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REVIEW

Ways to increase adherence to allergen immunotherapy

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ABSTRACT

Adherence to allergen immunotherapy (AIT) is crucial for its efficacy. Subcutaneous AIT requires monthly visits (or more extended in the case of venom immunotherapy), while sublingual AIT is performed with a daily intake of allergen drops. Non-adherence to an AIT schedule and premature discontinuation are common problems. Various studies have shown controversial results on the rate of AIT adherence. The aim of this review is to describe the problem of non-adherence and to offer some evidence-based advice to allergologists on how to increase it. Better patient education at the beginning of treatment, sharing with patients the decision on which type of immunotherapy to select and showing sincere interest in their treatment concerns are some tips that can help to increase adherence. A well organized allergologist time schedule not only increases safety but also offers the possibility of close follow-up and an increase in patient loyalty.

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Introduction

Allergen immunotherapy (AIT) is an effective treatment for respiratory allergy and venom hypersensitivity and the only causal treatment for these allergies^{1,2}. AIT for desensitization to airborne allergens can be performed via the subcutaneous (SCIT) or sublingual (SLIT) route, while Hymenoptera venom immunotherapy (VIT) is subcutaneous. Amelioration of respiratory symptoms, desensitization to the relative allergens, prevention of the onset of new sensitizations (applies to airborne allergens) and sustained effect that may persist for years after discontinuation are some of AIT's benefits^{1–3}.

Following the predetermined visits for allergy shots or the regular intake of scheduled SLIT doses for an extended time (at least 3 years for AIT to airborne allergens and 5 years for VIT) is mandatory in order to lead to the desired therapeutic outcomes⁴. Non-adherence to the time schedule and duration of AIT leads to significantly reduced efficacy of the therapy^{1,2,4}. Patients' adherence can highly influence the efficacy of AIT, as it does in the cases of any pharmacotherapies. Non-compliance is a common problem in medicine, often preventing the healing of a disease, increasing emergency hospitalizations and consuming public health resources^{5–8}.

The terms "compliance" and "adherence" are often mistakenly used as synonymous. The World Health Organization (WHO) adopted the definition of "adherence" as "the extent to which a person's behavior, such as taking medication, following a diet or executing lifestyle changes, corresponds with agreed recommendations from a health care provider"⁶ and is differentiated from the older term of "compliance" that presumes a more passive role of patients in their treatment plans. Concordance is a term focusing on the

patient–physician relationship and the degree to which a treatment represents a common decision⁸.

As reported by WHO, it has been shown that non-adherence to the treatment of chronic diseases is greater than for acute diseases while it becomes very high for preventive interventions⁶. Adherence to antihypertensives ranges 26–51%, adherence to antidepressant therapies 40–70%, while the relative one to antiretroviral agents for HIV infection is 37–83%⁶. Non-adherence to antiasthmatic therapy is 30–70% and is considered a major reason for poor asthma control^{6,9–12}.

AIT aims to offer a safe and efficacious treatment to cure allergy, but patients' adherence to the treatment is a factor that guarantees efficacy and safety. Like other specialists, allergologists are trying to find methods to increase patients' adherence and to prevent premature discontinuation of the treatment. The objective of this article is to describe the magnitude of the problem of non-adherence to AIT, to evaluate the current evidence regarding ways to improve it and to offer practical tips to physicians that perform immunotherapy.

The magnitude of the problem

A number of studies have attempted to accurately assess the magnitude of non-adherence to AIT, with contradictory results^{13–22}. Different methodologies have been used to assess adherence in these studies, which might be the main reason for the different results. A reason for heterogeneous results is that different routes of AIT require different approaches. Adherence to SCIT can be registered with more

accuracy than to SLIT; SCIT visits can be registered by the allergologist who performs it, while adherence to SLIT – that is based on patients' thoroughness – requires an appropriate methodology in order to assess it.

Since adherence to SLIT cannot be assessed with a direct method, such as measuring the concentration of the AIT's allergen in blood or urine, other indirect methods are used instead. These are based on information provided by the patients or by counting leftover doses. This information can be registered with a number of methods: with the use of diary cards or computer self-reports, by calculating the reorder interval for subscriptions, with structured questionnaires during visits or by phone calls¹³. However, these entries are highly dependent on the integrity and accuracy of patient input (or that of their caregivers)¹⁴.

Furthermore, there is data on AIT adherence from real-life studies and from clinical trials. Although most real-life studies show low adherence to AIT, clinical trials report unrealistically high adherence rates¹⁴. A hypothesis explaining this contradiction is a significant bias existing in clinical trials; patients are aware that adherence is the trial's aim, or are affected by the white-coat effect¹³. The "white-coat effect" of adherence during clinical trials is the regular intake of medications when a scheduled visit of the trial approaches in the calendar, causing a temporary "pseudo-adherence" that the patient reports as proper adherence¹⁵. The EASY project in Italy was a real-life study on children assessing non-adherence with the use of phone calls and registration of the remaining vials of monodose SLITOne¹⁶. Some studies have assessed adherence by measuring the remaining volume of extract in the returned medication vials and comparing them to the expected consumed amount either by pipette measurement or weighing^{17,18}. Refill data over a year or more can also provide useful information on adherence¹⁴.

Long-term studies on SLIT have reported a wide range of adherence (29–91%)¹⁹. Most of these studies do not distinguish the irregular intake of SLIT doses, that represents the actual non-adherence, from the discontinuation of SLIT that does not fall under the definition of adherence. Discontinuation is much easier to accurately assess than adherence in terms of regular uptake of SLIT. However, the range of discontinuation in the various studies has also been reported to be very wide; 6–84% for subcutaneous and 14–93% for sublingual¹⁹, which suggests that those studies that do not distinguish between irregularities in medication intake and discontinuation may have produced less reliable data. Different methodologies used in different studies can explain such a high range.

There have also been studies that directly compared the discontinuation of SCIT against the discontinuation of SLIT, all of them agreeing that patients tend to have a higher risk of discontinuing SLIT than SCIT^{20–22}. A wide range of discontinuation rates has also been reported in these studies. Nevertheless, most studies do not agree on the range of discontinuation risk of AIT; the discrepancy could be explained by the different methodologies used.

Reasons for reduced adherence and discontinuation of allergen immunotherapy

PASTE is a recent European study on adherence to AIT which took place in eight countries, lasted three years and required the regular online registration of data by allergologists, every four months²³. The preliminary results have reported excellent adherence (not missing any dose) for 88% of the patients that completed the study, while the discontinuation rates were 16% and 20.6% for SLIT and SCIT respectively²⁴. The main reasons for non-adherence included acute illness and forgetfulness, while discontinuation was reported to be mainly due to costs and various time/work commitments²⁴. Results showing adherence and discontinuation rates in the various countries that participated remain to be published.

The main reasons for discontinuing SCIT have been reported to be inconvenience (injections, many visits), financial reasons, patient perception of lack of symptom improvement and concurrent illness¹⁹. It appears that local adverse and systemic reactions are not the main reasons for discontinuation (6–11% and 1–16% respectively)¹⁹. On the other hand the main reasons for non-adherence and discontinuation of SLIT are the difficulties in adhering to its intake (forgetfulness, daily schedule), perceived poor efficacy, but also cost, adverse effects, concurrent illness and the time it requires^{19,25–29}. Other parameters connected with non-adherence to AIT include lower socioeconomic status, minority races, insurance coverage and moving residence^{14,19,28}.

The aforementioned data that has been reviewed by Cox et al. appears similar for both routes of AIT¹⁹. With respect to adverse reactions, they usually appear during the first visits and are certainly more frequent with SCIT than with SLIT. The fact that they appear to affect non-adherence and discontinuation of SLIT more than SCIT is controversial but might be due to patients' expectations; they are more aware of possible reactions due to SCIT and consent to remain in the doctor's office for a short time interval after the shot²⁹. On the other hand many patients under SLIT might not expect reactions so they are affected even though these are of much less severity and easier to treat¹⁹.

A retrospective study on AIT prescriptions, backtracking sales data for five years, has analyzed the discontinuation data from 86,000 patients³⁰. The comparison of perennial to preseasonal hypoallergenic pollen SCIT was useful, showing that discontinuation of preseasonal SCIT was much higher than for perennial (73% vs. 40% during the third year of AIT). It is also worth mentioning that they registered a high rate for SLIT discontinuation: 47% during the first, 74% during the second and 84% during the third year. Patients' age appeared to influence compliance, with adults showing the lowest compliance rates and children (5–11 years) being more compliant³⁰. This contrasts with another study that connected ages 16–25 to the highest levels of discontinuation while ages older than 40 were very compliant to AIT²⁸.

How can we improve adherence?

It often appears that patients' expectations do not coincide with those of doctors, e.g. allergologists expect a gradual decrease of symptom and medication scores while many patients anticipate immediate effects^{26,31}. Education and proper information on immunotherapy for candidate AIT patients is a tip that allergologists can follow to reduce discontinuation due to reactions, inconvenience issues or disappointment in efficacy³².

With the diagnosis of allergy patients should be informed about the various treatment approaches (allergen avoidance, pharmacotherapy and AIT) that can be combined to cure them. Both AIT route options (SCIT and SLIT) for the treatment of respiratory allergy should also be mentioned, if available in the patient's country. Well informed patients, that consent to follow a long-lasting treatment which offers slow symptom improvement and has the risk of potential reactions, are less likely to discontinue it³³.

An educational session is highly recommended during the administration of the first dose and is crucial especially for patients that will follow SLIT since they will continue the treatment at home³⁴. During this session, information on the expected magnitude of efficacy, the long-term efficacy of AIT, the side-effects, the cost and the expected degree of commitment should be provided. Simplified information on the modifying effect of AIT on allergy can motivate patients.

In a study performed in Italy a half-hour long educational session was offered to patients that would use SLIT³². The discussion included effects of SLIT, what to expect and when to expect improvement, possible side-effects and how to manage them, duration of therapy and how to store the product. Furthermore patients were followed up (phone calls) for refill and dropout evaluation. A year later, discontinuation of 12% was registered in this group, while discontinuation was more than double in patients included in a control group, not following the educational and follow-up procedure [32].

During the educational sessions the importance of keeping the indicated frequency of visits for SCIT or drop intake for SLIT should be emphasized, as well as the necessary length of time to render AIT efficacious. The outcome of two different studies in Israel and Thailand was that most patients knew that AIT would last more than one year but only 40% had realized that the total duration would be of 3 years^{31,35}. Mentioning the completion of time landmarks (first year or middle of therapy) can be a motivation tool to complete the AIT.

Frequent visits for SCIT may be inconvenient but they offer to patients the chance to meet their nurses and doctors often and address their questions. Supportive health professionals can enhance adherence during AIT visits and offer continuous education on AIT principles. Follow-up visits of patients under SLIT seem to increase adherence, maintaining a doctor-patient relationship; in a study on children treated with SLIT the 3 month interval of control visit was connected with better adherence compared to 6 month or yearly visits³⁶.

The effect of regular visits creates a different trend of adherence between perennial and preseasonal pollen SCIT: after the relevant season no symptoms exist so patients treated with preseasonal AIT are more likely to neglect visiting their doctors before the next season^{24,30}. Maintaining contact with our patients that chose preseasonal SCIT for pollen, and reminding them to renew their prescription before next year's season, can prevent discontinuing SCIT.

Long waiting hours at the practice for SCIT shots, and difficulties in contacting the personnel of an allergological unit, have been registered as reasons for low adherence^{25,37}. In the city of Brescia, Italy, it was noticed that about 75% of patients under SLIT were not renewing their prescriptions, which was attributed to the difficulty of patients in communicating with their doctors in order to get new prescriptions or to address questions on adverse reactions³⁷. The task of communication with patients was assigned to a secretary, who reminded them about refills and facilitated communication with their doctors. The secretary used an Excel database of the patients and performed random periodical calls or emailed them. It was noticed that discontinuation of SLIT decreased from 26.9% before to 2.9% after the secretarial intervention³⁷.

Patient-physician concordance can be achieved by sharing the decision on which route of AIT to choose^{8,14,29}. The provided information should be offered clearly and the desire of some patients to leave the choice of AIT to their physician must be respected¹⁴. With respect to patients deciding on their own which route to follow, it appears that they base their decision mainly on convenience and application technique²⁹. Some patients avoid SCIT due to the fear of needles, while others avoid SLIT, recognizing the probability of forgetting the drops²⁹. For patients feeling discomfort with injections there are commercially available devices offering great reduction in the experienced pain: a vibrating device with an iced interface and another with a surface of small plastic rounded nubs that can be pressed gently onto the skin.

In order to solve the adherence problem it is also suggested to focus on patient-centered care with a tailor-made approach and motivational interviewing^{8,14,26}. Bonding of people that meet professionally is highly influenced by local culture and affects the patient-doctor relationship too. A warm friendly doctor, demonstrating sincere interest in a patient's problem with patience, gains patient trust¹⁴. We should look into patients' eyes while speaking to them. Asking open-ended questions, i.e. ones that are not answered with yes or no, also creates a bond¹⁴.

In recent EAACI guidelines educating patients on how immunotherapy works and explaining the importance of compliance with the regular doses for three years of treatment is highlighted³. Regular visits every 3 months for patients under SLIT and the use of electronic reminders for our patients is also suggested³. The use of an electronic reminder device has been proved to be useful for SLIT³⁸. Alternatively, existing mobile applications can be used as electronic reminders, also providing information on AIT, and motivation with "push" messaging and AIT-themed gaming.

Table 1. Actions and suggestions for health providers towards decreasing the risk of non-adherence or discontinuation of AIT.

Action	Suggestions on how to support your action	Evidence
Inform patients	Educational sessions before the start of AIT. Explain to patients: how AIT functions with simple words, the time required to notice symptom improvement and the probable need for continuation of pharmacotherapy during AIT, possible side-effects and how to manage them, the duration of therapy and the storage of SLIT products.	Many patients on AIT haven't realized what the optimal duration of treatment is ^{32,34,35} . Education of patients beginning SLIT has been shown to significantly increase adherence in comparison to patients that haven't received a complete educational session ^{25,33} .
Follow up SLIT patients and suggest electronic reminders and apps	Schedule medical visits every 3 months. Check adherence discretely and motivate them to follow the advice in order to obtain high efficacy of AIT.	Follow-up every 3 months has been related to higher adherence than 6 months ³⁶ . Electronic reminders have been proved helpful to increase adherence ³⁸ .
Prefer perennial treatment	In the case that preseasonal SCIT is prescribed keep contact with patients and communicate with them to remind them about the scheduled visit for re-examination and prescription.	Perennial SCIT has higher rates of adherence compared to preseasonal ^{26,31} .
Ask for secretarial support	The help of a secretary is highly indicated. For allergy units that cannot support hiring a secretary, hiring professional telephone-center secretarial services is a cheaper alternative. Asking for help from your family members is an alternative.	Adherence of patients under SLIT has been increased after a secretary was assigned to communicate with them ³⁷ .
Reduce waiting hours	Program your AIT visits in a separate hour from others. Focusing on your AIT patients is also crucial for the immediate detection and treatment of a systemic reaction due to SCIT.	Long waiting hours and difficulties in contacting personnel have been registered as reasons for low adherence ^{26,27,37} .
Share the decision on AIT	Explain the options and try to get concordance. Accept making the decision if this is what the patient prefers.	Based on experience ^{8,14,30} .
Avoid inconvenience of injections	This applies mainly in children. Use noninvasive devices that are commercially available, to reduce pain.	Based on experience.
Bond with patients and be friendly	Show sincere interest in them. Look into their eyes during your conversation. Always try to smile. Ideally make a joke.	Based on experience.
Ask open-ended questions	Ask questions like: "how are you feeling since your last visit", or "when was the last time that you used rescue medicines".	Based on experience ¹⁴ .
Motivate patients	Mention the completion of time landmarks and remind them that signs of improvement appear slow but last for a long time after completing AIT.	Based on experience ^{8,14,27} .

Conclusions

Table 1 summarizes the suggested tips to increase adherence to AIT. The needs to be both "patient-centered" and "evidence-based" can conflict with each other, in the case that patients don't comply with AIT protocol⁸. It must be rendered clear to patients that in order to improve their health they have to be adherent to AIT. Safety of AIT is jeopardized when maintenance intervals of allergy shots or SLIT drops are not kept, while the impact of non-adherence on AIT's efficacy is also high. Allergologists can follow the suggested tips adapting them to patients' cultural, financial and professional background.

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