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Safety of ultrashort-term sit with pollen allergoids adjuvanted by monophosphoryl lipid A: a prospective italian survey

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Summary

A 3-year prospective post marketing survey on the safety of the recently developed ultra-short pre-seasonal subcutaneous immunotherapy (uSCIT-MPL4) with pollen allergoids adjuvanted with monophosphoryl lipid A was performed. A total of 510 patients received uSCIT-MPL4, 61% for grass, 35.7% for birch, 13.2% for parietaria and 3% for other pollens (ragweed, mugwort, and olive). A total of 3,308 injections were given and the mean duration of uSCIT-MPL-4 was 2.3 years. Overall, only 7 slight systemic reactions (SR) were observed in 510 patients (1.37%) and 2.11/1,000 injections suggesting that this treatment is even safer than traditional depot injection SIT.

The clinical efficacy of allergen specific immunotherapy for the treatment of respiratory allergy is well documented (1). However, its main drawback are the risk of systemic reactions and adherence, due to the long duration of the treatment. A recently developed immunotherapy with pollen allergoids adjuvanted with monophosphoryl lipid A involves an ultra-short pre-seasonal schedule, with only four injections (uSCIT-MPL-4), and therefore is expected to be convenient under the point of view of adherence. Several studies have demonstrated its clinical efficacy and tolerability in seasonal allergic rhinitis (2-4), but safety data in real life is still missing (5). In this study we prospectively assessed the safety of u-SCIT-MPL in a 3-year, multi-centre real-life trial.

Eight Italian allergy departments were involved in this prospective survey, which started in January 2006 and ended in December 2009. Physicians working at each center recorded both u-SCIT-MPL prescribed for respiratory allergy (seasonal rhinitis and/or asthma) and the adverse events observed during the course of the treatments in a standardized form. Immunotherapy was prescribed according to the recommendations of the European Academy of Allergology and Clinical Immunology (EAACI). The severity of asthma and rhinitis was graded according to GINA and ARIA guidelines (6, 7), respectively.

Each patient received four 1 ml subcutaneous injections (300, 800, 2,000 and 2,000 standardized units) of individually formulated u-SCIT-MPL using pollen allergoids (grass, tree, parietaria, ambrosia). The first three injections were administered at 1-2-week intervals, and the fourth after 1 to 4 weeks. The course was completed before the beginning of the relevant pollen season. The treatment was repeated for up to three consecutive years.

Table 1 - Details about the SR reported

Patient with SR	Sex/Age	Grade	Allergen	Disease	Epinephrine use	Concomitant risk factors	Dose
1	F/23	2	Grass	R	No	None	4
2	F/41	2	Grass	R and A	No	None	3
3	M/19	1	Birch	R and A	No	Viral infection	4
4	M/28	2	Ragweed	R and A	No	None	1
5	F/38	1	Parietaria	R and A	No	None	2
6	M/44	2	Birch	R and A	No	None	3
7	F/45	2	Grass	R and A	No	None	2

R: Rhinitis A: Asthma SR: Systemic Reactions; F: Females M: males

After each injection patients were kept under observation for 30 minutes by nurses and/or physicians. Allergen dose, changes in pharmacotherapy and systemic reactions (SRs) were carefully recorded. Peak expiratory flow values were also recorded before and after each injection in asthmatic patients. SRs were subdivided into immediate (occurring within 30 minutes) and late (onset > 30 minutes after injection) and their severity was graded according to the EAACI system (8). In case of SRs, an appropriate rescue treatment was given according to guidelines. For each SR, a detailed recording of demographic and clinical characteristics of the patient was performed. This included details on the phase of treatment and the presence of risk factors (infections, concomitant drugs, exposure to allergens, alcohol intake). The course of the SR and the actions taken were recorded as well.
A total of 510 patients (276 males and 234 females; age range 6-66 years) received uSCIT-MPL-4 in the study period (61% for grass, 35.7 % for birch, 13.3% for parietaria and 3% for ragweed); 18% received more than one extract. A total of 3,308 injections were given and the mean duration of uSCIT-MPL-4 treatment was 2.3 years. Overall, 7 SRs were observed, corresponding to 1.37% of patients and 2.11/1000 injections. All SRs were delayed (> 30 minutes) and Grade 1 or 2. Epinephrine was not required for any of the reactions. All reactions resolved spontaneously or after administration of oral antihistamine. Two of the patients with SRs discontinued the treatment, whereas the remaining five patients completed the treatment, with a dosage modification. In one patient, only a possible concomitant risk factor (viral infection) was identified. The details of the observed SRs are shown in Table 1.
Safety remains a major concern for subcutaneous immunotherapy and systemic reactions, although overall rare, seem to be unavoidable and unpredictable. For this reason we undertook this prospective post-marketing survey involving several allergy centers scattered in Italy, as the safety assessment is pivotal for every new immunotherapy. Safety of subcutaneous immunotherapy was addressed by several surveys mainly conducted in the USA, whereas less data are available for European countries (9, 10). These studies provided variable results according to the recording system, the country and the immunotherapy regimen, but the overall result is that, despite the general fear, subcutaneous immunotherapy is acceptably safe (9, 10). Based on the available data, this recently developed immunotherapy seems to be even safer than the traditional ones, though our results have to be confirmed in larger studies.
In conclusion, the low rate of SRs observed in this large prospective study suggests that allergoid uSCIT adjuvanted with monophosphoryl lipid A has an acceptable risk/benefit ratio, provided that it is carried out following the recommendations and according to the manufacturer's instructions.

References

1. Bousquet J, Lockey RF, Malling HJ. Eds. WHO Position Paper Allergen Immunotherapy: Therapeutic Vaccines for Allergic Diseases. Allergy 1998; (Suppl 44): 1-42.
2. Drachenberg KJ, Heinkill M, Urban E, Woronieck. Efficacy and tolerability of short-term specific immunotherapy with pollen allergoids adjuvanted by monophosphoril lipid A (MPL) for children and adolescents. Allergol Immunopathol 2003; 31: 270-7
3. Drachenberg KJ, Wheeler AW, Stuebner P, Horak F. A well-tolerated grass pollen-specific allergy vaccine containing a novel adjuvant, monophosphoril lipid A, reduces allergic symptoms after only four preseasonal injections. Allergy 2001; 498-505.
4. McCormack PL, Wagstaff AJ. Ultra-short-Course seasonal allergy vaccine (Pollinex Quattro). Drugs 2006; 66: 931-8.
5. Rosewich M, Schultze J, Fisher von Weickensthal-Drachenberg KJ, Zielen S. Ultra-short course of immunotherapy in children and adolescents during a 3-yrs post-marketing surveillance study. Pediatr Allergy Immunol 2010; 21: e185-e9.

6. Global Initiative for Asthma. www.ginasthma.org
7. Bousquet J, Cruz A, Ait Khaled N, Bachert C, Baena Cagnani C et al. Pharmacologic and anti-IgE treatment of allergic rhinitis ARIA update (in collaboration with GA2LEN). Allergy 2006 Sep; 61(9): 1086-96.
8. EAACI Immunotherapy position paper. Malling HJ & Weeke B edts, Allergy 1993; 48(supp 44): 9-35.
9. Schiappoli M, Ridolo E, Senna G, Alesina R, Antonicelli L, Asero R, Costantino MT, Longo G, Musarra A, Nettis E, Crivellaro M, Savi E, Massolo A, Passalacqua G. A prospective italian survey on the safety of subcutaneous immunotherapy for respiratory allergy. Clin Exp Allergy 2009; 39: 1569-74.
10. Windom HH, Lockey RF. An update on the safety of specific immunotherapy. Curr Opin Allergol Clin Immunol 2008; 8: 571-6.