

# Evidence of adherence to allergen-specific immunotherapy

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## Purpose of review

The main feature of allergen-specific immunotherapy is its capacity to modify the natural history of the disease, reducing the development of asthma and new sensitizations after 3–4 years of treatment. For this reason, adherence to the therapy is mandatory, as happens for all chronic medical treatment.

## Recent findings

Though subcutaneous immunotherapy is administered directly by physicians, the rate of adherence is surprisingly low, at less than 70%. The explanations for a poor subcutaneous immunotherapy adherence include inconvenience, lack of efficacy, costs and loss of working hours.

Local nasal immunotherapy has a very low adherence rate (27%), due to the local nasal side effects.

For sublingual immunotherapy, data are available from clinical trials and postmarketing surveys, which are favourable overall (rates of compliance >75%). Cost was the most common reason for discontinuation, followed by inconvenience, feeling of inefficacy and side effects.

## Summary

Studies addressing the adherence to allergen-specific immunotherapy in literature are lacking. In real life, costs and patient education are crucial issues in conditioning adherence to this treatment. Reduction of costs and more efforts in education of patients and also specialists may improve the adherence to immunotherapy.

## Keywords

adherence, allergen-specific immunotherapy, allergic asthma, allergic rhinitis, compliance

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## Introduction

Allergen-specific immunotherapy (SIT), together with allergen avoidance and pharmacotherapy, is a cornerstone in the management of allergic respiratory disorders. The main distinctive feature of SIT is its capacity to modify the natural history of the disease, especially preventing the onset of new allergen sensitizations and reducing the risk of asthma development [1]. In contrast with the use of anti-inflammatory drugs [2], SIT can maintain its clinical effects for years after discontinuation [1]. SIT given as subcutaneous injection (subcutaneous immunotherapy; SCIT) is well established over several decades and its efficacy has been confirmed in numerous clinical studies and meta-analyses [3–5]. During the past 20 years, due to the inconvenience and risk of systemic reaction of SCIT, the sublingual route (sublingual immunotherapy; SLIT) has been developed, in parallel with the local nasal route (local nasal immunotherapy; LNIT) [6]. The impressive number of randomized controlled

trials and meta-analyses published in the last decade [7,8,9,10] has led to the acceptance of SLIT as a viable alternative to SCIT for respiratory allergic diseases [10]. SLIT is currently commercialized by several manufacturers in Europe and other countries and it is largely used in clinical practice, whereas LNIT has been progressively abandoned.

SIT exerts its beneficial effects over long periods (i.e. weeks or months) and 3–4 years of treatment are required to obtain a favourable clinical and immunological response [11,12]. For this reason, specific allergen immunotherapy requires a strong commitment by the patients, and in this context compliance is essential, as happens for all chronic medical treatments [13,14]. The adherence for SCIT has been considered to be strong, as this is administered at regular intervals by physicians, whereas concerns have been raised regarding adherence to SLIT, which is managed by patients or parents at home without direct medical supervision.

**Table 1 Methods of measuring adherence**

| Tests                                                    | Advantages                               | Disadvantages                                                                            |
|----------------------------------------------------------|------------------------------------------|------------------------------------------------------------------------------------------|
| Direct methods                                           |                                          |                                                                                          |
| Directly observed therapy                                | Most accurate                            | Impractical in real life                                                                 |
| Measurement of the level of medicine in blood            | Objective                                | Expensive, individual variation of metabolism, selective drug                            |
| Measurement of the biologic marker in the blood          | Objective                                | Expensive, collections of bodily fluids                                                  |
| Indirect methods                                         |                                          |                                                                                          |
| Patient's questionnaires, patient's self-reports         | Simple, cheap                            | Susceptible to error with increased time between visits; easily modified by the patients |
| Pill counts                                              | Objective, easy to perform, quantifiable | Easily modified by the patients                                                          |
| Assessment of clinical response                          | Simple, easy to perform                  | Other factors can influence the clinical outcome besides adherence                       |
| Electronic medical monitors                              | Precise results easy to quantify         | Expensive, not practical                                                                 |
| Measurement of physiologic markers                       | Not always easy to perform               | False negative or false positive                                                         |
| Patient's diaries                                        | Simple                                   | Easily modified by the patients                                                          |
| Questionnaires for caregiver or teacher (paediatric age) | Simple, objective                        | Susceptible to distortion                                                                |
| Rates of prescription refills                            | Objective, easy to obtain data           | Patients cannot take drugs                                                               |

Reproduced from [13].

The aim of the present review is to evaluate the studies addressing the adherence to SIT in literature, in real life and in the recent big trials, which evaluating a large number of patients can be in a way assimilated to real life.

### Adherence

Adherence to (or compliance with) a medication regimen is generally defined as the extent to which patients take medications as prescribed by healthcare providers. Currently, the word 'adherence' is preferred because 'compliance' suggests that the patient is passively following the doctor's orders and that the treatment plan is not based on a therapeutic alliance established between the patient and the physician [15]. Rates of adherence for individual patients are usually reported as the percentage of the prescribed doses of the medication actually taken by the patients over a specified period. There is no consensual standard that represents an acceptable adherence rate; however, some trials consider that an adherence greater than 80% is adequate for most treatments [13].

The methods available for measuring adherence can be roughly divided into direct and indirect methods (Table 1) [13]. Each method has advantages and disadvantages and none of them can be considered the gold standard [16]. Also, it is important to remember that when adherence is the specific subject of a clinical trial and patients are aware of this, an intrinsic bias is immediately introduced.

### Adherence to subcutaneous immunotherapy

Though SCIT is directly administered by or under the supervision of a physician, the rate of adherence is surprisingly low, less than 70% in most of the studies

(Table 2) [17–24]. The earliest studies addressing the compliance of immunotherapy reported a rate of about 50% both in adults [17] and in children [18].

Lower *et al.* [18] reported that female patients and non-private patients were less compliant. In those studies, patients were treated according to a time-consuming traditional schedule, performed with weekly injections during the build-up phase and monthly injections during the maintenance period. Waste of time and annoyance were reported as the main causes for stopping treatment and this was more evident for rhinitis than for asthma [18]. The use of accelerated schedules seems to induce a slight improvement in the compliance rate [19]. In this study, the geographical distance from the clinic was determined as a negative factor influencing compliance rate.

In a population of 247 patients treated with SCIT, Ruiz *et al.* [20] reported that major causes of noncompliance were the cost of treatment, the worsening of symptoms and the shift to alternative/complementary medicines. In the study by Donahue *et al.* [21], the lowest compliance

**Table 2 Studies on compliance with subcutaneous immunotherapy**

| Reference                    | No. of patients | Age      | Follow-up | Compliance (%) |
|------------------------------|-----------------|----------|-----------|----------------|
| Lower <i>et al.</i> [18]     | 315             | Children | 4 years   | 44             |
| Cohn and Pizzi [17]          | 217             | Adults   | 4 years   | 48             |
| Tinkelman <i>et al.</i> [19] | 3349            | Adults   | 18 months | 65             |
| Ruiz <i>et al.</i> [20]      | 247             | Adults   | 18 months | 62             |
| Donahue <i>et al.</i> [21]   | 603             | Adults   | 4 years   | 33             |
| Rhodes [22]                  | 1033            | Adults   | 3 years   | 88             |
| More and Hagan [23]          | 381             | Adults   | 3 years   | 77             |
| Pajno <i>et al.</i> [24]     | 1886            | Children | 3 years   | 89             |

(33%) was observed. In this study, patients with asthma as the only indication would be more likely to abort or terminate immunotherapy more frequently or earlier. Record review showed that the majority of discontinuations were related to the patient's decision and were not related to side effects or asthma worsening.

The more reasonable explanations for a poor immunotherapy adherence include inconvenience, lack of efficacy, costs, concurrent diseases and severity of symptoms. A higher SCIT adherence rate was reported by Rhodes [22], though 12% of patients treated with the top dose stopped the therapy before the end of the third year because of relevant side effects, inconvenience or concurrent medical problems. The same reasons for stopping treatment were reported by More and Hagan [23], who studied 381 patients in a military setting. Patients treated with rush or accelerated schedules were less compliant, probably due to the higher frequency of side effects. Finally, in a longitudinal and comparative study performed by Pajno *et al.* [24] in children, the percentage of patients who abandoned the treatment was 5.6, 4.5 and 0.8% in the first, second and third year of treatment, respectively. Cost was identified as the main cause of withdrawal and poor compliance.

### Compliance with sublingual immunotherapy

Many of the factors that are reported to decrease adherence to SCIT, namely, side effects, inconvenience and fear of injections, are not present with SLIT. However, SLIT is a long-lasting home treatment that is directly managed by patients and parents, and therefore carries problems of adherence similar to all other drug therapies. In addition, as SLIT is self-managed at home without direct supervision, adequate adherence is mandatory. So far, several studies have specifically addressed this issue (Table 3) [24–28,29\*\*]. In a 3-year longitudinal trial properly designed to evaluate the clinical efficacy of SLIT in 319 patients, the adherence to the treatment was reported good (>80%) in 72% of study population and moderate (> 60%) in 18%. However, in this study, the methods for evaluating adherence were unclear and the reasons for nonadherence were not specified [25].

Three real-life studies [26–28] assessed the adherence to SLIT by means of unscheduled phone calls, in which

patients were asked to count the remaining doses (tablets or single-dose vials). In the first study by Lombardi *et al.* [26], mite-allergic patients were evaluated during the first year of treatment and pollen-allergic patients were called during the first pollen season. The range of adherence was 75–97%, both in seasonal and perennial allergy, without a significant difference. The other two real-life surveys were carried out in 443 adults and adolescents [27] and 71 children [28], respectively. In the first study, the rate of compliance was 76.3% after 3 months without significant changes after 6 months (74.8%). Four percent of patients stopped the treatment for different reasons unrelated to immunotherapy, whereas 1% discontinued SLIT due to side effects. Similar results were reported in the paediatric study [28]. The rate of compliance higher than 75% at 3 and 6 months was respectively 85 and 84% in the studied population. Cost was the most frequent reason for withdrawal, whereas side effects accounted for 1.4%. In another paediatric study by Pajno *et al.* [24], noncompliant patients accounted for 21.4% among 806 patients. A significant better compliance rate was registered in a hospital setting (90.5%), in comparison with private practice (61.2%). In this case also, cost was the most common reason for discontinuation (36.4%), followed by inconvenience, feeling of inefficacy and side effects [24].

A specific assessment of compliance in youngsters was performed by Roder *et al.* [29\*\*] during a 2-year randomized controlled trial. Participants who completed the follow-up and use more than 80% of the prescribed medication were considered adherent to medication intake, adherence being assessed by weighing the study medication. Interestingly, 77% of patients were considered adherent to the treatment, but the self-reported adherence was 99%. Of note, despite the good adherence, the mentioned trial failed to demonstrate any effect of SLIT on symptoms.

The efficacy of a compliance device was evaluated in 91 adult patients receiving SIT with allergen tablets in order to remind a regular use of treatment [30\*\*]. Patients were asked to fulfil a questionnaire at the end of treatment (8–10 weeks). Among responders, 82% reported using the device always or sometimes, 79% found the device easy to use but only 46% found that the device made it easier to remember a regular tablet intake and 61% indicate that they would consider using the device again.

**Table 3 Studies on compliance with sublingual immunotherapy**

| Reference                      | No. of patients | Age                | Follow-up             | Compliance (%) |
|--------------------------------|-----------------|--------------------|-----------------------|----------------|
| Marogna <i>et al.</i> [25]     | 319             | Adults             | 3 years               | 80             |
| Lombardi <i>et al.</i> [26]    | 86              | Adults             | 18 weeks to 13 months | 75–97          |
| Pajno <i>et al.</i> [24]       | 806             | Children           | 3 years               | 79             |
| Passalacqua <i>et al.</i> [27] | 443             | Adults/adolescents | 6 months              | 76             |
| Passalacqua <i>et al.</i> [28] | 71              | Children           | 6 months              | 85             |
| Roder <i>et al.</i> [29**]     | 154             | Adolescents        | 2 years               | 77             |

Recently, large studies have been performed to evaluate the clinical efficacy and safety of SLIT given as dissolving tablets in adults and in children. These studies are usually called 'big trials', as they involved more than 150 patients. Though these controlled trials and real-life studies represent different situations, the evaluation of adherence to medication in large trials can be assumed as a useful model to predict the potential drawbacks of the treatment in real life. In a trial involving more than 800 patients [31] with three different doses of allergen, the adherence is reported as high as 94–98%, and in another trial with more than 200 patients, the compliance ranged between 88 and 91% [32]. Concerning the paediatric trials, Wahn *et al.* [33] reported that 95% of patients had a compliance greater than 80% and in the study by Bufe *et al.* [34], the compliance was 93%.

### Compliance with local nasal immunotherapy

Only a comparative previously mentioned study [24] addressed the compliance with LNIT. A population study of 82 children, all treated in a private setting, was evaluated. The compliance rate was 27%. The main reason for withdrawal (56.6% of patients) was the local side effects after the administration of dose in the nose. Other causes of noncompliance were inefficacy and costs accounting for, respectively, 18.3 and 13.3%. Premedication with cromolyn, frequently used in controlled trials, significantly lowered the rate of side effects [34,35]. The use of allergen-coated strips for nasal application has been reported to improve the tolerability and adherence of LNIT [36].

### Conclusion

SIT is clinically used to reduce allergic symptoms on allergen exposure and to reduce the use of symptom medication, improving the quality of life of the individuals with allergic disease. It is well established that prolonged treatments are required to obtain a satisfactory immunomodulation of the disease and long-lasting efficacy [37]. Despite this, the adherence issue, which is crucial, has been addressed only recently. The available data from recently published literature suggest that the adherence to SCIT is far lower than expected, due to side effects and inconvenience. On the other hand, for SLIT, more data are available from clinical trials and postmarketing surveys. The data are overall favourable, with rates of compliance reported on average greater than 75%, but there is a great dispersion of figures and methodological bias is present. For those reasons, the official documents recommend that adherence has to be included as secondary outcome in future clinical trials of immunotherapy [38,39].

Several factors affecting the adherence rate must be found out. The cost is one of the most relevant [40••]

and this is clearly noticeable comparing the data of 'real-life' studies with the sales of immunotherapy. Costs may also account for the difference in adherence between SLIT and SCIT, as SCIT induces additional indirect costs such as loss of working hours, travelling expenses to hospital or medical private office. Another important factor to consider is patient's education and information about the clinical and immunologic benefits of specific allergen immunotherapy. The advantages and drawbacks of specific allergen immunotherapy have to be clearly evaluated together with the patient, before and during the treatment. Thus, education is mandatory to obtain an acceptable adherence. Nonetheless, it has been shown that according to allergists, the most important determinants of adherence to SIT are the perceived efficacy and the costs, whereas the patient's education is considered not relevant [41]. Similarly, a survey evidenced a lack of knowledge and several misconceptions among a substantial number of patients receiving immunotherapy for aeroallergens [42]. One-fifth of the study group did not know when improvement should be expected and 18% anticipated improvement to occur within days or weeks from the initiation of the treatment. Complete recovery of their allergies was expected by 39% of patients. Moreover, only 32% were aware that immunotherapy may have some potential risks. Finally, the schedule of treatment may also influence the adherence. It is reasonable to expect that regimens easy to follow and not time-consuming would increase the adherence to SIT.

In conclusion, it seems that there is room for improving the compliance by systematically assessing it and its determinants, by ameliorating the administration regimens and by putting more effort into educating patients and specialists.

### References and recommended reading

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 576–577).

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