

CORRESPONDENCE

Adherence to sublingual immunotherapy in preschool children

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Editor,

Specific immunotherapy is the only effective causal treatment that can modify the natural history of respiratory allergy (1). This effect is important in children, where a secondary prevention is desirable. Sublingual administration (SLIT) is accepted as a valid therapeutic option (2), and children represent an ideal population for SLIT, because of the good safety profile (2). Nonetheless, as per all chronic treatments, adherence is essential, but no data are available in preschool children. We assessed the adherence to SLIT in children aged <6 yrs and analyzed the factors possibly affecting adherence itself.

Children (age, 3–6 yrs) referred for respiratory diseases (bronchial asthma and/or rhinitis) and eligible for SLIT were enrolled. None had food allergy (possible confounding factor), and respiratory symptoms had to be present at least in the previous 6 months. The diagnosis of allergic asthma/rhinitis was made according to guidelines (3, 4). Patients receiving SLIT were stratified according to age: group A (3 ≤ yrs < 4.0), group B (4.0 ≤ yrs < 5.0), group C (5.0 ≤ yrs < 6.0). All the procedures involved standard clinical approaches; thus, the study was simply notified to the Ethical Committee of the University of Messina, and all parents provided written informed consent. Children were followed up during the 2-yr observation period with 3-month regular visits. SLIT extracts were from Stallergenes, Lofarma, ALK–Abellò, Allergopharma. Parents were allowed to choose drops or tablets, and SLIT was given according to manufacturers' recommendations. The administration technique was checked by pediatricians, using a placebo. Specific diary cards

to assess the adherence (pre-compiled list), side effects, and reasons for discontinuation/temporary interruption of SLIT (free answers) were given to parents and collected at each visit. The time and reasons for interruption/discontinuation were carefully recorded. The remaining vials/tablets were checked at control visits. If >80% of the scheduled doses were taken, the patient was considered adherent.

One hundred and fifty children (3–5.9 yrs, 86 boys) received SLIT for respiratory allergy (76% drops and 24% tablets). All suffered from allergic asthma and/or rhinitis from at least 6 months, and all received standard medications (antihistamines, intranasal corticosteroids, inhaled corticosteroids, bronchodilators). Mite SLIT accounted for 89.4% of prescriptions. Overall, 46% of 150 children discontinued SLIT. The percentage of discontinuations during the first year was significantly higher in group A than in groups B (52% vs. 18%, $\chi^2 = 12.7$, $p = 0.035$) and C (52% vs. 13%, $\chi^2 = 17.33$, $p = 0.032$), whereas during the second year, there was no difference between groups ($\chi^2 > 0.5$). The reasons for discontinuation, as determined by parents' interviews, are summarized in Table 1. The most common cause for withdrawal in group A was the subjective discomfort in keeping under the tongue drops/tablets, or children's refusal, without apparent side effects. The refusal was generally attributed to unpleasant taste. For groups B and C, withdrawals were attributed to ineffectiveness, or to family problems, not better defined. All withdrawals occurred during the first 3 months of treatment in group A, and within the first 6 months in the other groups. In those patients who did not discontinue SLIT, short interruptions (all <5 days), as a

Table 1 Cumulative frequencies and absolute number of the reasons for treatment discontinuation during the 2-yr period, according to age-group

	Group A		Group B		Group C	
Ineffective	4/50 (8%)		2/50 (4%)		2/50 (4%)	
	Drops 4/45	Tablets 0/5	Drops 2/36	Tablets 0/14	Drops 1/33	Tablets 1/17
Children's refusal/ local side effects*	24/50 (48%)		3/50 (7%)		2/50 (4%)	
	Drops 19/45	Tablets 5/5	Drops 2/36	Tablets 1/14	Drops 1/33	Tablets 1/17
Systemic side effects	1/50 (2%)		–		1/50 (2%)	
	Drops 1/45	Tablets 0/5	Drops 0/36	Tablets 0/14	Drops 1/33	Tablets 0/17
Time-consuming	3/50 (7%)		4/50 (8%)		4/50 (8%)	
	Drops 3/45	Tablets 0/5	Drops 3/36	Tablets 1/14	Drops 3/33	Tablets 1/17
Family problems	8/50 (16%)		7/50 (14%)		4/50 (8%)	
	Drops 8/45	Tablets 0/5	Drops 5/36	Tablets 2/14	Drops 3/33	Tablets 1/17
Total	35/50 (70%)		16/50 (32%)		13/50 (26%)	
	Drops 35/45	Tablets 5/5	Drops 12/36	Tablets 4/14	Drops 9/33	Tablets 4/17

*Group A vs. group B: $\chi^2 = 18.33$, $p = 0.002$; group A vs. group C: $\chi^2 = 19.02$, $p = 0.002$.

result of upper respiratory infections or accidental forgetting, were recorded, without differences between groups, and between tablets and drops, except for group A where tablets were discontinued in 100% of cases ($p < 0.01$ vs. drops). In patients who completed the 2-year course of treatment, adherence measured by returned doses remained over 80%. Adverse events occurred in 28 children (18.6%). Twenty-five had mild-moderate local reactions: tiredness and/or headache, abdominal pain, oral/lip itching. Those local reactions lead to SLIT withdrawal mainly in group A. Rhinoconjunctivitis was observed in two group C patients and wheezing in one group A patient who discontinued.

Poor adherence to therapy is a major factor contributing to poor disease control in allergic rhinitis/asthma. This holds true for SIT, which is a long-lasting disease-modifying treatment that requires optimal compliance. The available studies report high compliance rates, from 60% to 90% even in the long term (5). On the other hand, marketing data show a disappointing rate of discontinuations (6), that is, approximately 90% over 3 yrs. In this study, we specifically assessed the adherence to SLIT in children below the age of 6 yrs and found that children below the age of 4 had a lower adherence. The most common cause of treatment withdrawal below the age of 4 were local side effects or the refusal to keep in mouth drops or tablets. Of note, in very young chil-

dren, the appearance of itching in mouth is probably more troublesome than in other patients. Otherwise, a quite good adherence was seen from the age of four onwards. Another observation is that the majority of withdrawals in group A were recorded early in the treatment course. In this survey, the economic aspect was not a confounding factor, because SLIT was fully reimbursed by the healthcare system. Measures to enhance adherence include the use of reminders and frequent control visits (7).

To prevent poor adherence or immunotherapy refusal by young children, SLIT should be started preferably after the age of four. A strict monitoring of the adherence is anyway recommended.

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References

1. Passalacqua G. Specific immunotherapy: beyond the clinical scores. *Ann Allergy Asthma Immunol* 2011; **107**: 401–6.
2. Canonica GW (ed.). WAO Position Paper on Sublingual Immunotherapy. *Allergy* 2009; **66** (Suppl. 82): 3–33.
3. Bousquet J, Van Cauwenberge P, Kalthaev N (ed.). Allergic rhinitis and its impact on asthma (ARIA). Position paper endorsed by WHO. *J Allergy Clin Immunol* 2001; **108** (Suppl. 5): 147–334.
4. Global Initiative on Asthma Management (GINA Guidelines). Available at: <http://www.ginasthma.org>
5. Senna G, Ridolo E, Calderon M, Lombardi C, Canonica GW, Passalacqua G. Evidence of adherence to allergen-specific immunotherapy. *Curr Opin Allergy Clin Immunol* 2009; **9**: 544–8.
6. Senna G, Lombardi C, Canonica GW, Passalacqua G. How adherent to sublingual immunotherapy prescriptions are patients? The manufactures' viewpoint *J Allergy Clin Immunol* 2010; **126**: 668–9.
7. Vita D, Caminiti L, Ruggeri P, Pajno GB. Sublingual immunotherapy: adherence based on timing and monitoring control visits. *Allergy* 2010; **65**: 668–9.