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# Sublingual immunotherapy for allergic respiratory disease in elderly patients: a retrospective study

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**Key words**

*Elderly patients, Monosensitized, Sublingual immunotherapy, House dust mite, Respiratory allergy*

**Summary**

***Background:*** *Very few studies have evaluated the effects of sublingual immunotherapy (SLIT) in elderly adults with either rhinitis or bronchial asthma. The aim of this study was to ascertain whether SLIT is effective in these patients.* ***Methods:*** *One hundred and sixty seven patients (aged 18-65 years) with persistent rhinitis and mild asthma, selected from 573 subjects allergic to house-dust mites, were treated with either standard chronic pharmacotherapy or SLIT plus drugs on demand. Monthly symptom/drug scores, respiratory function, methacholine (MCh) challenge and eosinophil count were scheduled at the beginning and end of the study.* ***Results:*** *We analysed two age groups (18-28 years, 49 patients) and 55-65 years, 40 patients). There were no differences between the groups at baseline but MCh sensitivity was lower in the older patients. At the end of treatment, SLIT achieved improvement in all variables ($p<0.001$) in both age groups, but the global symptoms were lower in the younger patients ($p=0.002$). There were also fewer new sensitizations in the SLIT groups ($p=0.03$) than in the "control" patients given standard pharmacotherapy, but with no relation to age. Asthma became worse only in the control groups, regardless of age.* ***Conclusions:*** *SLIT reduces symptoms, drug consumption and the progression of the disease in both young and elderly subjects allergic to house-dust mites, with persistent rhinitis and mild bronchial asthma.*

## Introduction

Rhinitis and allergic bronchial asthma are very common in people of all ages, with a prevalence of approximately 10% in western countries (1). During the last 15 years, it has gradually become clear that rhinitis and asthma are two distinct clinical aspects of a single disease that involves the entire respiratory system (2). The progression from atopic dermatitis to asthma is generally known as the atopic march (3): in atopic children the disease initially arises as atopic dermatitis and food allergies, which subsequently evolve into rhinitis and asthma. Skin manifestations are less frequent in patients whose symptoms started during adulthood, but the march from rhinitis to asthma proceeds nevertheless, together with the possibility of new sensitizations (4-7).

The natural history of the disease has changed significantly over the last few decades, especially with emerging pollinoses from allergens such as birch (8, 9) and ragweed (10, 11). Often the patient does not present with a background of atopic constitution, the average age is higher than for other pollinoses, and the onset is after 45 years of age in up to 20% of cases; in some patients the symptoms first appear even after the age of 70 (12). These patients

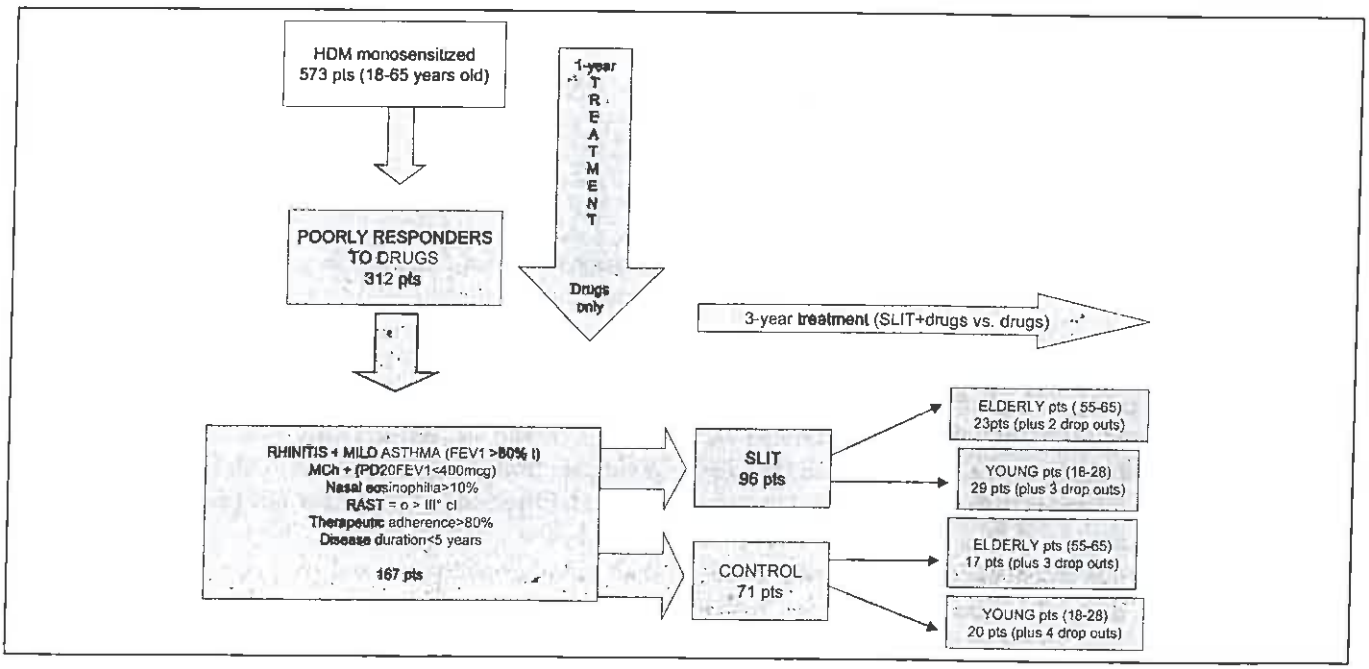
often started an allergen-specific immunotherapy (SIT) on account of the severity of the symptoms and inadequacy of control with standard drug therapy.
Although SIT is deemed the only treatment that can at least partly modify the natural course of the disease during its initial stages, its use in elderly patients is still debated. There are only few studies for injective SIT (13, 14), and none at all for non-injective SIT, or sublingual SIT (SLIT) in particular.
It is obvious that SIT is less indicated for elderly patients with a long history of allergic respiratory disease due to remodelling of the respiratory tract, which produces chronic and irreversible ultrastructural changes. However, elderly patients with a recent history of allergies seem to be ideal candidates for investigating the efficacy of SIT during their last decades.
Presented here are the findings of an observational, retrospective study regarding the use of SLIT in patients aged 55-65 years with respiratory disease (rhinitis and asthma) caused by *Dermatophagoides*, compared to younger patients (aged 18-28 years) with similar allergic and functional characteristics, who were also treated with SLIT, and two other groups of patients (of the same ages) who were given drugs alone.
The main purpose of the study was to establish whether SLIT plus drugs on demand provided control of symptoms and helped to prevent the progression of the respiratory disease and the onset of new sensitizations in these patients better than the standard chronic pharmacotherapy plus drugs on demand. The study also looked for any differences in the effect of SLIT in younger and elderly patients.

## Materials and methods

### *Patients*

We retrospectively evaluated 167 adult patients who had had persistent rhinitis and mild asthma for no more than five years, selected from a total of 573 patients monosensitive to *Dermatophagoides* and receiving medical care between 1994 and 2006 (Figure 1). Sixty-six patients (39 assigned to the active group and 27 controls) were not included because they were aged between 29 and 54 years. Among the 101 eligible patients (aged 18-28 or 55-65 years old) there were 12 spontaneous drop-outs, five from the active group (n=57) and seven from the control group (n=44). None were because of side effects.
The following diagnostic-therapeutic protocol has been implemented in the respiratory Allergology Clinic at the Cuasso al Monte Hospital (VA) since the early 1990s:

*Figure 1* - Study design



1) At the first visit (admission): skin prick tests, full spirometry with body plethysmography, methacholine (MCh) challenge, assays of specific IgE for the main pneumoallergens, eosinophil count in nasal secretions.
2) During the first year: treatment with drugs and monitoring based on clinical diaries of the symptoms and drugs consumed.
3) During the next three years patients who had not responded to standard treatment with drugs after the first year were asked for informed consent, and were given SLIT, usually for moderate-to-severe rhinitis and for rhinitis with asthma.
4) Re-evaluation of the immunoallergic profile after three years of SLIT.

After receiving only scant clinical benefit from treatment with drugs alone for one year, these 312 "poor responders" were also given the option of SLIT for three years plus drugs only on demand.

All the patients presented as follows at baseline:

1) Clinical profile of rhinitis and mild asthma ($FEV_1$ >80% of the expected value);
2) Positive MCh challenge for $PD_{20}FEV_1$ (or $PD_{35}Sgaw$) <400 μg;
3) Moderate-to-severe nasal eosinophilia (>10%);
4) RAST/CAP for *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* Class II or more;
5) Duration of disease less than five years.

*Treatment*

After one year of treatment with drugs patients had two options: to continue standard pharmacotherapy alone, i.e. cetirizine 10 mg/day and cromolyn sodium nasal 10 mg/day chronically plus inhaled salbutamol (100 μg 1-2 puffs) and nasal steroids (beclomethasone dipropionate, 1 puff per nostril once or twice per day) on demand, or else to select SLIT, based on a carbamylated monomeric allergoid in tablet form (Lais®, Lofarma S.p.A., Milan, Italy), plus drug therapy on demand. Ninety-six patients moved to SLIT and 71 preferred to continue with the drugs alone. The main reasons were: the higher cost of SLIT in comparison to the drugs, the patient's GP's opinion about immunotherapy, and the patient's own opinion.

SLIT was administered in accordance with the latest Position Paper (15, 16), using the therapeutic protocol recommended by the manufacturer. The therapy involved a mixture of monomeric allergenic extracts (50% *Dermatophagoides pteronyssinus*, 50% *Dermatophagoides farinae*) at the following allergy unit (AU) doses: 25, 100, 300, 1000. The extract was standardized by EAST-inhibition in comparison with an internal standard.

The treatment was designed with a dose-increasing phase of 14 weeks during which each dose was taken three times a week in accordance with a schedule provided by the manufacturer, and a maintenance phase during which the maximum dose of 1000 AU was taken once a week for the next three years. The cumulative annual average dose taken was approximately 60,000 AU.

After three years we re-evaluated the 89 patients to compare the results of SLIT + drug on demand with the schedule of drug alone taken chronically + drug on demand, in the two age groups, to verify whether SLIT gave better control of the symptoms than drugs alone, and whether there was any age-related difference in clinical and preventive efficacy with SLIT.

***Table 1*** - Clinical parameter values at baseline (mean and Standard Error of Mean, SEM) of younger (18-28 years) and older (55-65 years) patients in treated (SLIT) and control group (NO SLIT)

| | NO SLIT | | | | SLIT | | | |
|---|---|---|---|---|---|---|---|---|
| | 18-28 yy | | 55-65 yy | | 18-28 yy | | 55-65 yy | |
| | Mean | SEM | Mean | SEM | Mean | SEM | Mean | SEM |
| SMS BAS | 393.6 | 17.1 | 422.2 | 16.4 | 384.4 | 11.8 | 415.0 | 14.9 |
| FEV1 BAS | 86.9 | .8 | 86.8 | .7 | 86.7 | .7 | 87.5 | .6 |
| MEF25 BAS | 55.4 | 1.6 | 57.4 | 2.8 | 59.1 | 1.2 | 57.3 | 1.3 |
| MCh BAS | 204.8 | 23.6 | 149.8 | 24.4 | 151.2 | 16.3 | 253.6 | 20.4 |
| EOS BAS | 32.1 | 2.0 | 27.6 | 2.4 | 29.4 | 1.7 | 26.0 | 1.9 |
| B2 BAS | 18.8 | 1.1 | 21.7 | 1.1 | 21.3 | .8 | 20.9 | 1.4 |
| NCS BAS | 27.3 | 1.3 | 23.8 | 2.0 | 17.0 | .9 | 21.4 | 1.7 |

*Diagnosis*

Prick tests were done in accordance with international guidelines (17) using standardized commercial extracts (ALK Abellò, Lainate, Milan, Italy) for the following allergens: *Dermatophagoides pteronyssinus* and *farinae*, grass, *Artemisia*, ragweed, pellitory, dog and cat dander, birch, olive, *Alternaria* and *Cladosporium*.
Respiratory function was tested by computerized spirometry with plethysmography to study specific conductance and resistance (Masterlab Yaeger, Wurtzburg, Germany). The MCh challenge was done using a dosimeter (Yaeger) activated by inhalatory effort in response to increasing doses of MCh: 30, 60, 120, 240, 390, 690, 1290 μg (18, 19). Patients observed a 48-h wash-out period for beta-stimulants before the test.
Eosinophils in the nasal secretions were counted using a nasal tampon from the front nasal cavity. The material collected was smeared onto glass slides and dried, stained using the May Grünwald-Giemsa method, and read under an optical microscope with an immersion lens. The eosinophil count (number of eosinophils per 100 white blood cells in the nasal secretion) was classified as mild (<10%) or moderate-severe (>10%). Patients gave informed consent to the prick test and the MCh challenge.

*Patients' diaries*

Patients were instructed how to keep a clinical diary recording their symptoms and drug consumption each month during the period November-February from the beginning to end of treatment (three years), for SLIT or chronic standard drug therapy plus drug on demand for both groups. The clinical efficacy of the treatment was assessed on the basis of the following parameters: coughing, wheezing, dyspnea, nasal obstruction, nasal itching, rhinorrhea, sneezing, conjunctival itching, conjunctival redness, watery eyes. Each symptom was rated using the following scale: 0=absent, 1=mild, 2=moderate, 3=severe.
Both groups recorded the consumption of symptomatic drugs taken on demand (salbutamol 1 puff=1 point, beclomethasone dipropionate 1 puff per nostril=1 point).

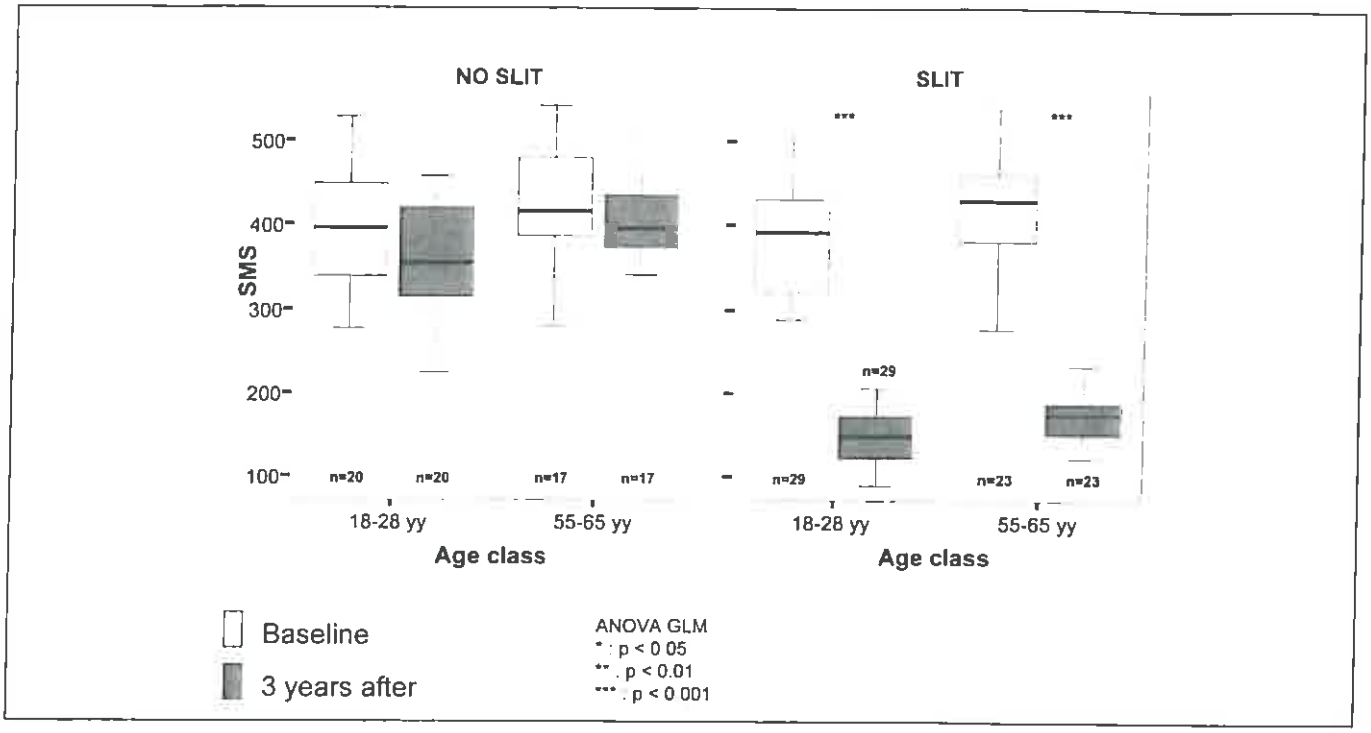
*Statistical analysis*

The sex ratios in the two treatment groups at baseline were compared by Fisher's exact test (20, 21), and differences in the clinical parameters at baseline were tested by GLM MULTI-way ANOVA (analysis of variance by a general linear model), using treatment and sex as fixed factors.
The effect of the treatments and the course of the parameters from baseline over the three years were then modelled using a modified ANOVA for repeated measures (repeated measures GLM) (22). The multivariate effects (overall clinical changes in all parameters) were tested by using Pillai's trace, and the within- subject effects were tested by the Greenhouse and Geisser method (23).
The probability levels for Pearson's Chi-Square were computed using a complete randomization method (permutation or exact test; $P_{Exact}$) or by a Monte Carlo simulation based on 100,000 sampled tables ($P_{MC}$) (24, 25) when the permutation method was not feasible.
All statistical analyses were done using the Statistical Package for Social Sciences version 13.01 (SPSS®).

**Results**

There was no difference in the sex ratios at baseline in the SLIT groups and the No-SLIT groups (respectively $X^2$ = 0.009, df = 1, $P_{Exact}$ = 1.000 and $X^2$ = 0.187, df = 1, $P_{Exact}$ = 0.746). Similarly, there were no differences in sex ratio when grouped by age (young, old) and comparing SLIT with No-SLIT (old, $X^2$ = 0.051, df = 1, $P_{Exact}$ = 1.000 and young, $X^2$ = 0.113, df = 1, $P_{Exact}$ = 0.777).
There were no differences in treatment, sex, and age class in the groups at baseline as regards the Symptom Medication Score (SMS), $FEV_1$, and $MEF_{25}$ (Figures 2, 3), but there were differences in MCh when treatment and age groups were combined ($F$ = 13.311, df = 1, $P$ < 0.001), with the older patients in the No-SLIT group showing lower MCh sensitivity than the younger ones (Figure 4A; 151.7 ± 23.8 and 203.5 ± 22.4), while the opposite was seen in the SLIT group (254.7 ± 20.6 and 150.4 ± 18.3). The EOS count also differed at baseline between the two age classes ($F$ = 4.984, df = 1, $P$ = 0.028) with the younger patients having significantly more eosinophils than the older patients (Figure 4B; 31.2 ± 1.3 and 26.8 ± 1.5). Finally, the use of nasal corticosteroids (NCS) differed significantly between the two groups at baseline ($F$ = 17.872, df = 1, $P$<0.001), with the SLIT group using NCS less than the controls (Figure 5B; 19.1 ± 0.9 and 25.4 ± 1.1).
The effect of treatment significantly affected the overall clinical scenario (multivariate effect; Pillai's trace, $F_{7,79}$ = 68.590, $P$ < 0.001), as did age ($F_{7,79}$ = 2.243, $P$ = 0.039), but the effect of age was no longer detectable after three

*Figure 2* - Symptom medication scores (SMS) in young patients (18-28 yrs) and elderly patients (55-65 yrs) at baseline (white boxes) and after three years of treatment with drugs (NO-SLIT) or allergoid SLIT (SLIT) during a four-year study in Cuasso al Monte Hospital, Italy. Boxes represent the first quartile (25%, lower box extreme), second quartile (median, thick bar), and third quartile (75%, upper box extreme), and whiskers indicate the extreme values. GLM ANOVA results are reported: *** = $P < 0.001$




years (Age*Time, $F_{3,79} = 1.262$, $P = 0.101$). Individually, all the parameters showed significant changes after three years (Figures 2-5) ($P < 0.001$), with a consistent change due to treatment ($P < 0.001$), but irrespective of age ($P > 0.050$), except for the eosinophil count ($F = 5.280$, $P = 0.024$) which was higher in younger patients (Figure 4B). Analysing the effects on each single parameter, treatment affected all parameters ($P < 0.050$), while age affected only the global symptoms (SMS, Figure 2; $F = 10.310$, $P = 0.002$). A combination effect of age and treatment was also detected for $\beta_2$ (Figure 5A; $F = 7.148$, $P = 0.009$) and NCS ($F = 6.247$, $P = 0.014$).

The rate of new sensitizations differed significantly between the treated and control subjects for both the older ($X^2 = 5.673$, df = 1, $P_{Exact} = 0.030$) and the younger patients ($X^2 = 5.979$, df = 1, $P_{Exact} = 0.020$), but there were no differences due to age in either group (controls $X^2 = 0.187$, df = 1, $P_{Exact} = 0.746$; SLIT $X^2 = 0.092$, df = 1, $P_{Exact} = 1.000$).

Some worsening of asthma (mild progressed to moderate asthma) was detected only in the controls, not in the SLIT patients. No age-related differences were detected in the control groups ($X^2 = 0.011$, df = 1, $P_{Exact} = 1.000$).

No noteworthy side effects were reported during the study. This is probably explained by the kind of SLIT employed (a modified allergoid) and the relatively low dosage.

## Discussion

The medical literature reports no studies specifically evaluating the efficacy of SIT in general or, in particular, in elderly patients. This is probably for two reasons: firstly, most patients attending the reference allergy centers are children, adolescents and young adults and, secondly, many of the older patients who come in for an allergy evaluation have a history of allergic respiratory disease that has persisted for many years which – it is generally held - renders them ineligible for allergen-specific immunotherapy (26, 27).

In our retrospective evaluation, we found that SLIT was equally effective in both young and elderly patients as long as the disease had started fairly recently. Long-term compliance (three years) to this SLIT schedule (tablets to be taken once a week) was also very good (only five spontaneous drop-outs out of 57 patients). We also did not

find any appreciable side effects. This can probably be ascribed to the type of SLIT utilised (a modified allergoid) and the relatively low dosage.

A double-blind, placebo-controlled trial would certainly have been a more appropriate tool to assess the indication for SLIT in elderly patients. However, a similar real-life evaluation during normal clinical practice in our allergy center would create ethical problems, particularly as regards the randomization of active treatments and placebo, and also because of the need to conduct the study for at least three years in order to verify specific changes in the patients' clinical, immunological, cytological and functional profiles (6, 28, 29). We therefore believe that a rigorously conducted retrospective evaluation comparing two treatments (SLIT *versus* chronic standard drug therapy) can nevertheless provide useful information on a practical allergological level to define the benefits of SLIT in elderly patients.

Like the younger patients, elderly patients treated with SLIT enjoyed significant improvement in their symptoms and a reduction in the use of drugs on demand. We also observed a tendency to improvement in respiratory function parameters and a decrease in eosinophil infiltration in the nasal mucosa, as well as a higher aspecific bronchoreactivity threshold to MCh challenge.

*Figure 3* - Functional expiratory volume ($FEV_1$, A) , and $MEF_{25}$ ($MEF_{25}$, B) in young patients (18-28 yrs) and elderly patients (55-65 yrs) at baseline (white boxes) and after three years of treatment (No-SLIT and SLIT) during a four-year study in Cuasso al Monte Hospital, Italy. Boxes represent the first quartile (25%, lower box extreme), second quartile (median, thick bar), and third quartile (75%, upper box extreme), and whiskers indicate the extreme values. GLM ANOVA results are reported: *** = $P < 0.001$

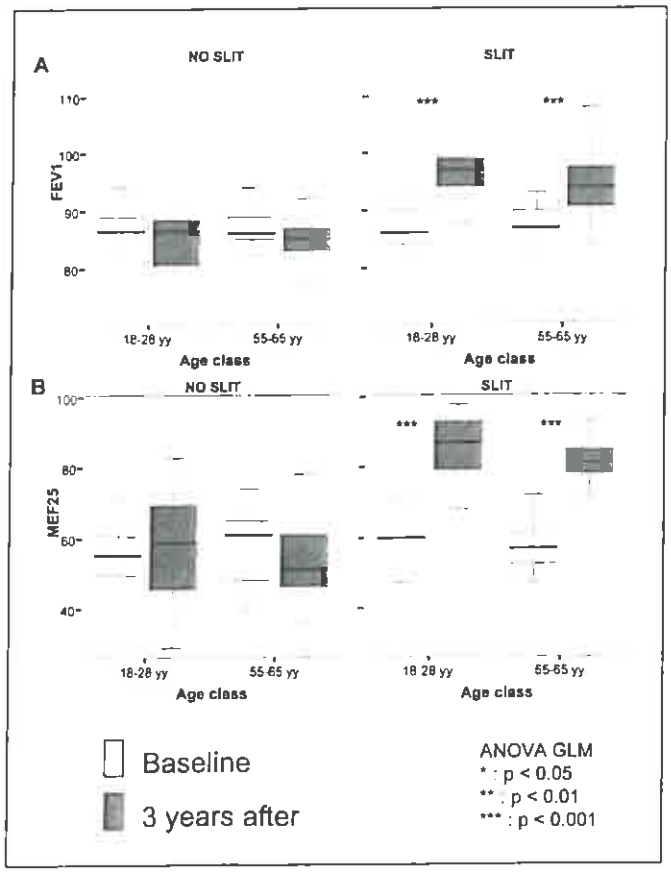



*Figure 4* - Methacholine sensitivity (MCh, A), and eosinophils count (EOS, B) in young patients (18-28 yrs) and elderly patients (55-65 yrs) at baseline (white boxes) and after three years of treatment (NO-SLIT and SLIT) during a four-year study in Cuasso al Monte Hospital, Italy. Boxes represent the first quartile (25%, lower box extreme), second quartile (median, thick bar), and third quartile (75%, upper box extreme), and whiskers indicate the extreme values. GLM ANOVA results are reported: *** = $P < 0.001$

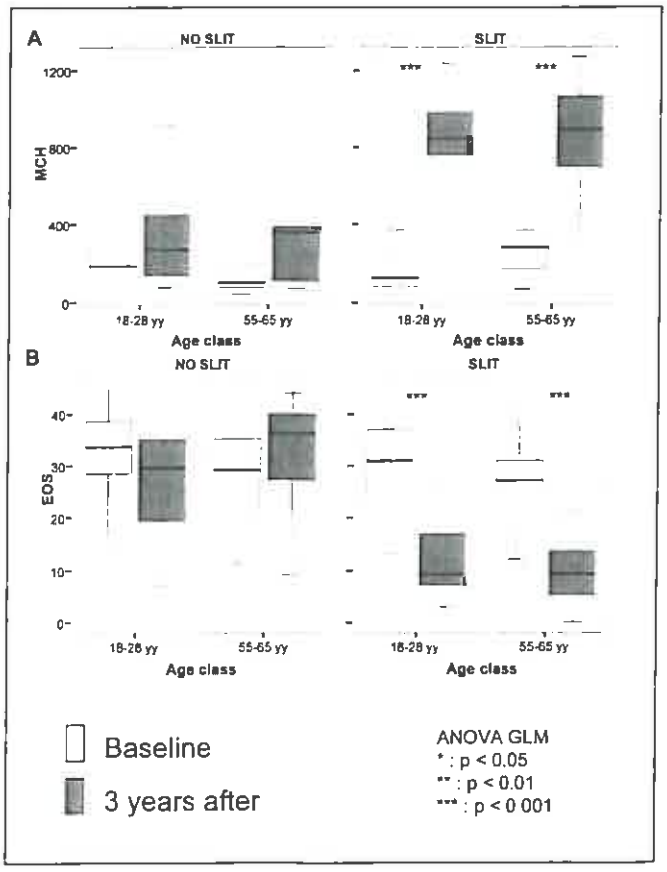
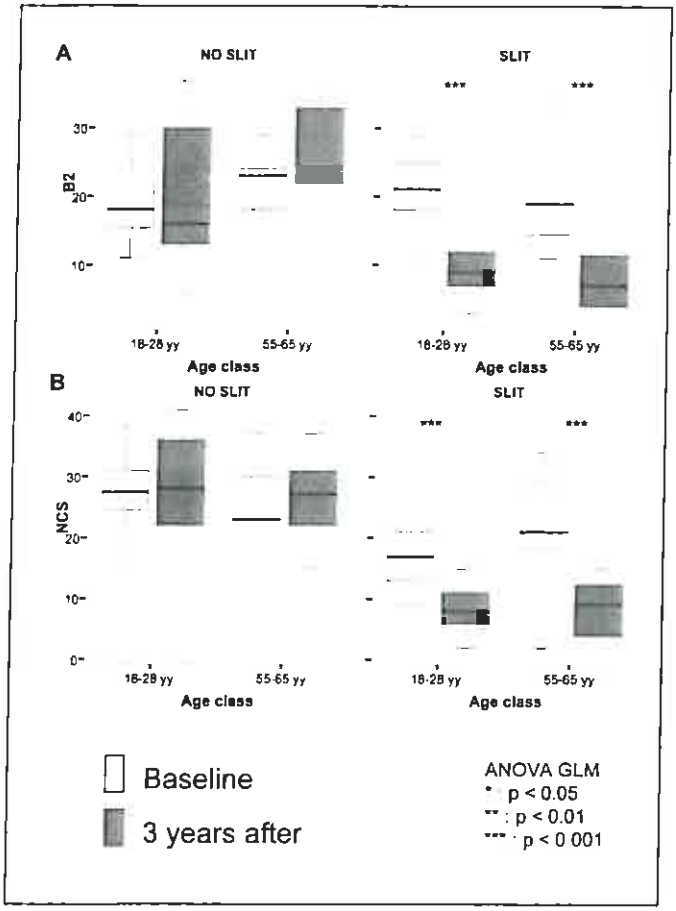


*Figure 5* - Beta-2 ($\beta_2$, A), and nasal corticosteroids (NCS, B) use in young patients (18-28 yrs) and elderly patients (55-65 yrs) at baseline (white boxes) and after three years of treatment (NO-SLIT and SLIT) during a four-year term study in Cuasso al Monte Hospital, Italy. Boxes represent the first quartile (25%, lower box extreme), second quartile (median, thick bar), and third quartile (75%, upper box extreme), and whiskers represent the extreme values. GLM ANOVA results are reported: *** = $P < 0.001$




Lastly, like in the younger patients, there was some prevention of the progression of the respiratory allergic disease, with fewer new sensitizations and less worsening of asthma. On the other hand, and again without any significant differences between young and elderly patients, many of the patients in the two control groups showed no real changes in the severity of their respiratory allergy profile, with many patients reporting some worsening of their clinical condition. Based on these considerations, SLIT can probably be considered a valid therapeutic option in elderly patients, as long as their history of disease is relatively short.

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