Pro/Con Review

Are Allergen Immunotherapy Dose Adjustments Needed for Local Reactions, Peaks of Season, or Gaps in Treatment?

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INTRODUCTION

We have been asked to debate the merits of dose adjustments for local reactions (LRs), pollen seasons, and gaps in therapy for subcutaneous allergen immunotherapy (SCIT). As allergists are aware, SCIT is a highly effective therapy for allergic rhinitis, asthma, atopic dermatitis, and stinging insect hypersensitivity. Severe and life-threatening events due to SCIT appear to be declining and are relatively rare, but they do occur.[1-5] Since 1973, at least 84 fatalities from SCIT in the United States and Canada have been reported.[1-8] There have been at least 4 confirmed fatalities since 2008, with 2 of these occurring under the care of allergists.[4,5] Based on data from the American Academy of Allergy, Asthma, and Immunology/American College of Allergy, Asthma, and Immunology (AAAAI/ACAAI) national surveillance study, systemic reactions (SRs) occur in 0.1% of injection visits, and there were at least 63 World Allergy Organization grade 4 SCIT reactions between 2012 and 2013.[5] Given that the significant benefits of SCIT are coupled with very real risks of adverse outcomes, allergists must evaluate strategies that will balance both sides of this equation.

ALLERGEN IMMUNOTHERAPY DOSE ADJUSTMENTS ARE NEEDED FOR LRs

Pro position

Disclosure: This is not necessarily my own opinion.

Given the risk of severe and potentially life-threatening reactions from SCIT, prescribers should take a conservative approach to minimize risks. This includes lowering doses and/or slowing down the build-up after LRs, and especially with large local reactions (LLRs) to SCIT. The immunotherapy practice parameters state that "Published studies indicate that individual local reactions do not appear to be predictive of subsequent systemic reactions"; however, they also admit that "some patients with a greater frequency of large local reactions might be at an increased risk of future systemic reactions."[9]

More than 90% of allergists adjust doses after LRs. Reasons for adjustment that are commonly cited include concern that LRs cause discomfort that lead to patient noncompliance (88.9%), concern that LRs are predictive of future LRs (45.7%), and concern that LRs are predictive of future SRs (29.2%).[10] One of the difficulties in interpreting the literature for LRs is that definitions for LRs versus LLRs vary. Small LRs have recently been defined as erythema and/or swelling of more than 5 mm and less than or equal to the size of the patient's palm at 30 minutes, or just any reaction that is smaller than the palm of the hand.[11,12] LLRs have variably been defined as more than 25 mm induration for at least 12 hours, more than 20 mm for at least 24 hours, more than 40 mm, or larger than the patient's palm.[13,14] In a survey of 249 patients who were active-duty or retired military personnel and their spouses and children, the authors reported that 71% experienced LRs, but that 96% would not stop SCIT because of LRs; however, only 20.3% of these reactions were larger than the palm of the hand. Even with the majority of reactions not meeting the definition for LLRs in this study, 13.6% of patients found reactions moderately bothersome and 5.1% found them extremely bothersome.[12]

Tankersley may attempt to dissuade practitioners from concerns regarding LRs based on data from retrospective studies that include LRs of various sizes. Regarding whether LRs predict future LRs, Tankersley may argue that only 27% of LRs (of all sizes) are followed by another LR, and 6% of LLRs are followed by another LLR.[11] However, in that same publication, Calabria et al[11] admit that "future studies measuring the ability of local reactions of a specific size (i.e., 50 mm and so forth) to predict local reactions would further add to the local reaction and immunotherapy literature." Tankersley may also present data indicating that LRs do not predict SRs with the next injection; however, in a retrospective review of a large multicenter allergy practice that adjusts doses for LLRs (defined as >25 mm, the size of a quarter), patients with SRs experienced LLRs in 35.2% of visits versus 8.9% of visits in a group matched for age, sex, and allergen sensitivity ($P < .001$).[15] In that study, although 33% of the SRs were immediately preceded by an LLR, individual LLRs were not predictive of future SRs with the next dose, but LLRs preceded SRs in approximately one-third of cases. In another retrospective 1-year, single-site study involving 360 patients, those experiencing SRs were also more likely to have experienced LLRs, defined as larger than the patient's palm. In that study, of those patients who experienced an LLR, 41.7% also experienced an SR, whereas only 10.7% of non-LLR patients had an SR.[16] Tankersley may also argue that studies have found that

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Abbreviations used
AAAAI/ACAAI- American Academy of Allergy, Asthma & Immunology/American College of Allergy, Asthma and Immunology
LR- Local reaction
LLR- Large local reaction
SCIT- Subcutaneous immunotherapy
SR- Systemic reaction

reducing doses with LLRs does not decrease SR rates; however, the practice parameters acknowledge insufficient data in this area and state that "Prospective studies investigating the sensitivity and specificity of large local reactions and the effect of immunotherapy modification on them are needed."[9]

In conclusion, we should adjust doses for LRs, and especially for LLRs, to SCIT, given that (1) we do not have extensive prospective, multicenter data from which to draw firm conclusions; (2) various cutoff points used to define LRs and LLRs confound interpretation of existing literature; and (3) there is a potential link between increased rates of LLRs and SRs for some patients. If more than 90% of allergists adjust doses after LRs, could all these allergists be wrong? See Table I for a summary of the Pro position.

Con position

Disclosure: I have not routinely dose adjusted for LRs since 1998.

I agree with Epstein that, as allergists, we should implement conservative measures to minimize SR risks for our patients. However, any measure undertaken should be evidence-based so that in an effort to provide benefit we do not actually create harm to those we serve. Over the last 2 decades a significant amount of literature has accumulated that clearly lays out 4 reasons that allergists should not routinely dose adjust for LRs.

First, LRs are not predictive of SRs. Allergists have historically considered an LR to be a flashing yellow traffic light warning us to yield and "do something" to avoid an impending SR with a future SCIT injection. In the 1990s, we found among our SCIT population at Wilford Hall in San Antonio, Texas, that we had several patients who could never attain a maintenance dose because of our dose adjustment protocol for LRs. Thus, we designed a protocol to prospectively evaluate over a 9-month period whether a no-dose adjustment schedule for LRs impacted SR rates compared with the previous 9 months before the initiation of this study.[17] In this prospective study, SR rates were not significantly different, with a rate of 0.8% under the dose adjustment schedule (65 SRs/8076 injections) and 1.1% under the no-dose adjustment schedule (49 SRs/4850 injections) ($P = .24$). See Figure 1. This study was significant because it was the first to specifically evaluate what happens at the injection visit immediately following an LR. The sensitivity of an LR predicting an SR was only 15% and the positive predictive value of an LR predicting an SR was also poor at 17%. The inability of an LR to predict an SR has also been supported in another prospective study,[18] and 2 additional studies have had the same conclusions.[19,20] Finally, the above referenced REPEAT study by Calabria was notable for 3 reasons: (1) a no-dose adjustment protocol was followed for LLRs, (2) it was only in a subpopulation of patients with LLR that an increased SR rate was seen (58.3% of patients who had an LLR never had an SR), and (3)

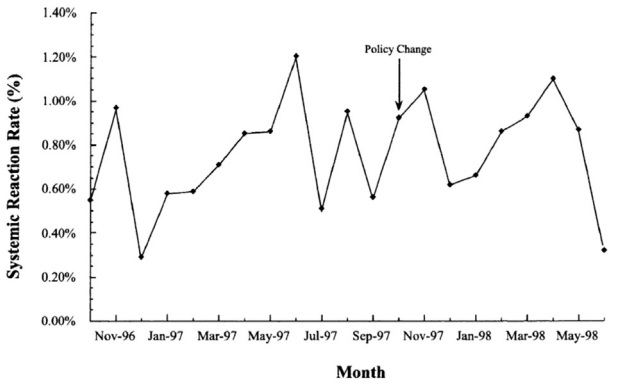

FIGURE 1. Monthly rates of systemic reactions after allergen injections.[17] Dose adjustment for LRs was discontinued on October 1, 1997.

patients with 1 or more LLR did not have an increased SR risk.[16] Thus, the LLR-SR association is seen among a subpopulation of patients with LLR regardless of whether you adjust the dose or not, so why dose adjust?

Second, LRs are not predictive of LRs.[9] Some allergists justify a dose adjustment due to concerns that an LR predicts a subsequent, potentially larger, LR, and so adjust doses to prevent a subsequent LR.[10] In the LOCAL study, both sensitivity (26.2%) and positive predictive value (27.2%) for an LR predicting a subsequent LR were poor.[11] It was actually the specificity of the absence of an LR predicting the absence of a subsequent LR that was more reliable (85.5%). Again, though well intended by the allergist, dose adjusting for an LR should not be used to prevent an LR at the next injection.

Third, LRs are not bothersome to patients. Although almost 90% of allergists reported dose adjusting for LRs due to a concern that patient discomfort would lead to noncompliance,[10] when we asked 249 patients on SCIT at our clinic (100% response rate) the overwhelming majority (81.9%) deemed their LR not bothersome at all or only slightly bothersome.[12] Because dose adjustments increase patient visits and costs, a dose adjustment protocol may more likely result in an unintended decrease in compliance. Unnecessarily increasing visits and costs is bothersome to patients.

Fourth, LRs are an uncommon reason that patients discontinue SCIT. Again, although noncompliance is a concern for allergists,[10] 96% of patients stated they would not stop SCIT because of LRs.[12] In addition, when 381 active SCIT charts from a military medical center were analyzed under a no-dose adjustment protocol for LRs and noncompliant patients were contacted, inconvenience (34.5%) was the single most important reason for discontinuation.[21] LRs were an uncommon reason for discontinuation and reported as a reason in only 5.5% of those who stopped SCIT. Of interest, there was a high compliance rate (77.4%) under this no-dose adjustment for LR protocol. These military data are applicable to all practice types.[22]

In light of this extensive literature, why would allergists continue to dose adjust for LRs? The evidence supports that SCIT dose adjustments are not needed for LRs. Dose adjustments for LRs delay achievement of a therapeutic dose, increase costs, introduce additional visits, create inconvenience, decrease compliance, and put the patient at increased risk of