

LONG-TERM AND PREVENTIVE EFFECTS OF SUBLINGUAL
ALLERGEN-SPECIFIC IMMUNOTHERAPY:
A RETROSPECTIVE, MULTICENTRIC STUDY

E. MADONINI,¹ F. AGOSTINIS,² R. BARRA,³ A. BERRA,⁴ D. DONADIO,⁵
A. PAPPACODA,⁶ E. STEFANI⁵ and E. TIERNO⁷

¹Villa Marelli Institute, Respiratory Allergy Department, Ospedale Niguarda Cà Granda, Milano,
²Pediatric Unit, Ospedali Riuniti, Bergamo, ³Pediatric Unit, Ospedale Moscati, Avellino,
⁴Respiratory Allergy Clinic, Ospedale G. da Procida, Salerno, ⁵Allergy Department, Azienda
Ospedaliera S. Giovanni di Dio e Ruggi d'Aragona, San Leonardo, Salerno, ⁶Pneumology Centre,
Ponte S. Pietro, Azienda Ospedaliera Treviglio, Bergamo, ⁷Pediatric Unit, Ospedale F. Palasciano,
Capua, Caserta

Received April 11, 2002 – Accepted July 26, 2002

There is now an increasing body of evidence to support the practice of allergen-specific sublingual-swallow immunotherapy (SLIT) in the treatment of IgE-mediated respiratory allergies. Recent studies on traditional injection therapy have pointed out that this form of treatment is not only capable to decrease actual allergic symptoms, but may also have long-term clinical and preventive effects and may influence atopy natural history. In the year 2000, our group published a retrospective, multicenter study showing the efficacy and safety of SLIT in a survey of 302 patients. We now carried out a second study on the same patients, with the aim of investigating long-term and preventive effects of SLIT. Beside the well-known safety and efficacy of this treatment (80.8 % of patients reported clinical benefits), SLIT proved also to elicit long term clinical effects: over a mean follow-up of 11.6 months after the end of treatment, 80.8 % of patients still maintained the previously achieved benefits. During the follow-up period, only 1% of non-asthma patients reported an onset of respiratory symptoms, and only 9.6 % of patients undergoing new skin tests showed new sensitizations. All the clinical benefits were strongly linked to the length of treatment: patients with long-lasting benefits were treated for a mean length of 29.1 months, while patients showing a return to pre-SLIT condition were treated for a mean 13.3 months. SLIT can obtain long-term and preventive effects so far attributed to injection immunotherapy.

There is now an increasing body of evidence to support the practice of allergen-specific sublingual-swallow immunotherapy (SLIT) in the treatment of IgE-mediated respiratory allergies. (1-3)

As a result of several controlled clinical studies published in recent years, the 1998 WHO Position Paper "Allergen Immunotherapy: Therapeutic Vaccines for Allergic Diseases" adopted for the first time an official position concerning local immunotherapy, stating that sublingual

immunotherapy "may be a viable alternative to parenteral injection therapy". (4)

Following the publication of the WHO document, additional controlled studies concerning efficacy and tolerability of SLIT have been presented in peer-reviewed journals. In the year 2000, our group published an open, retrospective, multicenter study about this treatment, involving 302 patients treated in seven different Allergy Centers (5). Notwithstanding the obvious limitations inherent in the study design, this investigation largely

Key words: sublingual allergen-specific immunotherapy; length of treatment; long-term effects; preventive effects

Mailing address: Dr. Enzo Madonini
Istituto Villa Marelli-Ospedale Niguarda Ca' Granda
Viale Zara 81 - 20159 Milan
Italy
E-mail: enzo.madonini@iol.it

0394-6320 (2003)

Copyright © by BILIFE, s.a.s.
This publication and/or article is for individual use only and may not be further reproduced without written permission from the copyright holder.
Unauthorized reproduction may result in financial and other penalties

confirmed the high efficacy and safety of this form of treatment, as already reported in previous controlled studies conducted on smaller-scale surveys. That study focused on treatments carried out in the years 1995 and 1996: at the time of the study, 256 treatments out of 302 (84.8 %) were still ongoing and the average length of treatment was 18 months (min. 3, max. 46). Only 59 patients (19.5 %) had been treated for at least 24 months.

Five years later, we carried out a new survey on the same patients, with two main purposes. First of all, assuming that all the treatments had by now been concluded, we wanted to collect more data about SLIT safety and efficacy in a large number of patients treated for a longer and adequate period of time. The ultimate study objective, however, was to collect information about patient follow-up, particularly about long-term benefits of SLIT and its possible capability to influence atopy's natural history.

In recent years, there has been mounting interest in these new aspects, since "classic" clinical benefits due to allergen-specific immunotherapy (SIT) have now largely been established. Some studies have already highlighted the long-term efficacy of SIT even after its discontinuation (6-9), a clear advantage over the results observed with pharmacological therapy (10). As for atopy natural history, several studies have already indicated that SIT seems to be able to prevent the frequent progression of rhinitis into asthma (11-13) and the onset of new sensitizations (14).

In light of the above, a recent Consensus Conference on SIT describes four levels of SIT efficacy:

- *Early effect*, achieved after initiation of SIT
- *Persisting effect*, persisting during SIT
- *Long-term effect*, after discontinuation of SIT
- *Preventive effect*, prevention of new sensitivities and exacerbation of disease (15).

These effects are usually referred to the conventional injection therapy. In this study, we evaluated for the first time the same effects or SLIT.

MATERIALS AND METHODS

A questionnaire carrying the name of every single patients had been sent to the seven Allergy Centers participating to the first survey, with the following questions:

- state and final treatment duration
- adverse reactions, if any, observed since the first survey
- clinical results at the end of treatment
- length of follow-up
- clinical results during the follow-up
- results of allergy test, if carried out after the end of treatment
- onset of new sensitizations, if any
- onset of asthma during follow-up of non-asthma patients
- asthma classification in asthmatic patients at the end of treatment and during follow-up
- patients satisfaction about treatment.

Being a retrospective survey, all the clinical results were expressed only in terms of physician's report, based upon a personal pool of objective and subjective evaluations.

281 questionnaires out of the original 301 patients (93,04%) have been returned. Patients in this second study are divided in 156 males (55.5 %) and 125 females, mean age 21.0 years (min 2, max 68, SD: 13,08). Demographic characteristics of these patients are comparable to the first survey. Table I shows the extract compositions used in the treatment of subjects participating in this second survey

Also the extract compositions are comparable to the first survey. Aqueous glycerinated standardised extract solutions (Allergopharma, Reinbek, Germany now supplied by Merck, Milan, Italy) were employed.

Rhinitis was reported as the most severe symptom by 125 subjects (44.5 %), asthma by 81 patients (28.8 %), dermatologic symptoms by 46 (16.4 %) and ocular symptoms by 29 patients (10.3 %). Even symptoms distribution is comparable to the first survey.

RESULTS

State and final treatment duration

All the treatments were concluded at the time of the present study. The definitive average duration was 26.4 months (min 7, max 72, SD 12.0). Considering the extract composition, the average length was 29.6 months for grasses, 26.0 for house-dust mites and 23.8 for parietaria.

Clinical results at the end of treatment

Table II shows the clinical evaluation expressed at the end of treatment. The vast majority of patients reported very good /good results (80.8 %).

Tab. I. *Extract Composition.*

ALLERGENS	No	%
House-dust mites	147	52.3
Grasses	72	25.6
Parietaria	57	20.3
Grasses 50%+Parietaria 50%	5	1.8

Tab. II. *Clinical evaluations at the end of treatment.*

CLINICAL EVALUATION	No	%
Very good / good	227	80.8
Moderate	50	17.8
Poor	4	1.4

Tab. III. *Clinical evaluations at the end of treatment according to the extract compositions.*

COMPOSITION	% Very good/good	% Moderate	% Poor
Mites	85,7	11,6	2,7
Grasses	83,3	16,7	0
Parietaria	64,9	35,1	0

Tab. IV. *Evaluation of SLIT results during follow-up visits.*

EVALUATION	N° Pts	%
Benefits maintained	227	80.8
Slight worsening	26	9.3
Marked worsening	2	0.7
Return to the pre-SLIT condition	26	9.3

Tab. V. *Average length of SLIT in different follow-up results.*

EVALUATION	N° Pts	AVERAGE SLIT LENGTH (months)
Benefits maintained	227	29.1
Slight worsening	26	16.7
Marked worsening	2	14.5
Return to the pre-SLIT condition	26	13.3

Tab. VI. *Follow-up evaluation in patients treated with house-dust mites, with a minimum 6-mo post-treatment observation.*

EVALUATION	N° Pts	%
Benefits maintained	48 No	78.7
Slight worsening	8 No	13.1
Return to the pre-SLIT condition	5 No	8.2

Table III shows the clinical evaluations according to the extract compositions. Clinical results were very positive and comparable in patients treated with grasses and mite extract (80.7 % and 83.3 % respectively). Clinical benefits were less evident in patients treated with parietaria extract. (64.9 %)

Clinical results appear to be related to the length of treatment, as shown in Fig. 1. Patients with good/very good results were treated for an average of 28.9 months (min 10, max 72), while patients with moderate results were treated for an average of 17.2 months (min 8, max 60) and finally patients whose results were defined as "poor" were treated for a mean 8.5 months (min 7, max 11).

The importance of a long SLIT duration is even more clear when evaluating SLIT results in terms of "years of treatment". (Fig. 2) Patients treated for less than one year reported very poor results, compared to patients treated for 2 and 3 years.

Follow-up of clinical results

The average length of patients monitoring has been 11.6 months (min 1, max 28). We asked the Investigators to compare the clinical conditions at the most recent follow-up visit with the results attained at the end of treatment.

As shown in Table IV, 80.8 % of patients maintained the positive results achieved at the end of treatment. This evaluation is also related to the length of treatment (Tab. V).

Since different pollen seasons may produce some variability, we choose to evaluate follow-up results in 147 patients treated with house-dust mites SLIT for perennial allergy. The average length of follow-up in these patients was 11 months, and we focused our attention on 61 patients with a minimum period of observation of 6 months after the end of SLIT (See Tab. VI). Once more, the length of treatment is of paramount importance to obtain good follow-up results (Tab. VII).

Allergy tests results and new sensitizations

Allergy tests have been repeated in 156 patients (55,5 %) after the SLIT conclusion. In 131 patients (84,5 %) a decreased response to the treated allergen was observed, while the response was unchanged in 25 subjects (15,5 %). In 15 patients (9,6 %) 20

Tab. VII. Average length of SLIT in different follow-up results. Patients treated with house-dust mites, with a minimum 6-mo post-treatment observation.

EVALUATION	Average length of SLIT (months)	MIN	MAX	SD
Benefits maintained	26,8	16	70	9,8
Slight worsening	15,2	10	24	5,0
Return to the pre-SLIT condition	11,4	8	14	2,6

Tab. VIII. New sensitizations

Allergen	N° pts
Parietaria	5
Olive	5
Mix Trees	4
Alternaria	3
Grasses	2
Animals	1

new sensitizations were found, which are shown in Table VIII.

Onset of asthma in non-asthmatic patients

A total of 200 patients did not report asthma symptoms at the start of treatment. These subjects have been followed for an average 9.6 months after the end of SLIT, and only 2 patients (1%) showed a new onset of asthma.

Asthmatic patients

At the start of treatment, 81 patients reported asthma symptoms and were followed for an average 16.4 months after the end of therapy. Out of these 81 patients, 50 (61.7 %) reported "absence of asthma" at the end of SLIT and at the more recent follow-up control. A further 9 patients (11.1%) reported "no asthma" at the follow-up, while asthma symptoms were still present in the other 22 (27.2%) patients at the end of treatment, either "mild intermittent" or "mild persistent", according to the NIH classification (16). In 5 subjects (6.2 %) asthma symptoms were worse at the follow-up control then at the end of SLIT.

Adverse reactions since the first study

The seven Centers did not report any adverse reaction.

Patients satisfaction

Patients opinion about SLIT efficacy has been collected in 277 subjects. The majority of patients (83.7 %) expressed satisfaction with the results achieved, while the remaining 45 patients (16.3 %) were unsatisfied. Average SLIT duration was much longer in satisfied patients (28 months) as compared with patients with no satisfaction (average duration 14 months).

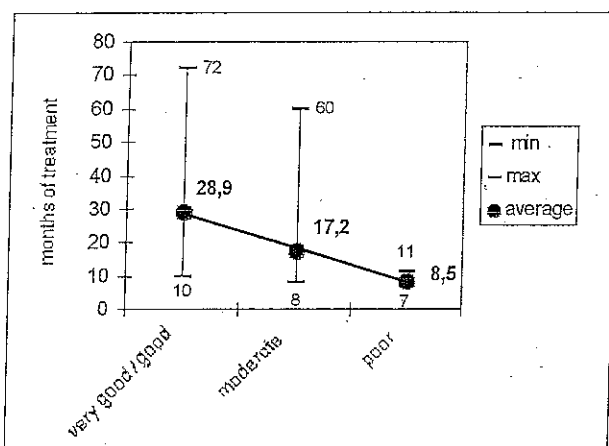


Fig. 1. Clinical results according to average SLIT duration.

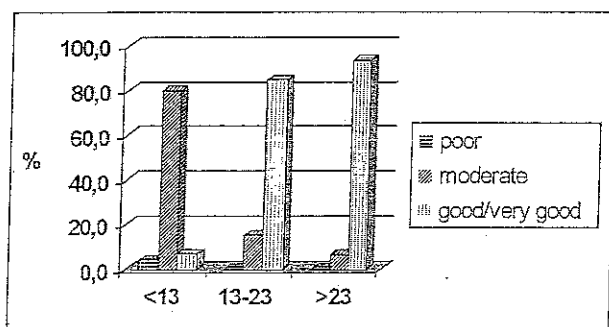


Fig. 2. Clinical results at the end of SLIT according to months of treatment.

DISCUSSION

In 1998, the "Allergen Immunotherapy" WHO Position Paper had considered local routes of immunotherapy, officially stating for the first time that SLIT could provide an effective alternative to the traditional injection therapy, although implying some reservations with the expression "Maybe..." and still not endorsing the routine use of this treatment (4). Following the publication of that document, several controlled studies have been performed, as recommended by the document itself and by many Authors. Several editorial reviews have also appeared, and these serve to further document the efficacy and safety of SLIT (3,17,18) and even go one step further than the Position Paper, by stating that SLIT can be administered either to adults and children due to the absence of severe side effects (19).

"Traditional" clinical results of the present survey, even if limited by the study design, are nevertheless fully consistent with the conclusions of several controlled studies: out of 281 patients included in this second survey, 80.8 % benefited from SLIT. Clinical results were positive and comparable in patients treated with grass extracts (83.3 %) and house-dust mites extracts (85.7 %). Results appeared less favourable in the overall group of patients treated with *Parietaria* extracts (64.9 % of positive reports). A possible explanation could be that these patients have been treated for a shorter mean length of time (23.8 months) compared with grasses (29.6 months) and mites (26.0) treatments. As a matter of fact, 30 patients treated with *Parietaria* extract for at least 24 months (min 24, max 48) reported an incidence of positive results comparable to the other groups (83.3%). As discussed below, the length of treatment is strongly correlated with all the observed clinical benefits.

Recent published documents emphasize that SIT can achieve more significant clinical benefits than merely "reducing allergic symptoms", underlining the long-term effects of SIT and its influence on atopy natural history (19-23). These effects were studied and attributed in the past to the traditional injection SIT. In this study, we extended these evaluations for the first time to SLIT, in an open, retrospective multicenter study, carried out in a large number of patients (281) in

seven different Allergy Centers. After a mean follow-up of 11.6 months, 227 patients (80.8 %) still maintained clinical benefits achieved at the end of treatment. This observation becomes all the more significant when considering patients with perennial mite allergy only, and particularly 61 subjects with such allergy and a minimum follow-up period of 6 months. The mean follow-up of these patients was 8.3 months, and 47 subjects (78%) had long-term benefits from SLIT, still maintaining the positive results observed at the end of treatment. Furthermore, after a mean treatment length of 32.5 months and a further follow-up period of 16.4 months, 59 patients with initial asthma out of 81 treated (72.8 %) were respiratory symptom-free. To better appreciate the clinical and financial benefits achieved with SLIT, we must recall the observations made with traditional pharmacological therapy, where symptoms and signs of asthma exacerbate very soon, after the discontinuation of treatment, even after prolonged steroid therapy (10).

During the combined 4 year treatment period and follow-up observation, only 2 patients out of 200 with no asthma symptoms at the beginning of SLIT reported respiratory problems (1 %). Despite the lack of a control group, such incidence can be considered very successful compared to the rate of asthma development in rhinitis patients, as usually referred in epidemiological studies covering atopy natural history (19, 24-25).

In a study by Des Roches et al. it was demonstrated that SIT treatment in children monosensitized to house-dust mite was capable of preventing the onset of new sensitizations, in comparison with a non-treated control group (14). In our survey, allergy tests were repeated during the follow-up of 156 out of 281 treated subjects and new sensitizations were detected in only 15 subjects (9.6 %). The magnitude of the skin response to the treated allergen was decreased in 84.5 % of subjects, thus indirectly confirming that clinical benefits are supported by immunological mechanisms.

One of the most relevant observations emerging from this study is the clear relationship between the length of treatment and the clinical results: actually, both early benefits from SLIT, observed at the end of treatment, and long term persistence of such benefits are correlated to the length of

treatment. A 3-yr length of treatment is generally considered to be adequate in order to achieve long-lasting clinical benefits (27), although no specific studies investigating the relationship between length of SIT and clinical results have been conducted. This study clearly shows that this relationship does exist for SLIT: only 6.6 % of patients treated for less than one year reported clinical benefits, versus 94 % of subjects treated for more than two years. (Fig. 2) With regard to follow-up results, patients showing long-lasting clinical benefits had been treated for an average of 29.1 months: a progressive reduction of the length of treatment was observed in the other "groups of results", down to 13.3 months of treatment in patients complaining a "return to the pre-SLIT clinical condition".

This is the first study in which SLIT is evaluated with different and more current clinical criteria. Notwithstanding the limitations of a retrospective, uncontrolled study, the results in particular point to the long-term and preventive effects of SLIT benefits that have thus far been attributed only to traditional injection SIT. The study also underlines the need to carry out the treatment for an adequate length of time, in light of the clear relationship between treatment duration and clinical benefits.

Taking into account these positive results, along with the well-documented safety of this treatment, SLIT can be considered an effective alternative to injection therapy in IgE-mediated respiratory allergies.

REFERENCES

- Holt P., P.D. Sly and W. Smith. 1998. Sublingual immunotherapy for allergic respiratory disease. *Lancet* 351:613.
- Malling H.J., J. Abreu-Noguiera, B. Alvarez-Cuesta et al. 1998. Local immunotherapy. *Allergy* 53:933.
- Frew A.J. and H.E. Smith. 2001. Sublingual immunotherapy. *J. Allergy Clin. Immunol.* 107:441.
- Bousquet J., R.F. Lockey and H.G. Malling. 1998. WHO Position Paper. Allergen Immunotherapy: Therapeutic Vaccines for Allergic Diseases. *Eur. J. Allergy Clin. Immunol.* 53(5):1.
- Madonini E., F. Agostinis, R. Barra et al. 2000. Safety and efficacy evaluation of sublingual allergen-specific immunotherapy. A retrospective, multicenter study. *Int. J. Immunopathol. Pharmacol.* 13:77.
- Des Roches A., L. Paradis, J. Knani, et al. 1996. Immunotherapy with a standardized Dermatophagoides pteronyssinus extract. Duration of the efficacy of immunotherapy after its cessation. *Allergy* 51:430.
- Costa J.C. 1996. Effects of immunotherapy on symptoms, PEF, spirometry and airway responsiveness in patients with allergic asthma to house-dust mites (*D. pteronyssinus*) on inhaled steroid therapy. *Allergy* 51:238.
- Shaikh W.A. 1997. Immunotherapy vs inhaled budesonide in bronchial asthma; an open, parallel, comparative trial. *Clin. Exp. Allergy* 27:1279.
- Naclerio R.M., D. Proud, B. Moylan et al. 1997. A double-blind study of the discontinuation of ragweed immunotherapy. *J. Allergy Clin. Immunol.* 100:293.
- Magnussen H, U. Willembrock and R. Torres. 1992. Airway responsiveness, lung function and symptoms after cessation of high dose inhaled corticosteroids in patients with bronchial asthma. *Am. Rev. Respir. Dis.* 145:A498
- Johnstone D.E. and A. Dutton. 1968. The value of hyposensitisation therapy for bronchial asthma in children: a 14 year study. *Pediatrics* 42:793.
- Mosbech H and O. Osterballe. 1988. Does the effect of immunotherapy last after termination of treatment? Follow-up studies in patients with grass pollen rhinitis. *Allergy* 43:523.
- Jacobsen L., S. Dreborg, C. Moller, E. Valovirta, U. Wahn et al. 1996. Immunotherapy as preventive allergy treatment (PAT). *J. Allergy Clin. Immunol.* 97:232 (abstract).
- Des Roches A, L. Paradis, J-L Ménardo, S. Bouges, J-P Daurès and J. Bousquet. 1997. Immunotherapy with a standardized Dermatophagoides pteronyssinus extract. VI. Specific immunotherapy prevents the onset of new sensitizations in children. *J. Allergy Clin. Immunol.* 99:450.
- Proceedings of the "Immunotherapy in Allergic Asthma Consensus Conference" August 19-20, 2000. 2001. *Ann. Allergy Asthma Immunol.* 87:1.
- National Asthma Education and Prevention Program Expert Panel Report 2. 1997. Guidelines for the Diagnosis and Management of Asthma. Bethesda, Maryland: National Institute of Health Publication No 97-4051.
- Clavel R., J. Bousquet and C. Andre. 1998. Clinical efficacy of sublingual-swallow immunotherapy: a double-blind, placebo-controlled trial of a standardized five-grass-pollen extract in rhinitis. *Allergy* 53:493.
- Torres Lima M, D.R. Wilson, A. Roberts, S.M. Walker and S.R. Durham. 2001. Grass pollen sublingual immunotherapy (SLIT) for seasonal rhinoconjunctivitis.

- A randomized controlled trial (abstract). *J. Allergy Clin. Immunol.* 107:S256.
19. Lockey R.F. 2001. "ARIA": Global guidelines and new forms of allergen immunotherapy. *J. Allergy Clin. Immunol.* 108:497.
 20. Marogna M., A. Tiri and G. Riva. 2001. Clinical practice improvement program for immunotherapy of respiratory allergic diseases. *Int. J. Immunopathol. Pharmacol.* 14:93.
 21. Scala E., M. Giani, L. Pirrotta, E.C. Guerra, O. De Pitta and P. Puddu. 2001. Occupational asthma due to metoclopramide hydrochloride (MCPH). *Int. J. Immunopathol. Pharmacol.* 14:145.
 22. Bruno G., P. Andreozzi, L. Magrini, G. Santangelo, U. Graf and A. Angelino. 2001. Serum tryptase in allergic rhinitis: effect of Ceterizine treatment. *Int. J. Immunopathol. Pharmacol.* 14:147.
 23. della Volpe A., G.W. D'Agostino, A.M. Varricchio and N. Mansi. 2002. Sublingual allergen-specific immunotherapy in allergic rhinitis and related pathologies: efficacy in a paediatric population. *Int. J. Immunopathol. Pharmacol.* 15:35.
 24. Settignano R.J., G.W. Hagy and G.A. Settignano. 1994. Long-term risk factors for developing asthma and allergic rhinitis: a 23-year follow-up study of college students. *Allergy Proc.* 15:21.
 25. Linna O, J. Kokkonen and A. Lukium. A 10-year prognosis for childhood allergic rhinitis. *Acta Paediatr.* 81:100.
 26. Bousquet J, P. van Cauwenberge and N. Khaltaev. 2001. Allergic rhinitis and its impact on asthma. ARIA Workshop Report. *J. Allergy Clin. Immunol.* 108:S147.
 27. Des Roches A, L. Paradis, J. Knani et Al. 1996. Immunotherapy with a standardized Dermatophagoides pteronyssinus extract. Duration of the efficacy of immunotherapy after its cessation. *Allergy* 51:430.