

A look at adherence with subcutaneous immunotherapy without out-of-pocket patient costs

Jun Mendoza, MD^{*}; Geoffrey Carlson, MD[†]; Priya Nath, MD[‡]; James Quinn, MD[§]

^{*} 10th Medical Group Allergy Clinic, Colorado Springs, Colorado

[†] 60th Medical Group Allergy Clinic, Fairfield, California

[‡] 316th Medical Group Allergy Clinic, Suitland, Maryland

[§] Wilford Hall Allergy Clinic, San Antonio, Texas

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ABSTRACT

Background: Subcutaneous Immunotherapy (SCIT) provides long-lasting benefits when administered for 3 to 5 years.

Objective: We evaluated SCIT adherence and factors associated with adherence in a military health care system with no out-of-pocket expenses.

Methods: We performed a combined retrospective and prospective observational electronic medical record review of SCIT from 2005 to 2012 to determine the start of therapy, time to maintenance dose (MD), duration of MD, and associated factors.

Results: We enrolled 897 patients selected for SCIT. A total of 421/897 (47%) were of male sex, 269/897 (30%) had asthma, and 113/897 (13%) had a systemic reaction. Ages ranged from 1 to 74 years (mean 34.8). There were 751/897 (84%) who were on aeroallergen immunotherapy, 108/897 (12%) on imported fire ant immunotherapy, and 54/897 (6%) on venom immunotherapy. Therapy was not initiated in 130/897 (14%) patients. There were 538/897 (60%) who received at least 1 MD; 307/897 (34%) completed 3 or more years of MD SCIT, 26% completed 4 or more years of MD SCIT, and 19% completed 5 years or more of MD SCIT. For those reaching MD, the mean total duration was 4.23 years and the mean time on MD was 3.17 years. Men were 271/421 (64%) more likely to reach MD ($P = .01$). The presence of asthma, age, venom immunotherapy/fire ant immunotherapy vs aeroallergen immunotherapy, and systemic reaction were not associated with reaching MD. After achieving MD, none of the identified factors were associated with SCIT duration.

Conclusion: Even with no out-of-pocket expenses, adherence to an adequate course of SCIT was 34%. Only the male sex was significantly associated with reaching MD. No factors were associated with the duration of SCIT after MD.

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Introduction

Physicians allocate a great deal of time diagnosing and treating their patients, yet little attention is focused on adherence to therapy. Chronic illnesses, long-term maintenance treatments, extremes of age, socioeconomic status, relationship with the physician, the attitude of the physician toward treatment, the amount and frequency of dosing, and the location of treatment are all suspected to affect patient compliance with medical therapies.¹ Dr C. Everett Koop, former Surgeon General of the United States, shed light on this difficult

truth of medicine with the statement, “Drugs don’t work in patients who don’t take them.”

Subcutaneous immunotherapy (SCIT) involves the gradual administration of increasing quantities of an allergen to develop tolerance to the allergen. Types of SCIT include aeroallergen immunotherapy (AIT), venom immunotherapy (VIT), and imported fire ant immunotherapy (IFAIT). The current recommended duration for AIT,² VIT,³ and IFAIT³ is 3 to 5 years. At least 3 years of SCIT can provide persistent benefits and immunomodulatory effects.² However, many patients fail to achieve this goal and there has been ongoing interest in the factors associated with its adherence.^{4–14} Young age, lack of health insurance, non-White, the female sex, and shots done outside an allergist’s office is recognized as negative predictors of SCIT adherence.^{4,15} Other studies point solely to financial barriers as the major reason for early discontinuation.^{13,14} At our center, all patients are insured by TRICARE (Falls Church, Virginia) by virtue of their association with the military. Under TRICARE, annual premiums for treatment

Address correspondence to: Jun Mendoza, MD, USAF, MC, Allergy/Immunology 10th Medical Group, 4102 Pinion Drive, Colorado Springs, CO 80840.

E-mail: junmendoza24@gmail.com.

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at a military treatment facility (MTF) depend on the type of military association, ranging from \$0 to \$942 annually. Aside from annual premiums, all care and medications at the MTF (including all allergy services) are free of charge including no copayments and no deductibles. The purpose of our study was to evaluate the factors associated with reaching maintenance dosing (MD) for AIT, VIT, and IFAIT, and subsequent adherence at 3 and 5 years of therapy for patients without out-of-pocket expenses.

Methods

This was a combined retrospective and prospective observational electronic medical record review of SCIT from 2005 to 2012 at an MTF in San Antonio, Texas. Before 2008, patients were retrospectively enrolled and followed. From 2008 to 2012, patients were prospectively enrolled and followed. Information was collected regarding the start of therapy, the time to MD, the duration of MD, and the end of therapy. Patients were grouped by demographic and health factors including age, sex, asthma, type of SCIT, and systemic reactions (SRs). Study approval was obtained from the 59th Medical Wing institutional review board. All initial evaluations, extract prescriptions, and allergy injections were done at a single center. Allergen extracts were ordered through the Extract Laboratory Management System online application and prepared at the US Army Centralized Allergen Extract Laboratory.

The risks and benefits regarding treatment were discussed at the time of enrollment. Written consent was obtained on initiating therapy. Allergy injections consisted of a build-up phase (1–2 injections per week) with 37 venom rush buildups, followed by a maintenance phase (1 injection per month). Causes of dose reductions include the event of a previous SR, late injections, or the start of a new allergy extract vial. Dose reductions were generally not done for a history of large local reactions or during peak pollen season for aeroallergen SCIT. Treatment with an antihistamine at least 1 hour before injection was encouraged to reduce the frequency of severe SR and to improve chances of achieving MD.¹⁶ The observation time after each injection was 30 minutes unless extended by the physician because of concern for a delayed SR with injections. The SCIT was not performed in patients with uncontrolled asthma, given that this has been found to increase the risk of fatal reactions.¹⁷ Other relative contraindications that were considered include the use of a β blocker, high-risk comorbid conditions, pregnancy, or young age.

Patients were included in the study if they received SCIT to aeroallergens, flying Hymenoptera venom, or IFA whole-body extract. Patients were excluded from the study when there was no documented start date for therapy, no documented end date for therapy, or when they were only on sublingual immunotherapy. When no doses were recorded for allergy shots, then the patient was determined to have not started therapy. When a patient underwent multiple courses of SCIT for the same indication, then the longest period of therapy with a known start date, MD date, and end date was chosen. In the event in which only the month was documented for the start date, MD date, or end date, then the date was listed as the 15th day of that month. When a patient's AIT prescription was revised to include new allergens, then this was considered to be the start of a new course of therapy. When a delay in injections required a patient to restart at the beginning SCIT dose, then this was considered to be the start of a new course of therapy. Adherence was defined as receiving MD SCIT for at least 3 years. The presence of asthma was defined as recorded peak flows during therapy or documentation of asthma in the medical record. Patients undergoing either VIT or IFAIT were combined into 1 single group called the Hymenoptera immunotherapy (HIT) group.

Table 1
Baseline Characteristics of the Patient Population

No. Pts (N)	897
Child <18 y	147 (16%)
Adult $\geq$ 18 y	750 (84%)
Male sex	421 (47%)
Asthma	270 (30%)
History of SR on SCIT	113 (13%)
Did not initiate SCIT	130 (14%)
Received at least 1 MD	538 (60%)

Abbreviations: MD, maintenance dose; Pts, patients; SCIT, subcutaneous immunotherapy; SR, systemic reaction.

Results

A total of 897 patients undergoing SCIT were included in this study per the inclusion and exclusion criteria above. The baseline characteristics of the patient population are listed in Table 1. Ages ranged from 1 to 74 years old, with a mean age of 34.8 years old. A total of 16% (147/897) were children, 47% (421/897) were of the male sex, 30% (270/897) had asthma, and 13% (113/897) had an SR while on MD SCIT. Of the 897 patients enrolled, 14% (130/897) of patients did not initiate therapy whereas 60% (538/897) received at least 1 MD. There were 34% (307/897) who completed at least 3 or more years of MD SCIT. Furthermore, evaluating the 34% who reached 3 years of MD, 7% completed only 3 years, 8% completed only 4 years, and 19% completed 5 years or more (Fig 1). For those patients achieving MD, the mean total duration was 4.23 years, whereas the mean time for MD was 3.17 years. Only 7% of patients reaching MD underwent rush IT for the HIT group; 84% (751/897) were on AIT and 18% (162/897) were on HIT, with 2% (16/897) of patients on both AIT and HIT.

χ^2 tests and independent *t* tests were performed to evaluate the associations between variables. Significance was set to *P* less than .05. Male patients were 64% more likely to reach MD (*P* = .01). The type of SCIT (AIT vs HIT), the presence of asthma, age (child vs adult), and history of SRs were not significantly associated with reaching MD (Table 2). Of the 113 patients experiencing an SR, 61% (69/113) reached MD, which was not statistically different from the 60% (469/784) of patients who did not experience an SR (*P* < .84). The type of SCIT, presence of asthma, age, history of SRs, or sex was not significantly associated with the duration of SCIT (Table 3). Figure 2 illustrates the overall adherence rates for SCIT.

Discussion

We evaluated factors associated with reaching MD and subsequent adherence with SCIT. A total of 60% of patients reached MD, but only 34% remained adherent to therapy at the 3-year mark. This is not surprising as poor compliance is a common theme among many SCIT studies.^{5–12} However, our study is unique in that it highlights most patients failing to adhere to the recommended duration of SCIT regardless of no out-of-pocket expenses. Despite a typically held view, this would suggest that factors other than cost should be the focus of improved adherence. We did not report any fatalities with therapy or find SR to be significantly associated with reaching MD or with the duration of SCIT.

Our study found male patients to be significantly more likely to reach MD, but the reason for this remains unclear. In a retrospective review of patients on SCIT for the treatment of allergic rhinitis, Lower et al⁴ similarly identified male patients as slightly more adherent than female patients with therapy. Data on such results are controversial. Some studies find men to be more adherent to therapy in general,^{18–21} another study finds men to be less likely to follow their prescriptions,²² and other studies find no sex discrepancy at all.^{23–25} In a postal questionnaire

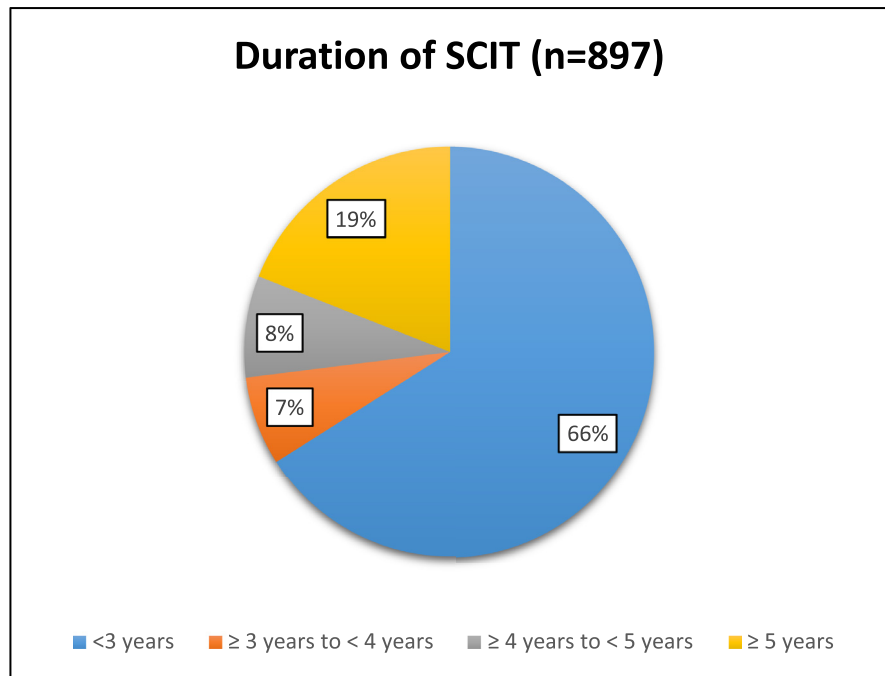


Figure 1. Total number of patients for the duration of SCIT. SCIT, subcutaneous immunotherapy.

Table 2
Characteristics of Patients Who Did and Did Not Reach MD

Characteristics	Reached MD	Did not reach MD	P value
Total no. patients	538/897 (60%)	359/897 (40%)	—
Male sex	271/421 (64%)	150/421 (36%)	.01
Female sex	267/476 (56%)	209/476 (44%)	
AIT ^a	453/751 (60%)	298/751 (40%)	.78
HIT ^a	95/162 (59%)	67/162 (41%)	
Asthma	158/270 (59%)	112/270 (41%)	.44
No Asthma	380/627 (61%)	247/627 (39%)	
Child	84/147 (57%)	63/147 (43%)	.44
Adult	454/750 (61%)	296/750 (39%)	
History of SR	69/113 (61%)	44/113 (39%)	.83
No history of SR	469/784 (63%)	315/784 (40%)	

Abbreviations: AIT, aeroallergen immunotherapy; HIT, Hymenoptera immunotherapy; MD, maintenance dose; No., number; SR, systemic reaction. The bold value is a significant P value less than .05

^aTotal number of patients is 913 as a result of 16 patients receiving both AIT and HIT.

Table 3
Characteristics of Adherent Patients at 3 Years and 5 Years

Duration of SCIT	Only 3 y	≥ 5 y	P value
Total No. patients	63/897 (7%)	173/897 (19%)	—
Male sex	34/421 (8%)	77/421 (18%)	.28
Female sex	29/476 (6%)	96/476 (20%)	
AIT ^a	57/751 (8%)	137/751 (18%)	.19
HIT ^a	6/162 (4%)	36/162 (22%)	
Asthma	19/270 (7%)	49/270 (18%)	.79
No Asthma	44/627 (7%)	124/627 (20%)	
Child	13/147 (9%)	21/147 (14%)	.26
Adult	50/750 (7%)	152/750 (20%)	
History of SR	14/113 (12%)	23/113 (20%)	.99
No history of SR	49/784 (6%)	150/784 (19%)	

Abbreviations: AIT, aeroallergen immunotherapy; HIT, hymenoptera immunotherapy; MD, maintenance dose; No., number; SCIT, subcutaneous immunotherapy; SR, systemic reaction.

^aTotal number of patients is 913 as a result of 16 patients receiving both AIT and HIT.

regarding adherence to prescription drugs, Sundbom et al²⁶ found that the rates of adherence can be similar between sexes but differ in their reasons for behavior. Forgetting to take the medicine, changing the dosage, or recovery from the illness were reasons cited by men for poor adherence to treatment while filling the prescription, but not taking the drug or adverse drug reactions were reasons cited by women.²⁶ Unlike medications, SCIT requires significant time, and for many, significant need to coordinate around work, family, and other responsibilities. In our society, the disproportionate burden of child care and household responsibilities, in addition to paid work, falls on women.²⁷ Although not evaluated in our study, this would be an important area for future studies to explore as a possible explanation for the sex disparity in adherence.

Our study did not find any significant predictors for the duration of SCIT, but many studies continue to look into this area of interest. Inconvenience is a common reason for discontinuing SCIT (ranging from 34.5%⁹ to 45%⁸), but Cohn et al⁸ found that inconvenience may be indirectly related to the underlying disease. In a review of practice records, the authors found that 45% of patients on aeroallergen SCIT discontinued therapy because of inconvenience.⁸ However, a subgroup analysis found that 55% of patients with allergic rhinitis discontinued treatment because of inconvenience, whereas 22% of patients with allergic rhinitis and asthma stopped for this same reason.⁸ Conversely, 25% of patients in the allergic rhinitis and asthma group stopped SCIT because they felt “better with medication,” whereas 0% in the allergic rhinitis group stopped for this same reason.⁸ Asthma is generally perceived as a more consequential illness than rhinitis, making inconvenience less likely a factor. A vast armamentarium of medications is also available for the treatment of asthma, which may lead patients to feel “better with meds.” In our study, however, conditions of greater medical consequence, such as asthma and venom allergy, did not seem to lead to greater adherence.

Limitations of our study were that it was, in part, retrospective and observational, and only looked at demographic factors toward

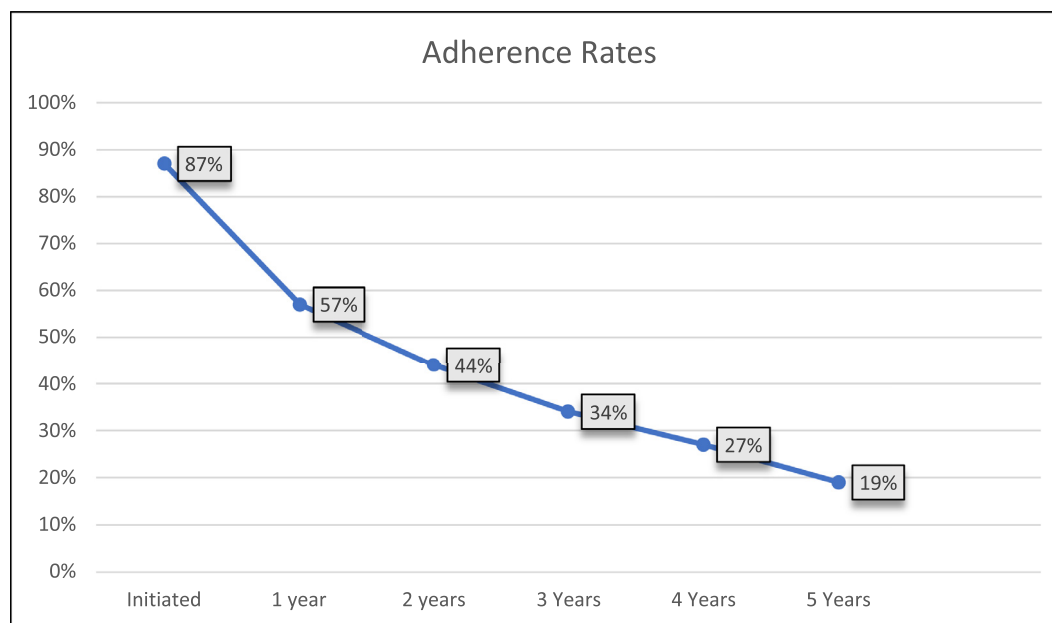


Figure 2. SCIT adherence rates. SCIT, subcutaneous immunotherapy.

reaching MD and subsequent adherence with SCIT. The database that was used did not collect information on whether a patient was military on active duty or civilian, so there may be confounding factors that may not apply to the general population. Our study also included members of a mobile military population who may face challenges to staying in 1 area for at least 3 years to receive SCIT. Some military members are given temporary duty assignments in another city, which can interrupt their continuity of shots, whereas others may be deployed overseas, which can disrupt therapy altogether. Despite our best efforts to put a system into place to continue SCIT at other military bases uninterrupted, this service remains base dependent and is not always available. Although this study was performed at an MTF, the mobility of our patient population is not unique to the military and is likely applicable to our increasingly mobile society in which Americans move an average of 11.7 times in their life, with 9.8% moving in any given year.²⁸ Any patients that left the local area and went to another MTF were assumed to have discontinued therapy as their records were no longer available. It is possible that some of these patients continued SCIT at their new location, which could lead to a falsely elevated level of noncompliance. Finally, we did not survey our patients for reasons or explanations for their adherence, but this would be an important area to pursue in future studies. Strengths of this study include long-term follow-up and continuous data collection from a single center. To our knowledge, this is the largest study investigating patient compliance with SCIT that eliminated direct medical cost as a cofactor and that distinguishes 3- and 5-year outcomes.

Conclusion

The decision of whether to start SCIT is a shared medical decision between the provider and the patient, but the reasons for not adhering to therapy remain a challenge for optimal medical care. We found that male patients were significantly more likely to reach MD, whereas SCIT adherence overall remained low despite no out-of-pocket expenses. Further studies surveying patients to understand the reasons for nonadherence may help to improve the disappointing outcomes of adherence. We hope the factors that we have evaluated will focus on the future approach to improving adherence, such as sex, although deemphasizing factors that may be less relevant such

as cost, age, and co-morbid asthma. Other studies looking into adherence with costly therapies within the military health care system will also allow thoughtful selection of patients and prudent use of government resources.

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