

Changing the route of immunotherapy administration: An 18-year survey in pediatric patients with allergic rhinitis and asthma

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ABSTRACT

Immunotherapy can be administered either sublingually (sublingual immunotherapy [SLIT]) or subcutaneously (subcutaneous immunotherapy [SCIT]). The rate of route switching, required by patients, can provide an indirect evaluation of patients' preferences and adherence. The authors retrospectively reviewed patients' files over an 18-year period to quantify the changes in the route of administration. The clinical records of children referred for respiratory allergy between 1994 and 2011 and prescribed with SLIT or SCIT were reviewed. The specific causes of the shift from SLIT to SCIT and vice versa were always assessed, with a special attention to adverse events. The records of 4933 children (2289 male patients, aged 4–18 years) were reviewed. Six hundred forty-eight patients received SCIT and 4285 patients received SLIT. Of the 4285 SLIT patients, 340 (7.9%) shifted to SCIT, mainly with *Parietaria judaica* and grasses. The 85.8% of the changes were caused by a perceived low efficacy. None of the parents required the route change for side effects. Of the 648 patients initially treated with SCIT, 54 (8.3%) shifted to SLIT, 85% of them for local or systemic side effects, but none for poor efficacy. The rate of SCIT/SLIT changes is, overall, low and because of poor efficacy for SLIT and side effects for SCIT.

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Allergic respiratory diseases (rhinitis and asthma) are constantly increasing worldwide and represent a common health care problem, with economic implications. Despite there are evidence-based guidelines addressing the pharmacologic treatment of symptoms,^{1,2} allergen-specific immunotherapy (AIT) still remains the only allergen-oriented therapeutic approach that can modify the immunologic response to allergens.^{3,4} This implies not only the reduction in symptoms and drug intake, but also a long-lasting effect and an interference with the natural evolution of the disease (e.g., development of asthma in patients with rhinitis).⁵

AIT can be administered either by injection (subcutaneous immunotherapy [SCIT]) or sublingually (sublingual immunotherapy [SLIT]),^{6–9} and the two routes proved equivalent in terms of efficacy in some head-to-head comparisons.^{10,11} On the other hand, the more recent guidelines on how recommendations should be made, take into account not only the clinical efficacy and the quality of evidence, but also safety, costs, and patient's preference and adherence.^{12–15} In the case of AIT, however, few data are currently available on the

patient's preference¹² about the two routes of administration. A possible evaluation of this aspect can be performed by assessing the rate of changes from SLIT to SCIT (and *vice versa*) as required by patients. Thus, we retrospectively reviewed the patients' files in an 18-year period of time to evaluate the changes in the routes of administration.

METHODS

The clinical records of children referred for respiratory allergy to the Pediatric Allergy Unit of the Department of Pediatrics of University of Messina–Italy Clinic between 1994 and 2011 were reviewed. Our clinical records always report, in detail discontinuations, side effects and administration route replacements. Only those receiving AIT (either SLIT or SCIT), prescribed according to guidelines,^{6,7} were considered. AIT was given for allergic rhinitis and/or asthma, which were diagnosed according to guidelines. In particular, the positivity of skin-prick test or CAP assay for at least one of the locally relevant allergens (dust mite, grass, *Parietaria*, olive, cypress, cat, dog, ragweed, mugwort, *Aspergillus*, and *Alternaria*) had to be documented. Both SLIT and SCIT were given according to the manufacturers' recommendations. AIT manufacturers were Stallergens (Antony Cedex, France), Lofarma (Milan, Italy), Alk Abellø (Hørsholm, Denmark), Allergopharma (Reimbeck, Germany), and Anallergo (Florence, Italy).

As per routine practice, the SCIT maintenance dose was given monthly. In the case of SLIT, regular visits

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Table 1 Demography and clinical characteristics of the patients

	Total	SCIT	SLIT	$p \chi^2$ SCIT vs SLIT
Patients	4933	648	4285	<0.001
M/F (%)	2289/2644 (46)	304/344 (47)	21,992/4285 (47)	NS
Age range (yr)	4–18	7–18	4–18	—
Rhinitis (%)	1221 (25)	235 (36)	986 (23)	NS
Asthma (%)	1018 (21)	98 (15)	920 (21)	NS
Asthma + rhinitis (%)	2694 (54)	315 (49)	2379 (56)	NS
Grass only	925 (19)	190 (29)	735 (17)	NS
<i>Parietaria</i> only	1244 (25)	236 (36)	1008 (23)	NS
Olive only	164 (3)	67 (10)	97 (2)	NS
Dust mite only	765 (15)	72 (11)	693 (16)	NS
Grass + mite	316 (6)	4 (0.6)	312 (7)	NS
Grass + par	198 (4)	21 (3)	177 (4)	NS
Par + mite	395 (8)	15 (2)	380 (9)	NS
Other	17 (0.3)	3 (0.3)	14 (0.4)	NS

NS = not significant; SCIT = subcutaneous immunotherapy; SLIT = sublingual immunotherapy.

(at 3- to 4-month intervals) were always scheduled to achieve a satisfactory adherence.¹⁶ The parents of allergic children were carefully instructed about the administration of SLIT and the management of the possible side effects. Those patients who underwent AIT for <2 years were excluded.

SCIT was administered to patients in our allergy unit by trained pediatricians. The specific causes of the shift SLIT/SCIT and *vice versa* were always assessed and reported. In particular, adverse events were documented. For SLIT, tiredness, headache, itching in mouth and throat, itching and swelling lips, abdominal pain, nausea, vomiting, diarrhea, urticaria, wheezing, rhinoconjunctivitis, hypotension, and anaphylactic reactions were documented. For SCIT, tiredness, headache, local swelling, redness, itching, induration, urticaria, wheezing, rhinoconjunctivitis, and hypotension anaphylactic reactions were documented. The files were also examined for shifting causes other than side effects, such as lack of adherence due to children's refusal, family problems, time-consuming (<80% of the scheduled doses taken and discontinuation during the first pollen season), or low efficacy. Only the data regarding house-dust mites, *Parietaria* grass, and olive tree pollen were considered, because of the very small number of children treated with other therapeutic allergens. The study was approved by the Ethics Committee of the University Hospital of Messina.

RESULTS

The records of 4933 children (2289 male patients; mean age, 11 year; age range, 4–18 years) were reviewed. The diagnosis was rhinoconjunctivitis alone in 1221 patients (25%), asthma alone in 1018 patients

(21%), and asthma plus rhinitis in 2694 patients (54%). Of them, 648 (304 male patients; mean age, 13 years; age range, 7–18 years) patients received SCIT, and 4285 (1985 male patients; age range, 4–18 years; mean age, 10 years) patients received SLIT. The demographic and clinical details are summarized in Table 1.

Among the reviewed patients, of the 4,285 with prescribed SLIT, 340 shifted to SCIT (7.9%). SLITs were most frequently interrupted and shifted to SCITs with *Parietaria judaica* pollen (4.29%) followed by grass (2.56%). Considering single allergens the rate of *Parietaria* reached 11.73%, and grass reached 8.95%. Among the 340 patients shifting from SLIT to SCIT, 292 (85.8%) were ascribed to a perceived low efficacy of sublingual route, whereas 48 patients' parents (14.2%) reported lack of adherence (forgetting the daily dose or refusal not because of side effects). None of the parents required the route change for local or systemic side effects (Table 2). Of the 648 patients initially treated with SCIT, 54 (8.3%) shifted to SLIT. According to each single allergen, *P. judaica* achieved a rate of 10.62% and grass received a rate of 8.32%. Among these, patients 46 (85%) shifted to SLIT because of the appearance of local side effects (large local reactions or induration at the site of injection); 3 patients (6%) shifted for systemic reactions and 5 patients (9%) for lack of adherence. None of the parents required the replacement of the administration route for perceived inefficacy.

Systemic side effects (e.g., urticaria and/or asthma and/or rhinitis) occurred in 36 SLIT patients (0.84%) over 18 years, in five cases with two organs involved. In none of them a switching to SCIT was requested, although SLIT was discontinued in the majority of those patients. With SLIT, no reactions or multiple

Table 2 Changing SLIT to SCIT and *vice versa*

	SCIT TO SLIT (n = 54/648)	SLIT TO SCIT (n = 340/4285)	$p\chi^2$
%	8.3	7.9	NS
Nonadherence	5 (9.25%)	48 (14.12%)	NS
Side effects	49 (90.75%)	0	<0.001
Inefficacy	0	292 (85.88%)	<0.001
<i>Parietaria</i>	29 (4.47%)#	184 (4.29%)*	NS
Grass	18 (2.77%)#	110 (2.56%)*	NS
Dust mite	5 (0.77%)	41 (0.95%)	NS
Olive	2 (0.30)	5 (0.11%)	NS

Numbers, percentages, and reasons for shifting the regimen.
#SCIT for single allergen: *Parietaria*, 10.62%, and grass, 8.32%.

*SLIT for single allergen: *Parietaria*, 11.73%, and grass, 8.95%.

NS = not significant; SCIT = subcutaneous immunotherapy; SLIT = sublingual immunotherapy.

organ life-threatening or epinephrine-requiring events occurred. With SCIT, one anaphylactic reaction occurred, caused by a *Parietaria* vaccine. The patient (female), aged 14 years, was successfully treated at the emergency department with i.m. epinephrine, i.v. betamethasone, and oral cetirizine. In this patient AIT was permanently discontinued, without shifting to the other route.

DISCUSSION

AIT is a long-term treatment, and it should be continued for 3–5 years to achieve an optimal disease control with a possible long-lasting effect. There are now two available routes of AIT administration: the SCIT traditional and the SLIT.⁷ Poor adherence to therapy is a major factor contributing to the poor disease control in allergy rhinitis/asthma.

For the first time we performed a particular retrospective study, to examine the frequency of replacement of one administration route of vaccines to the other. A similar, limited rate of patients shifted from SLIT to SCIT (7.93%) and *vice versa* (8.33%). However, differences were reported on the cause(s) of the shifting. The most common reason reported in allergic children who shifted from SLIT to SCIT was a perceived low efficacy of the treatment.

On the other hand, side effects caused by injections were the causes reported by the majority of patients who interrupted SCIT and shifted to SLIT. Among them, adolescents had frequent discomfort during injections with the appearance of recurrent swelling or urticaria on the arms. Girls also claimed beauty concerns caused by the local side effects. This study was of note retrospectively with the aim to verify in real life

both the rate and the reason of replacement(s) of administration routes of vaccines.

Recently, a meta-analysis suggested that SLIT vaccines for grass pollen is less effective than SCIT,¹⁷ but the head-to-head clinical trials failed to show a difference between the two routes.^{10,11} On the other hand, it is well known that SCIT can cause severe reactions including fatalities,^{18–20} although the more recent survey reported no fatality over a 3-year period.²¹ In addition, no fatal event and only 11 reported anaphylactic reactions have been so far described with SLIT.^{20,22}

Altogether, the absolute rate of “shifting patients” is low, <10% in both groups of patients. The replacement of different routes is requested by some allergic patients to avoid a real interruption of treatments(s). Therefore, to comply with them is reasonable, to improve efficacy and safety of allergen immunotherapy, also considering the different regulatory rules existing in the United States and in the European community.^{23,24}

REFERENCES

1. Bousquet J, Van Cauwenberge P, and Khaltaev N. Aria Workshop Group; World Health Organization. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 108(suppl 5): S147–S334, 2001.
2. Global Initiative on Asthma. Available online at www.ginasthma.org; accessed July 2012.
3. Soyer OU, Akdis M, and Akdis CA. Mechanisms of subcutaneous allergen immunotherapy. *Immunol Allergy Clin North Am* 31:175–190, 2011.
4. Jutel M, and Akdis CA. Immunological mechanisms of allergen-specific immunotherapy. *Allergy* 66:725–732, 2011.
5. Passalacqua G. Specific immunotherapy: Beyond clinical scores. *Ann Allergy Asthma Immunol* 107:401–406, 2011.
6. Bousquet J, Lockey R, and Malling HJ. World Health Organization Position Paper. Allergen immunotherapy: Therapeutic vaccines for allergic diseases. *Allergy* 53(suppl 44):1–42, 1998.
7. Frieri M. New frontiers in immunotherapy. *Allergy Asthma Proc* 20:281–288, 1999.
8. Malling H-J, Abreu-Nogueira J, Alvarez-Cuesta E, et al. EAACI position paper on local immunotherapy. *Allergy* 53:933–944, 1998.
9. Canonica GW, Bousquet J, Casale T, et al. Sub-lingual immunotherapy: World Allergy Organization Position Paper 2009. *Allergy* 64(suppl 91):1–59, 2009.
10. Khinchin S, Poulsen LK, Carat F, et al. Clinical efficacy of sublingual and subcutaneous birch pollen allergen-specific immunotherapy: A randomized, placebo-controlled, double-blind double-dummy study. *Allergy* 59:45–53, 2004.
11. Eifan AO, Akkoc T, Yildiz A, et al. Clinical efficacy and immunological mechanisms of sublingual and subcutaneous immunotherapy in asthmatic/rhinitis children sensitized to house dust mite: An open randomized controlled trial. *Clin Exp Allergy* 40:922–932, 2010.
12. Brozek JL, Baena-Cagnani CE, Bonini S, et al. Methodology for development of the Allergic Rhinitis and Its Impact on Asthma guideline 2008 update. *Allergy* 63:38–46, 2008.
13. Reisacher WR, and Visaya JM. Patient adherence to allergy immunotherapy. *Curr Opin Otolaryngol Head Neck Surg* 21: 256–262, 2013.
14. Scurati S, Frati F, Passalacqua G, et al. Adherence issues related to sublingual immunotherapy as perceived by allergists. *Patient Prefer Adherence* 4:141–145, 2010.

15. Bukstein D, Luskin AT, and Farrar JR. The reality of adherence to rhinitis treatment: Identifying and overcoming the barriers. *Allergy Asthma Proc* 32:265–271, 2011.
16. Vita D, Caminiti L, Ruggeri P, and Pajno GB. Sublingual immunotherapy: Adherence based on timing and monitoring control visits. *Allergy* 65:668–669, 2010.
17. Di Bona D, Plaia A, Leto-Barone MS, et al. Efficacy of subcutaneous and sublingual immunotherapy with grass allergens for seasonal allergic rhinitis: A meta-analysis-based comparison. *J Allergy Clin Immunol* 130:1097–1107, 2012.
18. Epstein TG, Liss GM, Murphy-Berendts K, and Bernstein DI. Immediate and delayed-onset systemic reactions after subcutaneous immunotherapy injections: ACAAI/AAAAI surveillance study of subcutaneous immunotherapy: Year 2. *Ann Allergy Asthma Immunol* 107:426–431, 2011.
19. Cox L, Calderon M, and Pfaar O. Subcutaneous allergen immunotherapy for allergic disease: Examining efficacy, safety, and cost-effectiveness of current and novel formulations. *Immunotherapy* 4:601–616, 2012.
20. Burks AW, Calderon MA, Casale T, et al. Update on allergy immunotherapy: American Academy of Allergy, Asthma & Immunology/European Academy of Allergy and Clinical Immunology/PRACTALL consensus report. *J Allergy Clin Immunol* 131:1288–1296, 2013.
21. Bernstein DI, Epstein T, Murphy-Berendts K, and Liss GM. Surveillance of systemic reactions to subcutaneous immunotherapy injections: Year 1 outcomes of the ACAAI and AAAAI collaborative study. *Ann Allergy Asthma Immunol* 104:530–535, 2010.
22. Passalacqua G, Baena Cagnani CE, Canonica GW, et al. Grading the local side effects of sublingual immunotherapy: Speaking the same language. *J Allergy Clin Immunol* 132:93–98, 2013.
23. Cox L, Compalati E, Kundig T, and Larche M. New directions in immunotherapy. *Curr Allergy Asthma Rep* 13:178–195, 2013.
24. Nelson HS. Is sublingual immunotherapy ready for use in the United States? *JAMA* 309:1297–1298, 2013. □

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