

SURVEY ON THE SAFETY OF A NO-UPDOSING REGIMEN OF SUBLINGUAL IMMUNOTHERAPY

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Sublingual immunotherapy (SLIT) is now recognized as a viable alternative to the injection route (1). Its efficacy in respiratory allergy has been repeatedly proven in numerous clinical trials and, concerning rhinitis, it is also supported by meta-analyses in children and adults (2, 3). A remarkable characteristic of SLIT is the very favourable safety profile, which has been confirmed in several post-marketing surveys involving also children below the age of five years (4, 5). Due to the optimal safety, and the absence of severe side effects, it was suggested that a slow up dosing phase maybe not necessary, and recent trials showed that starting the SLIT course with the maintenance dose does not lead to remarkable increase in side effects (6). On the other hand, a build-up phase with increasing doses is mandatory for injection immunotherapy for safety reasons, as suggested by the increased rate of side effects when accelerated or rush protocols are used (7). Omitting the up dosing phase, which requires the use of different vials of the product, is expected to make the treatment more patient-friendly and to avoid dosing mistakes. Based on this background we performed a large population-based survey in real life to evaluate the safety of the no-up dosing schedule in allergic patients.

All patients seen at our centres from January 2005 to March 2006, were prescribed SLIT in a no-up dosing regimen and the occurrence of side effects was evaluated by a dedicated diary card. A clear diagnosis of IgE-mediated respiratory allergy was required, and SLIT was prescribed according to guidelines (1) in persistent or moderate/severe rhinitis with or without mild to moderate asthma. The absence of contraindications to immunotherapy was carefully evaluated as well. SLIT, standardized in STU, was given as the commercial preparation (SLITone, ALK-Abellò,

Lainate, Milano) of single-dose containers to be assumed once daily. The usual regimen involves a build-up phase of 10 days, with increasing daily doses from a separate vial. In this survey, the up dosing phase was omitted and the patients were instructed to start immediately their SLIT course with the maintenance dose. All patients (or parents) were carefully instructed on the rationale and use of SLIT, on the possible side effects and on how to manage them. A physician was available at each centre for any possible problem and regular visits were planned as made in the routine practice. Patients were given a structured diary card where they had to record any adverse event occurring with SLIT. Adverse events were subdivided into local (oral itching/swelling) and systemic (urticaria, asthma, rhinitis, gastrointestinal complaints, anaphylaxis) and graded as mild (no need for treatment or dose adjusting), moderate (need for drugs/medical advice or dose adjusting), and severe (life-threatening or hospitalization or emergency care or discontinuation needed).

Between January 2005 and February 2006 the no-up dosing SLIT was prescribed to 156 patients (65 female and 91 male, mean age 19.83, range 5-54 yrs). One hundred and seventeen patients received SLIT for a single allergen (53 mite, 34 parietaria, 19 grass, 6 olive, 4 alternaria, 1 mugwort); 10 patients were treated with two separate extracts (6 parietaria and mites, 1 parietaria and grass, 1 parietaria and olive, 1 mite and grass, 1 parietaria and mugwort); 18 patients received a manufactured mix SLIT (17 grass+olive, 1 grass+mugwort) and 11 patients were treated with three allergens in various combinations. A continuous maintenance was given for mite, alternaria and parietaria (118 treatments), whereas for the other pollens a pre-seasonal regimen was recommended. Overall, during the survey, about 33,660 doses were given and the duration of the follow-up ranged from 4 to 15 months. One single adverse event due to SLIT was reported, i.e. mild oral and pharyngeal itching 15 minutes after the first dose. This side effect self resolved, disappeared after 15 minutes and was no more

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present at the subsequent doses. The overall rate of side effects resulted to be 0.7% of patients and less than 0,03 per 1,000 doses.

As it happened with injection immunotherapy, the simplified administration schedules for SLIT have recently gained the attention of clinicians. In fact, the updosing phase is time-consuming, requires the use of vaccines prepared in multiple blisters or vials at different concentrations and may represent a source of errors. The updosing phase cannot nevertheless be avoided with injection immunotherapy, whereas with SLIT the ultra rush and accelerated schedules have been proved safe (8, 9), and there are also reports on the tolerability of no-updosing (10, 11). The present survey was conducted in a large population of patients in real life and with a commercial product prepared as single-dose vials. The results confirm that starting the SLIT with the maintenance dose is a safe approach and the rate of adverse events does not differ with that observed in other surveys (4, 5) using the traditional regimen. In conclusion we suggest that the no-updosing administration can be a suitable and patient-friendly modality of administration of SLIT.

References

1. World Health Organization Position Paper. - Allergen immunotherapy : therapeutical vaccines for allergic diseases. Bousquet J, Lockey R, Malling HJ eds. *Allergy* 1998;53(suppl.):1-33.

2. Wilson D.-R., Torres L.-I., Durham S.-R. - Sublingual immunotherapy for allergic rhinitis (Cochrane review). *Cochrane Database Syst Rev.* 2003;(2):CD002893.
3. Penagos M., Compalati E., Tarantini F., Baena-Cagnani R., Passalacqua G. et al. - Meta analysis of the efficacy of sublingual immunotherapy in pediatric patients. *Ann Allergy Asthma Immunol* 2006 in press.
4. Fiocchi A., Pajno G., La Grutta S., Pezzuto F., Incorvaia C., Sensi L., Marcucci F., Frati F. - Safety of sublingual-swallow immunotherapy in children aged 3 to 7 years. *Ann Allergy Asthma Immunol.* 2005 Sep;95(3):254-8.
5. Di Rienzo V., Minelli M., Musarra A., Sambugaro R., Pecora S., Canonica W.-G., Passalacqua G. - Post-marketing survey on the safety of sublingual immunotherapy in children below the age of 5 years. *Clin Exp Allergy.* 2005 May;35(5):560-4.
6. Grosclaude M., Bouillot P., Alt R. et al. - Safety of various dosage regimens during induction of sublingual immunotherapy. *Int Arch Allergy Immunol* 2002;129:248-253.
7. Lockey R.-F., Nicoara-Kasti G.-L., Theodoropoulos D.-S., Bukantz S.-C. - Systemic reactions and fatalities associated with allergen immunotherapy. *Ann Allergy Asthma Immunol.* 2001;87(Suppl 1):47-55.
8. Rossi R., Monasterolo R.-E. - A pilot study of feasibility of ultra-rush (20-25 minutes) sublingual-swallow immunotherapy in 679 patients (699 sessions) with allergic rhinitis and/or asthma. *Int J Immunopathol Pharmacol.* 2005;18(2): 277-85.
9. Tripodi S., Di Rienzo Businco A., Benincori N., Scala G., Pingitore G. - Safety and Tolerability of Ultra-Rush Induction, Less than One Hour, of Sublingual Immunotherapy in Children. *Int Arch Allergy Immunol.* 2005 Dec 22;139(2):149-152.
10. Guerra L., Compalati E., Rogkakou A., Pecora S., Passalacqua G., Canonica W. - Randomized open comparison of the safety of SLIT in a no-updosing and traditional updosing schedule in patients with Parietaria allergy. *Allergol Immunopathol* 2006 in press.
11. Dahl R., Stender H., Rak S. - Specific immunotherapy with SQ standardized grass allergen tablets in asthmatics with rhinoconjunctivitis. *Allergy.* 2006;61:185-90.

