A. Musarra[1], D. Bignardi[2], C. Troise[2], G. Passalacqua[3]

Long-lasting effect of a monophosphoryl lipid-adjuvanted immunotherapy to parietaria. A controlled field study

[1] Allergy Unit, National Healthcare System, Reggio Calabria; [2] Allergy Unit, Azienda Ospedaliera S. Martino, Genoa; [3] Allergy and Respiratory Diseases, University of Genoa

Key words

Monophosphoryl lipid adjuvant, immunotherapy, long lasting effect, rhinitis, asthma.

Summary

Background: *The clinical efficacy of Monophosphoryl lipid A-adjuvanted immunotherapy (MPLA-SCIT) is ascertained, but there are no data on its possible long-lasting effect. We assessed in a real-life setting the persistence of the clinical effect five years after discontinuation.* ***Methods:*** *Patients with parietaria-induced respiratory allergy and fulfilling the criteria for immunotherapy prescription were evaluated at baseline, after the third year of MPLA-SCIT and five years after discontinuation. Visual analog scores, severity of the disease, pulmonary function and skin reactivity were assessed. Matched subjects who refused immunotherapy served as controls.* ***Results:*** *Twenty nine patients received MPLA-SCIT and 28 were the control group. There was a significant clinical improvement, as assessed by VAS only in the active group after 3 years that remained significant at 5 years versus baseline and controls. The distribution of severity of rhinitis was overall decreased at 3 and 8 years as well. The number of patients with conjunctivitis in the active group decreased from 19 to 6 at the end of the treatment and to 9 after 5 years. There was also a decrease in the number of patients with asthma symptoms (from 6 to 2 to 4), which doubled in the control group. A significant reduction in the wheal of the Parietaria skin test was seen in the active group at the end of the treatment (9.5±2.1 mm VS 6.4±2.6 mm; p=.01), but this reduction was lost at the 5-year. No relevant change was overall detected in pulmonary function.* ***Conclusion:*** *MPLA-SCIT is effective, and the clinical efficacy is maintained after 5 years of discontinuation.*

Introduction

Allergen specific immunotherapy (SIT) is widely used in the management of respiratory allergy, and the subcutaneous administration (SCIT) has represented the standard treatment for one century (1). During the last twenty years, numerous attempts were made to improve both the safety of SCIT (e.g. by the chemical modification of allergens to obtain allergoids)(2), or by changing the modality of administration (e.g. intralymphatic injection) (3). Another field of research was aimed at improving the efficacy, to obtain favourable clinical effects with smaller amounts of allergens. One of this approaches involves the administration of adjuvants together with the allergen. Adjuvants are non-immunogenic molecules that enhance the immunological effects of the antigen, but to be suitable for the human use, they should obviously be non toxic and non irritating. The monophosphoryl lipid A (MPLA), derived by the cell wall of a non-pathogenic Salmonella, was identified as an ideal candidate for this use. MPLA was demonstrated capable to enhance the Th1 response, and to increase the response to allergens

(4-6). Therefore, a MPLA-adjuvanted immunotherapy was prepared, tested in clinical trials (7, 8) and subsequently commercialised. Nowadays, MPLA-SCIT is widely used in routine clinical practice in many European countries.

In addition to the well-known clinical effects, namely the reduction of symptoms and/or medication intake, specific immunotherapy possesses additional properties, including the prevention of the onset new sensitisations and of the development of asthma. One of the most important additional properties is the long-lasting effect, that is the persistence of the clinical benefit for several years after discontinuation (9). The long-lasting effect can be interpreted as the result of a profound immunological modification of the immune response, with a Th1 skew partly mediated by allergen-specific T regulatory cells (10). The persistence of the clinical benefit has been consistently confirmed for the traditional SCIT in several trials (11), but there is so far no data on MPLA-SCIT. Based on this, we performed a prospective controlled trial to assess if MPLA-adjuvanted immunotherapy exerts a long-lasting effect.

Methods

The trial was designed as prospective, open, and nonrandomized. Patients with respiratory allergy due to Parietaria were prescribed a 3-year course of MPLA-SCIT. They were assessed for clinical characteristic at baseline, at the end of immunotherapy and 5 years later. A matched group of patients who refused SCIT served as controls.

Inclusion criteria were those recommended by guidelines for the prescription of immunotherapy: i) mild persistent or moderate/severe rhinitis (12) with or without asthma, ii) proven sensitisation to parietaria (assessed by skin prick test or CAP RAST), iii) presence of symptoms during the Parietaria season. Exclusion criteria were severe or uncontrolled asthma, mild intermittent rhinitis, previous courses of specific immunotherapy for Parietaria. Patients with malignancies, systemic immune diseases or major anatomical abnormalities of the nose were also excluded, as recommended by guidelines (1).

The MPLA-SCIT was given according to the manufacturer's instructions, with four pre-seasonal injections given at weekly intervals, at the doses of 300, 800, 1,000 and 2,000 units. The course was repeated before the season for 3 years. All the subjects received the same standard drug therapy for the treatment of rhinitis, conjunctivitis and asthma, according to current guidelines (12, 13). All patients, receiving or not MPLA-SCIT, underwent the same diagnostic procedures at baseline, after 3 years (end of SCIT) and after 8 years from baseline (5-year discontinuation). The following evaluations were made:

- clinical assessment of the presence and severity of rhinitis, conjunctivitis and asthma. Rhinitis was classified as mild intermittent or persistent, and moderate/severe intermittent or persistent according to ARIA (12). Asthma was graded in severity according to GINA (13);
- skin prick test with a standard panel of allergens including mites, grasses, parietaria, olive, birch, cypress, ragweed, cat and dog dander. The skin test for Parietaria was performed in duplicate and the mean diameter of the wheal (major diameter plus orthogonal) was recorded;
- pulmonary function test, to record FEV_1 and FVC;
- visual analog scale (VAS). This consisted of a 10 cm line, where the patients had to mark their perceived well-being during the past season, from 0 (very troublesome symptoms) to 10 (total absence of symptoms).

Statistical analysis was performed by a computerized program. Student's t test was used for inter-group and intra-group comparisons. The chi-square test was applied to categorical data.

Results

Twenty nine patients (15 male, mean age 33.4 years, age range 18-60) were prescribed MPLA-SCIT. Twenty-eight matched patients (13 male, mean age 34.1 years, age range 10-59), who refused SCIT served as control group. The two groups resulted to be homogeneous for the clinical and demographic characteristics at baseline (Tab. 1). In particular, asthma was present in 19% and 20%, and conjunctivitis in 65% and 66% of the active and placebo group, respectively. The rate of monosensitized subjects was slightly greater in the control group (53% vs 41%; p= .02). The pattern of skin positivities in the polisensitized subjects is shown in Table 2. There was a significant clinical improvement, as assessed by VAS, only in the active group after 3 years, whereas no change was seen in the control patients. The clinical improvement versus baseline and versus the end of SCIT was maintained at the 5-years assessment (Fig. 1). Also, the distribution of severity of rhinitis was overall decreased at 3 and 8 years in the active group, with no apparent change in the controls (Fig. 2). Of note, the number of patients with conjunctivitis in the

Table 1 - Baseline characteristics of the two groups

	MPLA-SCIT n=29	CONTROLS n=28	P chi square
Mean age ± SD	33.4±11.8	34.1±13	NS *
Age range	18-60	10-59	-
Male (%)	15 (52)	13 (46)	NS
Conjunctivitis (%)	19 (65)	18 (66)	NS
Asthma (%)	6 (19)	6 (20)	NS
Mild persistent rhinitis (%)	6 (19)	6 (20)	NS
Moderate/sev intermittent rhinitis (%)	0	2 (5)	NS
Moderate/sev persistent rhinitis (%)	23 (62)	20 (75)	NS
Mean FEV1% ± SD	100±.8	96±9	NS *
Mean FCV% ± SD	101±9	100±10	NS *
Parietaria wheal mean diameter ± SD	9.5±2.1	8.9±1.6	NS *
VAS score ± SD	2.9±1.5	2.7±1.1	NS *
Monosensitized	12 (41)	15 (53)	.02

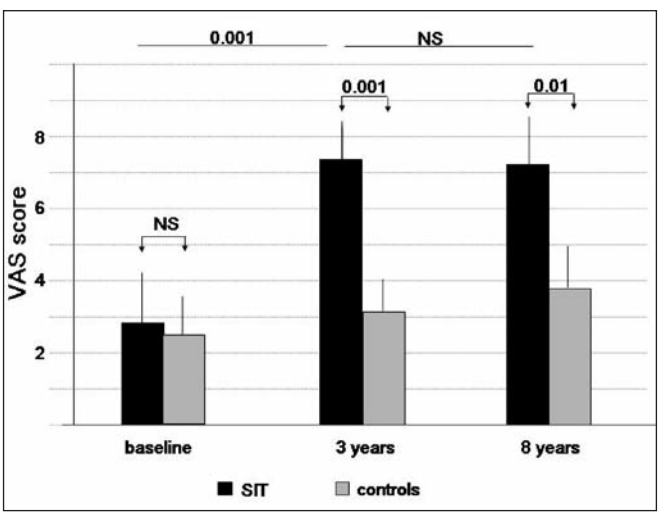
* Student's t

Table 2 - Pattern of sensitisation in polysensitized subjects

	MPLA-SLIT n = 17	CONTROLS n = 13
Grass, n (%)	6 (35)	4 (30)
Mite, n (%)	5 (29)	3 (23)
Olive, n (%)	5 (29)	3 (23)
Cypress, n (%)	2 (12)	2 (15)
Hazelnut, n (%)	3 (18)	1 (8)
Cat, n (%)	2 (12)	3 (23)
Mugwort, n (%)	2 (12)	2 (15)

active group decreased from 19 to 6 at the end of the treatment and was of 9 after 5 years of discontinuation. In parallel, there was a decrease in the number of patients with asthma symptoms (from 6 to 2 to 4). In the control group there was no change in the number of patients with conjunctivitis, whereas those with asthma were doubled after 8 years. A significant reduction in the mean wheal diameter of the Parietaria skin test was seen in the active group at the end of the MPLA-SCIT (9.5±2.1 mm VS 6.4±2.6 mm; p=.01), but this reduction was lost at the 5-year follow up (9.5±2.1 mm VS 8.4±2.7mm; p= NS). No change was observed in the control group (8.9±1.6 mm VS 8.8±1.1 mm VS 8.1±1.5 mm). Concerning the spirometric parameters, in the control group there was a slight decline over time in the FEV_1 and FVC, but a significant

Figure 1 - Visual Analog Scale score (mean and SD) at the three time-points. The 3-year point corresponds in the SCIT group to the end of the treatment. The significant differences are plotted above the bars



difference was detected only for FEV_1 at 8 years versus baseline (Fig. 3). At the end of the follow up only one out of the 12 monosensitized patients in the active group had developed new sensitizations, whereas this happened in 6/15 monosensitized of the control group. The behaviour of the main clinical parameters during follow-up is shown in table 3. The treatment was overall well tolerated. Only

four patients displayed a large local reaction during the first course with the 2,000 U dose. The dose was repeated the next week without further problems.

Discussion

The so-called "additional effects" of immunotherapy, namely the preventive action and the long-term persistence of the clinical effects, make this treatment profoundly different from the standard medications. In particular, the long-lasting effect was clearly demonstrated for the traditional SCIT (for review see 9, 11), although only few randomized double blind trials were specifically designed to assess this effect (14-17). No datum is so far available for the adjuvanted SCIT, which is largely used in clinical practice since about ten years. Thus, we designed this study to evaluate the persistence of the clinical benefit of MPLA-SCIT for Parietaria. In order to have available all the data in the long-term, the design had to be kept as simple as possible, and adherent to the real-life. For this reason, only those parameters which are usually employed to evaluate the effects of immunotherapy were chosen, namely the clinical assessment of disease's severity (1) and the patient's reported perception of the well being. The main limitation of the study stands in the open non randomized design. Nonetheless, in real life, it is not feasible to have a double blind approach maintained for such a long time, and in fact an open design was used in

Figure 2 - Percentage distribution of the severity of rhinitis (according to ARIA) at the three time-points in the SCIT and control groups. Chi-square p values are reported above the bars

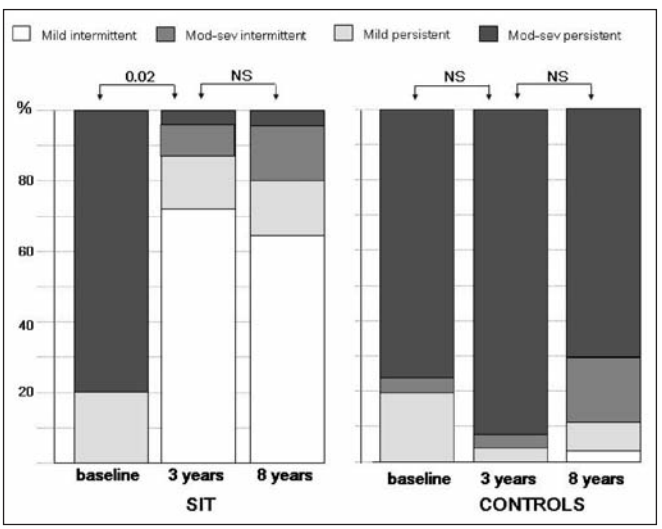


Figure 3 - Mean (SD) values of FEV1 and FVC measured at the three timepoints. Significant p value differences are reported above the bars

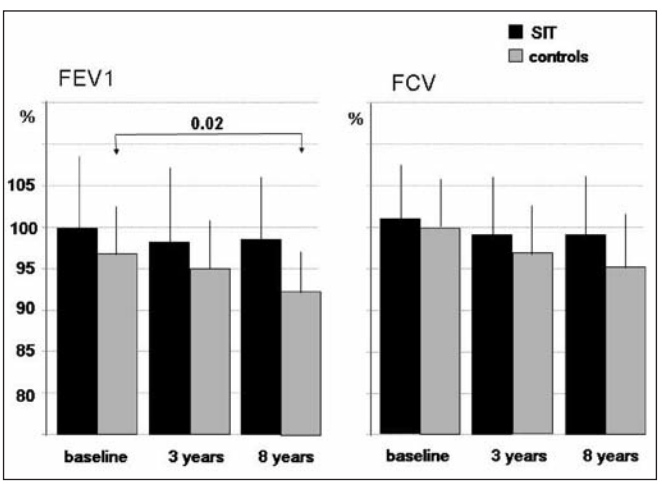


Table 3 - Summary of the clinical characteristics of the patients in the two groups

	SCIT (N= 29)			Controls (N=28)		
	Baseline	3 yrs	8 yrs	Baseline	3 yrs	8 yrs
Conjunctivitis (%)	19 (65)	6 (20)	9 (31)	18 (66)	21 (75)	21 (75)
Asthma (%)	6 (20)	2 (7)	4 (14)	6 (20)	9	12
Mild intermittent (%)	0	21 (72)	19 (65)	0	0	2 (7)
Mild persistent (%)	6 (20)	4 (14)	4 (14)	6 (20)	1 (3)	3 (10)
Mod/sev intermitt (%)	0	3 (11)	5 (8)	2 (7)	1 (3)	4 (14)
Mod/sev persist (%)	23 (80)	1 (3)	1 (3)	20 (73)	26 (94)	19 (68)
Monosensitized (%)	12 (41)	11 (38)	11 (38)	15 (53)	12 (43)	9 (32)
Wheal mean diameter	9.5±2.1	6.4±2.6	8.4±2.7	8.9±1.6	8.8±1.4	8.1±1.5

other studies to assess the long-term effect of sublingual immunotherapy (18). For the same reasons, it was not feasible to have a detailed recording of the medication intake, although this would have added a relevant and confirmatory information. In addition, the study was not designed to assess the efficacy of the treatment, but the persistence of the effects on the long term. Finally, the absence of a randomization is counterbalanced by the ascertained homogeneity of the two groups at baseline. As far as the clinical parameters are concerned, it was observed that the overall severity of the disease (rhinoconjunctivitis) was decreased after MPLA-SCIT, and that the improvement was maintained at 5 years after discontinuation. The reduction of the skin reactivity at the 3rd year can be interpreted as an indirect marker of the immunological effect. This is also corroborated by the prevention of the onset of new sensitisations in monosensitized patients after discontinuation, which is similar to that described elsewhere (19).

In conclusion also the relatively new immunotherapy with an MPLA adjuvant results to have a long-lasting carry-over effect, which is similar to that of traditional SCIT. This encourages the use of this modality of treatment (20), in order to combine a good safety profile (21) with the achievement of beneficial effects for years after the discontinuation.

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