

Quantitative assessment of the compliance with once-daily sublingual immunotherapy in children (EASY Project: Evaluation of A novel SLIT formulation during a Year)

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Compliance is a major determinant for allergy treatment, especially in children. Sublingual immunotherapy (SLIT) is self-managed at home, and no quantitative data on pediatric adherence are available. We studied the compliance in a large real-life setting. A simplified schedule of SLIT was used, consisting of a 10-day up dosing phase followed by maintenance treatment in monodose containers to be taken daily (SLITone®). Italian specialists throughout Italy assessed the compliance in children who were newly prescribed SLIT according to guidelines. Parents were contacted with unscheduled telephone interviews at the third and sixth month of therapy and asked to count at that moment the remaining vials. Data from 71 children (38 boys, age range 2–13 yr) were enclosed in the database. Thirty had rhinoconjunctivitis, four asthma and 37 rhinoconjunctivitis + asthma. SLIT was prescribed for: mites in 57 (81%) subjects, grasses in 11 (15%) and 3 (4%) grass + olive mixture. Compliance data were available for all children at 3 months, and for 56 at 6 months. At 3 months, 85% of subjects had a compliance rate > 75% (69% of them adhered > 90%). At 6 months, 84% had a compliance rate > 75% (66% of them adhered > 90%). In four cases SLIT was discontinued for economical reasons, and in one case (1.4%) for side effects probably related to therapy. These data obtained in a quite large sample of children and in real-life confirm that the compliance with SLITone® is good, despite the therapy managed at home.

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Allergen-specific immunotherapy (IT) is the practice of giving increasing amounts of allergen(s) in order to achieve an immunomodulatory effect and to reduce the symptoms during exposure to allergen(s). Subcutaneous immunotherapy (SCIT), which remained for several decades the only administration route, is effective and safe when properly prescribed and administered,

but a remote risk of severe side effects is present (1). For this reason, the international guidelines consider the age below 5 yr a relative contraindication to SCIT (2–4). On the contrary, sublingual immunotherapy (SLIT) seems to be safe and is presently considered as a viable alternative option to the traditional subcutaneous route (2, 3). The favorable safety profile, has been

confirmed repeatedly in post-marketing surveillance studies (5–8), involving also children aged between 3 and 5 yr (7, 8). In addition to the safety profile, SLIT is also convenient because no injection is needed and it can be managed at home. Recently, simplified administration schedules (short build-up and once-daily dosing) have been introduced in order to make the SLIT even more user-friendly. All the mentioned characteristics would suggest a good compliance rate, but as the treatment is self-managed at home, concerns about the compliance with SLIT in a real-life setting have been raised (9).

Compliance is defined as the degree to which the patient's behavior coincides with the medical prescription (10). Suboptimal compliance is a common problem with all kinds of medications that are taken by the patient at home, without the direct supervision of the physician (11). In allergic diseases, the poor compliance is generally identified as one of the main causes of treatment failure. So far, there are very few data concerning compliance with SLIT, especially in children. For this reason, an observational multicenter study (EASY: Evaluation of A novel SLIT formulation during a Year) (12) was specifically designed to measure the compliance to SLIT in a real-life setting. The present article describes the results concerning a pediatric population.

Methods

Study design

This survey was limited to the compliance aspect and not intended as an efficacy evaluation. It was designed as multicenter and observational study in a real-life setting, and conducted with SLIT prepared in plastic single dose containers to be taken once daily (SLITOne®; Alk-Abelló, Lainate, Milan, Italy). Pediatric outpatients suffering from allergic rhinoconjunctivitis and/or asthma and eligible for IT, were enrolled throughout Italy. At unscheduled telephone interviews, parents were contacted during the SLIT course and asked to count the remaining unused single dose vials.

Patients and diagnosis

Pediatric allergists distributed over the entire Italian territory were asked to record the compliance data of all children to whom SLIT for respiratory allergy was newly prescribed. As a general indication, data from 5–10 patients were required. Data were collected from January 2004 to June 2005.

Children were diagnosed with allergic rhinitis and/or asthma according to guidelines (3, 13), based on clinical history, symptoms and positivity of skin prick tests (and/or radioallergosorbent test). Skin tests were performed with a panel of standardized extracts (Alk-Abelló) including: house dust mites, grasses, *Parietaria*, olive, birch, ragweed, hazelnut, *Cladosporium*, *Alternaria*, cat and dog dander, plus a negative and a positive control.

SLIT and concomitant treatments

Sublingual immunotherapy was prescribed as routinely done to patients with comorbid rhinitis and asthma, with persistent moderate/severe rhinitis, or when rhinitis (although intermittent) was particularly troublesome during the allergen exposure. The parents were informed in detail about the rationale of SLIT and about the treatment modality.

Sublingual immunotherapy treatment, in its commercial preparation, began with a short up-dosing phase, involving the administration of 1–10 drops from a 200 STU/ml vial in days 1–10. Starting from day 11, the maintenance dose, prepared in disposable single-dose containers (200 STU/vial), was taken daily in the morning before breakfast. Each package of SLITOne® comprised 90 monodose containers for a full 3-month treatment period. A continuous treatment to be prosecuted for 3–5 yr was prescribed for mites, whereas for pollens a pre-seasonal regimen was applied. The manufacturer provided detailed printed instructions on the SLIT schedule, and the parents received additional oral explanation on how to manage the therapy. The prescribing physician, or a physician at each center, was designated for phone contacts.

Assessment of compliance and safety

All families were contacted unscheduled by telephone during the third (day 60–90) and sixth (day 150–180) month of therapy. During the telephone interview, parents were asked: (a) if the child was still taking the SLIT, (b) to count at that moment the unused single-dose containers remaining in the blister package. A computerized program, based on the starting date of SLIT, calculated the expected consumed and the expected remaining containers at a given date. Therefore, for each patient, compliance could be calculated as:

$$\frac{\text{Expected consumed} - \text{Remaining}}{\text{Expected consumed}} \times 100.$$

The empty vials had to be returned at the visits. A diary card for side effects was also given (8). Side effects were grouped as local (oral itching/swelling, edema of lips/tongue, nausea or vomiting) and systemic (rhinitis, conjunctivitis, asthma, urticaria/angioedema). The severity was graded as: mild (no medical advice or treatment required, no interference with activities, no discontinuation), moderate (interference with everyday activities, need for drug treatment and/or SLIT discontinuation), or severe (life-threatening events needing hospitalization and/or emergency care).

Results

By June 2005, 71 children (38 boys, mean age 9.43 yr, age range 2–13 yr) received a SLIT prescription by the participating physicians. Thirty subjects had rhinoconjunctivitis (six with atopic dermatitis), four had asthma and 37 had rhinoconjunctivitis plus asthma (four with atopic dermatitis). SLIT was prescribed for: mites in 57 (81%) subjects, grasses in 11 (15%) and three (4%) with a grass plus olive mixture. Compliance data were available for all children at the first telephone interview (during the third month of treatment), whereas at the second interview (sixth month of treatment), data were collected for 56 patients only, as 10 had been prescribed a pre-seasonal SLIT of 3–5 months and five had discontinued the treatment. A summary of the compliance data is reported in Table 1. Out of 71 patients, 85% had a compliance rate >75% in the third month, and in the sixth month 84% of subjects had a compliance rate >75%. In four cases SLIT was discontinued as the cost was not affordable. Only in one child (1.4%) SLIT had to be discontinued due to a side effect (i.e., recurrent edema of the hands) that was judged by the physician probably but not certainly related to therapy. In none of the patient the compliance measured by the formula was >100%. In all cases, the parents of the children who were still on SLIT reported occasional omission of doses

due to negligence or forgetting. Immunotherapy in Italy is a 'patient-named' product and its cost is differently reimbursed depending on the regional area. In our sample, 20% of patients had SLIT reimbursed, 10% partially reimbursed, and 70% had to fully pay for it. Nevertheless, the reimbursement modality did not affect the compliance in a relevant way (chi-square $p = \text{NS}$). Moreover the socioeconomic situation of the family (education, occupation), the age and the type of disease did not affect the adherence (data not shown).

Discussion

Compliance is regarded as one of the major determinants of a successful treatment (11), and this is of particular relevance in pediatric patients (14, 15), where the compliance with, for example, anti-asthma medications is generally far from being optimal (15–17). An objective and quantitative measurement is difficult to perform in real-life. Simply asking the patient if he/she had taken all the doses is a hardly reliable information. With inhaled drugs, weighting the canisters can be useful, but this does not provide information on the quantity of drug really taken (18). In some cases it is possible to use electronic devices applied to the drug package (19), but this approach is quite expensive and not applicable to all drugs.

In SCIT, it is commonly believed that as the physician gives injections, the adherence is optimal (virtually 100%). Nevertheless, looking at the available literature, with SCIT the compliance is far from being optimal, mainly due to the discomfort of injections (20–21). On the contrary, SLIT is safe (5–8) and can be self-managed by the patient. For the latter reason, compliance could be expected to be lower than that of subcutaneous immunotherapy (where the patient receives medication in the doctor's office). Indeed, in some surveys in adults (12, 22, 23) the compliance was satisfactory, whereas there is one single study in children (24). In the present survey, SLIT was prepared in single-dose containers, making it easier to count the doses taken. By calling the parents without warning them in advance and asking to count the remaining containers at the moment, it is possible to avoid the bias related to the intention to exhibit a good compliance. It is quite unlikely that parents can calculate the correct number of remaining doses and the expected consumption in a few seconds. Thus we are confident that the results herein provided truly reflect the compliance of patients, although this method does not allow to deter-

Table 1. Compliance with sublingual immunotherapy measured at 3 and 6 months of treatment

Compliance (%)	Third month (71 pts), n (%)	Sixth month (56 pts), n (%)	Chi-square <i>p</i>
>90	49 (69)	37 (66.1)	NS
75–89.9	11 (15.5)	10 (17.9)	
50–74.9	5 (7)	5 (8.9)	
25–49.9	0 (–)	1 (1.8)	
<25	4 (5.5)	0	
Discontinued	2 (3)	3 (5.3)	

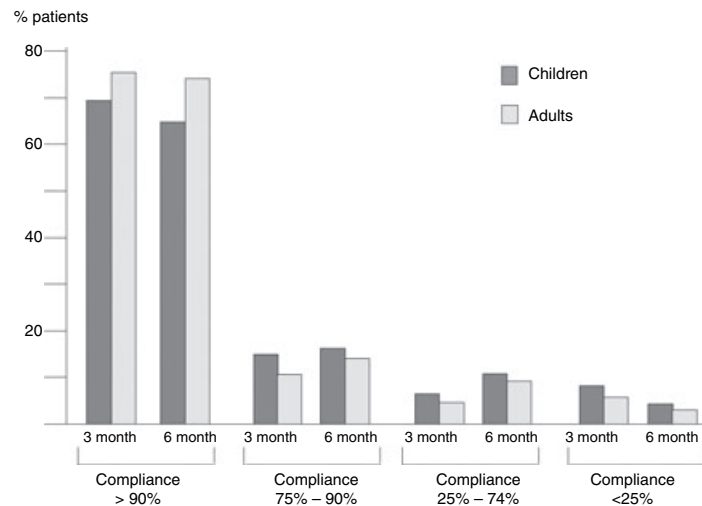


Fig. 1. Compliance rates at 3 and 6 months measured with the same methodology in children (present study) and adults (12).

mine whether the patients took their medication daily. Overall the results were satisfactory, as about 66% of the children had taken more than 90% of the prescribed doses, and the compliance was >75% in about 85% of the patients. Unfortunately, due to its short duration we were unable to assess the compliance in the up-dosing phase. Our results partly differ from those described by Pajno et al. (24). Nevertheless, the authors did not assess quantitatively the adherence, but only the discontinuation rate over a 3-yr period. Of note, in our study the adherence rate was only slightly inferior to that obtained in adults within the same type of survey (12), as shown in Fig. 1. SLIT was discontinued after the first 3 months in 7% of cases, but only in one case discontinuation was caused by side effects possibly related to the treatment.

The data provided herein are of particular relevance as they were obtained in a real-life setting, in which it is known that compliance is lower than that of controlled studies (11). In conclusion, compliance with SLITOne® is good and even better than that observed with conventional pharmacologic treatments (25–26) despite self-administration at home. The convenience of once-daily administration, similar to drugs, and the simple up-dosing schedule are factors likely to play a relevant role in improving compliance.

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References

1. Committee on the Safety of Medicines. CSM update. Desensitizing vaccines. *Br Med J* 1986; 293: 948.
2. World Health Organization Position Paper. Allergen immunotherapy: therapeutic vaccines for allergic diseases. In: BOUSQUET J, LOCKEY R, MALLING HJ, eds. *Allergy* 1998; 53 (Suppl.): 1–33.
3. BOUSQUET J, VAN CAUWENBERGE P, eds. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001; 108 (5 Suppl.): S146–50.
4. Allergen immunotherapy: a practice parameter. American Academy of Allergy, Asthma and Immunology. American College of Allergy, Asthma and Immunology. *Ann Allergy Asthma Immunol* 2003; 90(1 Suppl 1): 1–40.
5. DI RIENZO V, PAGANI A, PARMIANI S, PASSALACQUA G, CANONICA GW. Post-marketing surveillance study on the safety of sublingual immunotherapy in children. *Allergy* 1999; 54: 1110–3.
6. LOMBARDI C, GARGIONI S, MELCHIORRE A, et al. Safety of sublingual immunotherapy in adults: a post marketing surveillance study. *Allergy* 2001; 56: 889–92.
7. DI RIENZO V, MUSARRA A, SAMBUGARO R, et al. Post marketing survey on the safety of sublingual immunotherapy in children below the age of 5 years. *Clin Exp Allergy* 2005; 35: 560–4.

8. FIOCCHI A, PAJNO G, LA GRUTTA S, et al. Safety of sublingual-swallow immunotherapy in children aged 3 to 7 years. *Ann Allergy Asthma Immunol* 2005; 95: 254–8.
9. NELSON HS. Advances in upper airway disease and allergen immunotherapy. *J Allergy Clin Immunol* 2003; 111: S793–8.
10. HAYNES RB. Introduction. In: HAYNES RB, TAYLOR DW, SACKETT L, eds. *Compliance in Healthcare*. Baltimore, MD: John Hopkins University Press, 1979: 262–268.
11. OSTERBERG L, BLASHKE T. Adherence to medication. *N Engl J Med* 2005; 353: 487–97.
12. PASSALACQUA G, MUSARRA A, PECORA S, et al. Quantitative assessment of the compliance with a once-daily sublingual immunotherapy regimen in real life (EASY Project: Evaluation of A novel SLIT formulation during a Year). *J Allergy Clin Immunol* 2006; 117: 946–8.
13. Global Initiative for Asthma. Guidelines 2006. <http://www.ginasthma.com> (last accessed October 2006).
14. ADAMS CD, DREYER ML, DINAKAR C, PORTNOY JM. Pediatric asthma: a look at adherence from the patient and family perspective. *Curr Allergy Asthma Rep* 2004; 4: 425–32.
15. O'CONNOR SL, BENDER BG, GAVIN-DEVITT LA, WAMBOLDT MZ, MILGROM H. Measuring adherence with the Doser CT in children with asthma. *J Asthma* 2004; 41: 663–70.
16. BECKER AB. Challenges to treatment goals and outcomes in pediatric asthma. *J Allergy Clin Immunol* 2002; 109 (6 Suppl.): S533–8.
17. IQBAL S, RITSON S, PRINCE I, DENYER J, EVERARD ML. Drug delivery and adherence in young children. *Pediatr Pulmonol* 2004; 37: 311–7.
18. BENDER B, WAMBOLDT FS, O'CONNOR SL, et al. Measurement of children's asthma medication adherence by self report, mother report, canister weight, and Doser CT. *Ann Allergy Asthma Immunol* 2000; 85: 416–21.
19. CHOO PW, RAND CS, INUI TS, et al. Validation of patient reports, automated pharmacy records, and pill counts with electronic monitoring of adherence to antihypertensive therapy. *Med Care* 1999; 37: 846–57.
20. TINKELMAN D, SMITH F, COLE WQ Jr, SLIK HJ. Compliance with an allergen immunotherapy regimen. *Ann Allergy Asthma Immunol* 1995; 74: 241–6.
21. LOWER T, HENSY J, MANDIK L, JANOSKY J, FRIDAY GA Jr. Compliance with allergen immunotherapy. *Ann Allergy* 1993; 70: 480–2.
22. MAROGNA M, SPADOLINI I, MASSOLO A, CANONICA GW, PASSALACQUA G. Randomized controlled open study of SLIT for respiratory allergy in real life: clinical efficacy and more. *Allergy* 2004; 59: 1205–10.
23. LOMBARDI C, GANI F, LANDI M, et al. Quantitative assessment of the adherence to sublingual immunotherapy. *J Allergy Clin Immunol* 2004; 113: 1219–20.
24. PAJNO GB, VITA D, CAMINITI L et al. Children's compliance with allergen immunotherapy according to administration routes. *J Allergy Clin Immunol* 2005; 116: 1380–1.
25. CARTER ER, ANANTHAKRISHNAN M. Adherence to montelukast versus inhaled corticosteroids in children with asthma. *Pediatr Pulmonol* 2003; 36: 301–4.
26. SHERMAN J, PATEL P, HUTSON A, CHESROWN S, HENDLES L. Adherence to oral montelukast and inhaled fluticasone in children with persistent asthma. *Pharmacotherapy* 2001; 21: 1464–7.