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SAFETY AND EFFICACY OF SUBLINGUAL SPECIFIC IMMUNOTHERAPY TO HOUSE DUST MITE USING A DIFFERENT DOSAGE: A PILOT STUDY

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The aim of this randomized open study was to evaluate the safety and efficacy of different dosages (2000 UI vs 4000 UI) of sublingual immunotherapy (SLIT) in patients with allergic diseases such as asthma associated to rhinitis and rhinoconjunctivitis sensitized to house dust mites. We enrolled 61 patients with a history of allergic asthma, and a positive skin prick test for *Dermatophagoides (D.) pteronyssinus/farinae*. Patients were randomly assigned to receiving SLIT at dosage of 2000 UI (Group A) or 4000 UI (Group B) maintenance dose. We evaluated: subjective symptoms using a Visual Analogic Scale (VAS), the amount of prescribed symptomatic drugs, bronchial reactivity to methacholine and side effects using a specific questionnaire. A significant improvement in symptoms, assessed by VAS, was observed with both SLIT doses with no significant differences between groups. The provocation dose of methacholine inducing a 20% fall of FEV1 significantly increased after 12 months only in the 4000 UI dose group. In conclusion, both monomeric allergoid dosages of SLIT (2000 UI and 4000 UI) are a safe and efficacy option to reduce symptoms in patients with allergic asthma caused by house dust mites. Moreover, both dosages are efficacious even to protect against airway reactivity but it seems that monomeric allergoid of SLIT at higher dosage (4000 UI) is better than at the lower dosage (2000 UI).

Asthma is one of the most common chronic diseases in children. It is estimated that the number of people in the world suffering from asthma can reach approximately 300 million (1, 2), representing a major cause of hospitalization, access to emergency care, school absence and poor quality of life, as demonstrated also in children with allergic rhinitis (3, 4). It is also clear that, among patients with asthma, there is a considerable range of phenotypes,

significant heterogeneity concerning function of the airway epithelium, the degree of airway inflammation and airway hyper-responsiveness (5-7) and variable responsiveness to anti-inflammatory drugs, so that it would be more appropriate to refer to asthma as a syndrome, rather than a disease. In recent years allergen-specific sublingual immunotherapy (SLIT) has emerged as an effective and safe treatment option to prevent the progression

Key words: immunotherapy; sublingual; house dust mite; bronchial hyper-reactivity; safety; efficacy; dosage

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of allergic diseases (8, 9) influencing an increase of patient adherence to this therapy (10). SLIT has been proved effective at a large range of doses, from five to three hundred times the doses used for the traditional subcutaneous immunotherapy (11). To date, there is no final agreement on the most advantageous dosage, and it is noteworthy that, although uncommon, potentially fatal side effects have been reported also with SCIT (12). Therefore the aim of this study was to evaluate the safety and efficacy of different dosage (2000 UI vs 4000 UI) of SLIT in patients with asthma sensitized to house dust mites.

MATERIALS AND METHODS

In this randomized, open study we enrolled 61 patients, both children and young adults with a history of allergic asthma associated to rhinitis or rhinoconjunctivitis and a positive skin prick test for *Dermatophagoides (D.) pteronyssinus/farinae*. Patients sensitized to seasonal allergens were excluded. All patients, in stable condition, were treated with a monomeric allergoid in tablets (Lais R, Lofarma SpA, Milan, Italy) containing both *D. pteronyssinus* and *farinae* (50% each). After three days of induction treatment with increasing doses of SLIT, patients were randomly assigned to *Group A* receiving a maintenance dose of 2000 allergic units (AU)/week and *Group B* receiving 4000 AU/week. All patients were guaranteed with symptomatic pharmacological treatment (antihistamines and nasal steroid). During the study period (1 year) we evaluated: 1) subjective symptoms using a Visual Analogic Scale (VAS) where a 0 score indicated no symptoms and 10 most severe symptoms; 2) amount of symptomatic drugs needed; 3) bronchial reactivity to methacholine; and 4) side effects, using a specific questionnaire. Safety and clinical assessment was performed every 4 months. Patients were asked to record in a diary any local or systemic side effects after administration of each dose. Bronchial challenge with methacholine was performed at baseline and after 12 months of treatment.

A total of 31 patients were included in the lower

dose group and 30 in the higher dose group with no significant differences between groups for age, body mass index and pharmacological treatment. Asthma severity in most of the patients of both two groups resulted moderate persistent.

All characteristics of the patients are described in Table I.

RESULTS

A significant improvement of symptoms was observed in patients using a SLIT dose of 2000 UI (VAS score before and after treatment $P < 0.001$), as well as using a SLIT dose of 4000 UI (VAS score before and after treatment $P < 0.001$) (Fig. 1) with no significant differences between the two groups ($P = 0.638$). Moreover, there was no significant difference between groups concerning the use of additional anti-allergic medications. The provoking dose (PD20) of methacholine producing a 20% fall of FEV1 significantly increased after 12 months in patients using a SLIT 4000 UI dose (PD20 at baseline and after treatment, $P < 0.001$) but not in the patients using a 2000 UI dose (PD20 at baseline and after treatment $P = \text{ns}$) (Fig. 2). During the entire study period no systemic side effects were reported by the patients in either group.

DISCUSSION

The scientific debate aiming to define the best dosage in terms of safety and efficacy on the use of SLIT is still open, since this treatment seems to be effective within a wide range of doses. Our pilot prospective study performed on both adult and paediatrician patients sensitized to house dust mite showed that the two different dosages of SLIT (2000 UI vs 4000 UI) had similar safety and clinical efficacy in patients with allergic asthma, in terms of disappearance of symptoms and use of other anti-allergic medication. This is not in agreement with a recent meta-analysis in which patients with seasonal allergy treated with higher dosage of SLIT showed better results than patients treated with lower dosages (13).

Today it is known that among children with

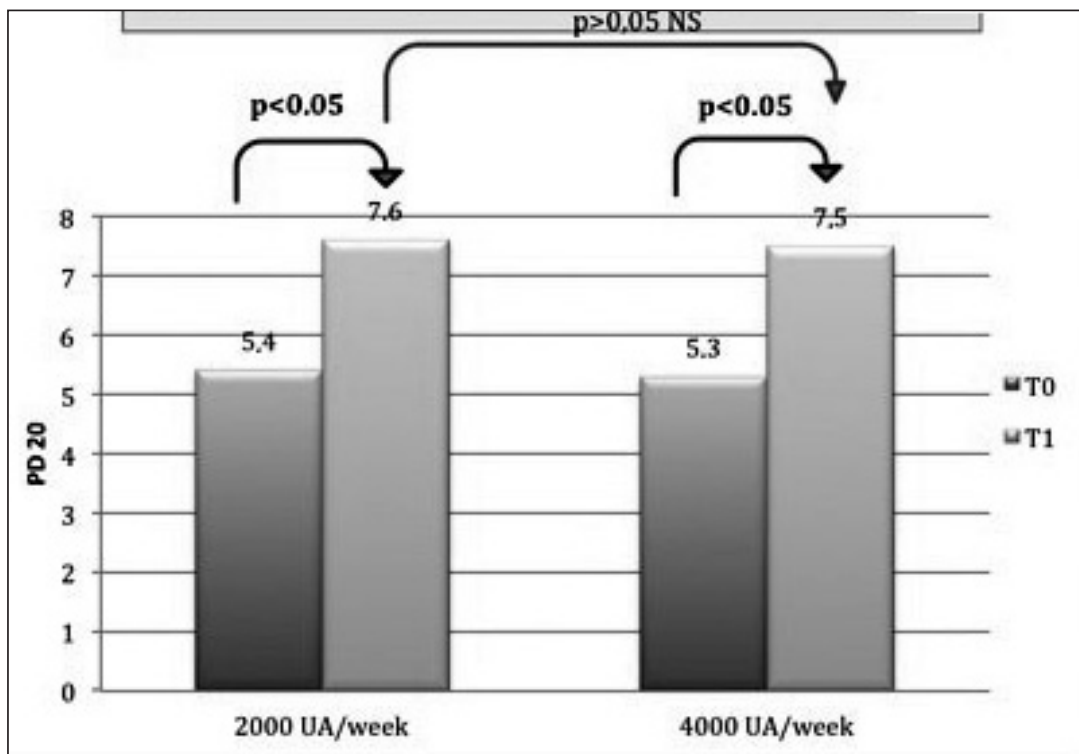


Fig. 1. Changes in intra and inter-group V.A.S. at T0 and T1.

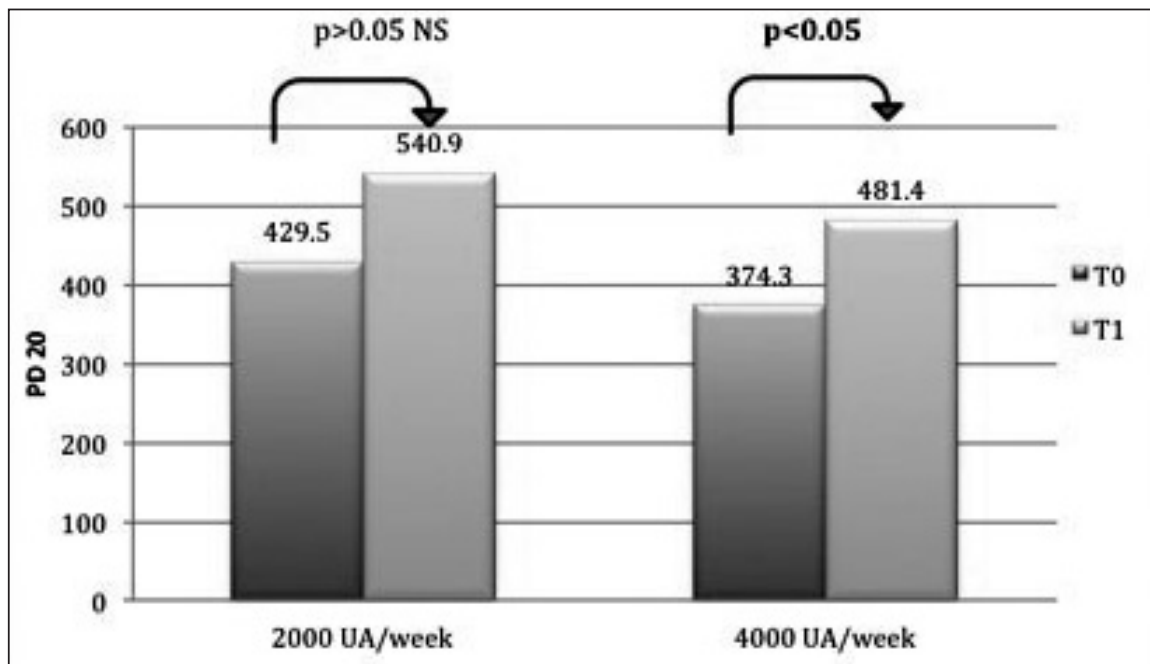


Fig. 2. Variations intra- and inter-group PD20 at T0 and T

asthma, there is a considerable range of phenotypes, significant heterogeneity concerning mucosal immunity, the degree of airway inflammation and airway hyper-responsiveness (14-17) and even serum markers (18-24) and this issue could play a key role on the open question regarding the “best dosage”.

Effect of SLIT in bronchial hyperreactivity, airway inflammation and mucosal immunity was shown in our previous study (25). However, in the present study we found a significant improvement of bronchial hyperactivity only in children treated with higher dosage (4000 UI), while in the other group (2000 UI) we found no significant difference.

As progression of allergic rhinitis toward allergic asthma is a major objective to pursue with immunotherapy, the more significant effect of higher dosage on bronchial reactivity may justify the use of SLIT at a higher safe dosage.

In addition, the use of high dosage of the allergoid is encouraged by the lack of side effects and the

optimal adherence to treatment, which is probably due to its low level of allergenicity (26-28).

In conclusion, we think that a dosage of 4000 UI or more of SLIT with a monomeric allergoid is as safe an option to reduce symptoms as a dosage of 2000 UI, and it seems to be more efficacious to protect against airway reactivity in patients with allergic asthma caused by house dust mites.

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Table I. *Characteristics of patients.*

	Group A : 2000 UA/week	Group B: 4000 UA/week
Number of patients	31	30
Sex (M/F)	21/10	18/11
Age (years)	26.5±12.8	28.2±18.9
Weight (kg)	65.6±17.8	63.8±16.9
Height (cm)	163.1±16.4	164.8±14.9
Clinical condition		
Asthma	1	1
Rhinitis and asthma	25	23
Rhinoconjunctivitis and asthma	5	6
Severity		
Mild Persistent	26	25
Moderate Persistent	3	5

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