

Expert Opinion

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Polysensitization as a challenge for the allergist: the suggestions provided by the Polysensitization Impact on Allergen Immunotherapy studies

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Introduction: Polysensitization, that is, sensitization to more than one allergen family, is a common feature of patients with allergic rhinitis (AR) and significantly impairs their quality of life (QoL). Allergen-specific immunotherapy is the only causal treatment for AR. However, the polysensitization phenomenon may represent a crucial obstacle as far as it concerns the choice of the allergen extract to be used for immunotherapy.

Areas covered: A series of real-life based multi-center studies, named POLISMAIL (Polysensitization Impact on Allergen Immunotherapy), have been designed with the aim of evaluating the behavior of allergists in managing polysensitized AR patients. The effect of immunotherapy treatment in these patients was also evaluated. A single allergen extract was used in two-thirds of patients, whereas a mix of two allergens was chosen in the remaining. The severity grade of AR and the QoL were significantly improved by immunotherapy. Both outcomes confirmed that immunotherapy with one or two allergen extracts achieves a significant improvement in polysensitized patients.

Expert opinion: In conclusion, POLISMAIL studies demonstrate that polysensitization should not represent a counter-indication for prescribing immunotherapy. The choice of limiting sublingual immunotherapy to one to two allergen extracts, preferably separated and at high dosages, is sufficient and effective in improving symptoms and QoL.

Keywords: allergic rhinitis, polysensitization, quality of life, sublingual immunotherapy

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1. Introduction

Allergic rhinitis (AR) is the most frequent IgE-mediated disease as it may affect up to 40% of the general population [1] that results in substantial social and economic costs [2]. In fact, school or work performance and absences (including parents' work absences), daily activities and play, and quality of sleep are significantly impaired in both children and adults with AR [3]. AR may be also frequently associated with asthma and is considered the main risk factor for development of asthma, as underlined by the ARIA (Allergic Rhinitis and its Impact on Asthma) document [4]. These issues make AR a relevant disease deserving adequate attention and management.

Moreover, the increasing number of sensitizations (the so-called phenomenon of polysensitization) in the same allergic patient seems to characterize the natural history and may represent a common feature of allergic patients [5]. It has been documented that atopic infants start always with monosensitization, that is, sensitization to only one class of allergens [6]. In fact, AR patients debut with monosensitization, but soon

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tend to become sensitized to further allergens over time [4]. Polysensitization is an immunological phenomenon that is clinically significant and relevant from an epidemiological point of view. Indeed, polysensitization has been well documented in several studies conducted both in children and in adults, during a general population survey or in allergic population-based studies [7-13]. The increasing number of sensitizations seems to characterize the natural history of allergic patients and may represent a typical evolution of allergy. The percentage of polysensitized patients ranges from 20 to 90% in the studied populations [13]. Polysensitization may be also associated with a different clinical picture with respect to monosensitized patients and especially with a more impaired quality of life (QoL) [14,15]. A study demonstrated that allergic children had a higher frequency of sensitizations than their parents, especially in families with polysensitization [16]. In another study, analyzing retrospectively 165 asthmatic patients who were monosensitized in a first survey, Silvestri *et al.* found that 43.6% of the patients became polysensitized on a second survey [17]. The transition from monosensitization to polysensitization observed in the entire population was present also in preschool- and in school-aged children separately analyzed. In addition, they found that house dust mite sensitization and, at a lower degree, pollen sensitization, seem to play a 'triggering' role in the development of polysensitization, as a high proportion of children originally monosensitized to house dust mites or to pollens became polysensitized. Instead, it has been recently reported that in childhood allergic asthma, total and mite-specific sIgE levels are strictly linked to markers of allergic inflammation, that is, the fractional exhaled NO levels or blood eosinophilia, without being affected by the presence of multiple sensitizations [18].

Another study reported that polysensitized patients had more severe symptoms than monosensitized ones [11]. Moreover, it has been observed that polysensitized patients with rhinitis more frequently present associated asthma than monosensitized ones [15]. On the other hand, there are patients who remain monosensitized during their life. A very recent study suggested in a functional defect of T-regulatory cells an immunological hypothesis to explain the trend to develop polysensitization [19]. Children with persistent monosensitization produced higher quantity of IL-10 and IFN- γ than children developing polysensitization [19]. This fact might suggest the existence of two different phenotypes for mono- and poly-sensitized patients.

2. Allergen immunotherapy in polysensitized patients

Allergen-specific immunotherapy (SIT) 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 [20]. Sublingual immunotherapy (SLIT) is currently the most commonly prescribed form of SIT in many European countries and its efficacy is recognized in consensus documents [4] and evidenced by meta-analysis [21].

However, polysensitization may have a profound influence in clinical practice: for example, it may represent a crucial obstacle as far as it concerns the choice of the allergen extract that should be used for immunotherapy. For this reason, many physicians prefer to renounce prescribing SIT in polysensitized patients. In this regard, the evaluation of immunotherapy efficacy in polysensitized patients still represents an unanswered question and there are few studies on this issue. Adkinson *et al.* performed a controlled trial of subcutaneous immunotherapy (SCIT) in children with allergic asthma using several (up to seven) allergens and found no discernible benefit [22]. However, there were major methodological problems in the Adkinson study, primarily use of mostly seasonal allergens in treating children with perennial asthma (excluding cockroach and animal dander allergens which may well have been the most important in mixed inner city and suburban children). 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 QoL in patients with seasonal AR due to double sensitization [23]. 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 [24]. SLIT with only grass pollen achieved some improvement in the season of birch pollen and vice versa; the authors attributed this outcome to possible cross-reactivity of the two pollen allergens or induction by the first SLIT treatment of production of IL-10, which exerts a partially nonspecific immunologic regulatory effect. However, SLIT with both pollens provided the best clinical outcome. In addition, the effective use of multiple allergen immunotherapies has been reported in three studies summarized by Nelson [25].

For these reasons, we designed a series of real-life based multi-center observational studies, named POLISMAIL (Polysensitization Impact on Allergen Immunotherapy), to try to provide responses to these unanswered questions, mainly concerning the relevance of polysensitization in the clinical practice. These studies also aimed at evaluating the characteristics of polysensitized AR patients and the behavior of allergists treating them. The effect of a 2-year SLIT treatment in such patients was also evaluated in different times.

The rationale of POLISMAIL studies was based on several issues: i) the polysensitization phenomenon may start from early childhood, ii) it progresses with aging, iii) up to 80% of allergic adults may be polysensitized, iv) it may depend on Treg defect, v) it may significantly affect QoL, vi) it may be associated with more severe symptoms than monosensitized subjects and vii) it may prevent immunotherapy prescription.

These studies were conducted in 11 allergy centers that were homogeneously distributed in Italy. The study design should include samples representative of the general population. These studies were approved by the review board of each participating center and an informed consent was obtained from each patient. All patients were evaluated at baseline and after 1 and 2 years of SLIT.

Cohorts of patients with AR (possibly 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 done on the basis of AR symptom duration and kind of symptoms combined with positive skin prick test according to ARIA criteria [2].

The diagnosis of asthma and the severity assessment was 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) [25]. 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 [26].

SLIT was administered according to the build-up and the maintenance schedules suggested by the manufacturer. The choice of the allergen extract used in SLIT was based on the demonstration of the relationship between sensitization 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. The statistical analysis was performed by appropriate tests.

The first study investigated the clinical characteristics of 418 polysensitized patients [15]. The analysis showed that 220 patients had AR and 198 had AR associated with asthma. AR patients were classified as having mild intermittent in 8.1%, moderate-severe intermittent in 18.9%, mild persistent in 20.3% and moderate-severe persistent in 52.6% of cases. Asthma classification showed that 51.3% of subjects had intermittent asthma, 23.2% mild persistent, 22.2% moderate persistent and 3% severe persistent. The mean number of sensitizations was 3.65. Comparing polysensitized patients with a group of monosensitized subjects, a significant difference in more severe symptoms in polysensitized than in monosensitized patients was found, both concerning nasal and bronchial complaints. The most relevant causative allergens were: grass pollen (76.4%), house dust mites (47.4%), *Parietaria* pollen (38.9%), *Betulaceae* pollen (38.3%), olive pollen (26.7%), ragweed pollen (23.3%), cat epithelium (22.5%), dog epithelium (13.2%), *Alternaria* (10.4%) and cypress pollen (9.6%) (Figure 1).

A second POLISMAIL study investigated the clinical characteristic of polysensitized children [27]. The pediatric cohort consisted of 139 children (mean age 11.8 years): 117 were polysensitized, 71 had AR alone and 68 AR plus asthma. The classification of rhinitis was: 7.2% for mild intermittent, 21.6% for moderate-severe intermittent, 24.4% for mild persistent and 46.8% for moderate-severe persistent. The classification of asthma was: 44% for intermittent, 22% for mild persistent, 32% for moderate persistent and 2% for severe persistent. Also, this study confirmed that polysensitized children reported more severe (nasal and bronchial) symptoms than monosensitized ones. The distribution of the most prevalent allergen cause of sensitization was: grass pollen (90%), house dust mites (65%), cat epithelium (34%), *Betulaceae* pollen (33%) and *Parietaria* pollen (32%).

A third POLISMAIL study investigated the allergist attitude for decision making in choosing allergens for immunotherapy and the 1 year immunotherapy efficacy [28]. This study was performed on 244 patients. A total of 230 patients were treated with SLIT for 1 year: 165 with a single allergen extract and 65 with two different extracts (Figure 2). SLIT treatment significantly improved disease staging, and reduced symptoms severity and drug use. No systemic reaction was reported. This study reported that immunotherapy was effective and safe in polysensitized patients after 1 year of treatment also using a single extract; therefore, polysensitization did not represent an obstacle for immunotherapy prescription in these patients.

A fourth POLISMAIL study evaluated the effect, in real-life clinical practice, of 1 year immunotherapy on QoL in polysensitized patients [29]. This study prospectively evaluated 167 consecutively enrolled polysensitized patients with AR. QoL was assessed using the RQLQ at baseline and after 1 year of SLIT treatment. The mean values of all the QoL items improved significantly (Figure 3). This study, therefore, showed that QoL can be improved in polysensitized patients treated with SLIT and that the use of just one or two allergen extracts seemed to be sufficient and effective in terms of improving QoL.

A fifth POLISMAIL study aimed at evaluating the clinical effectiveness of 1 year of SLIT in a cohort of 51 polysensitized children [30]. Forty-two children were treated with a single extract, four with two different extracts and three with a mix of allergens (data from 2 patients were missing). SLIT treatment induced a significant reduction in the number of sensitizations; significant improvement of AR classification and severity; and significant reduction of ocular, nasal and bronchial symptoms, and drug use (Figure 4). No systemic reactions to SLIT were observed. Also, this study thus showed that polysensitization was not an obstacle for prescribing SLIT in these polysensitized children.

The last POLISMAIL study aimed at evaluating both the behavior of some allergists managing polysensitized AR patients and the effect of 2 year SLIT treatment in such patients [31]. A single allergen extract was used in two-thirds

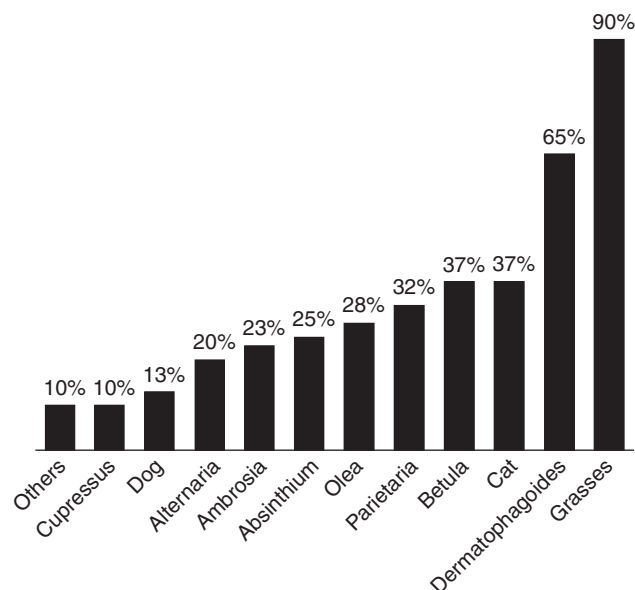


Figure 1. Prevalence of allergen sensitizations in the first POLISMAIL study.

POLISMAIL: Polysensitization Impact on Allergen Immunotherapy.

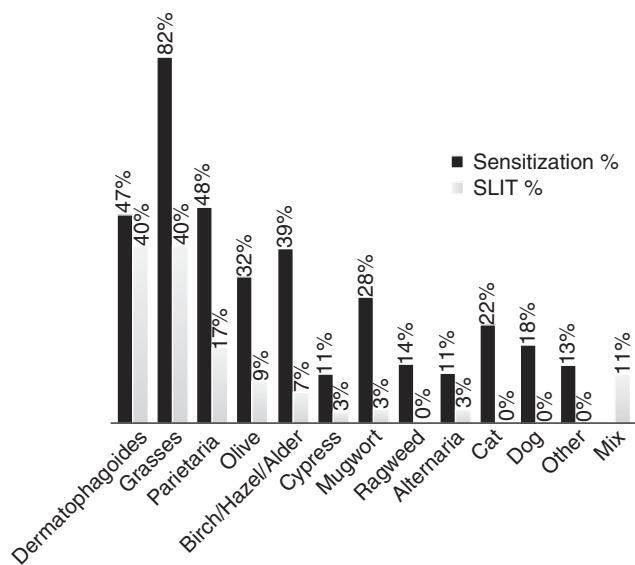


Figure 2. Distribution of polysensitizations and allergen extracts chosen for immunotherapy.

of patients, whereas a mix of two allergens was chosen in the remaining. The severity grade of AR and the type of diagnosis were significantly improved by 2 year SLIT. In addition, SLIT significantly improved QoL (Figure 5). Both outcomes confirm that SLIT with one or two allergen extracts achieves a significant improvement in polysensitized patients. Therefore, this study also demonstrated that polysensitization should not represent a counter-indication for prescribing

immunotherapy. The choice of limiting SLIT to one to two allergen extracts was sufficient and effective in improving symptoms and QoL.

3. Conclusion

In conclusion, all these studies clearly indicate that polysensitization should not constitute an impediment to SLIT prescription if only few allergens are chosen. Moreover, this choice seemed to be correct as SLIT efficacy was confirmed in those cohorts also limiting the number of used allergens. In particular, the suitability of the allergen choice was confirmed by SLIT effectiveness on the reported improvement of AR and asthma classifications and severity. Therefore, the choice of limiting SLIT to one to two allergen extracts, preferably separated and at high dosages, was sufficient and effective in improving symptoms and QoL in polysensitized patients.

4. Expert opinion

Allergen immunotherapy was introduced 100 years ago [32], but remained an empirical treatment until the first controlled trial in 1954 paved the way to the scientific era [33]. Today, the clinical efficacy of immunotherapy in both its forms of subcutaneous (SCIT) and sublingual (SLIT) administration is demonstrated by a number of meta-analyses, recently reviewed by Compalati *et al.* [34]. Typically, an immunotherapy trial includes patients sensitized to only one allergen or to other allergens unable to bias the observations; for example, a trial on SCIT or SLIT with a grass-pollen extract may include patients sensitized to cypress pollen that has a completely different flowering season. However, in real-life conditions, and especially concerning adults, most allergic patients are sensitized to many allergens, thus defining the state of polysensitization [4,5]. In the US, this is not perceived as an obstacle, and many patients are treated with mixes including all the allergens eliciting a positive response to allergy tests. However, a double-blind, placebo-controlled trial of multiple-allergen immunotherapy in 121 allergic children with moderate-to-severe asthma for over 2 years showed that such kind of immunotherapy was of no discernible benefit in allergic children with perennial asthma who were receiving appropriate medical treatment [22]. Indeed, in Europe the option to treat allergic patients by using mixes of multiple allergens is generally disregarded. Such an attitude is influenced by the awareness that when many allergens are used in a mixed extract, the dose of each allergen is much lower than the dose administered with extracts of single allergens. In fact, the dose dependence of efficacy of immunotherapy is a solid concept for SCIT [35] and was recently confirmed also for SLIT [36,37]. Apart from such a concept, the fact that polysensitized patients cannot be treated at all with immunotherapy is not supported by scientific data. This was the reason for us to perform a series of real-life based multi-center observational studies under the name POLISMAIL, with the aim of evaluating the characteristics of polysensitized patients, the behavior of allergists treating them

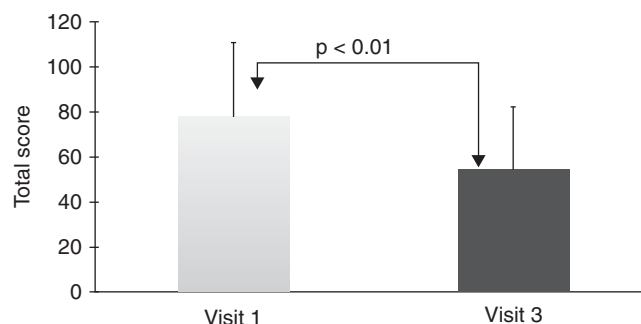


Figure 3. Improvement in quality of life in the fourth POLISMAIL study.

POLISMAIL: Polysensitization Impact on Allergen Immunotherapy.

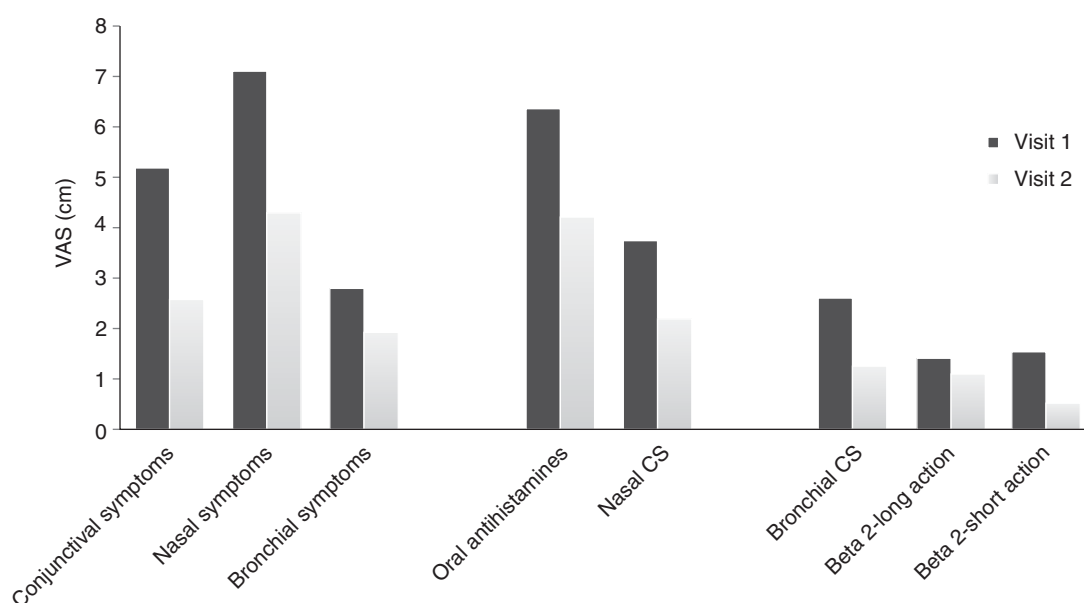


Figure 4. Improvement in symptom score, drug use for rhinitis and asthma in polysensitized children treated with immunotherapy.

and the effect of a SLIT treatment conducted for 2 years in such patients.

A population of patients (adults and children) suffering from AR (also if associated with asthma) referring to the 11 allergy centers in Italy participating in the POLISMAIL study was prospectively evaluated. In all patients, the clinical definitions of AR according to ARIA criteria [2] and of asthma according to GINA criteria [8] were obtained. Also, QoL assessment by the RQLQ was an integral part of the evaluation of patients.

In the first study, investigating the clinical characteristics of 418 polysensitized patients, 220 patients with only AR and 198 with AR and asthma, a mean number of 3.65 sensitizations was found [15]. The comparison of polysensitized with monosensitized subjects showed that polysensitized patients have significantly more severe nasal and bronchial symptoms. In the second study, only polysensitized children

were investigated [27]. This population consisted of 139 children, 71 with AR and 68 with AR and asthma; confirmation was obtained for more severe nasal and bronchial symptoms reported in polysensitized than in monosensitized children. The third POLISMAIL study approached the issue of SLIT prescription and efficacy in 230 patients treated for 1 year. In 165 patients a single allergen extract and in 65 two different extracts were used. A significant improvement of disease staging, symptom severity and drug use was observed showing that SLIT was clinically effective in polysensitized patients also using a single extract and, thus, that polysensitization should not prevent its prescription. The fourth study addressed the effectiveness of 1 year of SLIT with one or two allergen extracts on QoL by prospectively evaluating 167 polysensitized patients with AR, and found a significant improvement of the mean values of all the QoL items [29].

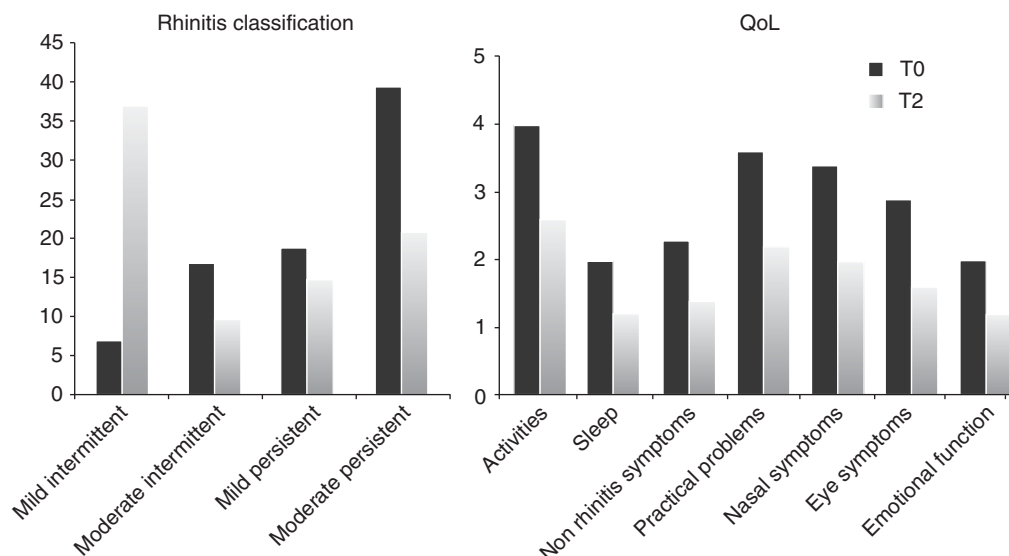


Figure 5. Improvement in severity of rhinitis classification and quality of life in polysensitized patients treated with immunotherapy for 2 years.

The fifth study was aimed at evaluating the effectiveness of 1 year of SLIT in a group of 51 polysensitized children, 42 treated with a single extract, 4 with two different extracts and 3 with a mix of allergens [30]. Also in this case, SLIT significantly reduced the eye, nose and bronchial symptoms, the drug consumption and the number of sensitizations, and improved the AR staging and severity, reasserting that polysensitization is not an obstacle for prescribing SLIT also in polysensitized children. The latest POLISMAIL study investigated the behavior of allergists managing polysensitized AR patients and the effect of 2 year SLIT treatment in such patients by using a single allergen in about 65% of patients and two allergens in the remaining [31]. Once more, a significant improvement of AR symptoms and QoL was achieved.

It is notable that all these observations were obtained in real-life setting; this fact may present some benefits, such as the possibility of enrolling large cohorts and overall of observing that occurs in the common practice. On the other

hand, observation real-life studies are less methodologically rigorous than formal clinical trials. Therefore, the conclusions should be considered in a broader perspective. Anyway, these POLISMAIL studies should convince the allergists as well as other specialists managing allergic patients, such as pneumologists, dermatologists and ENT specialists, that polysensitization should no more represent a handicap for prescribing SLIT because a treatment limited to one to two allergen extracts is clearly effective in improving the clinical symptoms and QoL of patients, while maintaining the well-known safety of this therapy [38].

Declaration of interest

G Ciprandi and C Incorvaia are scientific consultants for Stallergenes Italia. P Puccinelli, S Soffia and S Scurati are employees of Stallergenes Italia. F Frati is medical and scientific director of Stallergenes Italia.

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