

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)

To the Editor:

Allergen-specific immunotherapy given as subcutaneous injections (SCIT) remained for decades the only available administration route. SCIT is effective and safe when properly prescribed and administered, but a remote risk of severe side effects exists. The problem of the risk/benefit ratio stimulated the search for safer administration routes, including sublingual immunotherapy (SLIT), introduced in 1986. Currently SLIT is considered a viable alternative to SCIT^{1,2} and is supported by many clinical trials.² The favorable safety profile (no severe adverse event in more than 15 years) was confirmed in several postmarketing surveillance studies.^{3,4} SLIT is convenient for the patient (no need for visits and injections), and a simplified administration schedule (short up dosing and once-daily administration) would make it even more user-friendly. These characteristics would suggest a potentially good compliance.

Compliance is defined as the degree to which the patient's behavior coincides with the medical prescription⁵ and is a common problem with all medications taken by the patient without a direct medical supervision.⁶ To date, there are very few data concerning the compliance with SLIT in the clinical trials. Thus, we designed a study (EASY: Evaluation of A novel SLIT formulation during a Year) to measure the compliance in a real-life setting.

This survey, limited to the compliance aspect, was designed as multicenter and observational. It was conducted with SLIT prepared in plastic monodose containers to be taken once daily (SLITone; ALK-Abelló, Lainate, Milan, Italy).

Allergists distributed over the entire Italian territory were asked to record the compliance data of 5 to 10 consecutive outpatients to whom they had prescribed SLIT. Data were collected from January 2004 until June 2005. Patients were diagnosed with allergic rhinitis and/or asthma according to guidelines² based on the clinical history, symptoms, positivity of skin prick tests (and/or RAST), and pulmonary function test when appropriate.

Skin tests were performed with a panel of standardized extracts (ALK-Abelló, Lainate, Italy) including mites, grasses, *Parietaria*, olive, birch, ragweed, hazelnut, *Cladosporium*, *Alternaria*, and cat and dog dander, plus a negative and a positive control.

Sublingual immunotherapy was prescribed to those patients with comorbid rhinitis and asthma, with persistent moderate/severe rhinitis, or with rhinitis (although intermittent) that was particularly troublesome during the allergen exposure. The economic aspect was also considered. The patients were informed in detail about the rationale of SLIT and the modality of the treatment. In the case of multiple sensitizations, or when it was not clear

which was the responsible allergen, specific nasal challenges were performed to identify a single allergen for immunotherapy.

Sublingual immunotherapy began with a short up dosing phase, involving the administration of 1 to 10 drops from the 200 Standard Therapeutic Units (STU)/mL vial in days 1 to 10. Starting from day 11, the maintenance dose, prepared in disposable monodose containers (200 STU/vial), was taken daily in the morning before breakfast. Each package of SLITone contained 90 monodose containers for a 3-month treatment period. Continuous treatment was prescribed to patients with dust mite allergy, whereas pollen allergy was treated preseasonally.

The manufacturer provided detailed printed instructions, and the patients received additional explanation on how to take and manage the therapy. The prescribing physician, or a physician at each center, was designated for telephone contacts if further information was needed. In addition to SLIT, all patients received the proper drug therapy as recommended in the guidelines.²

All patients were contacted by unscheduled telephone call during the 3rd (day 60-90) and 6th (day 150-180) month of therapy. During the telephone interview, each patient was asked whether he or she was still taking the SLIT, and was asked to count at that moment the remaining monodose containers in the blister. A computerized program, based on the starting date of SLIT, calculated the expected consumed and the expected remaining vials at a given date. Compliance was calculated as follows:

$$\frac{\text{Expected consumed} - \text{remaining}}{\text{Expected consumed}} \times 100$$

The patients recorded on a diary card the possible side effects after each dose of SLIT, as previously reported.³ 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 temporary discontinuation), moderate (need for drug treatment and/or SLIT discontinuation), or severe (life-threatening events needing hospitalization and/or emergency care).

By June 2005, 443 adult and adolescent patients (211 male subjects, 232 female subjects; mean age, 31.3 years; age range, 14-68 years) were included in the database. Two hundred seventeen had rhinoconjunctivitis, 196 rhinitis and asthma, and 30 only asthma. Prescribed SLITs were 220 mites (50%), 116 grass (26%), 69 *Parietaria* (16%), and 23 trees (5%). The remaining 3% of patients received mixed allergens. Data on compliance were obtained at the 3rd month for all 443 patients, and at 6 months for 266 patients, because the remaining 217 subjects had received a preseasonal treatment lasting 3 to 4 months only. The overall compliance data are summarized in Table I. In all cases, patients who were still on SLIT reported occasional

TABLE I. Compliance with SLIT measured at 3 and 6 months of treatment

	3rd mo (443 patients)	6th mo (226 patients)	P value
Compliance (%)	Patients, N (%)	Patients, N (%)	χ^2
>90	338 (76.3)	199 (74.8)	NS
75-89.9	48 (10.8)	37 (13.8)	NS
50-74.9	20 (4.5)	18 (6.7)	NS
25-49.9	4 (0.9)	5 (1.8)	NS
<25	7 (1.6)	3 (1.2)	NS
Discontinued	22 (5.0)	4 (1.7)	.01
Not started at all	4 (0.9)	—	NS

omission of doses because of negligence or forgetting. At the first phone contact, 22 patients (5.0%) had discontinued the treatment, and 4 patients had not taken SLIT at all. At 6 months, 4 additional patients had discontinued SLIT. The reasons for discontinuation, where available, are listed in Table II. Moderate side effects possibly related to treatment caused discontinuation in 4 of 443 (0.9%) patients.

Age, sex, education, and occupation did not influence the adherence rates, as confirmed by the χ^2 test, as well as the severity of the disease (data not shown). The cost of the treatment represented a major problem only in 2 of 443 patients who did not purchase it at all. There was no difference in compliance rates according to reimbursing modality. Of the patients with the higher compliance, 81%, 70%, and 82% had the treatment fully, partially, or not reimbursed, respectively. The percentages were 13%, 14%, and 11% in the patients with a compliance of 75% to 90% (again, no significant difference).

Compliance is one of the major determinants of a successful treatment,⁶ but an objective quantitative measurement is difficult to perform in real life. Asking the patient about the doses taken and weighing the canisters of inhaled drugs are imprecise methods, whereas electronic devices applied to drug packages are reliable, but quite expensive and not applicable to all drugs.

In the case of SCIT, it is believed that the adherence is virtually 100%, but looking at the literature, the compliance is far from being optimal.^{7,8} On the contrary, SLIT is safe and convenient, but self-managed by the patient; thus, the compliance could be expected to be lower than with SCIT. A direct comparison of the compliance between SLIT and SCIT is not possible, because different compliance measures would be required. Also, the measurement of the compliance with SLIT alone implies technical problems. One possible solution, applicable to liquid vaccines, is to measure the volume of the extract remaining in returned vials. One study used this method and reported a satisfactory compliance rate.⁹ With SLIT in tablets, the compliance can be assessed by asking the patient (without being warned in advance) to count the remaining tablets at a given moment.¹⁰ These methods may have intrinsic pitfalls, but the main problem is essentially the small number of subjects; thus, a large population study was needed. In

TABLE II. Number of patients who discontinued or did not start SLIT during the 6 months of observation and reasons for discontinuation

Reason	N (%)	Description
Discontinued for unknown reasons	10 (2.3)	Refused to provide explanation (4 discontinued between 3 and 6 mo)
Side effects not related to SLIT	6 (1.4)	Halitosis, panic attacks, acne
Side effects possibly related to SLIT	4 (0.9)	3 oropharyngeal itching, 1 general malaise
Did not begin the treatment	2 (0.5)	Refused to provide explanation
Required to be switched to injection immunotherapy	2 (0.5)	Judged the subcutaneous route easier to manage
Unaffordable cost	2 (0.5)	Did not purchase the prescribed SLIT
Intercurrent surgery	2 (0.5)	Hospitalized
Car accident	1 (0.3)	Hospitalized for major fractures
Pregnancy	1 (0.3)	Discontinuation suggested by the obstetrician for prudence
Total	30 (6.7)	

the present survey, SLIT was prepared in monodose containers for once-daily administration, and it was possible to count the doses taken by calling the patients randomly and asking them to count the remaining vials at the moment. It is unlikely that patients could perform the calculation of the correct number of doses in a few seconds; therefore, the results represent a realistic estimate of the compliance. According to this method, overall 75% of the patients took more than 90% of the prescribed doses, and the compliance was more than 75% in about 88% of the patients. In only 0.9% of the patients, discontinuation was caused by side effects possibly related to the treatment. There was a greater discontinuation rate at the first interview (Table II), but we cannot interpret this fact, because the 4 patients who discontinued after 3 months refused to provide an explanation.

These data obtained in a real life setting with SLITone show that the compliance is satisfactory despite the fact that the treatment is self-administered at home. The once-daily administration and the simple up dosing schedule are likely to play a relevant role in improving compliance.

We thank Prof G. W. Canonica for his helpful comments. We thank all the participating specialists for their cooperation: F. Benassi, D. Berra, L. Billeri, P. Borrelli, D. Bruzzese, S. Cabras, P. Candi, C. Caramazza, S. Casanova, S. Casotto, C. Castagneto, F. Castellano, M. Cilia, S. Crescioli, A. Cristaudo, A. Curcio, P. Dall'Aglia, S. Daniele, F. Della Torre, A. Ebbli, G. Feyles, A. Fiorina, M. Franzini, A. Giaccone, G. Giro, O. Grimaldi, G. Iannello, A. Ingrassia, E. Kugler, G. Loi, M. Marino, M. Mauro, G. Minore, P. Morandi, A. Moschella, R. Niniano, P. Omodeo, R. Pellegrino, E. Piuanti, L. Quaglio, F. Reccardini, F. Romano, E. Savi, S. Scaccianoce, G. Scarantino, M. Scarlato, S. Scarpa, P. Scavalli, E. Serpe, P. Serra, V. Sillano, L. Strazzeri, M. Torrazza, T. Truffelli, N. Verna, and M. Zambito.

Giovanni Passalacqua, MD^a
 Antonino Musarra, MD^b
 Silvia Pecora, MD^c
 Saverio Amoroso, MD^d
 Leonardo Antonicelli, MD^e
 Gianni Cadario, MD^f
 Mario Di Gioacchino, MD^g
 Carlo Lombardi, MD^h
 Erminia Ridolo, MDⁱ
 Guido Sacerdoti, MD^j
 Domenico Schiavino, MD^k
 Gianenrico Senna, MD^l

From the ^aAllergy and Respiratory Diseases, Department of Internal Medicine, University of Genoa, Pad Maragliano, I go R Benzi 10, 16132 Genoa, Italy;

^bAllergy Unit, National Healthcare System, Reggio Calabria; ^cALK-Abelló Italy, Lainate, Milan; ^dCivic Hospital of Palermo; ^eAllergy Unit, Azienda Ospedaliera-Universitaria Ospedali Riuniti, Ancona; ^fDivision of Allergy and Clinical Immunology, S. Giovanni Battista Hospital, Turin; ^gAllergy Unit, Policlinico Colledara, Chieti; ^hPneumoallergology Unit, FBF S. Orsola, Brescia; ⁱDepartment of Clinical Sciences, University of Parma; ^jPoliclinico Federico II, Naples; ^kAllergy Unit, Policlinico Gemelli, Rome; ^lAllergy Unit, Verona General Hospital, Verona, Italy.

Disclosure of potential conflict of interest: S. Pecora is employed by ALK-Abelló. The rest of the authors have no conflict of interest to disclose.

REFERENCES

1. World Health Organization position paper: allergen immunotherapy: therapeutic vaccines for allergic diseases. Bousquet J, Lockey R, Malling HJ, editors. *Allergy* 1998;53(suppl):1-33.
2. Allergic rhinitis and its impact on asthma. Bousquet J, Van Cauwenberge P, editors. *J Allergy Clin Immunol* 2001;108(suppl 5):S146-50.
3. Lombardi C, Gargioni S, Melchiorre A, Tiri A, Falagiani P, Canonica GW, et al. Safety of sublingual immunotherapy in adults: a post marketing surveillance study. *Allergy* 2001;56:889-92.
4. Di Rienzo V, Musarra A, Sambugaro R, Minelli M, Pecora S, Canonica GW, 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.
5. Haynes RB. Introduction. In: Haynes RB, Taylor DW, Sackett L, editors. *Compliance in healthcare*. Baltimore: John Hopkins University Press; 1979.
6. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med* 2005;353:487-97.
7. Tinkelman D, Smith F, Cole WQ 3rd, Slik HJ. Compliance with an allergen immunotherapy regimen. *Ann Allergy Asthma Immunol* 1995;74:241-6.
8. Lower T, Hensy J, Mandik L, Janosky J, Friday GA Jr. Compliance with allergen immunotherapy. *Ann Allergy* 1993;70:480-2.
9. 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.
10. Lombardi C, Gani F, Landi M, Falagiani P, Bruno M, Canonica GW, et al. Quantitative assessment of the adherence to sublingual immunotherapy. *J Allergy Clin Immunol* 2004;113:1219-20.

doi:10.1016/j.jaci.2005.12.1312

Airway inflammation in occupational asthma caused by styrene

To the Editor:

Styrene or phenylethylene has rarely been reported as a causative agent of occupational asthma.¹⁻⁴ This volatile monomer is widely used in the production of polymers, copolymers, and reinforced plastics and is a reactive solvent in the manufacture of unsaturated polyester resins. Styrene is known as an irritant to the skin and mucous

membranes and has been associated with dysfunction of the central nervous system. Workers in auto body shops may be exposed to styrene, because they use polyester resins in paints and car putty.

A 31-year-old man, a nonatopic and nonsmoker with persistent asthma, was referred for evaluation to the outpatient allergy clinic of our hospital. He had worked as a painter in an auto body shop for 4 years on a regular 8-hour shift during the day. He did not wear any protective equipment. During the last year, he had experienced sneezing, nasal discharge, ocular itching, and nasal stuffiness as well as dyspnea, dry cough, and wheezing when working. Asthma symptoms were more intense at the end of the work shift and at night, and he remained symptom-free during holidays and days off work. He handled paints containing hexamethylene diisocyanate (HDI) and polyester resins and hardeners that included in their composition styrene at a concentration of 10% to 25%, as disclosed by product labels and material data safety sheets.

He was evaluated 4 months after he had left his job because of asthma symptoms. After obtaining written informed consent, 3 single-blind specific inhalation challenges (SICs) were performed in a 7-m³ challenge chamber on separate days. This chamber is made of lacquered stainless steel (Telstar Projects SA, Madrid, Spain) and equipped with vacuum exhaust and high-efficiency particle arrest filtration. On visit 1, PC₂₀ was measured, and sputum induction was performed. On visit 2, the patient painted placebo solution (polyol) with a brush onto a cardboard for 5 minutes. Spirometry was performed at 5, 10, 20, 30, 40, and 60 minutes after the inhalation challenge. From that moment, peak expiratory flow and FEV₁ were measured hourly with a computerized flowmeter (Amos, Jaeger, Germany) for 24 hours after challenge, respecting sleeping time. On visit 3, the patient underwent a SIC with HDI. Twenty-four hours later, on visit 4, methacholine inhalation test and sputum induction were performed again. Three days later, on visit 5, the patient painted the styrene solution (20 mL) on a cardboard for 4 minutes, and the following day, on visit 6, a methacholine inhalation test and sputum induction were performed.

Physical examination, blood tests, and spirometry results were normal. Specific IgE against diisocyanates measured in the patient's serum was negative. Specific IgE against styrene was assayed in duplicate by ELISA, using a concentration of 20 µg/mL and serum dilution series starting from 1:2 as described elsewhere,⁵ and was also negative. Sputum was induced by hypertonic saline inhalation and processed as previously described (both with and without dithiothreitol).⁶ Sputum samples were analyzed using flow cytometer scan cytometry (FACSCalibur flow cytometer; Becton Dickinson, San José, Calif). mAbs (Pharmingen, San Diego, Calif) used to identify cells were CD19, CD3, CD4, CD8, CD16, CD45, CCR3 (B and T lymphocytes, neutrophils, and eosinophils), CD63, and CDw125 (activated basophils).

At baseline (visit 1), PC₂₀ methacholine was 1 mg/mL. On visit 2 (sham exposure), no significant changes in FEV₁ were observed over the next 24 hours. On visit 3,