

SUBLINGUAL IMMUNOTHERAPY IN POLYSENSITIZED ALLERGIC PATIENTS WITH RHINITIS AND/OR ASTHMA: ALLERGIST CHOICES AND TREATMENT EFFICACY

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Polysensitization is very common in allergic patients and was previously reported to be associated with more severe symptoms and impaired quality of life. Polysensitization is often considered as a contraindication for specific immunotherapy (SIT). This study is aimed at evaluating the allergist attitude for decision making in choosing SIT in a cohort of Italian polysensitized patients. Moreover, the 1-year effectiveness of the prescribed sublingual immunotherapy (SLIT) in this cohort was evaluated. The study was performed on 244 patients (109 males, 135 females, mean age 28.7 years, S.D. 12.0) with allergic rhinitis (assessed by ARIA criteria) and/or mild to moderate asthma (assessed by GINA criteria) treated with SLIT for 1 year. The kind and the number of prescribed allergen extracts, type of diagnosis, severity of symptoms, use of drugs, and adverse events were evaluated at baseline and after 1 year. A total of 230 patients were treated with SLIT: 165 with a single extract, and 65 with two different extracts (mix). SLIT treatment significantly improved disease staging, and reduced symptom severity and drug use. No systemic reaction was reported. In conclusion, these findings provide preliminary evidence that SIT is effective and safe in polysensitized patients after 1 year of treatment also using single extracts, and thus does not represent an obstacle for prescribing SIT.

Allergic rhinitis (AR) is very frequent as it concerns up to 40% of people (1) and its prevalence is still increasing (2). Social and economic costs are related to quality of life problems and its prevalence

affects medical costs (3). AR classification has been recently revised by the "Allergic Rhinitis and its Impact on Asthma" (ARIA) group (1). This classification includes a comprehensive assessment

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of the frequency and duration of the symptoms. Intermittent AR (IAR) is defined by symptoms occurring for <4 days/week or <4 consecutive weeks. Persistent AR (PER) is defined by symptoms occurring for >4 days/week and >4 consecutive weeks. Additionally, a severity scale of mild to moderate-severe (based on the AR impact on both daily activities and quality of life) was included in the revised classification.

Moreover, it is well known that AR is frequently associated with asthma (4-5). Asthma is classified by GINA guidelines on the basis of severity of symptoms as mild, moderate or severe, and by duration of symptoms as intermittent or persistent (6).

AR is frequently associated with the phenomenon of polysensitization, i.e. allergic patients tend to become sensitized to more allergens over the years (7). Indeed, a recent study provided evidence that 72% of patients with allergic rhinitis are polysensitized (8). This fact may result in problems when the allergist has to prescribe specific immunotherapy (SIT) as it could be difficult to choose the allergen to use. In this regard, a very recent study confirmed for polysensitized patients the relevance of ARIA classification of AR (9). PER is the most common form of AR in these patients, symptoms are frequently moderate-severe, and asthma is associated to rhinitis in about half of the patients.

The major aim of this study is to evaluate the allergist's attitude for prescribing SIT in a cohort of polysensitized patients suffering from AR and eligible for SIT. Moreover, the 1-year efficacy and safety of the prescribed sublingual immunotherapy (SLIT) was evaluated.

MATERIALS AND METHODS

Study design

This is an open observational study, which was named POLISMAIL after the Italian words "Polisensibili: Storia della Marcia Allergica durante Immunoterapia a Lungo termine" (in English: history of the allergic march during long-term immunotherapy). This multicenter study was conducted in 26 Allergy Centres homogeneously distributed in Italy. It was designed to include samples representative of the general population and to have the ability to identify the new diagnosed cases according to

validation (1). Patients were evaluated before starting SLIT and after 1 year. The study was approved by the Review Board of each participating center and informed consent was obtained from each patient. As the study was observational, each allergist was free to prescribe SLIT following ethical rules of good clinical practice. The allergen extract for SLIT was chosen on the basis of its clinical relevance.

Subjects

A total number of 244 patients (109 males, 135 females, mean age 28.7 years, S.D. 12.0) with allergic rhinitis and/or asthma were prospectively and consecutively evaluated. A detailed clinical history was taken and a complete physical examination was performed. The patients were included in the study on the basis of a diagnosis of allergic rhinitis and/or asthma and documented polysensitization, as all subjects included in this study had >2 sensitizations as assessed by skin prick testing.

Skin prick tests (SPT) were carried out according to the European Academy of Allergy and Clinical Immunology (10). The panel consisted of: house dust mites (*Dermatophagoides farinae* and *pteronyssinus*), cat, dog, grasses mix, mugwort, ragweed, *Parietaria officinalis*, birch, hazel, olive tree, cypress, *Alternaria tenuis*, *Cladosporium*, *Aspergillus* mix (Stallergenes, Milan, Italy).

The diagnosis and severity classification of intermittent or persistent allergic rhinitis was made on the basis of a history of nasal symptoms and positive skin prick test according to validated criteria (1). The diagnosis and severity classification of asthma were made according to GINA criteria (6). Moreover, patients gave a subjective judgment of both the severity of their symptoms and the use of drugs by a visual analogue scale (VAS) according to validated criteria (11). Symptoms were globally evaluated, by cumulatively considering eye itching, epiphora and redness, nasal itching, rhinorrhea and obstruction, cough, wheeze and dyspnea.

Patients were evaluated at baseline (V1) and after 1 year (V2). Adverse events to SLIT were adequately recorded.

Statistical Analysis

Continuous and/or discrete parameters were reported as mean, SD, third quartile, and frequency. Categorical parameters were reported in contingency tables. Homogeneity of data was evaluated by χ^2 Fisher exact test. The significance of the values concerning the principal parameters between V1 and V2 was calculated by Student's t test for paired data and by non-parametric Wilcoxon test for continuous parameters. Confidence Interval at 95% (CI) was reported for the mean of the

Table I. Distribution of positive results to SPT and allergen extracts chosen for SLIT.

Allergen	N	%	Immunotherapy	%
Dermatophagoides	114	46.7	97	39.8
Grasses	199	81.6	97	39.8
Parietaria	118	48.4	42	17.2
Olive	79	32.4	23	9.4
Birch/Hazel/Alder	95	38.9	17	7
Cypress	27	11.1	6	2.5
Mugwort	69	28.3	8	3.3
Ragweed	33	13.5	0	0
Alternaria	27	11.1	8	3.3
Cat	54	22.1	0	0
Dog	43	17.6	0	0
Other	32	13.1	1	0.4
Mix			27	11.1

differences between V1 and V2. McNemar test was used for categorical or discrete parameters. The p value concerning the 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).

RESULTS

The most relevant allergens in the polysensitized patients are reported in Table I. Grasses were the most important cause of sensitization, giving positive SPT in 199 (81.6%) patients, followed by *Parietaria*, positive in 118 (48.4%) patients and *Dermatophagoides*, positive in 114 (46.7%). The mean number of sensitizations per patient was 3.65. Seventy patients had 2 sensitizations, 71 had 3 sensitizations, 41 had 4 sensitizations, 28 had 5 sensitizations, 19 had 6 sensitizations, and 15 had more than 6 sensitizations. Table I reports the distribution of positive results to single allergens and the allergen extracts chosen for SLIT. A total of 230 patients were treated with SLIT: 165 with a single extract, 58 with 2 different extracts, and 7 with more than two extracts (grass pollen, *Parietaria* pollen, olive pollen, birch pollen, and dust mites being the allergen most frequently included). Overall, grasses and *Dermatophagoides* were the most common extracts prescribed: both in 97 (39.8%) patients, followed by numerous pollens as reported in Table I.

The following distribution of diagnosis was observed: 132 (54.1%) patients had AR alone, 103 (42.2%) had AR associated with asthma, and 9

(3.7%) asthma alone at baseline. After 1 year, 148 (60.7%) patients had AR alone, 90 (36.9%) had AR associated with asthma, and 6 (2.5%) asthma alone: the McNemar test provided a borderline significance for these comparisons ($p=0.05$).

Concerning the severity of AR, 42 (20.9%) patients had IAR: 6 of them with mild symptoms and 36 with moderate-severe symptoms; 193 (79.1%) patients had PER: 44 with mild and 149 with moderate-severe symptoms at baseline (Fig. 1). After 1 year of SLIT treatment, 111 patients had IAR: 70 with mild and 41 with moderate-severe symptoms; 122 patients had PER: 75 with mild and 52 with moderate-severe symptoms. All these differences were statistically significant to McNemar test ($p<0.0001$). In particular, about 30% of patients was without or with mild symptoms of IAR after 1 year of SLIT. Concerning asthma severity in the 112 asthmatic patients, 56 had an intermittent form and 56 a persistent form (28 mild, 27 moderate, and 1 severe) at baseline. After 1 year of SLIT treatment, asthma was present in 92 patients, 58 with the intermittent form and 34 with the persistent form (18 mild and 16 moderate). The difference between asthma severity at the two visits was significant to McNemar test, with $p=0.0004$.

Fig. 2 shows the mean (+ SD) of ocular, nasal, and bronchial symptoms assessed by VAS at baseline and after 1 year. A significant decrease was found in ocular ($p<0.01$), nasal ($p<0.01$) and bronchial symptoms ($p<0.01$). Likewise, the use of drugs significantly diminished after 1 year of

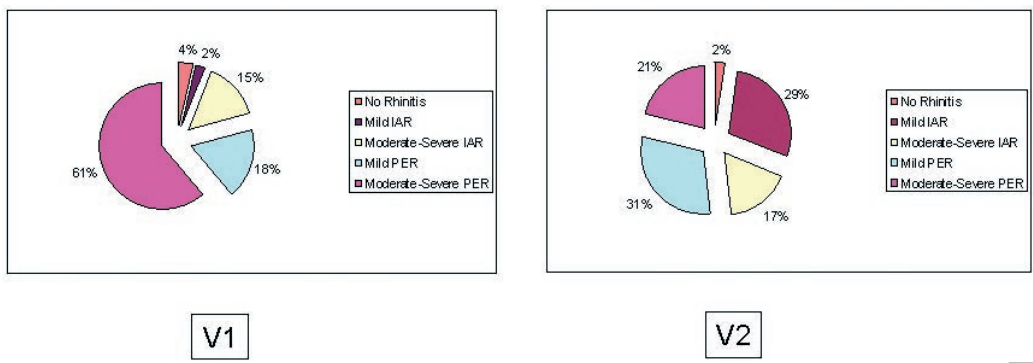


Fig. 1. Type and severity of rhinitis before and after 1 year of SLIT.

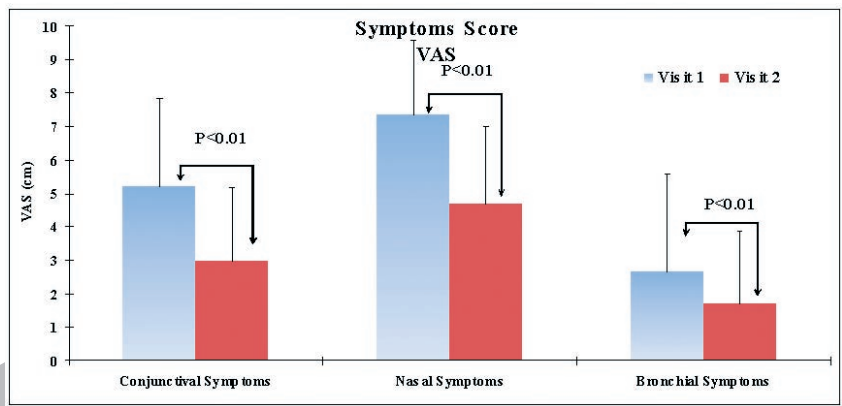


Fig. 2. Symptoms severity assessed by VAS before and after 1 year of SLIT.

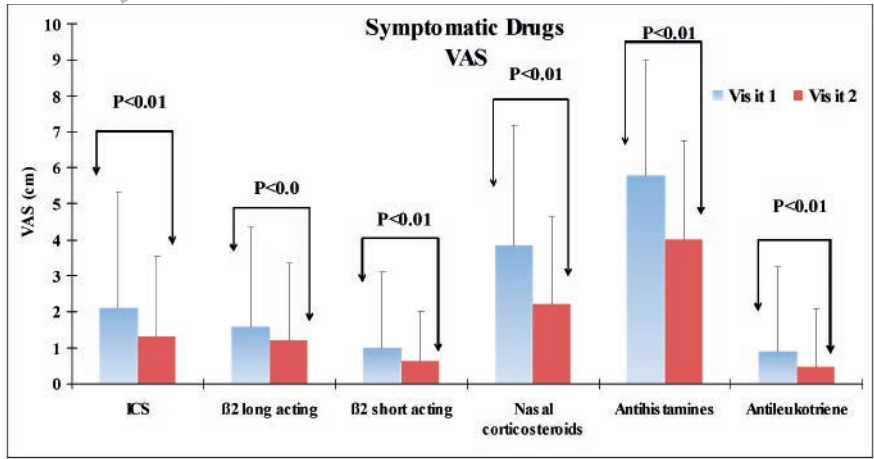


Fig. 3. Drug use assessed by VAS before and after 1 year of SLIT.

SLIT treatment concerning inhaled corticosteroids, short- and long-acting B2-agonists, intranasal corticosteroids, antihistamines, and antileukotrienes ($p < 0.01$ for all) as reported in Fig. 3.

With regard to the adherence to the treatment, 155 (71.1%) had a complete adherence with no interruption of the schedule, 33 (15.1%) patients had only one interruption, and 19 (8.7%) had two interruptions. No systemic reactions were observed. The reported adverse reactions were: 57 local reactions, all mild and self-resolving, 24 gastrointestinal reactions, also mild and self-resolving, and 3 respiratory reactions. However, there were 3 drop outs (all to grass pollen treatment): in 2 patients for heartburn and in one patient for abdominal colic. All adverse reactions were independent of clinical severity.

DISCUSSION

Polysensitization is an immunological phenomenon that is clinically significant and relevant from an epidemiological point of view, as recently reported in recent surveys (7, 12-13). The increasing number of sensitizations seems to characterize the natural history of allergic patients and may represent a typical development of the allergic reaction. Polysensitization may be associated with a different clinical picture in respect to mono-sensitized patients, and especially with a more impaired quality of life (9).

This study is primarily aimed at evaluating the allergist attitude in prescribing SIT in a large cohort of Italian polysensitized patients suffering from AR and asthma. Moreover, the study evaluates the 1-year effectiveness of the prescribed sublingual immunotherapy (SLIT) in this cohort. The analysis of the basic characteristics of patients showed that the majority of them (about 80%) have the PER form and the moderate-severe form as the most frequent clinical expression. This finding may be partially explained by the relevant number of sensitizations per patient (i.e. 3.65) in our cohort and may depend on the type of studied populations, confirming previous studies (12-14). Secondly, about half the patients with AR also have asthma, which therefore represents an important co-morbidity for AR, as stated in the ARIA document (1). With

regard to asthma severity, most patients had the intermittent form, whereas almost all patients with persistent asthma had mild-moderate severity of symptoms. This finding is partially conflicting with other surveys on asthma (4, 15). The presence of concomitant AR, which is a well-known worsening factor for asthma (1), may possibly explain such discrepancy. Furthermore, the clinical relevance of polysensitization is confirmed by both the high mean number of sensitizations and the possible influence on the attitude of physicians in managing allergic patients, mainly concerning the prescription of immunotherapy. Indeed, many physicians when confronted with such sensitizations prefer to avoid prescribing SIT.

The present study, based on real life clinical practice, provides some interesting outcomes on this issue. Firstly, grasses were the most relevant allergen, followed by house dust mites; this finding confirms previous studies conducted in Italy (15). Although the mean number of sensitisations is 3.65, a single extract was chosen in about two-thirds of patients, and few allergens were used in the others. This model indicates that polysensitization should not constitute an impediment to SLIT prescription if only few allergens are chosen. On the other hand, this choice seems to be correct as the SLIT effectiveness is confirmed in this cohort also limiting the number of used allergens. In particular, the suitability of the allergen choice is confirmed by SLIT effectiveness on the improvement of AR and asthma classifications. Indeed, asthma becomes less frequent and IAR becomes more frequent. Equally, the severity of symptoms significantly decreases after SLIT treatment. A further confirmation of the validity of such a strategy is the perception of symptom severity and drug use assessed by patients. Probably, these findings also result from both a close adherence to the schedule and an optimal safety profile of SLIT. Few studies investigating the effects of immunotherapy with multiple allergens are available (17-19). Adkinson et al. conducted a controlled trial of subcutaneous immunotherapy (SCIT) on children with allergic asthma using several (up to 7) allergens and found no discernible benefit (17). By contrast, Alvarez-Cuesta et al. demonstrated in a placebo controlled study that SCIT, with both grass and olive pollen, was able to significantly improve the quality

of life in patients with seasonal allergic rhinitis due to double sensitisation (18). A recent open study used SLIT to evaluate the respective efficacy of treatment with grass pollen, birch pollen, or both, in patients with double sensitization to such pollens (19); however, 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) (19) or to induction by the first SLIT treatment of production of interleukin 10, which exerts a partially non-specific immunologic regulatory effect, SLIT with both pollens provided the best clinical outcome. However, it is to note that the diagnosis with conventional extracts does not permit the distinction from *bona fide* polysensitization from pan-allergen reactive patients. This applies in particular to birch-plus-grass allergic individuals, where reactivity to Bet v 2/Phl p 12 or Bet v 4/Phl p 7 imply positive skin and *in vitro* tests with both extracts, also in the absence of IgE reactivity to major allergens from the two allergen sources. Widespread use of a new recombinant diagnostic tool is expected to improve the capability to make correct prescription of immunotherapy in polysensitized patients.

Our results, obtained on a large number of patients, confirm that SLIT with one or two allergen extracts achieves a significant improvement in rhinitis and asthma in most polysensitized patients. In conclusion, this study strengthens the concept that polysensitization is a relevant aspect in allergic patients and must be carefully evaluated, mainly if immunotherapy is considered as treatment. In any case, polysensitization should not represent a counter-indication for prescribing immunotherapy. The choice limited to 1-2 allergen extracts revealed to be sufficient and effective in improving allergic symptoms. However, further controlled multicenter studies are necessary to fully confirm these findings.

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