

# Adherence to Sublingual Immunotherapy

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**Abstract** Adherence is a major issue in any medical treatment. Allergen immunotherapy (AIT) is particularly affected by a poor adherence because a flawed application prevents the immunological effects that underlie the clinical outcome of the treatment. Sublingual immunotherapy (SLIT) was introduced in the 1990s, and the early studies suggested that adherence and compliance to such a route of administration was better than the traditional subcutaneous route. However, the recent data from manufacturers revealed that only 13 % of patients treated with SLIT reach the recommended 3-year duration. Therefore, improved adherence to SLIT is an unmet need that may be achieved by various approaches. The utility of patient education and accurate monitoring during the treatment was demonstrated by specific studies, while the success of technology-based tools, including online platforms, social media, e-mail, and a short message service by phone, is currently considered to improve the adherence. This goal is of pivotal importance to fulfill the object of SLIT that is to modify the natural history of allergy, ensuring a long-lasting clinical

benefit, and a consequent pharmaco-economic advantage, when patients complete at least a 3-year course of treatment.

**Keywords** Adherence · Compliance · Allergen immunotherapy · Sublingual immunotherapy · Efficacy · Long-lasting effects

## Introduction

The issue of adherence and compliance concerns any medical treatment. The two terms refer to the extent to which patients follow the physician's prescription, but adherence implies also that patients and physicians agree on the therapeutic plan [1]. Globally considering drug treatment, it was estimated that about half of all patients receiving a prescription by a physician do not adhere to medication regimens [2•]. Allergen immunotherapy (AIT) is the practice of administering increasing doses of a specific allergen to induce clinical tolerance to that allergen [3•]. In its long history, AIT was performed only by the injective form of subcutaneous immunotherapy (SCIT) until the mid-1980s, when sublingual immunotherapy (SLIT) was introduced [4]. The early studies on compliance were performed on SCIT, detecting low values that ranged from 45 to 60 %. The demanding schedules used, with very frequent injections, were blamed for this, as shown by patients' recognition of inconvenience as the major cause of noncompliance [5•]. SLIT, which is administered at home by patients themselves, is free from such a problem and should have adherence characteristics similar to drug treatment. Indeed, the first studies on SLIT reported a very good compliance, ranging from 79 to 97 % [5•]. However, such a brilliant outcome was not confirmed when the data from manufacturers were analyzed. In fact, calculating the rate of spontaneous discontinuations derived from sale data of two large manufacturers in

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Italy over a 3-year period demonstrated a decrease from 100 to 43.7 % in the first year, to 27.7 % in the second year, and to 13.2 % in the third year [6•].

A poor compliance is a general issue for prolonged medical treatments, but is particularly detrimental for AIT because an insufficient duration prevents the occurrence of the immunological changes that underlie the clinical efficacy and, especially, the persistence of the clinical effects after stopping AIT [7], which must be administered for at least 3 years [8]. This makes the achievement of a good adherence of critical importance.

### Adherence to SLIT in Controlled Trials and in Real Life

Actually, in the rigid organization of controlled trials, the compliance to both SCIT and SLIT was usually good. A recent systematic review evaluated the dropout rate (a clear-cut index of nonadherence) in published double-blind, placebo-controlled randomized clinical trials of SLIT for respiratory allergy. A total of 81 studies, comprising 9998 patients, were included. Dropouts were analyzed with regard to allergen, formulation, treatment schedule, participant age, study size, number of centers, and type of allergic disease. The composite dropout percentage was 14 % (95 % CI 11.9–16), and no difference was found comparing active with placebo-treated participants [9]. As reported above, the first real-life studies showed SLIT compliance and adherence rates often higher than 80 % [5•]. Many of these studies are limited by the low number of patients evaluated. In a study including a very high number of patients, the compliance with SCIT and SLIT was compared according to hospital or private office setting administration. With SCIT, instituted in 1886 subjects, 207 (10.9 %) were noncompliant, with no significant difference between the two settings. The major reasons for withdrawing were the cost (35 %), family problems (21 %), inconvenience (20 %), lack of efficacy (16 %), and adverse reactions (7 %). SLIT was used in 806 patients, 173 of whom (21.4 %) were noncompliant, with a highly significant difference for better results in the hospital setting (90.5 %) compared to the private office setting (61.2 %); also with SLIT, the most common reason of withdrawal was the cost of treatment (36.4 %), followed by inconvenience, feeling of inefficacy, and side effects [10].

The most recent studies limited the investigation to the rate of compliance and adherence to SLIT, reporting much worse outcomes, similar to the manufacturer-based data reported by Senna et al. [6•]. For example, in a recent retrospective analysis by Dutch authors of data from 6486 patients starting immunotherapy between 1994 and 2009, 2796 patients receiving SCIT and 3690 receiving SLIT, only 18 % reached the minimally required duration of treatment of 3 years (SCIT,

23 %; SLIT, 7 %). Median durations for SCIT and SLIT users were 1.7 and 0.6 years, respectively. These findings are likely a result of the fact that this is not a clinical research study but were, as noted by the authors reinforce, “an urgent need for further identification of potential barriers and measures that will enhance persistence and compliance” [11•]. In another study, German sale data for different preparations of a single allergen manufacturer were retrospectively evaluated for 5 consecutive years, based on prescriptions per patient. Pollen SLIT and high-dose hypoallergenic (allergoid or unmodified depot pollen and mite preparations for SCIT) were used, 85, 241 patients receiving pollen or mite SCIT and 706 patients receiving pollen SLIT. Prescriptions for at least 3 years were noted in 42 % of patients with pollen SCIT and for 45 % of patients with mite SCIT. Compliance with SLIT was seen in 16 % of patients receiving prescriptions for at least 3 treatment years [12]. Also in the pediatric age, an adherence to SLIT lower than reported in previous surveys [5•, 10] was found in a recent study with 2 years of follow-up, corresponding globally to a rate of adherence of 54 % but with significantly worse rates in children aged less than 4 years during the first year [13].

### Issues Related with Nonadherence

Nonadherence concerns all treatments of respiratory allergy. For example, in allergic rhinitis, studies reported adherence as low as 48.7 % for antihistamines [14], and fewer than half of prescribed doses of intranasal corticosteroid medication were taken [15•]. A number of determinants of nonadherence to drug treatment have been identified, including patient-related factors (age, cognitive difficulties, comorbidities, social and family support, coping style), disease-related factors (chronicity, presence or absence of symptoms), treatment-related symptoms (number of daily doses to take, complexity of the regimen, ease of assumption, side effects), physician-related factors (poor relationship with the patient, behavioral inappropriateness, inadequate patient’s involvement), and healthcare system-related factors (difficulties of access to health services and poor treatment by clinic staff, high medication costs) [14]. Lack of efficacy has been reported as the major reason for discontinuing the intake of medications prescribed for nasal allergies [16]. Indeed, the literature thus far available, as reported above, suggests that the most important factors affecting adherence and compliance to SLIT are the cost of treatment, the inconvenience, the feeling of inefficacy, and the side effects. The cost of treatment particularly affects SCIT because the cost of the allergen extract must be added to that of the injections [17], but remains very important also for SLIT. A questionnaire-based survey of 296 Italian allergists examined factors influencing the adherence to SLIT. The factor ranking first was the patient’s perception of clinical

efficacy, confirming the importance of lack of efficacy as the major factor associated to nonadherence to treatments we reported above. The cost of treatment, expressed as the possibility of reimbursement, ranked second. Then followed by the absence of side effects. Patient education, regular follow-up, and ease of assumption of SLIT were perceived as less important [18].

### Proposed Methods to Improve Adherence to SLIT

Although the approaches to improve compliance and adherence to AIT, and particularly to SLIT, were proposed when the available data were more encouraging, they are still valid. The most important appear to be patients' education and appropriate timing of control visits. Concerning education, a better compliance was reported in patients receiving a complete educational program regarding SLIT with written instructions compared with patients receiving verbal information alone [19•]. This was confirmed in a study based on an educational/follow-up plan of 149 patients treated with SLIT compared to 90 patients not participating to the plan. In the first group, discontinuations at 4 months were 5 vs. 18 % in the controls and 12 % of patients in the active group vs. 35 % in the control group after 1 year. The authors concluded that "An adequate education and a strict follow-up can significantly reduce SLIT discontinuations" [20]. Regarding the timing, Vita et al. performed a study on three groups of SLIT-treated patients, the first with a control visit scheduled at a 3-month interval, the second at a 6-month interval, and the third with only one visit/year. The best compliance was found in patients who received four visits per year [18.5 % of withdrawals], while children in the other two groups abandoned SLIT with a rate of 32.3 % in patients with two visits and 70.4 % in patients with one visit/year, respectively [21•]. In particular, the rate of adherence of 29.6 % in the one visit/year group is comparable to the poor results from recent studies [11•, 12] and makes it likely that an adequate number of visits each year during the SLIT treatment could significantly improve the long-term adherence.

Also, other approaches that may improve the adherence to SLIT have recently been proposed. Tripodi et al. reported that using an online platform, Allergymonitor<sup>®</sup>, which requires patients to register daily or weekly the data concerning SLIT, resulted in a significantly better adherence (96 %) in the 27 patients, aged 6 to 20 years, compared with the 50 % of 18 patients followed by conventional methods [22]. Other technology-based tools, including social media, e-mail, and short message service by phone, are currently being considered to improve adherence to immunotherapy [23], but no studies on such tools are available yet. The most recent proposal to improve the adherence is to involve the patient in the choice of the route of administration of AIT. After receiving two educative sessions about SCIT and SLIT, 204 patients

chose the most appropriate route according to their characteristics. After 6 months, they were compared with 103 patients who underwent SCIT or SLIT according to the physicians choice. A total of 46 patients discontinued AIT, but the rate was 11 % in patients who chose the kind of treatment vs. 21 % in those who were treated according to the physician's choice ( $p \leq 0.05$ ) [24]. However, the significance of the data is limited by the short duration of the follow-up and small sample size.

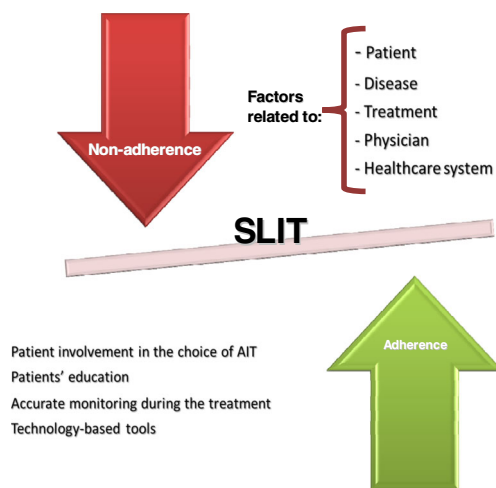
### Identifying the Actual Needs to Meet to Achieve a Satisfactory Adherence to SLIT

In a recent review, Antico discussed the large differences of compliance and adherence observed in the available studies. He suggested that the better outcome in placebo-controlled trials may depend on the patient's motivation, and particularly to the patient's decision to participate in the trial and to meet the researcher's expectations, defining a condition conceptually similar to concordance, which is a consultation process, based on the patient's belief and needs, that tends to establish a therapeutic alliance between the physician and patient [25]. This is in agreement with the role of patient's values and preferences in the Grading of Recommendations Assessment, Development and Evaluation [GRADE] approach to medical treatments [26••]. The results from the recent study by Sanchez, though based on a short monitoring period, offer confirmation to this concept [24]. As noted by Bender and Oppenheimer, little research has addressed the consequence of lack of adherence to SLIT [27], including the loss of its cost-effectiveness that was clearly demonstrated in specific studies when patients complete the 3-year course of treatment and continue to benefit the long-lasting effects of AIT after it was stopped that are related to the immunological effects [28].

It is likely that the study Prospective Adherence to Specific immunoTherapy in Europe (PASTE), developed by the European Academy of Allergy and Clinical Immunology and designed to prospectively evaluate adherence to SCIT and SLIT across different European countries, will expand our understanding of the factors influencing the adherence. Each participant in the study will be followed up for a total of 3 years; to assess adherence, a 4-monthly follow-up form detailing any missed doses and reasons will be completed online, and, in case of treatment discontinuation, reasons for this will be recorded [29].

### Conclusions

After the first optimistic reports in recent years on a very high adherence to SLIT, it became apparent that SLIT is plagued by the same issue of low adherence that affects drug treatment.



**Fig. 1** Factors influencing adherence to sublingual immunotherapy

The degree of adherence is particularly low at the third year of SLIT, and this prevents the disease-modifying effect on the natural history of allergy to be achieved, the occurrence of which ensures the long-lasting clinical benefit and the consequent pharmaco-economic advantage. The search for optimal adherence is a question of balancing a number of factors (Fig. 1). Improving adherence to SLIT is a major goal, and the recent studies suggest that patient education, accurate monitoring during treatment, and possibly technology-based tools are interventions that are likely to meet such a need.

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#### Compliance with Ethical Standards

**Conflict of Interest** Dr. Incorvaia reports personal fees from Stallergenes Italy. Drs. Mauro, Leo, and Ridolo declare that they have no conflicts of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of major importance

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