

How Should Allergists Deal With Local Reactions to Allergen Immunotherapy?

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Abstract Despite the well-known benefits of subcutaneous immunotherapy (SCIT), adverse reactions include both local reactions (LRs) and systemic reactions. An LR is a well-known adverse event associated with SCIT injections and is defined as any swelling located at or near the injection site following allergen injection. Concerns that LRs might predict systemic reactions have historically motivated allergists to dose adjust for LRs. More recent data have dispelled this notion, although many allergists continue to dose adjust for other reasons. This article discusses the historical response to LRs and dose adjustments and reviews the most recent literature addressing LRs to SCIT. Treatment options, although they are either unproven or not studied, are offered as an alternative to routine dose adjustments for LRs. Education remains the foundation of physician–patient communication concerning LRs.

Keywords Local reactions · Systemic reactions · Dose adjustments · Immunotherapy

Introduction

Since the observations of Wyman in 1835 and the unique self-experimentation of Blackley in 1873, allergists and the medical community have had the realization that pollen accounts for the symptoms of allergic rhinitis [1]. The first use of subcutaneous immunotherapy (SCIT) by the English

physicians Noon and Freeman in 1911 was based on the knowledge that pollen was the etiologic agent of seasonal allergic rhinitis and the success of active and passive immunization in controlling rabies, tetanus, and diphtheria. Cooke formally introduced SCIT to the United States around 1915, but the ensuing 10–20 years were chaotic, with empiricism and trial-and-error serving as the sole guidelines for further SCIT development. It was only natural for mistakes and abuses to occur, but empiric observations during this period established the foundation for later SCIT advances. The need for communication and standardization prompted the formation of the first allergy societies in 1923 and the *Journal of Allergy* in 1929. By 1945, 56 allergy clinics existed in 66 medical schools across the United States, with the first controlled study of SCIT published in 1949.

Despite the well-known benefits of SCIT, adverse reactions include local reactions (LRs) and systemic reactions, with the focus of this article being on the former. An LR is a well-known adverse effect associated with SCIT injections and is defined as any swelling located at or near the injection site following allergen injection (Fig. 1).

As the clinical allergist contemplates the potential adverse effects that might arise from SCIT, several questions arise regarding the clinical significance of LRs:

- Do they predict a systemic reaction?
- Do they predict future LRs?
- How much are patients bothered by them?
- Do they lead to SCIT noncompliance?
- How many allergists dose adjust for them?
- What is the rationale behind dose adjusting?
- Should we care about LRs?

The remainder of this article is devoted to addressing these and other LR questions.

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Fig. 1 Local reaction to immunotherapy

The History of Local Reaction Definitions

Various size definitions have been used within the allergy literature to describe LRs. A, B, and C reactions have been used during the past 40 years and were defined in a 1981 article reporting LRs: “A” reaction refers to induration of 15 to 20 mm; “B” reaction refers to induration of 20 to 25 mm; and “C” reaction refers to induration greater than 25 mm or 12 h [2]. Two years later, the second edition of Middleton’s *Allergy: Principles and Practice* textbook reported similarly, stating that swelling and erythema persisting longer than 24 h or reaching a size greater than 20 mm in diameter should be considered a significant LR [1]. Terminology differentiating a small LR from a large LR was also introduced to the allergy community around this time. At that time, small LRs were to be distinguished from large LRs (≥ 40 mm in diameter), as there was concern that large LRs might cause considerable discomfort and/or persist for 24 h or longer [1].

In 1996, the Joint Task Force Practice Parameters for Allergen Immunotherapy further subdivided LRs into early and late reactions [3]. Early LRs were those that occurred within 20 to 30 min after the injection (during the period of time that the patient was observed in a clinical setting) and late LRs were those that occurred more than 30 min after the injection but before the next injection. Other LR size definitions within the literature are shown in Table 1.

The History of Dose Adjustment Recommendations

Almost 30 years ago, the standard textbook of allergy and immunology alleged that severe LRs to a SCIT allergen to

Table 1 Local reaction size definitions

• “A” reaction: induration 15–20 mm
• “B” reaction: induration 20–25 mm
• “C” reaction: induration >25 mm or 12 h [2]
• Small local reaction <40 mm and large local reaction ≥ 40 mm [1]
• >20 mm and >24 h are significant [1]
• Early local reaction ≤ 30 min and late local reaction >30 min [3]
• Local reaction ≥ 40 mm [4]
• Small local reaction <20 mm and large local reaction ≥ 20 mm [5]
• Local reaction no larger than the size of the palm of the patient’s hand and large local reaction larger than the size of the patient’s palm (8–10 cm) [6]

which a patient was most sensitive would limit the amount of other allergens within that mixture that could be administered [1]. Thus, it was recommended that the allergen to which the patient was extremely sensitive should not be included in the SCIT mixture but instead given separately. Increasing dilution doses could only be administered if the initial dilutions were tolerated without significant LRs, with caution exercised in the patient who developed large LRs. This adjustment was suggested, as LRs were considered to be potential harbingers of a systemic reaction should the SCIT dosage be increased following an LR. Until recent literature changed the mindset, it appears that this flashing yellow light of the LR warning of the impending systemic reaction was the driving force behind the allergy community’s practice of dose adjusting for LRs.

A review of the literature reveals three articles that serve as the most likely sources of the beginning of dosage adjustment recommendations for LRs. In 1972, a 62-year-old physician on a single injection of a grass mixture was reported to develop an LR that spread down to his wrist within a few hours along with the simultaneous development of bronchospasm [4]. He received a dose adjustment and further smaller doses without incurring local or systemic reactions. A second article in 1981 by Ramirez et al. [2] described an approach in venom SCIT of reducing the incidence of systemic reactions [2]. Although the time needed to attain a 100- μ g maintenance dose was prolonged, this study described a dose adjustment schedule based on the size of the LR (Table 2). With this dose adjustment schedule, the investigators had no systemic

Table 2 Historical local reaction grading and recommended dose adjustments

• “A” reaction: induration 15–20 mm; repeat dose
• “B” reaction: induration 20–25 mm; return to dose without a reaction
• “C” reaction: induration >25 mm or 12 h; reduce dose 50%

reactions in their population of 18 patients. In addition, they commented that their subsequent clinical experience with venom SCIT seemed to confirm their observations in a large patient sample. Thus, they concluded that systemic reactions to venom SCIT might be lessened by dose adjustments after LR. The final source that may also form the basis for dose adjustments based on LR is the 1984 article by Mauriello et al. [5], which reported the risk of a systemic reaction in patients with a history of large LR to flying Hymenoptera stings to be about 10%. Extrapolating this clinical sting LR and subsequent systemic risk to the SCIT paradigm may have formed the basis of dose adjustments for LR in an effort to reduce systemic reaction risk.

However, a critical review of the literature over the past 25 years brings into question the traditional approach of dose adjusting for LR. In 1986, Nelson et al. [6] described a prospective study of 416 patients who received 26,645 injections, and examined the incidence of local and systemic reactions at any time during the course of SCIT. Although 93% of the patients had at least one LR, 88% of those with LR never had a systemic reaction. LR as a predictor of systemic reactions had a 64% sensitivity, a 1.2% specificity, a 12% positive predictive value, and a 14% negative predictive value. The authors concluded that the presence of LR was not helpful in predicting which patients would develop systemic reactions. A 1987 abstract by Hepner et al. [7] regarding 2989 patients on conventional SCIT reported that large LR usually did not precede systemic reactions. In a 1992 paper, the detailed measurement of the LR as a guide to subsequent doses began to be called into question because of the inherent variability of LR [8]. Although large LR (>15–20 cm) were suggested to potentially require some dose adjustment, LR were an unreliable predictor of the occurrence of future systemic reactions.

Despite evidence to potentially change US practice recommendations for LR, dose adjustment recommendations continued to be propagated. Middleton's 1993 *Allergy: Principles and Practice* edition stated that large LR (≥ 4 cm) might be associated with systemic reactions or create concern that further dosage increase would cause a systemic reaction [9]. Dose adjustments were recommended in addition to a cautious subsequent increase in dosages. Similar recommendations followed in 1996 from the Joint Task Force [3]. Safety monitoring and efforts to prevent anaphylactic SCIT reactions included monitoring for LR and possible dose adjustments for early or late large LR. If a patient experienced a large LR, adjustment of extract dosage was to be considered. Other descriptions in the literature also stated that LR might be associated with the risk of a systemic reaction from further dosage increase, with dose adjustments recommended [10]. Additionally, patients at risk of systemic

reactions to SCIT were reported to include those with a history of frequent large LR [11].

Interestingly, the 1998 World Health Organization position paper on SCIT, referencing the 1986 paper by Nelson et al. [6] and the 1987 abstract by Hepner et al. [7], stated that large LR did not predict the onset of subsequent systemic reactions [12]. In 2000, the World Health Organization again took the position that LR were not associated with increased risk of anaphylaxis, and subcutaneous nodules at the injection site did not require dose adjustment [13]. In the chapter authored by Nelson [14] in Middleton's 1998 *Allergy: Principles and Practice* textbook, he wrote that the occurrence of an LR to SCIT was not found to be predictive of the occurrence of a systemic reaction. Other than pain with 50% glycerin injections, there was no further mention of LR. This was the first time dose adjustments had not been mentioned in this fifth edition of the standard allergy textbook.

Current Local Reaction Literature and Recommendations

It was around the turn of the 20th century that we began to see an increase in publications further substantiating a scientific basis indicating that LR did not predict systemic reactions, and routine dose adjustments for LR were unnecessary. Not only were dose adjustments not necessary, but concern began to be raised that they actually might serve the opposite purpose and introduce additional visits and injections that then might increase the risk of administration errors and decrease patient compliance due to the additional visits and difficulty achieving maintenance [15]. In 2000, the first paper to evaluate local and systemic reaction rates during periods of both dose adjustment and no dose adjustment for LR demonstrated no difference in systemic reaction rates (0.8% vs 1.1%), LR rates in systemic patients (7.3% vs 4.7%), or LR rates preceding systemic reactions (18.8% vs 10.5%) [16]. During an 18-month period under the 9-month dose adjustment protocol and then subsequent 9-month no dose adjustment protocol for LR, the sensitivity of an LR for a systemic reaction was 15%, and the positive predictive value of an LR for a systemic reaction was only 17%. Of note, this study differed from the 1986 Nelson et al. [6] study in two respects in that patients received SCIT under a no dose adjustment protocol for LR during the second 9-month period. Also, the very next dose following an LR was examined during the entire 18-month period rather than any general time during SCIT therapy, as was examined in the Nelson et al. [6] study. It was concluded that dose adjustments for LR were unnecessary, delayed progression to maintenance, potentially increased administration errors,

and introduced additional injections and visits that hampered compliance and increased costs.

Despite this 2000 article, which concluded that dose adjustments were unnecessary [16], three additional sources were published over the next 4 years that continued to recommend routine dose adjustments for LR. In 2002, *Patterson's Allergic Disease* reported that large LR were a cause for concern, dosages should be reduced or repeated, and maintenance dosages should be lowered [17]. The 2003 edition of *Pediatric Allergy: Principles and Practice* recommended a dose repeat when the previous dose produced local swelling greater than 3 cm (the size of a silver dollar), and a twofold drop with local swelling of 5 cm or more [18]. Finally, the 2003 SCIT practice parameters recommended careful evaluation of any patient with a late LR more than 30 min after the SCIT injection as an action to reduce the risk of anaphylaxis [19]. Although it was admitted that published studies to date had not indicated that large LR were always predictive of subsequent systemic reactions, nevertheless, the experience of some experts concluded that a correlation existed between large LR and subsequent systemic reactions. In contradiction to these three sources, the 2003 edition of *Middleton's Allergy: Principles and Practice* once again made no mention of LR, with the exception of citing one paper that found the occurrence of an LR to not be predictive of a systemic reaction [6] and a second asserting that LR were an insensitive predictor of systemic reactions at the next SCIT injection, which concluded that LR do not require dose adjustments [16].

Additional LR data began to accumulate with a 2003 study examining whether a no dose adjustment schedule for LR would influence systemic reaction rates or result in self-discontinuation of SCIT [20]. The systemic reaction rate during a 3-year period did not differ statistically from the previous period operating under a dose adjustment protocol. In addition, during a 24-month period, SCIT compliance was 73.5%, with no patients discontinuing due to LR. This study concluded that there were fewer delays in reaching maintenance under a no dose adjustment protocol for LR, increased patient compliance, greater uniformity and simplicity, decreased additional costs, and potentially fewer dosing errors in those receiving two or more injections at each visit. In 2004, Kelso [21] reiterated previous conclusions by demonstrating that the rate of systemic reactions to SCIT was the same whether or not a dose adjustment occurred after an LR. A final report in 2004 evaluated whether a no dose adjustment protocol for LR at satellite clinics during SCIT would influence systemic reaction rates as compared with a similar no dose adjustment protocol within an allergist's clinic [22]. Nine satellite clinics under the supervision of primary care providers were compared

with a central regional clinic with an allergist who was also providing remote oversight to these same nine satellite clinics. During a 15-month period, systemic reaction rates were not statistically different ($P=0.26$) between the satellite clinics (0.68%; 6338 injections) and the central regional allergy clinic (0.84%; 10,636 injections). It was concluded that a no dose adjustment for LR at satellite clinics did not increase systemic reaction rates compared with the central regional allergy clinic also operating under a no dose adjustment protocol. Thus, a no dose adjustment protocol for LR can also be safely used in clinics giving SCIT under the supervision of a primary care provider.

The first study suggesting an association between an increased frequency of large LR and systemic reactions while on SCIT was reported by Roy et al. [23] in 2007. This study was a retrospective database review of 557 patients receiving SCIT under a dose adjustment protocol for LR. A 0.025% systemic reaction rate was reported among more than 1 million injections. A large LR was defined as 25 mm or greater. In those patients with systemic reactions, 35.2% of visits and 19.5% of injections were associated with large LR, whereas those without a systemic reaction had LR with only 8.9% of visits and 5.3% of injections. The authors concluded that patients with an increased frequency of large LR might have an increased risk of future systemic reactions and that recognizing the relevance of frequent, large LR was important for designing safer protocols for successful SCIT in those patients. This paper was cited in the 2007 allergen SCIT practice parameter [24] with the comment that some patients experiencing a greater frequency of large LR might be at an increased risk of future systemic reactions, although no intervention recommendation was made. This practice parameter concluded that although an individual large LR is not predictive of a subsequent systemic reaction, the evidence was unclear as to whether those with repeated large LR (≥ 25 mm) were at a potentially greater risk of a subsequent systemic reaction. In response to the findings from Roy et al. [23], a recent study evaluated the association of frequent LR with systemic reactions but did so under a no dose adjustment protocol [25•]. Although a similar association was found as in the Roy et al. [23] study, it was actually a subset of patients within the larger set of patients with frequent LR that accounted for the association. Two conclusions can be drawn from these two studies: 1) the association of frequent LR and increased systemic reactions occurs whether or not LR dose adjustments are made and 2) a generalization cannot be made to all patients with LR, so efforts to focus on all LR patients based on these two studies would result in unnecessary interventions that are not applicable to the entire LR population.

Monitoring Local Reactions

Recommendations have been made to monitor LRs in SCIT patients. The most recent practice parameter recommends the documentation of which arm an injection is administered with the rationale stated as potentially facilitating determination of the exact cause of the LR [24]. It is assumed that this would be in the situation in which a patient was receiving two separate injections. Although the etiologic vial could be determined, the exact allergen would be difficult to identify given the US practice of multi-allergen vials. In addition to LR documentation, the practice parameter recommends that each SCIT patient be questioned at each visit regarding delayed LRs occurring after the patient left the clinic from his or her previous visit. Documentation of LRs is a sound practice from a medical documentation perspective. This allows the practicing allergist a documentation source to correlate and substantiate any reports or questions that the patient might have concerning LRs he or she may be experiencing. This then allows the allergist to provide education to the patient concerning LRs and then to make a decision as to whether attempted interventions are necessary.

To Dose Adjust or Not to Dose Adjust Is the Question

Although most (92%) US allergists report that they dose adjust for LRs, the primary rationale provided in 2007 that motivated the practice was a concern that the LRs would lead to noncompliance [26]. Actually, the exact opposite has been demonstrated, as compliance may actually be improved by not dose adjusting and is typically not a reason patients discontinue SCIT [20]. Dose adjustments increase the inconvenience of SCIT for patients, and inconvenience is the primary reason patients discontinue SCIT [27]. In addition, when patients were queried about their concern with LRs, most (82%) deemed LRs not bothersome at all or only slightly bothersome, and among those patients who experienced an LR, 96% stated they would not stop SCIT because of these LRs [28•]. The data do not support dose adjustments based on allergists' concern for noncompliance.

The second motivating factor for dose adjusting among allergists in 2007 was a concern that LRs were predictive of future LRs [26]. To address this concern, Calabria et al. [29•] published the LOCAL study in 2009, which demonstrated that only 6% of large LRs were followed by another large LR. The sensitivity for a large LR predicting a subsequent large LR was 5%, and the positive predictive value for a large LR predicting another large LR was 6%. The clinical implication of this study is that LRs do not predict LRs at the next SCIT injection, and LRs should not

be used to make SCIT dose adjustments. Of interest, and in response to the LR literature published since 2000, a concern for LRs predicting a systemic reaction was a minor factor in allergists' rationale to dose adjust, as only 29% of allergists cited this [26]. Thus, routine dose adjustments for LRs are not supported by the current literature.

Prevention of and Symptomatic Therapy for Local Reactions

Although there is very little in the literature evaluating the effects of therapeutic interventions in preventing, minimizing, alleviating, or resolving LRs, clinical interventions are recommended in practice parameters and are also widely practiced in the United States. The most recent practice parameter recommendations for LRs include cool compresses, topical corticosteroids, oral antihistamines, dose adjustments for persistent large LRs causing patient discomfort, more frequent office visits for evaluation and management of LRs, depression of the plunger at a rate that does not result in wheal formation or excessive pain, and application of mild pressure at the injection site for 1 min after needle removal to reduce the chance of extract leakage [24].

In the GILL study published in 2008 out of the Wilford Hall Medical Center, small LRs (smaller than a patient's palm), but not large LRs (the size of or bigger than a patient's palm), increased with higher allergen concentration, number, and volume [30•]. However, higher glycerin concentrations (even 50%) were not associated with significantly higher small or large LR rates. The take-home message from this study is that concern for LRs should not be a reason to limit the glycerin or allergen content of immunotherapy extracts.

Additional recommendations for LR prevention within the literature have included increasing the interval between doses to at least 1 week and possibly 2 weeks, with the hypothesis being that this would permit a long time for immunity to develop after each injection [9]. In contrast to this recommendation, another source has stated that fewer reactions might occur with shorter intervals between injections; therefore, the interval between SCIT injections should be individualized to provide the greatest efficacy and safety for each patient [19]. Finally, a previous edition of Middleton's *Allergy: Principles and Practice* recommended attention to proper injection technique, which was purported to minimize the pain of injection and degree of local discomfort, and that the needle needed to be wiped free of antigen with a sterile swab before injection, which would reduce LRs alleged to be caused by antigen retained on the needle shaft [1]. Oral steroids for 2 days also have been stated as an indication for significant LRs [17]

Potentially the most practical bit of advice was found on the World Allergy Organization website in 2004, on which Canonica and Durham reassured the allergy community that in general, LR's following injections were to be expected, and no treatment was required other than reassurance, although they wrote that occasionally, the use of an antihistamine might be indicated [31]. One allergist uses a steroid (0.05–0.1 mL triamcinolone, 10 mg/mL) mixed with the allergen extract with anecdotal success and has reported no problems with local skin atrophy (Reisman, personal communication).

Despite all the recommendations apparently motivated by anecdotal experience, the only interventions that have been systematically studied for the prevention of LR's are oral antihistamines (terfenadine [32, 33], terfenadine + ranitidine [33], fexofenadine [34], loratadine [35], astemizole + ranitidine + prednisone [36], loratadine + topical anesthetic [37], and desloratadine [38]) and the leukotriene modifier montelukast [38]. Of note, neither of these were found to be effective in conventional SCIT and had their influence only in rush SCIT and the subsequent 3 weeks.

Although the rationale has varied, dose adjustments in SCIT have served as a mainstay of intervention. However, it is the opinion of this author that there is no literature to support dose adjustments for LR among our SCIT patients. Our large (>400 patients on SCIT at any one time) academic practice has not practiced dose adjustments for the past 12 years, with our historical systemic rates of 0.8% dropping to 0.4% during this time with no significant changes in our practice. We also continue to have high SCIT compliance rates compared with those of other institutes reported in the literature. This author does not advocate dose adjustment for LR's, as this may actually work against the intended desire and lead to noncompliance, increased costs, additional visits, failure to attain maintenance dosages either at all or in a timely fashion, and potentially lead to dosing errors in those patients on two separate injections. However, although unproven with conventional SCIT courses, interventions other than dose adjustments may be used and have been addressed in this article as pretreatment for prevention and/or amelioration, or after treatment for symptomatic relief.

The primary modality for LR's that should be addressed by the practicing allergist is that of education. It is not an issue of if an LR will occur but rather when an LR will occur. Education of the allergy office staff and the SCIT patient is essential to a successful SCIT practice. Education concerning LR's and their failure to predict further systemic reactions or other LR's, and the fact that patients are generally not bothered by LR's are key components to this education. Patients should be supplied with LR education before initiating SCIT, when they have an LR, and at routine follow-up appointments. Patients should be encouraged to notify the office staff and allergist if LR's are

bothersome so that pretreatment and symptomatic therapy may be prescribed. The educated patient is a patient who will rarely be bothered by an LR. Compassionate care and symptomatic therapy will alleviate and preclude patient anxiety and concern.

Conclusions

LR's are a common occurrence in the allergist's practice, with frequency rates of 26% to 82% reported during the course of SCIT, and a 0.7% to 4.0% LR rate per 100 injections [4, 6, 39]. Allergists have used a variety of interventions in their attempt to prevent, ameliorate, or symptomatically treat LR's over the years. During the past 10 years, several studies have looked at LR's and their association with systemic reactions and additional LR's. In addition, allergists and patients have been surveyed with regard to LR's. All these areas of study have been part of an attempt to address allergists' concerns about LR's.

LR's to SCIT is a vast area with significant clinical application waiting to be researched. The allergy community needs sound evidence to guide the practice of LR intervention. Convenience, comfort, compliance, cost, and confusion are all at stake when unnecessary dose adjustments or interventions are made for LR's.

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