

Allergy Immunotherapy Adherence and Delivery Route: Location Does Not Matter

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Allergic rhinitis (AR) is a chronic illness that imposes considerable clinical and economic burden. Children and adults with poorly controlled AR may experience substantial decrements in their quality of life and are at increased risk to develop allergic asthma, nasal polyps, otitis media, sleep disorders, and upper respiratory tract infections.¹⁻⁴ Allergic rhinitis accounts for 13.4 million office visits,⁵ 3.5 million lost workdays,⁶ and 2 million missed school days each year in the United States.⁶ Patients with allergic rhinitis spend an estimated \$11 billion dollars annually, \$7 billion for prescription and \$4 billion for over-the-counter medications. Whereas symptomatic drug treatment is effective for many patients, it only confers temporary relief. In contrast, allergen immunotherapy (AIT), either subcutaneous allergen immunotherapy (SCIT) or sublingual allergen immunotherapy (SLIT), modifies the course and complications of AR and possibly other allergic diseases. Clinical benefits include a reduction in the number and severity of allergic symptoms and a decreased reliance on the use of symptomatic drug treatments.⁷ Benefits can persist for up to 12 years after 3 to 5 years of AIT,⁷⁻²² and greater treatment duration is associated with longer-lasting clinical benefit.^{12,13,20,23} Patients who receive AIT for AR, compared with those who do not, have a 3- to 6-fold decreased risk of developing asthma.²⁴⁻²⁹ In addition, AIT may decrease the risk of developing new sensitivities to other inhalant allergens in both patients who are monosensitized and those who are polysensitized.^{7,13,29-34} Given the clinical and economic burden of poorly controlled AR and the documented benefits of AIT, it makes considerable sense to identify and treat patients with early in the disease course, to prevent the onset of new allergen

sensitizations, new allergic diseases and their concomitant complications.³⁵ Only a minority (2%-9%) of US patients who would potentially benefit from AIT receive such treatment.³⁶⁻³⁸

SLIT may soon become a commercially available alternative to SCIT in the United States. SCIT allergen vaccines are typically formulated by the physician based on their knowledge of local allergens, the patient's disease, and clinical sensitivity, and are given in a clinical setting with a physician present. In the near future, it is likely that at least 1 form of SLIT will be manufactured in tablet form for direct patient distribution through retail pharmacies for patient at-home administration. Whereas SCIT compliance can be monitored directly through patient clinic visits, SLIT adherence will likely be assessed more indirectly, possibly in a manner similar to other prescription medications (eg, pharmacy database).

Bender and Oppenheimer³⁹ write in this issue of *JACI: In Practice* about the special challenges of nonadherence with SLIT. They draw parallels between allergic diseases and other chronic and burdensome diseases, such as cardiovascular, respiratory, diabetes, and cancer. The similarities are noted between AIT used to treat allergic diseases and interventions used to treat other chronic diseases that require substantial patient commitment for extended time periods. Compelling data are cited in general medicine that demonstrate the relationships among improved adherence and increased clinical benefit, decreased health care utilization, and reduced direct and indirect costs. As additional forms of AIT are approved, discussions of AIT adherence should reflect not only the collective wisdom gleaned from patient adherence to other medications used to treat other diseases, but the specific wisdom gathered from more than a century of SCIT administration. Underlying reasons for poor adherence to AIT, whether by SCIT or SLIT, are well documented and summarized below.

In one of the earliest US studies to examine patterns of SCIT care, investigators contacted 217 patients who prematurely discontinued SCIT (defined as no SCIT-related outpatient visit for at least 6 months within 2 years of SCIT initiation) in a US study published in 1993.⁴⁰ Patients reported the following reasons for noncompliance: inconvenience of visits required for the injection (44%), ineffective treatment (8%), concurrent illness thwarted continuation (10%), satisfactory control of symptoms was sufficiently obtained with medications (7%), and without medications (7%). In another early US study, investigators reviewed 315 patient charts (patient age ranges, 5-18 years) of patients who were initially prescribed SCIT at a single medical center.⁴¹ One-hundred and thirty-eight patients prematurely discontinued SCIT (44%). The most common reasons reported for discontinuation were inconvenience (17) and symptoms unchanged (16) or improved (14).

Bender and Oppenheimer³⁹ in this issue of *JACI: In Practice* indicate that little is known about how to address poor adherence to SLIT. Although true, there is a small body of literature that may provide guidance on how to improve SLIT adherence.

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TABLE I. Rates of AIT discontinuation

Study	Sample	Design	Definition	Rate, %
Natural extract SCIT				
Mabry, ⁴⁴ 1982	25 Children and adults	Retrospective	Prematurely discontinued SCIT	72
Cohn and Pizzi, ⁴⁰ 1993	217 Adults	Retrospective	Did not renew SCIT prescription in past 6 mo and received <3 y of SCIT	50
Donahue et al, ³⁷ 1999	384 Children and adults	Retrospective	Received <61 SCIT injections over 3.5 y	67
Lower et al, ⁴¹ 1993	315 Children	Retrospective	Did not receive SCIT in past 6 mo and completed <2 y of SCIT	44
Tinkelman et al, ⁴⁸ 1995	13,157 Children and adults	Retrospective	Stopped SCIT without approval of allergist before 18 mo	17
Rhodes, ⁴⁵ 1999	1033 Adults	Retrospective	Stopped SCIT without formal approval before completing at least 3 y	12
More and Hagan, ⁴⁶ 2002	381 Children and adults	Retrospective	Did not receive SCIT in the past 3 mo, discontinued SCIT without approval and completed <5 y of SCIT	23
Dam Petersen et al, ⁴⁷ 2005	253 Adolescents and adults	Retrospective	Did not complete 15-wk up-dosing phase	6
Hankin et al, ³⁶ 2008	520 Children	Retrospective	Stopped SCIT before 3 y	84
Maresh et al, ⁵⁰ 2010	50 Children and adults	Retrospective	Received ≥10 doses but <2 y of SCIT	41
Sieber et al, ⁵² 2011	695 Children and adults	Retrospective	Did not renew SCIT prescription over 2 y	66
Hsu and Reisacher, ⁵¹ 2012	139 Children and adults	Retrospective	Stopped SCIT before 3 y	45
Allergoid SCIT				
Pajno et al, ⁴⁹ 2005	1886 Children	Retrospective	Stopped SCIT without authorization of prescribing physician during first 3 y	11
Sieber et al, ⁵² 2011	602 Children and adults	Retrospective	Did not renew SCIT prescription over 2 y	61
SCIT (unspecified type)				
Ruiz et al, ⁵³ 1997	247 Adults	Retrospective	Stopped SCIT before 18 mo	38
Kiel et al, ⁵⁷ 2013	2796 Adults	Retrospective	Stopped SCIT before 3 y	77
SLIT				
Pajno et al, ⁴⁹ 2005	806 Children	Retrospective	Stopped SLIT without authorization of prescribing physician during first 3 y	21
Chang et al, ⁵⁴ 2009	142 Children and adults	Prospective, observational	Stopped receiving SLIT before 6 mo	31
Incorvaia et al, ⁵⁸ 2010	52 Adults	Randomized, parallel-group	Stopped SLIT before 6 mo	14
Senna et al, ⁵⁵ 2010	2 Large SLIT manufacturers	Retrospective	Did not renew SLIT prescription over 3 y	87
Vita et al, ⁶⁰ 2010	300 Children and adults	RCT	Stopped SLIT before 2 y	40
Sieber et al, ⁵² 2011	112 Children and adults	Retrospective	Did not renew SLIT prescription over 2 y	49
Hsu and Reisacher, ⁵¹ 2012	78 Children and adults	Retrospective	Stopped SLIT before 3 y	41
Pajno et al, ⁵⁹ 2012	150 Young children	Prospective, observational	Stopped SLIT before 2 y	46
Trebuchon et al, ⁵⁶ 2012	1289 Children and adults	Retrospective	Stopped SLIT before completing prescribed regimen	27
Kiel et al, ⁵⁷ 2013	3690 Adults	Retrospective	Stopped SLIT before 3 y	93
Any AIT				
Hommers et al, ⁷⁶ 2007	296 Adults	Cross-sectional	Self-reported not completing AIT	65

RCT, Randomized controlled trial.

One important factor is the patient's knowledge of and expectation of the time from initiation to symptom relief and the degree of improvement to be achieved. Studies indicate that patients are ill informed about these issues. For example, an Israeli study of 132 adult and adolescent patients treated with SCIT queried about treatment knowledge and expectations.⁴² Thirty-nine percent of patients expected full recovery, 35% expected some improvement, 16% expected prevention of the development of new allergies, and 10% expected protection against the onset of asthma. Patients' knowledge regarding the duration of AIT was poor: 60% were unaware of optimal treatment duration, 8% expected life-long therapy, 21% expected longer than 1 year of therapy, and 10% expected several years of therapy. Thirty-three percent did not know

about the risk of adverse effects, 35% considered AIT to be entirely safe, 13% considered it to be sometimes associated with adverse reactions, and 19% recognized that AIT can be associated with significant risk. The following data indicate that patients were not knowledgeable about their own allergic problems. Twenty-three percent thought that they were receiving AIT for an allergen unrelated to their disease, and 24% failed to recognize at least 1 allergen, 9% recognized any allergen, and only 3% recognized all allergens involved in their treatment. Patients who initiated treatment within the previous 6 months had a better knowledge of such therapy than those who had been receiving the therapy for a longer period of time. In a survey of 100 patients who received SCIT for AR and/or allergic asthma at a hospital-based allergy clinic in Thailand,

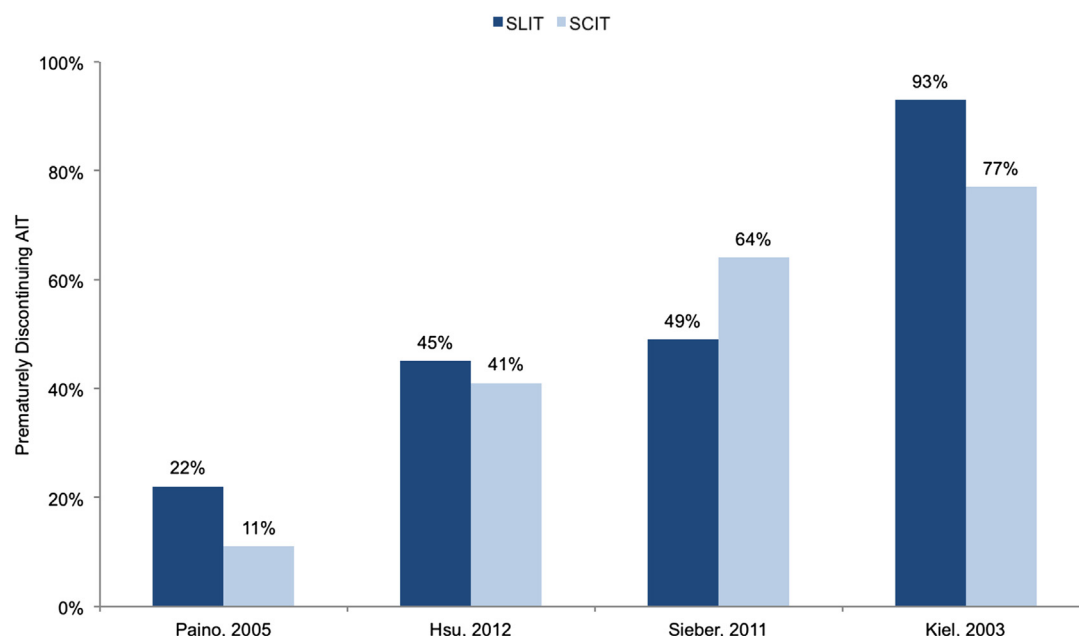


FIGURE 1. Legend SLIT versus SCIT adherence. Pajno 2005: A prospective study of 1992 Italian children who received SCIT ($n = 1186$) or SLIT ($n = 806$) during 1998 to 2003; found a significantly larger proportion of patients who were treated with SLIT and who prematurely discontinued treatment ($P < .0005$). Hsu 2012: Retrospective examination of the medical records of 217 US patients who received SCIT or SLIT during 2007 to 2010. Sieber 2011: Retrospective analysis of grass pollen AIT prescription renewal rates over 2 years. Kiel 2013: Retrospective analysis of pharmacy claims of 6486 Dutch adults who received SCIT ($n = 2796$) or SLIT ($n = 3690$) who completed 3 years of treatment.

42% reported that AIT would not provide symptomatic relief for at least 6 months, 62% were aware that therapy was to be continued for at least 3 years, 60% believed that it could prevent the onset of asthma, 28% expected prevention of new allergies, and 17% believed that it was rarely associated with severe adverse effects.⁴³

SCIT AND SLIT ADHERENCE RATES

Rates of SCIT discontinuation in 15 studies range from 6% to 84% (Table I),^{36,37,40,41,44-53} whereas premature discontinuation of SLIT in 10 studies ranged from 21% to 93% (Table I).^{49,51,52,54-60} Among 3690 Dutch adults who initiated SLIT, only 7% completed 3 years of treatment.⁵⁷ Two SLIT manufacturers found that fewer than 20% of SLIT prescriptions were continued 3 years after initiation.⁵⁵ In a study that examined SLIT prescription renewal rates, only 50% of patients renewed their prescriptions in the 2 subsequent years.⁵² SLIT discontinuation rates in 6 other studies, over at least 2 years, reported discontinuation rates that ranged from 21% to 46%.^{49,51,54,56,59,60}

STUDIES THAT DIRECTLY COMPARED SLIT VERSUS SCIT ADHERENCE

Four studies examined premature discontinuation among patients who received SCIT or SLIT (Figure 1). A study of 1992 Italian children who received SCIT ($n = 1186$) or SLIT ($n = 806$) from 1998 to 2003 found that a significantly larger proportion of patients treated with SLIT prematurely discontinued treatment during the first 3 years compared with patients treated with SCIT (22% vs 11%; $P < .0005$).⁴⁹ A retrospective study of

records of 217 US patients who received SCIT or SLIT during 2007 to 2010 revealed similar rates of discontinuation during the first 3 years (SCIT 45% vs SLIT 41%; $P =$ not significant).⁵¹ A retrospective analysis of grass pollen AIT prescription renewal rates in Germany found that 49% and 64% of patients did not renew their SLIT or SCIT prescription, respectively, over 2 years.⁵² A retrospective analysis of pharmacy claims of 6486 Dutch adults who received SCIT ($n = 2796$) or SLIT ($n = 3690$) found that a significantly greater proportion of patients treated with SLIT versus those treated with SCIT discontinued treatment before 3 years (93% vs 77%; $P < .001$).⁵⁷

ADHERENCE BASED ON THE DURATION OF THE STUDY

Long- and short-term adherence studies are summarized in Tables E1 and E2 (in this article's Online Repository at www.jaci-inpractice.org), respectively. Rates of SLIT adherence (generally defined as taking $\geq 80\%$ of prescribed medication) in 7 studies over 2 or 3 years ranged from 29% to 91%.^{29,34,57,59,61-63} Some studies assessed adherence quantitatively by measuring the amount of SLIT solution or tablets returned during clinical trials. They reported adherence rates of 72% to 91%.^{29,34,59,61,63} The lowest SLIT adherence rate was based on an estimate provided by Italian allergists, who indicated that only 29% of patients would be $\geq 80\%$ adherent to SLIT over 3 years.⁶² Only 38% of patients who received SLIT in another study were determined to be adherent in a retrospective claims analysis as defined by more than 3 months between SLIT prescriptions during treatment.⁵⁷ Other studies that quantitatively measured adherence to SLIT over 1 year or less reported high adherence rates (84%-97%)

(Table E2).⁶⁴⁻⁷² Physicians' estimates patient adherence in another study over 1 pollen season was 88%.⁷³

The most commonly cited reasons for SCIT discontinuation as listed in Table E3 (in this article's Online Repository at www.jaci-inpractice.org) were inconvenience, lack of efficacy, concurrent illness, and cost. Although cost was a barrier to SCIT continuation by only 4% to 6% of patients in 3 studies,^{41,45,46} 4 studies indicated that cost or lack of insurance was the reason for discontinuing such therapy in 30% to 40% of patients.^{49,51,53,74} The reasons for discontinuing or not adhering to SLIT were similar to SCIT (see Table E4 in this article's Online Repository at www.jaci-inpractice.org). However, a greater proportion of patients who received SLIT versus SCIT cited a lack of efficacy as a reason for poor adherence.^{49,51} A 2013 study evaluated the relationship between patient satisfaction with treatment, duration of SLIT, adherence to SLIT, and clinical improvement.⁷⁵ Patients who experienced a longer duration of treatment with SLIT (9-12 months) reported greater improvement in their AR symptoms and were significantly more satisfied with treatment than those who completed shorter treatment (4-6 months). Adherence to SLIT was significantly associated with patient satisfaction ($P < .0001$).

FACTORS THAT INFLUENCE AIT ADHERENCE

Three studies examined the effect of insurance coverage and/or reimbursement on AIT adherence.^{41,52,66} One study found that patients with nonprivate insurance were more likely to discontinue SCIT than those with private insurance⁴¹ and another that nonreimbursement increased the likelihood of discontinuation compared with full reimbursement.⁵² A third found no effect of reimbursement on discontinuation.⁶⁶ Diagnosis was related to SCIT discontinuation in 2 of 5 studies.^{37,46,48,50,76} Donahue et al³⁷ found that patients diagnosed with AR and asthma were more likely to complete AIT than those diagnosed with AR or asthma alone. Two studies found no effect of disease severity on SLIT adherence,^{63,66} and more frequent monitoring visits were associated with greater SLIT adherence.⁶⁰

CONCLUSION

AIT adherence is equally poor regardless of whether or not treatment is administered in a medically supervised setting (SCIT) or at home (SLIT) and comparable to poor adherence with long-term pharmacotherapy. Inconvenience, related to patient time and travel, is the most frequently cited reason for SCIT discontinuation. A common perception is that SLIT, a home-based treatment, which does not require clinic visits, would overcome this barrier and increase adherence. However, studies as cited in this editorial, suggest that SLIT adherence is equally poor to SCIT. Additional investigations are needed to better understand reasons for nonadherence for both SCIT and SLIT to institute interventions to increase adherence.

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TABLE E1. Rates of slit adherence: long-term studies

Study	Population	Design	Definition	Rate, %
Marogna et al, ^{E1} 2004	319 Adolescents and adults	RCT	>80% Adherent (percentage of expected consumption) over 3 y	72
Marogna et al, ^{E2} 2008	216 Children	RCT	≥80% Adherent (percentage of expected consumption) over 3 y	74
Roder et al, ^{E3} 2008	153 Children	RCT	≥80% Adherent (as measured by amount of medication returned) over 2 y	77
Ott et al, ^{E4} 2009	213 Children and adults	RCT	Percentage of used returned vials over 3 pollen seasons	91
Scurati et al, ^{E5} 2010	296 Allergists	Cross-sectional	Physician estimated % patients with ≥80% adherence over 3 y	29
Pajno et al, ^{E6} 2012	150 Children	Prospective, observational	Percentage of used returned SLIT among patients who completed 2 y of SLIT	>80
Kiel et al, ^{E7} 2013	3690 Adults	Retrospective	Among patients who completed at least 3 y of SLIT, Percentage with ≥1 gap between SLIT prescriptions of ≥3 mo	38

RCT, Randomized controlled trial.

TABLE E2. Rates of slit adherence: short-term studies

Study	Sample	Design	Definition	Rate, %
Lombardi et al, ^{E8} 2004	86 Adolescents and adults	Prospective, observational	Percentage of expected consumed tablets during 1 y (HDM allergy) or at the beginning (18 wk) of pollen season	97
Jansen et al, ^{E9} 2009	91 Adults	RCT	Percentage of expected consumed tablets during 1 pollen season	95
Durham et al, ^{E10} 2006	855 Adults	RCT	Percentage of expected tablets consumed (measured the patient-recorded tablet intake by using electronic diaries) during a mean of 18 wk of treatment	94-98
Passalacqua et al, ^{E11} 2006	443 Adolescents and adults	Prospective, observational	≥75% of expected consumed tablets at 6 mo	89
Passalacqua et al, ^{E12} 2007	71 Children	Prospective, observational	≥75% of expected consumed tablets at 6 mo	85
Cadario et al, ^{E13} 2008	34 Children and adults	RCT	100% adherent (as measured by volume of returned vials) over 1 y	67
Bufe et al, ^{E14} 2009	253 Children	RCT	Mean adherence (based on IMP accountability records) during preseasonal (17 wk) and seasonal (4 wk) SLIT	93
Shaikh et al, ^{E15} 2009	50 Adolescents and adults	Prospective, observational	Average adherence (patient diary card) over 1 y	84
Wahn et al, ^{E16} 2009	131 Children	RCT	≥80% adherent during 5 mo	94
Halken et al, ^{E17} 2010	278 Children and adolescents	RCT	≥80% adherent during 1 pollen season	94
Migueres et al, ^{E18} 2011	536 Children and adults	Prospective, observational	Percentage that physicians estimate as having "good" adherence while taking SLIT during 1 pollen season	88

RCT, Randomized controlled trial; HDM, house dust mite; IMP, investigational medicinal product.

TABLE E3. Patient-reported reasons for discontinuing SCIT

Reason	% Respondents, reference nos.
Inconvenience	11-66 ^{E19-E26}
Concurrent illness	8-22 ^{E19,E21,E22,E25,E26}
Not effective	2-13 ^{E20-E27}
Symptoms improved	6-41 ^{E20,E22,E27}
Changed residence or clinic	7-19 ^{E20-E22,E26,E27}
Adverse reaction	6-11 ^{E21,E25}
Systemic reaction	1-16 ^{E20-E22}
Local reaction	4 ^{E20}
Cost or lack of insurance	4-40 ^{E20-E22,E24-E27}

TABLE E4. Patient-reported reasons for SLIT discontinuation and/or nonadherence

Reason	% Respondents, reference nos.
Inability to take medication according to schedule and/or forgetting and/or noncompliance	27-32 ^{E8,E28,E29}
Time consuming and/or inconvenient	7-18 ^{E6,E24,E28}
Not effective	5-50 ^{E6,E24,E25,E28,E29}
Concurrent illness and/or medical condition	6-64 ^{E8,E11,E28}
Adverse effects	8-33 ^{E6,E11,E12,E25,E28,E29}
Cost	6-80 ^{E11,E12,E24,E25,E28}

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