Pro/Con Review

Should Epinephrine Autoinjectors Be Prescribed to All Patients on Subcutaneous Immunotherapy?

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Subcutaneous allergen immunotherapy (SCIT) clearly benefits appropriately selected patients with allergic rhinitis, asthma and anaphylaxis to stinging insects. Since inception of SCIT, systemic allergic reactions (SRs) and severe anaphylaxis have been risk management challenges facing the practicing allergist. Recently it has estimated that 14% of reported SRs begin at least 30 minutes after injection administration or after the 30 minute recommended clinic observation period. Faced with the possibility that SRs could occur after the patient leaves the clinic, some practicing allergists routinely prescribe epinephrine auto-injectors to all injection patients. This article summarizes the key arguments for and against routine prescription of epinephrine auto-injectors for all allergen injection patients, discussed in a PRO/CON debate at the 2015 AAAAI meeting. Currently, there is insufficient clinical evidence to make a strong recommendation for or against this practice. © **2016 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2016;■:■-■)**

Subcutaneous immunotherapy (SCIT) with aqueous allergen extracts has been practiced for more than 100 years.[1,2] In the last 4 decades, controlled clinical trials have demonstrated the efficacy of this modality in the treatment of patients with allergic rhinitis, asthma, and Hymenoptera allergy. Since its inception, the potential risk of severe systemic reactions (SRs) and rare fatal anaphylaxis associated with SCIT has been recognized. During the last 4 decades in the United States, retrospective surveys of the experience of practicing allergists and, more recently, annual surveillance studies have helped to define the frequency of rare fatal reactions (FRs) after administration of SCIT injections as well as factors that might increase their risk.[3-6] A recent annual surveillance study of clinical allergy practice in the United States indicates that SRs after SCIT injection reactions occur at 0.1% of all injection visits.[6] A retrospective study of SCIT FRs estimated that from 1990 to 2001, one fatal injection reaction occurred in every 2.5 million injection visits.[7] Investigation of potential risk factors in this and other surveys among practitioners revealed that uncontrolled asthma appeared to be the most commonly cited factor noted at the time of SCIT-related fatal events. Heightened awareness from discussions of severe SCIT reactions described in the aforementioned studies has led to the development of practice guidelines recommending routine preinjection screening of all asthmatic patients for asthma control and observing patients for a minimum of 30 minutes after SCIT injections.[8] Since 2008, it appears that the number of fatal SCIT reactions have declined.[6] In the annual surveillance study conducted in 2009-2010, only 3.4% of all reported SCIT-associated SRs would be classified as anaphylaxis and only 0.4% of these as delayed-onset anaphylaxis beginning after 30 minutes.[9] The available evidence suggests that most SRs occur within 30 minutes after injections but a minority of SRs (14%) begin after more than 30 minutes.[9] For this and other reasons, a minority of allergists have begun to routinely prescribe epinephrine autoinjectors to all patients receiving SCIT and provide training on self-administration in the event of a late-onset SR. A survey conducted among 273 practicing allergists in North America found a wide variation in this practice with 33% responding that self-injectable epinephrine was routinely prescribed to all their patients receiving SCIT injections; 53% of respondents indicated that they risk-stratify patients in arriving at a clinical decision to prescribe. It is noteworthy that 25% of survey participants were uncertain if epinephrine prescriptions had actually been filled and the majority of these physicians administered SCIT injections regardless of whether patients carried self-injectable epinephrine devices with them to their injection visits.[10] Arguments for and against this practice were recently debated in a Pro-Con Debate at the 2015 annual American Academy of Allergy, Asthma & Immunology (AAAAI) meeting. A summary of the debate favoring and opposing this practice is listed in Table I and detailed arguments are presented below.

PRO POSITION: EPINEPHRINE AUTOINJECTORS SHOULD BE PRESCRIBED FOR ALL PATIENTS RECEIVING SCIT

SCIT is unique as a medical therapy in that a known precipitant of anaphylaxis is being intentionally delivered. Although a highly efficacious option for atopic disease, rare but significant SRs including life-threatening anaphylaxis do occur. Any

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No funding was received for this work.
Conflicts of interest: D. J. Fitzhugh has received consultancy fees from ViroPharma; and has received payment for developing educational presentations from Prime Education, Inc. D. I. Bernstein has received research support from the American Academy of Allergy, Asthma & Immunology/the American College of Allergy, Asthma & Immunology, Amgen, Novartis, Genentech, Pearl, GlaxoSmithKline, AstraZeneca, Johnson & Johnson, Merck, Allergy Therapeutics, Sanofi, Boehringer Ingelheim, Pfizer, and Circassia; has received consultancy fees from Adamis, Teva, Circassia, merck, and Novartis; is on the Board of Directors for the American Board of Allergy and Immunology, Joint Task Force Practice Parameters; and has received lecture fees from AstraZeneca, Merck, and Boehringer Ingelheim.
Received for publication November 16, 2015; revised April 5, 2016; accepted for publication April 7, 2016.
Available online ■■
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2213-2198

http://dx.doi.org/10.1016/j.jaip.2016.04.007

Abbreviations used
FR- Fatal reaction
NFR- Near-fatal reaction
SCIT- Subcutaneous immunotherapy
SLIT- Sublingual
SR- Systemic reaction

clinician administering SCIT must be prepared to treat such reactions in the office. Safety can be maximized by making self-injectable epinephrine routinely available to all SCIT patients in the event of a delayed reaction outside the office. Although severe SRs occurring after the customary in-office 30-minute period are quite infrequent, systemic injection with epinephrine is nevertheless the only appropriate therapy for such reactions, which is the same as for any anaphylactic event.

A number of questions must be considered before issuing a recommendation to routinely prescribe self-injectable epinephrine to all SCIT patients:

1. What is the frequency of delayed SRs, and of these, how many are severe?
2. What is the efficacy of epinephrine for delayed SRs?
3. What is the cost of the intervention?
4. Can patients at elevated risk for delayed SRs be identified?

Severe delayed SRs to SCIT are overall rare. Using data from the prospective AAAAI/American College of Allergy, Asthma & Immunology (ACAAI) Immunotherapy Surveillance study, delayed SRs occurred at an incidence of 1 per 14,000 injection visits.[9] Of these, 12.5% were classified as severe (grade 3). Thus, the calculated incidence of severe, delayed SRs after SCIT is approximately 1 per 112,000 injection visits. Although such events are indeed infrequent, all patients receiving SCIT require an anaphylaxis preparedness plan for such an out-of-office event. Certainly, one strategy for managing a delayed SR could be for the patient to return to the administering physician's office or a nearby emergency facility. Although these strategies are not unreasonable, medical attention is not always readily available and anaphylaxis continues to evolve during any delay in receiving medical care. Having self-injectable epinephrine available to all SCIT patients ensures immediate access to potentially life-saving therapy in the event of a delayed SR to an SCIT injection.

Regarding efficacy epinephrine for delayed SRs, there is extensive, high-quality evidence that prompt administration of intramuscular epinephrine on recognition of anaphylaxis is the therapy of choice and all other therapies are essentially adjunctive.[11] Delayed administration of epinephrine is a contributing factor for some FRs to immunotherapy.[8] No study has been designed to compare outcomes of delayed SRs among patients who did or did not receive self-administered epinephrine. There is no reason to believe that the physiologic mechanism of anaphylaxis in delayed SRs operates differently than, say, food anaphylaxis and that administration of epinephrine should be any less efficacious. Indeed, in the AAAAI/ACAAI surveillance study, all of 9 patients with late-onset, severe SRs required and *eventually* received epinephrine. However, unfortunately, only a minority of these patients (4 of 9) had epinephrine autoinjectors previously prescribed and only 2 of these 4 actually self-administered epinephrine.[9]

Although the cost of autoinjectable epinephrine cannot be discounted, cost should not be a deterrent to prescribing the only accepted first-line treatment for anaphylaxis. Unfortunately, the average wholesale price of epinephrine autoinjectors continues to climb in the United States. The average wholesale price of autoinjectors was near $100 in 2011, whereas the retail price varies dramatically but can approach $300 per device.[12] However, cost defrayment mechanisms are available in the form of copay cards and patient assistance programs from all major manufacturers of autoinjectors.[12] The cost dilemma of providing epinephrine for SCIT patients is unfortunately no different than that faced by other patients who are at risk for anaphylaxis due to food or venom allergy. Finally, it is worth noting that if a recommendation for all SCIT patients to have epinephrine autoinjectors were implemented in the Allergen Immunotherapy (AIT) Practice Parameters, this would likely be covered as a no-cost preventative service to patients under the Affordable Care Act, irrespective of deductible or copay/coinsurance obligations.

Because delayed SRs to immunotherapy are overall rare, it would be highly desirable to establish which patients are at elevated risk for such reactions. This question is really the central axis about which the question to prescribe epinephrine autoinjectors to SCIT patients revolves: *are there any clear risk-stratification criteria to identify patients at increased risk for delayed SRs to immunotherapy who might benefit most from having self-injectable epinephrine available*? There are a number of risk factors that may predispose patients to SR, delayed or otherwise, most notably labile asthma or a history of prior SR.[13] The most recent update of the Immunotherapy Practice Parameter supports such a risk-stratification scheme, stating: "Some physicians might request that patients considered at increased risk of a serious systemic reaction outside of the office/medical clinic carry injectable epinephrine. These patients should be instructed in the use of epinephrine to treat a systemic reaction that occurs after they have left the physician's office or other location where the injection was given."[8]

The essence of this decision dilemma in assigning future risk to patients is that there are no reliable patient characteristics that predict which patients might experience a future delayed SR. Interestingly, in the AAAAI/ACAAI surveillance study, "among patients experiencing severe delayed-onset SRs for whom complete reaction details were available, *none had ever had a SR in the past.*"[9] Selectively prescribing self-injectable epinephrine only to patients deemed to be at higher risk, while commendable, ignores the fact that many SRs, including delayed SRs, occur without obvious risk factors.

Practical considerations involve whether patients prescribed self-injectable epinephrine actually have autoinjectors available in the event of a severe delayed SR or, if they do, whether or not they decide to promptly self-administer the drug. Failure to carry or to self-administer previously prescribed autoinjectable epinephrine is a challenge we commonly face in convincing patients at risk for severe anaphylaxis due to food or venom allergy. The data for timely self-administration of epinephrine are not encouraging. We must continue to educate our patients about the central role of prompt epinephrine delivery in the treatment of severe allergic reactions and ensure that patients, parents, and other caregivers have the confidence and experience to utilize the device when indicated.[12,13] Although we cannot assure that epinephrine will be delivered in all instances by patients in the field when we might give it in the clinic, it is fairly