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How adherent to sublingual immunotherapy prescriptions are patients? The manufacturers' viewpoint

To the Editor:

Adherence to prescriptions is crucial for all long-term treatments,¹ and this is true also for sublingual immunotherapy (SLIT), which is self-managed at home by the patients themselves. In fact, in the case of SLIT, medical supervision is usually limited to control visits or to prescription renewals. Available postmarketing studies indicate that the compliance with SLIT ranges from 50% to 95%, depending on age and on duration of treatment.² Nonetheless, the postmarketing surveys on compliance have an inherent limitation in that the observation itself can distort the results to some extent. In other words, when patients are aware that their compliance with treatment is recorded, they tend to be more adherent. Moreover, those studies assessed the adherence over limited periods, whereas SLIT should be continued for at least 3 years, according to recommendations. In everyday clinical practice, the general perception is that a large proportion of patients discontinues the prescribed SLIT, and this usually happens within the first year.

To address this latter aspect better, and to quantify the rate of discontinuations in real life, we collected the Italian sales figures from 2 large manufacturers (Stallergenes Italy, Milan, and ALK-Abelló Italy, Lainate, Milan), who kindly provided their data subdivided as per the 20 Italian administrative regions. It is to be noted that these manufactures account for more than 60% of the Italian immunotherapy market. To assess the discontinuation rates over at least 3 years, we counted, in cooperation with manufacturers' personnel, the number of SLIT treatments sold in 2006 as first prescriptions, and how many of the same SLIT prescriptions were still prescribed as renewals in the subsequent years, until 2009. This could be done easily because in Italy SLIT is a named patient product, and each treatment sold can be tracked. The figures were provided as percentages, with the initial sales in 2006 the 100% baseline. The data of the 2 manufacturers were analyzed pooled together, and subdivided per administrative region, per allergen (pollen/mite), and per modality of reimbursement.

The sales decreased from 100% to 43.7% $\pm$ 8% in the first year, to 27.7% $\pm$ 10.1% in the second year, and to 13.2% $\pm$ 7.5% in the third year. This means that, out of all the prescribed SLITs, less than 20% were continued after 3 years. No difference was detected between the 2 manufacturers in any of the 3 years (*t* test *P* > .1), and the results were consistent across the 20 administrative regions of Italy, where the figures ranged between 60% and 28% in the first year, 47% and 29% in the second year, and 16% and 6% in the third year. Of note, the lowest discontinuation rate was in the northern region Valle d'Aosta, with 60%, 47%, and 26% continuing treatment in the 3 years, respectively. The highest discontinuation rate was found in the southern region of Campania, with 28%, 17%, and 6% continuing treatment in the first, second, and third years, respectively.

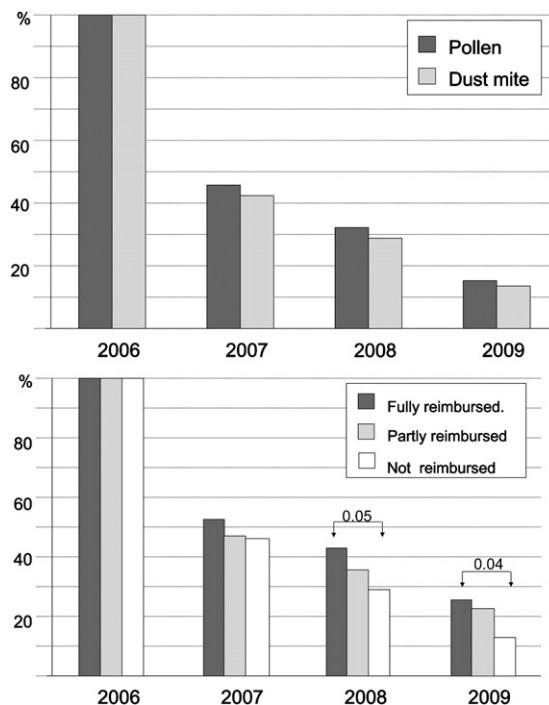


FIG 1. Percentages of SLIT treatments still ongoing at 1, 2, and 3 years after the initial prescription. *Upper panel*, Percentages for pollens and house dust mite SLITs. *Lower panel*, Percentages according to the reimbursement modality. Significant *P* values are indicated above the bars.

Some of the patients had more than 1 SLIT prescription, but none of them discontinued a single treatment only; thus, the percentages were unaffected. There was no difference between SLIT for pollens and SLIT for house dust mite, as shown in the *upper panel* of Fig 1; thus, the regimen of administration (preseasonal or continuous) does not seem to play a relevant role in the discontinuation rate. Surprisingly, the discontinuation rate was only marginally influenced by the modality of reimbursement, and a similar progressive decrease was seen in the Italian regions with full reimbursement, partial reimbursement, or no reimbursement at all (*lower panel*, Fig 1). Only in the second and third years, the difference between the regions with full reimbursement and no reimbursement became significant (*P* < .05).

Adherence to SLIT as assessed in postmarketing surveys is reported to be quite high,² reaching 95% of the prescribed doses in some cases.³ Nonetheless, these optimistic results do not fully reflect what happens in real life. In fact, the general perception of clinical allergists is that many patients discontinue their SLIT treatment and do not complete its 3-year course. The assessment of manufacturers' sales seemed to be a quite reliable approach for quantifying the phenomenon. Thus, we calculated the rate of spontaneous discontinuations by assessing the sales data of 2 large manufacturers in Italy over a 3-year period. According to these data, after 1 year from the prescription, only about 50% of the treatments were ongoing, and this percentage fell to almost 15% at 3 years. This behavior was consistent across the entire territory and identical for the 2 manufacturers. Certainly in such a survey, it was not possible to identify the reasons for discontinuation of SLIT treatments, although no discontinuation for severe adverse events was reported by the 2 producers. Among the reasons for discontinuing SLIT, the cost would be considered one

of the most relevant determinants,⁴ but in our evaluation, the difference between the regions with or without reimbursement was marginal and not sufficient to explain the high rate of discontinuations. On the other hand, a recent report suggested that the frequency of control visits strongly affects the adherence,⁵ which seems to be plausible but could be not assessed in this context.

In conclusion, sales data provided by manufacturers show an alarming rate of SLIT discontinuation, which is approximately 90% at 3 years after prescription. The phenomenon is uniform and consistent, and its causes need to be investigated urgently, because adherence is of primary relevance for the efficacy of SLIT. A stricter and closer collaboration between clinicians and manufacturers could be a reasonable approach to study the problem and, possibly, solve it.

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Wheezing in preschool children is associated with increased levels of cytokines/chemokines in exhaled breath condensate

To the Editor:

Although asthma is a common disease in children, only a minority of young children with respiratory symptoms, such as wheeze, will develop persistent symptoms. Mostly, preschool wheeze is associated with viral respiratory tract infections. These children are usually symptom-free at the age of 6 years. Airway inflammation is a central feature in asthma. Whether and to what degree airway inflammation is already a characteristic in wheezing preschool children is unknown. The current tools to assess airway inflammation, such as lung biopsy and bronchoalveolar lavage, are too invasive for routine use in young children. There is an increasing interest in the noninvasive assessment of inflammatory markers in exhaled breath such as fractional exhaled nitric oxide (FeNO) and solutes in exhaled breath condensate (EBC).

The aim of our study was to assess whether FeNO levels, inflammatory markers in EBC, and airway resistance are associated with wheezing in preschool children.

This study included children from the Asthma DEtection and Monitoring (ADEM) study that started in 2006 in the Netherlands (registered at clinicaltrials.gov: NCT 00422747).¹ A total of 258 preschool children (age range, 1.9-4.5 years) were selected: 57 children who never wheezed, 78 children with 1 to 3 wheezing episodes, and 123 children who experienced more than 3 wheezing episodes during life (defined as recurrent wheeze), as assessed by the International Study of Asthma and Allergies in Childhood questionnaire.² Clinical characteristics are summarized in Table I. If applicable, inhaled corticosteroids administration was stopped at least 4 weeks before the measurements. The offline measurements of FeNO, the collection of EBC, and the measurements of airway resistance have been described in detail previously.¹ In short, FeNO was collected offline in a 500-mL inert balloon during tidal breathing and analyzed by using a nitric oxide monitoring system (NIOX; Aerocrine, Solna, Sweden). To collect EBC, a closed glass condenser system with a breath recirculation unit was used, which was developed at our institute.¹ This efficient condenser system enables the recirculation of exhaled breath that does not directly condense. As a result, a high amount of EBC can be collected in a short time. Acidity of EBC was analyzed directly after collection (Radiometer Benelux B.V., Zoetermeer, The Netherlands). Inflammatory markers in EBC (Interleukin [IL]-1 α , IL-2, IL-4, IL-5, IL-8, IL-10, IL-13, soluble intercellular adhesion molecule [sICAM], TNF- α , RANTES [Chemokine (C-C motif) ligand 5 (CCL5)], and eotaxin [CCL11]) were measured using multiplex immunoassay (Luminex Corp, Austin, Tex). Airway resistance before and after a short-acting β_2 -agonist (300 μ g salbutamol; Teva Pharma, Haarlem, The Netherlands) was measured by using the MicroRint device (Micro Medical Ltd, Rochester, United Kingdom).¹

Differences among the 3 groups regarding their clinical characteristics and main outcome measurements were evaluated by means of nonparametric tests (Kruskal-Wallis or Mann-Whitney) and the χ^2 test for categorical variables (SPSS Inc, Chicago, Ill). Adjustment for multiple testing was conducted via the false discovery rate. Differences among groups were considered significant when the corrected false discovery rate *P* value was <.05.

The results showed that 97% of the children (N=251) were able to produce sufficient EBC with a mean volume of 498 μ L (range, 60-1410 μ L). Sudden anxiety was the major reason for dropout of the remaining 7 children. Successful FeNO, baseline airway resistance, and postbronchodilator airway resistance measurements were achieved in, respectively, 99%, 96%, and 92% of the children.

All ILs (IL-1 α , IL-2, IL-4, IL-5, IL-8, IL-10, IL-13) and sICAM significantly differed between groups (*P* < .05, Kruskal-Wallis test). Results of the *post hoc* pairwise comparisons are shown in Fig 1 (A-C), in which the significant pairwise comparisons are marked with an asterisk (*P* < .05, Mann-Whitney test). Levels of all ILs and sICAM were higher in the group of children with >3 wheezing episodes than in the children who never wheezed. In addition, levels of IL-2, IL-4, and IL-10 were higher in children with minor symptoms (1-3 wheezing episodes) than in children who never wheezed. Both levels of IL-13 and sICAM were elevated in children with >3 wheezing episodes compared