

Pro/Con Review

Injectable Epinephrine Should Be Prescribed to All Patients on Subcutaneous Aeroallergen Immunotherapy

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We have been invited to discuss the advantages and disadvantages of implementation of routine prescription of injectable epinephrine (IE) to all subcutaneous aeroallergen immunotherapy (SCIT) patients. We must emphasize that the strength of recommendation of our arguments, according to the existing guidelines, is based on evidence from nonexperimental descriptive studies (comparative, correlation, and case-control studies), namely strength of recommendation C. SCIT is an efficacious treatment for allergic rhinoconjunctivitis, asthma, atopic dermatitis, and venom hypersensitivity.¹ Although severe and life-threatening reactions to SCIT occur, these events are rare and are declining.² Seven fatalities due to SCIT have been reported since 2008.³ Consistent with previous data, the largest and most recent study on SCIT reaction rates reported that systemic reactions (SRs) occurred in 0.1% of injection visits between 2008 and 2016.^{1,3} Because of this, allergists/immunologists must consider methods to balance both the immense benefits and potentially life-threatening risks of SCIT.

This paper is not going to evaluate the pros and cons of prescribing IE in certain circumstances but will address the routine prescription of IE to all aeroallergen SCIT patients. There is no disagreement between the authors that SCIT should be performed with optimum, therapeutic, nonplacebo doses in a manner that places patients in the highest position to maximize their outcomes and minimize any adverse events. The patient is the number one priority. The authors will argue one item of how to operationalize this priority as it relates to the routine

prescription of IE to all patients on SCIT. It is assumed that all venom SCIT patients would already have an IE device, so the prescription of IE in this paper is in the context of aeroallergen SCIT.

PRO POSITION: EPINEPHRINE AUTOINJECTOR SHOULD BE PRESCRIBED TO ALL PATIENTS ON AEROALLERGEN SCIT

Subcutaneous allergen immunotherapy with natural aqueous allergen extracts is an effective treatment modality for allergic rhinitis, IgE-dependent asthma, and for preventing systemic anaphylaxis after Hymenoptera venom stings.⁴⁻⁶ Even though millions of SCIT injections are administered annually without adverse reactions, the annual rate of SRs in the North America is estimated at 0.1% (1 in 1000) of all injection visits occurring in 0.6% of all patients receiving SCIT.³ As a part of this surveillance study, from 2008 to 2016, 27% to 51% of American Academy of Allergy, Asthma, and Immunology (AAAAI)/American College of Allergy, Asthma, and Immunology (ACAAI) members completed an annual survey of SCIT-related SRs of varying severity. Data were gathered on 54.4 million injection visits (2008-2016). A severe grade 4 anaphylactic reaction has been estimated to occur in every 160,000 injection visits and in every 20,000 patients. Unfortunately, rare fatal reactions (FRs) continue to be reported.³ In a retrospective survey conducted in North America between 1990 and 2001, an FR occurred in every 2.5 million injection visits.⁷ Since 2008, a national surveillance study of immunotherapy safety cosponsored by AAAAI and ACAAI has conducted annual surveys of FRs and nonfatal allergic SCIT reactions. Although reported annual rates of fatal events seem to be declining, 7 injection-related FRs have been confirmed from 2008 to 2017.³ It is unknown to what extent fatal anaphylaxis after SCIT injections might be averted by early intervention with intramuscular self-injectable epinephrine. However, combined data from 2 separate retrospective surveys of FRs spanning 15 years (1985-1989 and 1990-2001) indicated that 43% of all fatal SCIT reactions were associated with a delay or failure to administer emergency epinephrine.^{7,8} In some cases, treatment delays were attributed to early departure of the patient from the clinic during the required observation period. In other cases, early symptoms of fatal anaphylaxis may not have been recognized and treated in a timely fashion by medical personnel at the injection facility. These documented experiences surrounding unpredictable fatal events would lend support to adapting the practice of routine prescription of IE to all patients receiving aeroallergen SCIT.

In choosing to recommend SCIT injections, the benefits must be weighed against the risks of injection-related anaphylaxis.

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Many risk factors for postinjection anaphylaxis have been identified that could require emergency administration of IE by the health care provider or the patient. Uncontrolled and labile asthma is the major contributing factor identified by treating physicians often associated with severe and fatal SRs to SCIT.^{2,7} In addition to uncontrolled asthma, other factors recognized to contribute to life-threatening systemic allergic reactions include errors in allergen dosing, failure to observe a 30-minute post-injection observation period, injection administration during peak pollen seasons, and delays in administration of IE. In 17% of FRs identified in retrospective surveys, no contributing factor was identified by treating physicians.^{7,8}

There are various scenarios where patients may be required to self-administer IE epinephrine for SRs after allergen injections. FRs were reported in patients leaving the clinic early after injections as well as in settings (eg, home administration) where health care professionals were unavailable to manage anaphylaxis and administer epinephrine in a timely fashion. Published reports have documented that 15% to 50% of SRs occur >30 minutes after SCIT administration and outside the injection clinic.^{9,10} Therefore, routine prescription of epinephrine autoinjectors to all patients receiving SCIT in combination with adequate training on self-administration is a rational strategy for early treatment of SRs occurring away from a medical facility.

Concern has been raised by the frequent occurrence of late SRs. Single practices have reported a high proportion of SRs beginning after 30 minutes.¹⁰ The annual incidence of delayed onset SRs (>30 minutes) was assessed twice in the National Surveillance Study of practicing allergists in North America. In the first survey conducted in 267 clinical practices, 14% of SRs began after 30 minutes.⁹ In the second national survey conducted in 2014 to 2016, 30% of all SRs were initially reported to begin after 30 minutes. However, when those clinics strictly observing a 30-minute waiting period were considered, 15.5% of SRs in those practices began after 30 minutes.³ Fortunately, the AAAAI/ACAAI Surveillance Study indicates that the proportion of practices observing a 30-minute waiting time increased from 57% to 73% between 2010 and 2016.³ Thus, it is likely that the overall proportion of delayed onset SRs is at least 15%, a higher than expected proportion of all SRs. This finding alone builds a compelling argument for routinely prescribing IE to all SCIT patients. Although nearly all delayed onset reactions were graded by respondents as mild or moderate in severity, severe potentially life-threatening SRs were reported in 9 patients representing 3% of all delayed onset SRs. In 5 of these patients for whom detailed information was provided, self-injectable epinephrine was clearly required; 3 patients required emergency department (ED) treatment and 2 experienced hypotension.⁹

Uncontrolled asthma, prior ED visits, and hospitalizations for asthma exacerbations have been identified as leading contributing factors in the majority of FRs to SCIT injections.¹¹ It is noteworthy that 75% of practices participating in the North American Surveillance Study indicated that SCIT is sometimes administered to their patients with partially controlled asthma (defined by an Asthma Control Test score less than 20).² In fact, two-thirds of grade 3 and 4 SRs reported in the National Survey occurred in patients with asthma.³ Patients with uncontrolled asthma could represent the largest patient group at risk for grade 3 and 4 SRs, principally manifested by severe bronchospasm. Thus, there is enough evidence

to justify recommending IE to high-risk asthmatic patients receiving SCIT to assure timely treatment of life-threatening SRs, especially if some are delayed in onset and occur away from a medically supervised clinic.

The evidence derived from annual AAAAI/ACAAI-sponsored surveys and other reports suggests that SRs inevitably occur despite the best efforts of treating allergists to assess and mitigate risk. The unpredictable nature of the delayed onset SRs alone could justify the decision to recommend IE for all SCIT patients. However, one might also justify a more selective strategy in routinely prescribing IE to the following categories of patients: those choosing not to observe the 30-minute postinjection observation period; those who experienced previous immediate or delayed onset SRs; those receiving injections from other health care providers; uncontrolled asthmatic patients receiving SCIT, a group at the highest risk for life-threatening SRs.

It is noteworthy that only approximately 30% of allergists participating in the national survey routinely prescribe IE to all SCIT patients.³ The PRO position for prescribing autoinjectors to all patients might be more widely accepted among practicing allergists if not for the poor patient adherence to carrying autoinjectors to their injection visits and self-administering IE when SRs actually occur. This is apparent in a recent study published by Epstein et al,³ who evaluated 21 delayed onset grade 3 or 4 severe SRs reported by treating allergists in the North American survey (2014-2015) among patients who had been prescribed IE devices. Only 4 (19%) patients actually self-administered epinephrine during reported delayed severe SRs, highlighting poor compliance with this recommendation.³ Poor compliance with IE self-administration is also common in patients experiencing fatal food-induced anaphylaxis.¹² An unmet need exists to improve epinephrine autoinjector compliance via consistent patient education and re-education on self-management of SRs occurring outside the clinic. Factors that could account for poor compliance include the cost of autoinjector devices, health literacy of patients, reluctance to self-inject, and inconvenience of carrying the device. In recent years, cost has been much less of an issue as prices of certain IE devices have decreased substantially, thanks to wider availability of generic products and selling of one product at reduced cost to patients through a specialty pharmacy. To encourage a more formal mechanism to address health literacy, national reimbursement of IE administration education by clinic personnel similar to asthma metered dose inhaler technique education reimbursement (CPT 94664) may lead to greater adherence to using IE. Our national organizations might consider investing efforts toward this end. To address "injection phobias," development of devices featuring alternate routes of administration (eg, sublingual and intranasal epinephrine) with equivalent pharmacokinetic properties to approved IE devices seems attractive. If proven effective, these could positively impact patients' self-management of SRs occurring outside the clinic.

CON POSITION: EPINEPHRINE AUTOINJECTOR SHOULD NOT BE PRESCRIBED TO ALL PATIENTS ON AEROALLERGEN SCIT

The safe prescription and administration of SCIT is highly valued among allergists. With the administration of SCIT come valid risks of local, systemic, and fatal reactions.¹ However, there

TABLE I. Comparison of IE and ambulances as interventions, not preventions of fatality

	Systemic reactions to SCIT	Car accidents
Annual US fatalities	2-3	37,461 (7)
Grade 1	Urticaria	Car has ability to drive away
Grade 2	Chest tightness	Car totaled
Grade 3	Refractory asthma	Passenger injured
Grade 4	Hypotension	Ambulance transport
Intervention	IE prescription	Ambulance proximity <1 mile
Goal	Prevent fatalities	Prevent fatalities
prevention	Train patients to wait 30 min, shot room SOPs, correct dosing	Seat belt, speed limit, red lights, blinkers

IE, Injectable epinephrine; SCIT, subcutaneous aeroallergen immunotherapy; SOP, standard operating procedure.

are at least 4 reasons why IE should not be routinely prescribed to all SCIT patients.

Injectable epinephrine prescriptions are fear based

The SR rate per SCIT injection is 0.1% to 0.2%,^{1,3,13} and almost all severe SRs occur within 30 minutes of SCIT administration.¹ Life-threatening anaphylactic reactions occurring >30 minutes after SCIT injections are rare, as reported by several large studies.¹ In the largest and most recent study on SCIT reaction rates, it was reported that only 0.6% of SCIT patients (120 of 20,000) had an SR, and only 0.005% of treated patients (1 of 20,000) had a grade 4 life-threatening reaction.³ The routine prescribing of IE is suggested to attempt to treat the possible occurrence of delayed anaphylaxis (>30 minutes after injection) after a patient leaves the allergy clinic after an SCIT injection.¹⁴ However, of all SRs reported to occur >30 minutes after receiving an injection, 95% were graded as mild to moderate, 4.8% were graded as severe to very severe, and none were fatal.³

To make an analogy, there are 310,000, 520,000, and 815,000 deaths annually due to war, homicide, and suicide, respectively.¹⁵ Nuclear reactors cause less deaths per year than sunlight, and deer cause more fatalities than alligators, bears, sharks, and snakes. “None of this means that nuclear radiation is good for you, that rattlesnakes are harmless, or that the evils of war are overblown. What it does mean is that we are often most afraid of the least likely dangers (*i.e.* SCIT fatality after the patient leaves our office), and frequently not worried enough about the risks that have the greatest chances of coming home to roost (*dosing errors, in-office delayed administration of epinephrine, placebo dose SCIT, unnecessary dose adjustments for local reactions, SCIT noncompliance and wait-time noncompliance, etc.*)”¹⁵ It has been reported that 8621 patients would need to be prescribed IE to treat only 1 delayed severe SR.¹⁴ Similarly, there are over 37,000 annual fatalities due to car accidents¹⁶ but historically only 2 to 3 annual deaths due to SCIT. The implementation of routine IE prescription for a potentially fatal SCIT reaction is analogous to the theoretical placement of an ambulance every mile within a city for a potentially fatal motor vehicle accident, as shown in Table I. However, both IE and ambulances are interventions for potential fatalities, not preventions. Although having access to an ambulance less than 1 mile away seems like a great way to decrease mortality due to car accidents, this implementation would not directly *prevent* motor vehicle accidents and would be cost-prohibitive and impractical. Similarly, prescribing IE to all SCIT patients does not prevent FRs from

occurring. Conversely, implementations that ensure correct dose administration or refraining from giving injections to patients during asthma exacerbations have the potential to actually *prevent* FR occurrence. The notion to prescribe IE to all SCIT patients is grounded in the fear of a highly unlikely severe SR needing IE more than 30 minutes after a SCIT injection.

Injectable epinephrine prescriptions are cost-prohibitive

Australia, Canada, the United States, and the United Kingdom have all reported national shortages of IE.¹⁷ In 2016, the cost of a pack of IE rose to over \$600, despite manufacturing costs remaining only \$35 per device.¹⁷ Is prescribing IE to such a large group of SCIT patients who have a very low delayed severe SR rate worth the cost and diminished supply of IE for patients with medication, food, or venom allergy who have a higher rate of anaphylaxis?¹⁸ There are 3.5 million Americans on SCIT and 17 million American candidates for SCIT. If allergists were to prescribe IE to every American on SCIT assuming that the device is \$300, it would cost \$3.15 billion (3.5 million patients × \$300/device × 3 devices/patient over a 5-year period).¹⁷ Based on a previous report, it would cost \$7,758,900 (8621 patients × \$300/device × 3 devices/patient) to treat 1 severe delayed SR.¹⁴ Simply put, prescribing IE for every SCIT is cost-prohibitive.

Injectable epinephrine prescriptions are a barrier to compliance

Adherence to 3 to 5 years of SCIT is an ongoing issue.¹⁹ There are 2 questions that must be addressed in the discussion of whether to prescribe IE to all SCIT patients:

- (1) Does prescribing IE overemphasize the risk of SCIT?
- (2) Does the operationalization of prescribing IE influence some patients to decline SCIT, be nonadherent with SCIT, and/or choose SLIT?

Universal prescription of IE for aeroallergen patients would overemphasize SCIT risk and might inadvertently create anxiety leading to lower SCIT initiation and exacerbate difficulties with SCIT adherence. If prescribing IE to all SCIT patients were to become standard of care, the prescription program would need to be operationalized. The physician would have to explain to patients why he or she is prescribing IE, thoroughly educate patients on how and when to properly use IE, and then write the prescription. Patients would have to pay for IE and pick it up from the pharmacy. In addition, patients must bring IE to every

TABLE II. Pro-Con summary: injectable epinephrine prescriptions are needed for all subcutaneous immunotherapy patients

Pro
(1) Although life-threatening anaphylaxis is rare, timely self-administration of IE may reduce risk of fatal outcomes
(2) Delayed onset SRs are frequent unpredictable events (15%-50%) some of which are severe and require self-IE
(3) Injectable epinephrine devices have become very affordable in recent years
(4) Published reports of poor adherence to IE during anaphylaxis do not justify denial of a potentially life-saving intervention to patients at risk
(5) In SCIT populations, multiple risk factors exist that enhance the likelihood of severe SRs that may not be recognized and treated at injection facilities
Con
(1) Life-threatening anaphylaxis is rare ^{1,3}
(2) 90% of severe SRs occur within the recommended 30-min clinic wait time ^{1,3,5}
(3) Injectable epinephrine prescriptions are cost-prohibitive for SCIT patients ^{5,7,8,26}
(4) Adherence to injectable epinephrine use is poor as only 8%-26% of patients self-administer IE during a delayed grade 3-4 SR ^{3,10}
(5) Injectable epinephrine prescriptions for aeroallergen SCIT patients are not supported by evidence-based medicine and not recommended by the FDA, AAAAAI, or ACAAI ³

AAAAAI, American Academy of Allergy, Asthma, and Immunology; ACAAI, American College of Allergy, Asthma, and Immunology; FDA, Food and Drug Administration; IE, injectable epinephrine; SCIT, subcutaneous aeroallergen immunotherapy; SR, systemic reaction.

follow-up visit and, if they do not bring it with them, would be required to reschedule their SCIT appointment. Furthermore, for the implementation of IE prescription to be effective in treating delayed fatal anaphylaxis, patients must actually use IE when needed after they leave the clinic, and then finally go to the ED. In a study on the activation of emergency medical services (EMS) after IE use for peanut anaphylaxis, results showed that alerting EMS immediately after IE use for peanut anaphylaxis has excessive costs and minimal benefit.²⁰ In a similar vein, a paradigm suggesting that 100% of SCIT patients who administer IE should activate EMS, as is recommended for food allergy, would be excessively cost-prohibitive. In SCIT patients prescribed IE, there is very poor patient adherence to IE use with only 8% to 26% self-administered IE during delayed grade 3-4 SR.^{3,21,22} In summary, IE has not been proven to be an effective mechanism to treat severe delayed SRs, and the successful implementation of operationalizing an IE prescription program would lead to even higher nonadherence rates for SCIT due to overestimation of risk.

Injectable epinephrine prescriptions are not supported by evidence-based medicine

There is no randomized trial demonstrating the superiority of an IE prescription writing policy for aeroallergen SCIT patients in the prevention of fatal anaphylaxis or complications from anaphylaxis after an SCIT injection. In fact, more recent studies have shown that there is no statistically significant improvement in SR rates in those practices that are currently prescribing IE to >90% of their SCIT patients.³ Furthermore, routine IE prescriptions for all SCIT patients are not recommended by the Food and Drug Administration, AAAAAI, or ACAAI. There are black box warnings and recommendations for the prescription of IE for the use of sublingual immunotherapy^{3,23-25} but not for SCIT. The AAAAAI/ACAAI practice parameters state that the decision to prescribe IE to patients receiving SCIT should be at the physician's discretion, and does not suggest that IE should be routinely prescribed to all SCIT patients.¹

Exceptions and the implementation of safe practices

There are special cases in which prescription of IE should be considered. For example, if the allergist is part of a practice with an institutional policy to prescribe IE to all SCIT patients, then "When in Rome, do as the Romans do" (Saint Ambrose). In addition, IE prescription should be considered in patients

with venom allergy, delayed or previous reactions, and those with biphasic potential.^{1,26} As stated in the practice parameter, "biphasic immunotherapy reactions, defined as resolution of the initial reaction with recurrence at 2 to 24 hours, were reported in up to 23% of patients who experienced a systemic reaction after allergen immunotherapy in one study. Biphasic reactions were typically less severe than the initial reaction." Lastly, if the practice does not routinely and systematically enforce a 30-minute wait time for all SCIT patients, the allergist should consider prescribing IE. That being said, implementation of more cost-effective and safer practices, like enforcing a 30-minute wait time in the allergy practice after an injection as recommended in the practice parameter,¹ is a much more practical approach to addressing systemic and fatal reactions to SCIT than prescribing an expensive medication to every SCIT patient. One easy way to implement the 30-minute wait time is to have the nursing staff quickly check the SCIT patient's arm and document the time and presence of a local or systemic reaction at 30 minutes. This creates an environment where waiting 30 minutes after SCIT injections is expected. On the first violation of the 30-minute required wait time, the nursing staff could educate the patient on the importance of being monitored for 30 minutes. On the second violation, the allergist could educate the patient that SCIT will be discontinued if a third incident occurs. Finally, on the third violation, SCIT would be discontinued. This simple implementation assures that all SCIT patients are being monitored and held accountable during the time period that systemic and life-threatening reactions are most common. There are many other additional measures that can be used to prevent SRs, such as applying criteria for selecting patients for SCIT, implementing standard operating procedures for the mixing lab and shot room to minimize errors, adding preinjection screening questions to check for SR risk factors before administering SCIT, and using safe and recommended dosing regimens. In conclusion, there are numerous simple and cost-effective ways to decrease the likelihood of an SR that do not require the routine prescription of IE to all SCIT patients.

CONCLUSIONS

As articulated in this paper, there is disagreement between the authors whether the cumulative evidence would suggest that routine prescription of epinephrine autoinjectors is a

justifiable practice to manage delayed onset SRs to SCIT injections (Table II). Enthusiasm for this routine practice is tempered by poor patient compliance, and low benefit-cost ratio,²⁶ given the very low frequency of delayed onset grade 3 or 4 SRs combined with poor adherence. An alternative approach might be to refocus on those patients with known risk factors for postinjection SRs including those with prior immediate or delayed onset SRs, those with uncontrolled asthma, those receiving injections in inadequately supervised clinics, and those receiving cluster buildup. Focusing efforts primarily on continuous education of high-risk patients on self-management of SRs may improve adherence to timely self-administration of IE. There is, however, no current evidence to support the efficacy of the latter approach for preventing or attenuating severe or fatal SRs. The authors trust that the 2 perspectives challenge the reader's practice and position on this topic. As mentioned in the introduction, there is no disagreement between the authors that SCIT should be performed with optimum, therapeutic, nonplacebo doses in a manner that places patients in the highest position to maximize their outcomes and minimize any adverse events. The patient continues to be our number one priority. When performed appropriately, SCIT is safe and effective and serves as the core in what our subspecialty offers as a disease-modifying therapy for those who suffer with allergic rhinoconjunctivitis, asthma, and atopic dermatitis. In conclusion, it is appropriate to restate Summary Statement 36 from the immunotherapy practice parameters, "Summary Statement 36: Several large studies demonstrate that life-threatening anaphylactic reactions after the first 30 minutes are rare. Delayed and biphasic immunotherapy induced systemic reactions can occur outside of a supervised medical facility. Thus patients should be educated regarding the possible signs and symptoms of systemic reactions and to contact their health care professional or seek emergency medical attention, as indicated. The decision to prescribe epinephrine autoinjectors to patients receiving allergen immunotherapy is up to the physician's discretion and is based on a number of considerations."¹

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