



Patient adherence to allergy immunotherapy

William R. Reisacher and Jiovani M. Visaya

Purpose of review

This article reviews the literature on patient adherence to two different approaches to allergen-specific immunotherapy for allergic disease. Factors related to adherence in general, as well as the various methods used to measure adherence, will be discussed.

Recent findings

Although a complex interaction of factors related to both the physician and the patient influence the adherence to a particular therapeutic regimen, effective communication between these two parties and the simplicity of the regimen are frequently noted to be of primary importance. Variability with respect to the definition of adherence, the method of measuring adherence, and the length of the measuring period has resulted in a wide range of adherence rates to allergy immunotherapy reported in the literature. Patients most often cite inconvenience, side-effects, and poor efficacy as reasons for discontinuing allergy immunotherapy.

Summary

Adherence to therapy not only improves individual patient outcomes, but also helps determine the best treatment modalities and reduces the burden of disease on society. As new methods of delivering immunotherapy are being developed, such as allergy immunotherapy tablets and oral mucosal immunotherapy, the factors associated with patient adherence should be carefully considered.

Keywords

adherence, allergic rhinitis, SCIT, SLIT

INTRODUCTION

Over 2000 years ago, Hippocrates described how important it is for patients to adhere to their prescribed therapy, and very few people today would disagree with that statement. Patient adherence is closely tied with the success of therapy, the ability to conduct accurate outcomes research, and ultimately a better understanding of which therapies should be recommended. For example, a 50% reduction in adherence in a randomized controlled trial (RCT) would increase the required sample size by a factor of five in order to maintain the power of that study [1]. Also, if nonadherent patients are removed from clinical studies, this may skew the study population away from those with certain predisposing characteristics that may be related to the disease being studied [2].

It has been estimated that adherence is approximately 50% over time in patients with chronic diseases [3]. Poor adherence can subsequently lead to unnecessary suffering, hospitalization, decreased quality of life and increased costs to both the individual as well as society [4]. Clearly, the factors related to patient adherence are extremely complex, involving the patient, the physician, the treatment

itself and even the relationship between the physician, patient and pharmacist. The word 'compliance' is often used to describe this topic, but because of its less authoritarian connotation, adherence will be used in this article. Adherence is essentially defined as, 'the extent to which the patient's behavior matches the agreed recommendations from the prescriber(s)' [5]. It involves not only acceptance and understanding of the therapy recommended, but also the observance of treatment intake over the recommended period of time [6].

Allergen-specific immunotherapy has been used to treat allergic rhinitis and atopic asthma for the past 100 years. It has been found to produce long-term symptomatic relief even after the cessation of therapy and reduces the need for medications [7]. It also has been shown to reduce the risk of developing

Correspondence to William R. Reisacher, MD, FACS, FAAOA, Associate Professor of Otolaryngology – Head and Neck Surgery, New York-Presbyterian Hospital, Weill Cornell Medical College, 1305 York Avenue, 5th Floor, New York, NY 10021, USA. Tel: +1 646 962 2093; fax: +1 646 962 0100; e-mail: wir2011@med.cornell.edu

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KEY POINTS

- Factors related to adherence may be related to the patient, the care provider, and the treatment itself.
- Adherence for the treatment of chronic disease is estimated to be about 50%.
- For antigen-specific immunotherapy, adherence to the treatment is one of the most important factors related to efficacy.
- Poor adherence to immunotherapy for allergic disease is often attributed to side-effects, convenience, and the perception of efficacy.

asthma and new sensitizations [8]. However, successful therapy relies heavily on the consistent administration of allergy extract. Subcutaneous immunotherapy (SCIT) is given weekly to monthly in the physician's office, whereas sublingual immunotherapy (SLIT) is taken daily by the patient at home. Adding to this challenge, the patient may not see clear improvements for the first 6 months of therapy. Moreover, patients are typically offered immunotherapy only after they have failed environmental control strategies, which also require good adherence skills. Therefore, a thorough understanding of the factors related to patient adherence is of particular importance to physicians who recommend immunotherapy to their allergic patients.

FACTORS RELATED TO PATIENT ADHERENCE

Many strategies have been attempted through the years to maximize adherence, including patient handouts, follow-up phone calls, colorful labeling, pill reminder boxes and encouragement by the pharmacist at the prescription counter, but results have been inconsistent [9]. Behavioral models, such as the Health Belief Model (HBM) and Health Decision Model (HDM), have been built with the goal of improving adherence to medical therapy. The Beliefs about Medicine questionnaire (BMQ) is based on these models, assessing both qualitative and quantitative aspects of patient adherence, and it has been found that both specific as well as general beliefs have an effect on adherence [10]. Poor adherence to therapy can be defined in different ways, such as suboptimal (taking a lower dose than recommended), therapeutic gaps (inconsistent application of the therapy over time), nonpersistence (stopping therapy prematurely), and primary poor adherence (never starting the therapy) [6[•]]. Common methods used to measure patient adherence include pill

counting, medical and pharmacy records, self-reporting, electronic monitoring, health behavior testing, and appointment keeping [11].

Factors such as socioeconomic status, age, sex, race, and education level are believed to influence patient adherence, but they have not been demonstrated with any consistency to be independent predictors of it [5]. Certainly, the patient's attitudes and perceptions about the disease, along with the beliefs and expectations concerning the likelihood of success and fear of side-effects, play a role as well [1]. It has been found the adherence is higher if the patient is paying for the treatment [11]. Complex therapeutic regimens, including multiple medications, long duration, and frequent dosing, are commonly associated with poor adherence, but the occurrence of side-effects is reported as the reason for nonadherence in less than 10% of cases [12,13].

However, although research has helped identify which factors are associated with adherence to therapy, there is less information available on what patients actually want. In a pharmacoepidemiologic study of over 3000 patients with seasonal allergic rhinitis, 75% preferred oral treatments, whereas only 13% preferred local topical therapy [14]. In another study of 110 ambulatory care patients on long-term medications, the majority of patients preferred taking oral medication in the morning or evening instead of noon, independent of meals ($P < 0.001$) [15^{••}]. For some patients, having to take a medication makes them feel 'sick' and they may choose to suffer the physical consequences of poor adherence rather than suffer the mental anguish of feeling like a person with illness. This is particularly important for the allergy patient, who is often young and does not have any other experience with chronic illness and long-term medication use. A treatment method geared toward this concept is oral mucosal immunotherapy (OMIT) using an allergy-extract-infused toothpaste designed to maximize the adherence by combining immunotherapy with the daily ritual of tooth brushing (AllerDent, Allovate, New York, New York, USA).

Studies have repeatedly demonstrated that effective communication between the patient and physician is associated with better adherence [16,17]. It has been suggested that five factors should be present to optimize patient adherence after consultation with the physician: willingness to share power, open discussion of the options, sharing of information, listening as much as talking, and devoting an adequate amount of time during the encounter [18]. Cushing and Metcalfe [19] determined that patients can only recall about 60% of what they are told and they are more likely to

remember the first thing they are told. Cultural and ethnic differences between the physician and the patient have a significant impact on adherence to therapy, and this is becoming more important as the world is globalizing [4,20]. For example, it would be very important to understand the meaning of certain foods to a patient's culture or religion before making dietary recommendations for diabetes management.

In spite of good-faith communication efforts by prescribers, patients may nonetheless begin therapy with limited knowledge about their treatment. Sade *et al.* [21] used a questionnaire to evaluate patient understanding of the goals and effects of immunotherapy in an Israeli population. Most patients understood that symptomatic improvement would require several months, but some patients (18%) expected improvement in days to weeks, and other patients (20%) did not know how long to expect improvement. Only 19% reported knowing that immunotherapy can potentially cause severe reactions and 21% expected to complete their course of immunotherapy within 1 year of initiation. Only 3.3% of patients were able to correctly list the allergens for which they were receiving immunotherapy. These findings highlight the challenges that remain for improving patient education and communication in the setting of allergy immunotherapy.

LITERATURE REVIEW

The literature search for this review was conducted using PUBMED as the main source. Search terms that were used included 'adherence', 'compliance', 'immunotherapy', 'allergic rhinitis', and 'asthma'. Studies from the last 10 years were divided among general articles on adherence, articles specific to SCIT, and articles specific to SLIT. A second search was then performed based on the relevant references noted in the first set of publications. Studies which specifically listed adherence as the endpoint for SCIT are summarized in Table 1 [22–32,33*,34], whereas those for SLIT are summarized in Table 2 [29,33*,35–47].

SUBCUTANEOUS IMMUNOTHERAPY

Adherence to SCIT is typically reported as the percentage of patients who maintain an immunotherapy regimen over a defined period of time. Published adherence rates vary widely, ranging from a low of 13% [26] to a high of 89% [24,29]. Comparing the adherence rates between studies can often be misleading because definitions of adherence have not been standardized. Whereas many studies

calculate adherence over a 3–4 year period corresponding to a complete course of immunotherapy [27,30,31,33*], other studies utilize follow-up periods as short as 1 year [25,34]. Additional studies employ a cross-sectional analysis and define patients who have not received SCIT within several months as nonadherent [22–24,28,32]. Perhaps the most specific definition of adherence is utilized by Donahue *et al.* [26], who define a complete course of immunotherapy as 20 or more injections during the first 6 months of therapy, 30 or more injections over the first year, 31 injections over the next 2.5 years, and a minimum total of 61 injections over a 3.5-year period.

Many studies cite inconvenience as the primary reason for discontinuing SCIT [22,23,27–29,33*]. Other common reasons include unaffordable cost [25,29], adverse systemic reactions [27,28], and medical comorbidities [27,28]. Some patients withdraw from SCIT because their symptoms resolve prior to completion of a full course [22,23,25], whereas other patients discontinue immunotherapy because of perceived ineffectiveness [23,29]. Several characteristics may help identify patients at risk for withdrawing from therapy, including a history of medical noncompliance, psychological problems, and negative perception of immunotherapy [27,32].

Demographic factors have been shown to influence SCIT adherence. Lower *et al.* [23] identified male sex as a positive predictor of adherence in children, whereas Rhodes [27] found that men aged 16–25 were more likely to withdraw from their study. Older age has occasionally been associated with improved adherence [27,28]. Hispanic patients in one study were 1.5 times more likely to discontinue SCIT therapy [31], whereas Caucasian children demonstrated statistically higher adherence rates [23]. Patients with government-assisted health insurance in one study exhibited higher attrition rates than privately insured patients [23].

Several studies have drawn relationships between the adherence rates and the underlying allergic disease. Donahue *et al.* [26] found that patients with concurrent allergic rhinitis and allergic asthma were more likely to complete therapy than those with either of these conditions alone; ragweed allergy sufferers also exhibited improved adherence rates. In one population of German women, underlying allergic rhinitis, neurodermatitis, and food sensitization were all positively correlated with adherence [31]. In contrast, a study from India demonstrated that allergic rhinitis was an independent predictor of nonadherence [32].

The context in which immunotherapy is delivered can also affect adherence. Tinkelman *et al.* [24]

Table 1. Clinical studies examining adherence to SCIT protocols

Study	Adherence rate	Factors contributing to adherence	Principal reasons for discontinuation
Cohn and Pizzi, 1993 [22]	Allergic rhinitis: 50%	–	Inconvenience
	Allergic rhinitis and asthma: 52%		Improving symptoms
Lower <i>et al.</i> , 1995 [23]	59%	Male sex	Inconvenience
		Caucasian race	Symptoms not improved
		Private insurance	Symptoms improved
Tinkelman <i>et al.</i> , 1995 [24]	Patients receiving IT in allergy clinic: 89.23%	Administration of immunotherapy in allergist's office (as opposed to outside physician's office)	–
	Patients receiving IT in outside physician offices: 65.18%		–
Ruiz <i>et al.</i> , 1997 [25]	62%	–	Symptomatic improvement
			High cost
Donahue <i>et al.</i> , 1999 [26]	Rhinitis and asthma: 43%	Persons with both rhinitis and asthma	–
	Rhinitis alone: 28%	Ragweed allergy	–
	Asthma alone: 13%	Documented allergen	–
Rhodes, 1999 [27]	88%	–	Medical problems (psychological, pregnancy)
			Noncompliance
			Change in residence
			Inconvenience
More and Hagan, 2002 [28]	77.4%	Older age	Adverse systemic reaction
		Non active-duty military members	Inconvenience
		Conventional schedule (as opposed to rush schedule)	Precluding medical condition
Pajno <i>et al.</i> , 2005 [29]	89.1%	–	Adverse systemic reaction
			Expense
			Time consuming
			Family problems
Hommers <i>et al.</i> , 2006 [30]	65%	In women only:	Ineffectiveness
		Rhinitis	–
		Neurodermatitis	–
		Food sensitization	–
Hankin <i>et al.</i> , 2008 [31]	84% Completed less than 3 years	Non-Hispanic	–
	53% Completed less than 1 year		–
Mahesh <i>et al.</i> , 2010 [32]	58.6%	No family history of allergies	–
		No allergic conjunctivitis	–
		Positive perception of immunotherapy	–
		Decrease in medicine requirement	–
		Missing no more than 2 of last 10 doses	–
Hsu and Reisacher, 2012 [33 ^a]	55%	–	Inconvenience
Kuang <i>et al.</i> , 2012 [34]	73.6%	–	–

SCIT, subcutaneous immunotherapy.

found that SCIT adherence was significantly higher in patients who received their injections at their allergist's office (89.23%), compared to those who received immunotherapy at an outside physician's

office (65.18%). In another study from a military medical center, active duty members were more likely to deviate from a course of immunotherapy than retirees or family members [28].

Table 2. Clinical studies examining adherence to SLIT protocols

Study	Adherence rate	Factors contributing to adherence	Principal reasons for discontinuation or missed doses
Marogna <i>et al.</i> , 2004 [35]	85% of patients completed 3-year SLIT course	–	Worsening of symptoms
	72% of patients took more than 80% of prescribed immunotherapy drops		Adverse local effects
	18% of patients took 60–80% of prescribed immunotherapy drops		
Lombardi <i>et al.</i> , 2004 [36]	Pollen allergy: 96.8%	–	Concurrent illness
	Dust mite allergy: 97.6%		Negligence
			Side-effects
Pajno <i>et al.</i> , 2005 [29]	78.5% Completed 3-year SLIT course	–	Expense
			Ineffectiveness
			Time-consuming
			Family problems
Passalacqua <i>et al.</i> , 2006 [37]	75% of patients took more than 90% of prescribed doses	–	Unrelated side-effects (halitosis, panic attacks, and acne)
Passalacqua <i>et al.</i> , 2007 [38]	69% of patients took more than 90% of prescribed doses at 3 months	–	Unaffordable cost
	66% of patients took more than 90% of prescribed doses at 6 months		
Cadario <i>et al.</i> , 2008 [39]	Continuous dosing: 65% completed 1-year course without missing doses	–	–
	Intermittent dosing: 70% completed 1-year course without missing doses		
Roder <i>et al.</i> , 2008 [40]	75% of patients completed 2-year study	Younger age	Local side-effects
	77% of patients completing the study took more than 80% of prescribed doses	Symptomatic improvement with immunotherapy	Inability to take study medication according to schedule
		Able to understand medication administration instructions	
		Lower severity of symptoms prior to initiation of immunotherapy	
Shaikh and Shaikh, 2009 [41]	84.19%	Female sex	–
		Younger age group	
Chang <i>et al.</i> , 2009 [42]	69% Continued SLIT regimen for 1 year	–	Inability to take medication according to schedule
			Ineffectiveness
			Inconvenience
			Adverse effects
Jansen <i>et al.</i> , 2009 [43]	95%	Use of electronic compliance device	–
Ott <i>et al.</i> , 2009 [44]	91%	–	–
Vita <i>et al.</i> , 2010 [45]	4 Yearly visits: 76% continued IT for 2 years	Monitoring visits with immunotherapy prescriber 4 times yearly	–
	2 Yearly visits: 68% continued IT for 2 years		
	1 Yearly visit: 30% continued IT for 2 years		
Migueres <i>et al.</i> , 2011 [46]	88.2% of patients rated as having 'good' compliance by their physicians	–	–
Hsu and Reisacher, 2012 [33*]	59% of patients continued SLIT through 4-year study period	–	Efficacy concerns
			High cost

Table 2 (Continued)

Study	Adherence rate	Factors contributing to adherence	Principal reasons for discontinuation or missed doses
Pajno <i>et al.</i> , 2012 [47]	54% of patients continued SLIT for 2-year study period	–	Unpleasant taste
	80% of patients took more than 80% of prescribed doses		Local side-effects
			Family problems
			Time constraints
			Ineffectiveness

IT, immunotherapy; SLIT, sublingual immunotherapy.

SUBLINGUAL IMMUNOTHERAPY

Because SLIT is typically self-administered by the patient, nonadherence can represent a variety of scenarios ranging from inconsistent daily administration of extract to complete withdrawal from the immunotherapy protocol. For studies that define adherence as maintenance of an immunotherapy regimen over a specific period of time, published adherence rates vary between 30% over 2 years [45] and 85% over 3 years [35]. Sales data provided by two large Italian SLIT manufacturers suggest that real-world adherence may be even lower than described in published trials, with fewer than 50% of patients renewing their prescriptions after 1 year and nearly 90% discontinuing treatment by the third year [48].

Lombardi *et al.* [36] pioneered a novel method for assessing adherence, wherein patients are contacted unannounced via telephone and asked to count the number of tablets remaining in their medication container. Adherence is then reported as the percentage of expected doses that were actually administered. On the basis of this method, 72–80% of patients administer at least 80% of their prescribed immunotherapy doses [35,40,47], whereas 66–75% of patients administer at least 90% of their prescribed doses [37,38]. When all patients are averaged, SLIT adherence typically measures greater than 90% [36,43,44].

Local side-effects from SLIT (particularly oral cavity itching and swelling) were cited in multiple studies as common reasons for missed doses or discontinuation of therapy [35,36,40,42,47]. Other reasons included perceived ineffectiveness [29,33[■], 35,42,47], difficulty following dosing instructions [36,40,42], unaffordable cost [29,33[■],38], inconvenience [29,42,47], medical comorbidities [36,37], family problems [29,47], and unpleasant taste [47].

Only a handful of studies have identified independent predictors of SLIT adherence. Roder *et al.* [40] found that attrition was associated with older age in children, subjective lack of improvement, and

difficulty understanding medication instructions; patients with more severe symptoms prior to initiating immunotherapy also demonstrated poorer adherence. One study from India reported that female sex and younger age were positively associated with SLIT adherence in an adult population [41]. In another study, Vita *et al.* [45] found that the children who attended four allergy follow-up appointments each year exhibited higher adherence (76%) than those who only received two yearly visits (68% adherence) or one yearly visit (30% adherence).

Scurati *et al.* questioned 325 Italian allergists on their observations regarding immunotherapy adherence [49,50]. Most allergists listed the patient's perception of clinical efficacy as the most important factor influencing adherence. Other factors highlighted by the respondents included lack of side-effects and cost reimbursement by the National Health Service. Most allergists cited telephone calls as the most useful tool for improving patient adherence, followed by frequent follow-up visits.

CONCLUSION

Adherence to allergy immunotherapy remains a complex interplay of patient-related factors, physician-related factors, and treatment-related factors. Effective communication between the patient and physician, along with consideration for the patient's beliefs, abilities, and preferences, are of primary importance for maintaining proper adherence and maximizing efficacy for this treatment. As methods for delivering allergy immunotherapy continue to evolve, further research focused on identifying patient and physician factors which may improve adherence to allergy immunotherapy will become even more important.

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Conflicts of interest

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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 295).

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