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Efficacy, safety and tolerability of sublingual monomeric allergoid in tablets given without up-dosing to pediatric patients with allergic rhinitis and/or asthma due to grass pollen

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Key words

Asthma, carbamylated allergoid, pediatric patients, sublingual immunotherapy, rhinitis

Summary

The efficacy and safety of monomeric allergoid (Lofarma, Milan) have been demonstrated in adults but very few studies have examined it in children. This study therefore investigated the efficacy and safety of this sublingual immunotherapy (SLIT) at the dosage of 1000 AU five times a week without any up-dosing. Forty allergic children (17 M and 23 F, mean age 7 years, range 4-16 years), 16 with rhinitis and 24 with rhinitis and asthma, were randomized to SLIT or drug therapy. All the patients were sensitized to grass; some were also sensitized, though to a lesser extent, to Parietaria, Olea and Betulaceae. The patients were treated pre-/co-seasonally for two years. A visual analogue scale (VAS) was used at baseline and at the end of the first and second pollen seasons to rate the patients' well-being. The VAS score was significantly higher after both the first and the second year of treatment in the SLIT group than in the controls ($p<0.05$). It improved in comparison to baseline only in the active group. All 40 children tolerated the therapy very well. The monomeric allergoid at the dosage of 5000 AU/week thus appears to have a good efficacy and safety profile in children.

Introduction

Specific immunotherapy (IT) is important in the prevention and treatment of respiratory allergy and its clinical value is acknowledged today (1-3). In the last few years new routes of administration have been investigated and developed. The sublingual route (sublingual immunotherapy - SLIT) appeared the most promising alternative to the traditional IT (3-6). Some randomized clinical trials have demonstrated the efficacy and safety of SLIT in the management of respiratory allergy due to grass pollen, at least in adults (7-9).

A decade ago the EAACI-ESPACI position paper (10) did not recommend SLIT for normal use in pediatric practice, since only a few controlled clinical trials had evaluated its efficacy and safety in children. Many more trials have now been conducted in children, with rhinitis and asthma, and the efficacy and safety are good (11-16). However, some findings are still conflicting in terms of effectiveness, type of allergen and dose (17). The present study in a pediatric population allergic to grass pollen evaluated the efficacy, safety and tolerability of SLIT with a carbamylated monomeric allergoid during two consecutive pollen seasons, employing a dosage of 5000 allergenic units (AU) per week without any build-up phase.

Materials and methods

Study design

This prospective, open-label, randomized study included two parallel groups given either SLIT or standard pharmacotherapy, with a history of at least two years of intermittent or persistent rhinitis or rhinoconjunctivitis, and/or mild intermittent or mild persistent allergic asthma for at least one year (18). Both groups were allowed rescue medication on demand for a very short period (no more than a few days). There was no run-in period. All the patients had a baseline evaluation at the beginning of the study (Tab. 1). The endpoints were the occurrence of symptoms in the two groups and the differences between visual analogue scale (VAS) scores in the treated and control groups at baseline and after one and two years. The VAS rating system was used to assess the patients' well-being before and after therapy and thus, indirectly, the severity of symptoms during the SLIT. The best possible score for well-being was 10 and the worst 0.

Patients

Forty allergic children were enrolled (17 M and 23 F, mean age 7 years, range 4-16 years), 16 with rhinitis only and 24 both rhinitis and asthma. The allergies were caused by grass pollen in most of the patients. All 40 were in fact sensitized to grass as confirmed by a positive (>3 mm) skin prick test response (Lofarma S.p.A., Milan) and positive CAP-RAST assay (class II or greater) (CAP System EIA, Pharmacia, Uppsala, Sweden). Twenty percent of the patients were sensitized to other seasonal allergens such as Parietaria, Olea and Betulaceae, though to a lesser extent and without any associated symptoms.

Children with systemic or immunological diseases, major anatomical alterations of the upper airways, renal insufficiency, coronary heart disease, neurologic or psychiatric diseases, or requiring chronic corticosteroids were excluded from the study. The children's parents signed an informed consent form before the child entered the study.

Investigational SLIT and concomitant pharmacotherapy

The SLIT consisted of a monomeric carbamylated allergoid (Lais®, Lofarma S.p.A., Milan) biologically standardized (19) in AU and prepared as soluble tablets for oral use (allergoid SLIT). The tablets were taken in the morning on an empty stomach and kept under the tongue for 1-2 minutes so they dissolved before swallowing. There was no build-up phase. Patients were treated pre/co-seasonally for 12 weeks/year for two consecutive years. The maintenance dosage was 1000 AU five times a week for 12 weeks in each pollen season (total amount of allergen 60,000 AU/year). Treatment started eight weeks before the pollen season and continued for four weeks during it.

Rescue medication, used as needed to control acute symptoms, was as follows: cetirizine or desloratadine tablets, inhaled salbutamol, intranasal fluticasone. A short course of systemic steroid was allowed (1 mg/kg daily for three days) for severe symptoms that did not respond to standard treatment.

Clinical evaluation

The patient's parents were required to record the presence and severity of symptoms on a special diary form each day during the pollen season. The following symptoms were considered: sneezing, rhinorrhea, obstruction, tearing, cough, nocturnal and diurnal asthma. Each symptom was rated from 0 (absent) to 3 (severe). Parents were also asked to complete the VAS and record any adverse events (AE). AE were classified as local (oral itching, swelling of the tongue) and systemic (asthma, rhinitis, urticaria, abdominal pain/diarrhea, anaphylaxis).

Statistical analysis

The Mann-Whitney U test for intergroup comparison was used to establish whether a particular variable differed significantly between the two populations (active and

Table 1 - Patients characteristics at baseline

	5000 AU/Week (for 12 weeks)	Controls	p
Patients (n.)	20	20	NS
Sex (M/F)	9/11	8/12	NS
Mean Age (years ± SD)	9.1± 3.6	4.8±1.5	NS
Weight (KG)	36±14.8	19.6±5.6	NS
Height (cm)	139±22.0	113±11.3	NS
Disease:			
Rhinitis without asthma	9	7	NS
Rhinitis with astma	11	13	NS

control) at baseline. The Wilkinson Signed Ranks test was used to evaluate the differences in VAS scores within each group and the Mann-Whitney test to analyze these differences between cases and controls.

Results

The VAS score was significantly higher throughout the treatment period in the allergoid SLIT group than the control group ($p<0.05$). It improved from baseline only in the SLIT group (Fig. 1). The global symptom score was slightly lower in the active group but the difference from controls was not significant (Fig. 2). All 40 children tolerated the therapy very well, with no systemic or local AE.

Discussion

The clinical efficacy and safety of SLIT with oro-soluble tablets, with no up-dosing phase, has been demonstrated in recent placebo-controlled, randomized clinical trials in large numbers of adults allergic to grass pollen (7-9). SLIT improves the patients' quality of life (6) and can prevent the development of asthma in children with allergic rhinoconjunctivitis (20). That SLIT is effective in pediatric patients was shown by the two meta-analyses of Penagos et al. in rhinitic and asthmatic children (15, 16), and by Whan et al. in 278 children and adolescents with grass-pollen induced rhinitis treated with SLIT in tablets; there was significant improvement of allergic symptoms during the pollen season and no serious AE (14).

The present trial, though it did not show any dramatic improvement in the symptom score in the SLIT patients, found a significant increase in the VAS ratings whose reliability in assessing the efficacy of treatment for allergic rhinitis was recently reported by Bousquet et al. (21).

Side effects, always a deterrent to using SLIT in children, have been very few in most studies to date, particularly in those using the monomeric allergoid (5, 6, 8-12). This can probably be ascribed to the low IgE-binding activity of the active ingredient (19) which prevents the IgE-mediated allergen presentation by dendritic cells to T_H2 cells, which is the key mechanism explaining the large increase of allergen-specific IgE observed during SLIT with native grass allergens (8-10). No AE were observed in present study despite the absence of a build-up phase. This allows us to suggest that in the future treatment might start even in children younger than five years old, with possible benefits for preventing the "allergic march" and new sensitizations.

Figure 1 - VAS mean values at baseline and after 5, 12 and 24 months of treatment in the 2 groups of patients

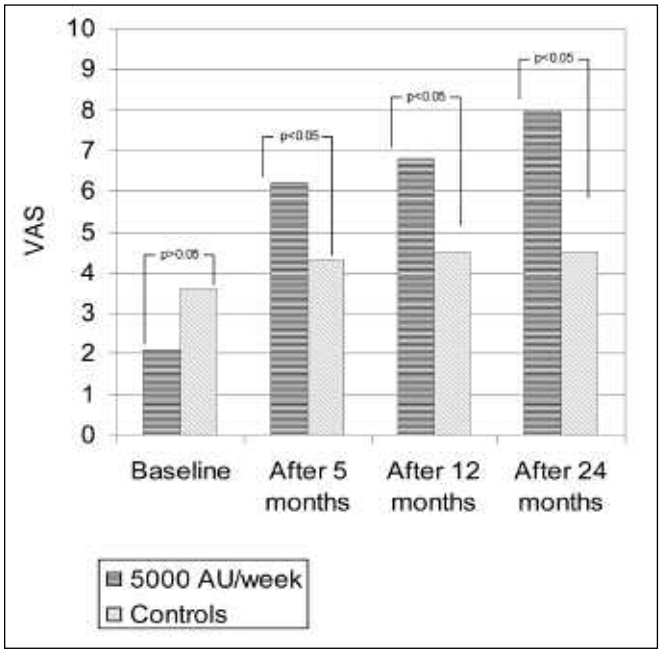
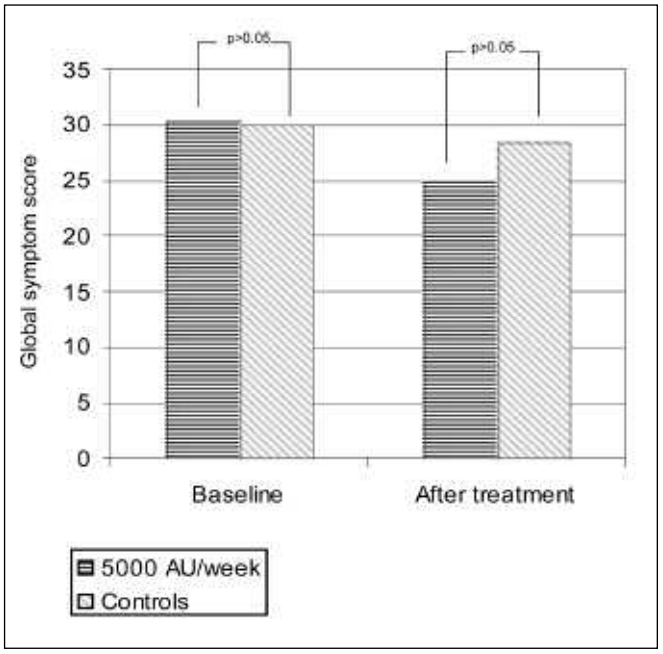


Figure 2 - Global symptom score in the 2 groups of patients before and after treatment



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