections [1,5–7]. The LOCAL study was performed to determine whether a local reaction predicted a local reaction at the next immunotherapy injection [8]. A retrospective analysis of an electronic database of subcutaneous immunotherapy was performed at a site that did not dose adjust for local reactions. Over a 12-month time period, 360 patients received a total of 9678 injections. Approximately 78% had at least one local reaction (defined as redness and/or swelling less than or equal to the size of the patient's palm) and 7.5% had a large local reaction (greater than the size of the patient's palm). For all the injections given, the total local reaction rate was 16.3%. Based on the data from this study, patients who experienced a local reaction after an injection experienced another local reaction at the next injection 27% of the time. This study indicated that the majority (almost three-quarters) of patients would not have a local reaction at the next injection. The study also found that both the sensitivity and the positive predictive value were low for the ability of a local reaction to predict a local reaction at the next injection. Consecutive large local reactions were infrequent in the LOCAL study; only 6% of large local reactions were followed by a subsequent large local reaction at the next injection [8]. Again, the investigators found the sensitivity and positive predictive value were low for the ability of a large local reaction to predict a subsequent small or large local reaction at the following injection. These findings were seen in a nondose-adjustment population receiving AIT.

Often implicated in local reactions is the glycerin content of the AIT prescription. Glycerin is a preservative commonly used in immunotherapy extracts and is a recognized irritant that can produce injection site pain. The GILL study was a 1-year retrospective analysis that set out to examine whether higher glycerin concentrations used in AIT extracts were associated with higher local reaction rates during immunotherapy [6]. The study demonstrated that the small local reaction rate (smaller than or equal to the size of the patient's palm) was higher with increasing allergen concentration but not with increasing glycerin concentration. Large local reactions were infrequent in this study group and did not increase significantly with either allergen

or glycerin concentrations. Glycerin concentrations as high as 50% were not associated with significantly higher small or large local reaction rates. The investigators also compared aeroallergen, flying Hymenoptera and imported fire ant immunotherapy local reaction rates, which were found to be similar. This finding was significant because the flying Hymenoptera immunotherapy extracts did not contain glycerin. This finding of comparable local reaction rates, in addition to the aforementioned findings of the study, add weight to the suggestion that the allergen concentration, and not the glycerin concentration, is more important in the etiology of local reactions.

■ Do local reactions predict systemic reactions with the next injection?

The relationship between systemic reactions and large local reactions has been investigated and debated in several studies [5,7,9]. Even the size criteria to define large local reactions has been debated among allergists, ranging from 25 mm [9] to larger than the palm of an average adult hand (8–10 cm) [5,7]. The REPEAT study sought to investigate the association between large local reactions and future systemic reactions within a practice that does not dose adjust for large local reactions [5]. They performed a retrospective analysis of an electronic database of subcutaneous immunotherapy during a 12-month period at a single site. Three hundred and sixty patients received a total of 9679 injections during this period. The large local reaction rate was 0.4% of injections given and the systemic reaction rate was 0.5% of injections given. Of those patients who experienced a systemic reaction, 78.3% had never had a large local reaction. Only ten patients (2.8%) experienced both large local reactions and systemic reactions. Patients with previous large local reactions experienced a higher frequency of systemic reactions and vice versa during their subcutaneous immunotherapy course. However, these large local reactions did not predict a systemic reaction at the next injection, because systemic reactions occurred an average of eight injections after the large local reaction.

In another study investigating this concept, Roy *et al.* performed a retrospective review of a database from a large, multicenter group that performed routine dose adjustments for large local reactions of 25 mm or greater [9]. During the 2-year surveillance period, 661,123 patient visits for AIT took place and a total of 1,108,621 injections were administered. The systemic reaction rate was 0.043% of all visits and 0.025% of all injections. A total of 33% of the systemic

reactions were immediately preceded by a large local reaction at the previous dose. The rate of large local reactions was almost four-times higher among patients who later experienced a systemic reaction, compared with the control group of patients (those who never experienced a systemic reaction). However, another third of the systemic reactors in this study had never experienced a large local reaction before the systemic reaction. Therefore, individual large local reactions did not predict subsequent systemic reactions but did occur at a higher rate among those who later experienced a systemic reaction. It is noteworthy that the definition of a large local reaction in this paper, of 25 mm or greater, was significantly smaller than the 80–100 mm (average adult palm size) large local reaction as reported in the previous four papers [5–8].

Two retrospective studies looked at the effect of not dose adjusting the immunotherapy dose in response to local reactions compared with the rate of systemic reactions following dose-adjustment protocols [7,10]. In the 2004 study by Kelso, most of the systemic reactions (67%) were not preceded by any local reaction, and of the cases that were preceded by a local reaction, only in one case had there been recurrent local reactions [10]. In 2000, Tankersley *et al.* reported that the sensitivity of a local reaction predicting a systemic reaction at the next immunotherapy dose was only 15% [7]. Both studies concluded that local reactions were insensitive and poor predictors of subsequent systemic reactions at the next allergen vaccine dose. Of interest, discontinuation of a dose-adjustment protocol for local reactions resulted in a decrease in local reactions, although this was not statistically significant [7].

■ Management of local reactions

Pretreatment with antihistamines has been shown to be efficacious in decreasing local reactions during cluster [11] and rush [12] AIT protocols used in venom immunotherapy. In a double-blind, placebo-controlled trial assessing pretreatment with fexofenadine in ultra-rush venom immunotherapy there was a significant decrease in cutaneous allergic symptoms such as itching, urticaria and angioedema [12]. Other cutaneous symptoms such as local flush, erythema and/or heat sensation were not reduced. This study also found no indication that there was a masking of more severe systemic allergic symptoms or of reduced efficacy of venom immunotherapy after premedication with antihistamines. Although commonly used, the effectiveness of premedication with antihistamines

in reducing local reactions during conventional build-up and maintenance immunotherapy injections has not been proven [1,8].

Leukotriene antagonists are the other drug class studied for their efficacy in reducing local reactions in AIT. A prospective, double-blind, placebo-controlled study of 15 patients with a history of severe anaphylactic reactions to Hymenoptera stings compared the effects of placebo, montelukast and desloratadine premedication on local reactions (which for this study were considered to be >3 cm) in a rush venom immunotherapy protocol [13]. This study demonstrated a significant delay in onset and a decrease in size of local reactions when montelukast, but not desloratadine, was used as premedication versus placebo. However, itching did not differ between the three groups.

Systemic reactions

A review of systemic reaction rates after AIT reported in the past 15 years found that the percentage of systemic reactions per injection for patients on conventional immunotherapy schedules is approximately 0.2% [14]. Although rare, the major risk of AIT is anaphylaxis, which can be fatal. A survey of fatal reactions related to immunotherapy injections taking place from 1990 to 2001 was conducted among members of the American Academy of Allergy, Asthma and Immunology [15]. Fatal reactions were estimated to occur once per 2.5 million injections, with an average of 3.4 deaths per year. Therefore, immunotherapy injections should be administered in a physician's office where procedures are in place that can reduce the risk of anaphylaxis. Should anaphylaxis occur, it can be promptly recognized and treated by a qualified provider. Epinephrine is the first-line treatment of choice for anaphylaxis.

As previously discussed, antihistamines may have a role in reducing local reaction rates in cluster and rush protocols of AIT, but have not been proven to have the same effect in conventional build-up and maintenance AIT. Several studies have examined the potential benefit of antihistamines for prevention of systemic reactions. In a double-blind, placebo-controlled trial assessing pretreatment with fexofenadine in ultra-rush venom immunotherapy, neither subjective nor objective systemic allergic reactions were reduced [12]. However, other studies have demonstrated the efficacy of antihistamine pretreatment in reducing systemic reactions. One such study was an open-label, multicenter protocol looking at administration of fexofenadine

(60 mg), compared with no pretreatment, 2 h prior to receiving a single AIT injection [16]. This study found a significant reduction in the occurrence of severe systemic reactions, an increase in the proportion of patients who were able to achieve target maintenance dose and a reduction in time to attain target maintenance dose. The second-generation H_1 antihistamine loratadine was also found to be effective in reducing both the number and the severity of systemic reactions in a double-blind, placebo-controlled study when given as pretreatment to patients receiving specific cluster immunotherapy for pollen allergy [11]. Another double-blind, placebo-controlled study of 22 children showed that premedication with a combination of H_1 and H_2 antihistamines plus an oral corticosteroid reduced the incidence of systemic reactions during inhalant allergen rush immunotherapy [17]. H_1 , but not H_2 , antihistamines may confer the protective effect in rush protocols. This was demonstrated in a prospective, randomized, double-blind, placebo-controlled study of 121 patients with Hymenoptera venom allergy treated with venom immunotherapy on a rush protocol [18]. They received pretreatment with either a combination of H_1 and H_2 antihistamines, an H_1 antihistamine alone or placebo. It was determined that pretreatment with an H_1 antihistamine, with or without the H_2 antihistamine, significantly reduced local and systemic reactions during AIT.

By contrast, other studies have not found premedication necessary or useful in reducing the systemic reaction rate. One of these studies, performed by Tankersley *et al.*, included patients with imported fire ant hypersensitivity in a 2-day rush immunotherapy protocol [19]. The patients were randomized to placebo or twice-daily terfenadine (60 mg), ranitidine (150 mg) and prednisone (30 mg) initiated 2 days before the protocol. Only three of the 58 patients who received injections in the rush protocol experienced mild systemic reactions. Two of these patients required treatment with epinephrine and the third patient's symptoms resolved without intervention. Among those who experienced a systemic reaction, there was no statistical difference between the placebo and active premedication groups. A second study performed a 1-day rush immunotherapy schedule without premedication in patients with imported fire ant hypersensitivity [20]. Thirty-seven patients underwent the rush protocol. Of those, nine patients experienced some type of reaction. Four patients complained of generalized pruritus; three complained of urticaria; one complained of nausea, chest tightness

and tachycardia; and one complained of dyspnea and throat scratchiness. The authors concluded that their 1-day protocol remained safe and effective. However, further studies using randomized placebo-controlled designs are needed to evaluate the role of premedication in these protocols.

Immunotherapy schedules & doses

■ Reductions during periods of exacerbation of symptoms

When a patient is exposed to increased levels of an allergen to which they are highly sensitive and concomitantly receive immunotherapy injections for that allergen, he or she might be at an increased risk of having a systemic reaction. This is especially true if the patient is experiencing a significant exacerbation of symptoms, particularly from asthma. According to the 2010 update of immunotherapy practice parameters, it is reasonable to consider not increasing, or even reducing, the dose of the AIT injection during the seasons when the patient is exposed to increased levels of the allergen to which they are highly sensitive, especially if their rhinitis or asthma symptoms are poorly controlled [1]. However, two large studies did not find an association between increased levels of allergen exposure and systemic reactions [21,22]. A prospective study of 4578 patients receiving allergen AIT was performed to identify risk factors for systemic reactions [21]. Systemic reaction rates were not found to correlate with pollen seasons. However, there was a correlation between increased reaction rates and increasing mold counts in summer and early fall months. Skin prick test positivity to molds was more frequent in those who had reactions than those who did not have reactions. A different prospective study, conducted over a 12-year period with 513,368 injections given, did not demonstrate an increase in systemic reactions during grass and ragweed pollen season for patients on grass and ragweed immunotherapy [22]. Therefore, only a theoretical risk exists that a highly sensitive individual may experience more systemic reactions during the respective pollen season. Most of these patients will do well without a need for dose adjustment [1].

■ Adjustments for missed doses

A pilot observational study of 16 missed-dose-adjustment protocols illustrates that a wide variety exists in these protocols [23]. Of the protocols, 50% calculated the late interval from the last dose received while the other 50% calculated this interval as starting from the missed scheduled dose. In addition, 41% of adjustments were based

on volume (reduction by a certain number of milliliters), 35% were based on 'steps' (reduction by a certain number of doses) and 24% required calculation of the reduced dose (reduction based on a certain percentage). Most of the providers used a single adjustment protocol. However, 31% used different dose-adjustment protocols for build-up and maintenance level immunotherapy injections. This study suggests a step-wise reduction protocol that reduces one dose for every week late beginning at 3 weeks late for build-up and 1 week late for maintenance. The recommended adjustments fall within the interquartile ranges for all 16 protocols studied. There are no evidence-based guidelines to support dose adjustment for missed immunotherapy injections according to the 2010 update of the immunotherapy practice parameters [1]. However, it has become customary practice to repeat or even reduce the dose of the immunotherapy injection depending on how long a time interval between injections has occurred. Further research is needed in this area.

■ Adjustments for local reactions

Dose adjustments for local reactions to AIT have primarily been used with the intent to reduce the occurrence of future local and systemic reactions. However, as previously reviewed, several studies have shown that a local reaction to immunotherapy is not predictive of future systemic reactions, and local reactions do not require dose adjustments [5,7,10]. Furthermore, local reactions have not been shown to predict local reactions at the next immunotherapy injection [8]. The question then arises as to why allergists continue to recommend and perform dose adjustments in response to local reactions. A study examined this question by sending electronic surveys to all practicing allergists of the American College of Allergy, Asthma and Immunology [24]. A total of 2797 electronic letters were sent and 761 (27.2%) responses were received. Of those respondents it was found that most allergists (91.9%) do indeed dose adjust for local reactions. Most of these dose adjustments are based on individual practice-specific written protocols that include criteria for repeating and decreasing the dose of immunotherapy as well as basing the dose adjustment on the size of the local reaction. Rationales used by allergists for dose adjustments for local reactions were also sought in the survey. These included the ideas 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%).

The same authors who surveyed the above allergists performed a survey to determine patient perceptions regarding local reactions from immunotherapy [25]. Their survey of 249 patients undergoing AIT showed that 71% of the patients reported local reactions. Of those with local reactions, 84.7% reported the local reaction to be smaller than the palm of the hand, and 81.4% deemed their local reactions not bothersome at all or only slightly bothersome. A total of 96% of the local reactors said they would not stop immunotherapy because of these local reactions. Even of the patients who reported local reactions larger than the palm of the hand, 58.3% deemed their local reactions not to be bothersome at all or only slightly bothersome. Of these large local reactors, 97.2% would not stop immunotherapy because of experiencing large local reactions. The findings were considered significant in light of the fact that the patients participating in this survey received their immunotherapy in a clinic that does not routinely dose adjust for local reactions.

With regard to compliance with AIT, the most common reason cited in the literature for patient noncompliance with AIT is inconvenience. In one study evaluating patient compliance, 381 active immunotherapy records were analyzed and patients who were defined as non-compliant were contacted for a telephone interview [26]. It was found that the most common reason for noncompliance was inconvenience of the AIT, as reported by 34.5% of the noncompliant patients interviewed. This was followed by a precluding medical condition in 18.2% of those interviewed and by the occurrence of an adverse systemic reaction to the immunotherapy in 16.4% of those interviewed. An adverse local reaction was an uncommon reason for noncompliance with immunotherapy, reported by only 5.5% of the patients interviewed. Another study reviewed 217 medical records of patients on AIT to identify who had discontinued treatment and their reasons for stopping [27]. Inconvenience was found to be the major contributing factor in noncompliance with AIT.

■ Adjustments after systemic reactions

After a systemic reaction, the allergen dose typically is reduced or immunotherapy is discontinued, especially if the reaction was severe. According to the 2010 update of AIT practice parameters, there are no evidence-based guidelines on dose adjustment after a systemic reaction [1]. Many allergists reduce the immunotherapy

dose to one that was previously tolerated, or to an even lower dose, depending on the severity of the reaction. A retrospective cohort analysis of a dose-adjustment schedule over a 4-year period was performed to analyze the systemic reaction rate immediately after dose adjustments were made following a systemic reaction [4]. For injections given immediately after a systemic reaction, the patient's AIT dose was reduced by one vial, a 90% reduction in dose, with subsequent resumption of the normal build-up schedule. The authors divided their results based on the safety of dose adjustment during build-up stage versus maintenance stage. There were 57 dose-adjusted build-up stage injections immediately after a systemic reaction, resulting in only one repeat systemic reaction. This was compared with the 66 systemic reactions in the nondose-adjusted build-up group. Between these groups, the authors did not find a statistically significant increased risk of a second systemic reaction after a dose adjustment for a previous systemic reaction. In the same study, 12 maintenance-stage injections immediately followed a systemic reaction and required dose adjustment. The authors found no additional systemic reactions

in this dose-adjusted group. Compared with the 15 systemic reactions from the nondose-adjusted injections, the dose-adjustment protocol after a systemic reaction was not associated with a statistically significant increased risk of systemic reactions, although admittedly the numbers were relatively small. In summary, there was no statistically significant increase in systemic reactions with any part of this study's dose-adjustment protocol.

If a systemic reaction occurs during build-up dosing, cautious increases in subsequent doses may be attempted. If the reaction occurs during maintenance dosing, one management consideration adopted by allergists/immunologists is to reduce the maintenance dose, provided the dose remains high enough to benefit the patient. However, prior to any dose adjustment a risk versus benefit assessment for continuing AIT in light of a previous systemic reaction to the immunotherapy should be undertaken [1].

Conclusion & future perspective

There have been a number of studies, primarily retrospective, reviewing the safety of subcutaneous AIT. The literature indicates that

Executive summary

Background

- Allergen immunotherapy should be considered in patients with allergic rhinitis, conjunctivitis or asthma with exposure to allergens.
- Immunotherapy is recommended for patients with a systemic reaction to Hymenoptera stings who demonstrate Hymenoptera-specific IgE antibodies.
- Immunotherapy is the only treatment in use that alters the natural course of allergic disease.
- The incidence of asthma can be reduced in patients with allergic rhinitis treated with immunotherapy.
- Venom immunotherapy reduces the incidence of venom-induced anaphylaxis in patients at risk.

Safety of immunotherapy: role of local reactions

- Local reactions from immunotherapy are common.
- Local reactions have not been shown to predict repeat local reactions with subsequent injections.
- The glycerin content of immunotherapy extracts has been implicated as an irritant that causes pain but not shown to cause local reactions.
- Local reactions have not been shown to predict systemic reactions with subsequent injections.
- Pretreatment with antihistamines decreases local reactions during cluster and rush protocols used in venom immunotherapy. This effect has not been shown in conventional build-up.
- Premedication with leukotriene antagonists may also decrease local reactions in rush venom immunotherapy protocols.
- The systemic reaction rate for patients on conventional immunotherapy schedules is approximately 0.2%.
- Epinephrine is the first-line treatment of choice for anaphylaxis.

Immunotherapy schedules & doses

- One should consider immunotherapy dose adjustment during seasons when the patient is exposed to increased levels of an allergen to which they are highly sensitive, especially if rhinitis or asthma symptoms are poorly controlled.
- There are no evidence-based guidelines to support dose adjustment for missed immunotherapy injections. It is customary practice to repeat or reduce the dose depending on the late interval.
- Several studies indicate that local reactions are not indications for dose adjustments.
- Inconvenience has been found to contribute most to noncompliance with immunotherapy.
- There are no evidence-based guidelines on dose adjustment after a systemic reaction. However, many allergists/immunologists reduce the dose to one that was previously tolerated, or even a lower dose if the reaction was severe.

individual local reactions are not predictive of subsequent local or systemic reactions. However, some patients with a greater frequency of local reactions may be at a higher risk for future systemic reactions. For patients who do experience local reactions, it appears that it is the allergen concentration, and not the glycerin concentration, of the extract that is more important in the etiology of these reactions. One of the problems for practitioners who prescribe and administer AIT injections is that no standardized protocol exists for dose adjusting. The impact of dose adjustment can have negative implications for the patient. Some of these include an increased cost, increased chance of dosing error and a delay or prolongation of therapy. Studies have not supported the idea that dose adjustment affects patient adherence or comfort significantly, suggesting that dose adjustments are made more

for the comfort and reassurance of the provider. Based upon available evidence, patients should be kept informed of the controversy regarding local reactions and the possibility of systemic reaction with subcutaneous AIT with or without dose adjustment. More opportunities to study this question of dose adjustment are needed with more patients in diverse clinical settings.

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