

LETTER TO THE EDITOR

THE POLISMAIL LESSON: SUBLINGUAL IMMUNOTHERAPY MAY BE PRESCRIBED ALSO IN POLYSENSITIZED PATIENTSG. CIPRANDI, C. INCORVAIA¹, P. PUCCINELLI², S. SCURATI² and F. FRATI²*Department of Internal Medicine, University of Genoa, Genoa; ¹Allergy/Pulmonary Rehabilitation, ICP, Milan; ²Scientific Department, Stallergenes, Milan, Italy**Received January 18, 2010 – Accepted April 16, 2010*

Polysensitization is a feature of allergic rhinitis (AR) that significantly impairs the quality of life (QoL) of AR patients. Allergen-specific immunotherapy is the only causal therapy for AR. However, the polysensitization phenomenon may represent a crucial obstacle as far as it concerns the choice of the allergen extract which should be used for immunotherapy. Therefore, a real-life based multi-centre study, named POLISMAIL, has been designed which aims at evaluating the behaviour of some allergists managing polysensitized AR patients. The effect of two-year SLIT treatment in those patients was also evaluated. A single allergen extract was used for two-thirds of patients, whereas a mix of two allergens was chosen for the remaining patients. The severity grade of AR and the type of diagnosis were significantly improved by 2-year SLIT. In addition, SLIT significantly improved QoL. Both outcomes confirm that SLIT with one or two allergen extracts achieves a significant improvement in polysensitized patients. In conclusion, the POLISMAIL study demonstrates that polysensitization should not represent a counter-indication for prescribing immunotherapy. The choice to limit SLIT to 1-2 allergen extracts was sufficient and effective in improving symptoms and QoL.

Allergic rhinitis (AR) is the most frequent IgE-mediated disease, as it may affect up to 40% of the general population (1). AR is frequently associated with asthma as underlined by the Allergic Rhinitis and its Impact on Asthma (ARIA) document (2). In addition, AR is considered the main risk factor for asthma inception (3). These issues make AR a relevant disease deserving adequate attention and management.

Polysensitization is a feature of AR: this phenomenon is so typical of allergic patients that it is quite rare to find monosensitized adult patients. In fact, AR patients debut with monosensitization, but soon tend to become sensitized to more allergens over time (4). It has been shown that polysensitization

significantly impairs Quality of Life (QoL) of AR patients (5).

Allergen-specific immunotherapy is the only causal therapy for AR, as it is able to reduce the allergic symptoms and the need of medications by inducing clinical and immunological tolerance to the causal allergen (6). Sublingual immunotherapy (SLIT) is currently the most commonly prescribed form of allergen-specific immunotherapy (SIT) in many European countries and its efficacy is recognized in consensus documents (2-3) and evidenced by meta-analysis (7).

However, polysensitization may represent a crucial obstacle as far as it concerns the choice of the allergen extract which should be used for

Key words: allergic rhinitis, polysensitization, sublingual immunotherapy, Quality of Life

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0394-6320 (2010)

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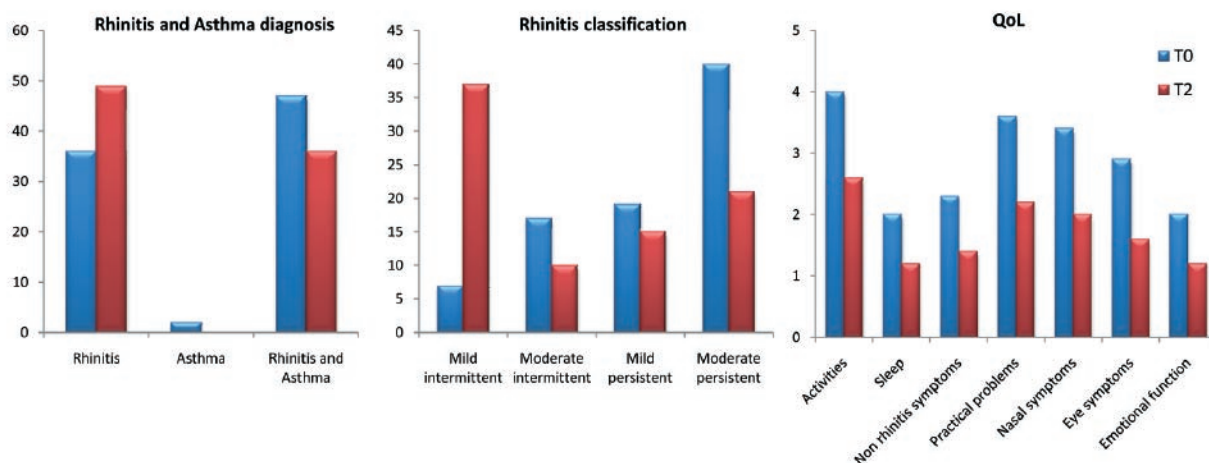


Fig. 1. Left quadrant: rhinitis and asthma diagnosis at baseline and after 2 years; middle quadrant: ARIA classification at baseline and after 2 years; right quadrant: Quality of Life items at baseline and after 2 years.

Table I. SPT results expressed as absolute and relative value.

SPT	No.	%
House dust mites	40	46
Grasses	56	64.4
Parietaria	32	36.8
Betulaceae	30	34.5
Olive	20	23
Absinthium	20	23
Cypressus	18	20.7
Alternaria	12	13.8
Cat	10	11.5
Dog	8	9.2
Ragweed	4	4.6

immunotherapy. For this reason, many physicians prefer to not to prescribe SIT in polysensitized patients. We designed a real-life based multi-centre observational study, named POLISMAIL, which aimed at evaluating the behaviour of allergists treating polysensitized AR patients. The effect of two-year SLIT treatment in those patients was also

evaluated.

The study was conducted in 11 Allergy Centers that were homogeneously distributed in Italy. It was designed to include samples representative of the general population. The study was approved by the Review Board of each participating center and an informed consent was obtained from each patient. All patients were evaluated at baseline (T0) and after 2 years of SLIT (T2).

Eighty-seven patients (42 males, 45 females, mean age 29.7 years, SD 10.8 years) with allergic rhinitis (eventually associated with asthma) were prospectively evaluated. A detailed clinical history was taken and a complete physical examination was performed at baseline. The patients were included in the study on the basis of a diagnosis of respiratory allergy and documented polysensitization. The diagnosis of intermittent or persistent AR and its severity was made on the basis of AR symptom duration and kind of symptoms combined with positive skin prick test (SPT) according to ARIA criteria (2). The diagnosis of asthma and the severity assessment were made according to Global Initiative for Asthma (GINA) criteria (8).

Health-related QoL assessment included the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ), which consists of 28 items distributed in seven domains: sleep problems (3 items), general problems (7 items), practical problems (3 items), nasal problems (4 items), eye symptoms (4 items), activities (3 items), and emotions (4 items) (9).

Responses to the items are scored on a 7-point Likert scale, while domains and overall scores are scored on a 0-6 scale, the lower the score, the better the QoL. When evaluating the effects on QoL of a treatment, a reduction of at least 1 point after treatment is considered clinically relevant (9).

SLIT was administered according to the build-up and the maintenance schedules provided by the manufacturer. The choice of the allergen extract employed in SLIT was based on the demonstration of the relationship between sensitisation and history, thus identifying the causal allergen(s) by a cause-effect connection between allergen exposure and symptom occurrence in each patient. Only use of rescue medication was allowed for better assessing the SLIT efficacy: therefore, patients could assume only antihistamines or short-acting bronchodilators on demand. All adverse events to SLIT were recorded in diary cards.

Statistical analysis was performed considering continuous and/or discrete parameters, reported as mean, SD, median, first and third quartile, and frequency. Categorical parameters were reported in contingency tables. The significance of the score differences between T0 and T2 of the items of the RQLQ was calculated by Student's *t* test for paired data. Confidence Interval at 95% (CI) was reported for the mean of the differences between T0 and T2. The analysis considered also the grade of severity, the type of sensitisation, and the type of used allergen at the SLIT start. The *p* value indicating statistical significance was set at 0.05. Statistical analysis was performed by statistical package BMDP Dynamic produced by BMDP Statistical software, Inc (Los Angeles, CA, USA).

The most frequent causes of sensitization were grass pollen, house dust mites, and Parietaria pollen, as reported in Table I. The mean number of sensitizations per patients was 3.5.

SLIT was carried out on 59 patients (67.8%) with one extract and on 28 (32.2%) with two extracts. House dust mites were the extract most commonly employed, followed by grasses. The grade of AR severity significantly decreased after 2-year SLIT ($p<0.0001$) as reported in Fig. 1A. The grade of asthma severity decreased after SLIT, even though non-significantly ($p=0.06$). The number of patients with asthma significantly diminished after SLIT

($p<0.01$), as reported in Fig. 1B. Finally, all QoL items significantly decreased at the end of SLIT therapy ($p<0.01$ for all), as reported in Fig. 1C.

There was no significant difference concerning the number of new sensitization at T2. Side effects were as follows: 6 local mild reactions and two gastroenteric side effects. No severe systemic reaction was reported. Only four patients dropped out for personal reasons.

Polysensitization is an immunological phenomenon that is clinically significant and relevant from an epidemiological point of view (10). The increasing number of sensitizations in an allergic patient seems to characterize the natural history and may represent a typical development of IgE-mediated hypersensitivity. Polysensitization may be associated with a different clinical picture in respect to monosensitized patients, and especially with a more impaired quality of life (5). Furthermore, the clinical relevance of polysensitization concerns the possible influence on the attitude of physicians in managing allergic patients, mainly concerning the prescription of immunotherapy. Indeed, many physicians faced with many sensitizations prefer not to prescribe SIT. On the other hand, an allergist, when managing polysensitized patients, tends to usually choose one (or two) allergen extracts for SLIT. Therefore, the POLISMAIL study, conducted in real-life clinical practice, provides some interesting outcomes on this issue.

First, all enrolled polysensitized patients were treated with SLIT: using a single extract for two-thirds of the patients, whereas a mix of two allergens was chosen for the remaining patients. This demonstrates that polysensitization is not an obstacle for SLIT prescription and the allergen choice is restricted preferably to one extract, keeping in mind that the mean number of sensitizations was 3.5.

Secondly, the severity grade of AR and the type of diagnosis were significantly improved by 2-year SLIT as was also QoL. These outcomes show that SLIT with one or two allergen extracts achieves a significant improvement in polysensitized patients. It is interesting to note that there was no clinical outcome difference between patients treated with mono-allergen SLIT and those treated with multiple-allergen SLIT. Moreover, the 2-year SLIT was safe and well tolerated. In addition, the present study

confirms a recent open study that used SLIT to evaluate the respective efficacy of treatment with grass pollen, birch pollen, or both, in patients with double sensitization to such pollens (11); although also SLIT with only grass pollen achieved some improvement in the season of birch pollen, and vice versa (attributed by the authors to possible cross-reactivity of the two pollen allergens) SLIT with both pollens provided the best clinical outcome.

In conclusion, the POLISMAIL study demonstrates that polysensitization should not represent a counter-indication for prescribing immunotherapy. The choice to limit SLIT to 1-2 allergen extracts was sufficient and effective in improving symptoms and QoL. However, for definitive conclusions a further study including a placebo-group should be performed.

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