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- **Dr. Riccardo Asero** – Ambulatorio di Allergologia – Clinica S. Carlo – Via Ospedale, 21 – I-20037 Paderno Dugnano (MI) – E-mail: r.asero@libero.it
- **Dr. Carlo Lombardi** – Servizio di Allergologia, Unità Operativa di Medicina Generale, Ospedale Sant’Orsola-Fatebenefratelli – Via Vittorio Emanuele II, 27 – I-25122 Brescia – E-mail: carlo.lombardi@poliambulanza.it
- **Dr. Alberto Tedeschi** – Unità Operativa di Allergologia e Immunologia Clinica, Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena – Via Pace, 9 – I-20122 Milano – E-mail: alberted@alice.it

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1 Section of Allergy and Clinical Immunology, Dept. of Internal Medicine, University of Bari, Bari, Italy
2 Allergy Unit, Dept. of Respiratory and Allergic Diseases, Azienda Ospedaliera Umberto I, Torrette, Ancona, Italy
3 Institute of Translational Pharmacology, Italian National Research Council, Second University of Naples, Naples, Italy
4 Section of Allergy and Clinical Immunology, Internal Medicine Unit, Ente Ecclesiastico Ospedale “F. Miulli”, Acquaviva delle Fonti, Bari, Italy
5 Section of Immuonoallergology, University of Florence, Florence, Italy
6 Laboratories of Analysis, Istituto Giannina Gaslini, Genoa, Italy
7 Allergy and Respiratory Diseases, IRCCS IST San Martino, University of Genoa, Genoa, Italy
8 Allergy Unit, Azienda Ospedale Università, Verona, Italy
9 Immunoallergology Unit, University of Salerno, Salerno, Italy

Key words
Component Resolved Diagnostic; Immuno Solid-phase Allergen Chip (ISAC); Italian Board for ISAC

Summary
The Component Resolved Diagnostic (CRD) approach has been developed when highly purified or recombinant allergen molecules have become available. These molecules are the allergenic proteins toward which the specific and clinically relevant IgE immune response is directed. So, the identification of protein families and cross-reactivity patterns of importance in allergy have been possible. The Italian advisory BOARD for ISAC was born: to evaluate the advantages, disadvantages and placement in diagnosis of CRD studying its application in allergic patients; to facilitate the interpretation of molecular diagnostics for clinical allergists; to evaluate the effectiveness of CRD in improving diagnostic risk assessment and early preventive treatment of allergic diseases. In the last years, its fields of interest have been: the evaluation of the performance of CRD on multi-sensitized allergic patients with respiratory symptoms and on poly-sensitized athletes; the evolution of IgE repertoire directed to single allergenic components by evaluating allergic patients with different age at a molecular level; the relevance of results obtained using allergen microarray technique for describing the IgE repertoire in allergic patients by reviewing the main articles focused on CRD published in the last 2 years; the need for an educational program focused on this new diagnostic tool also through the creation of an exhaustive and interactive explanation of the laboratory report molecular allergy; the investigation of the performance and potential additional diagnostic values of the ISAC microarray in a real-life clinical setting, taking into account also the economic values.

Introduction
Many different allergens share common protein epitopes, and the same specific IgE (sIgE) antibody can bind to proteins with similar structures present in different allergen sources, thus recognizing homologous allergens from different sources. Skin Prick Test (SPT) or allergen-sIgE tests cannot resolve this question (1). Also, a common assumption in SPT allergy diagnostic practice is that only a limited number of allergens are routinely assayed using both SPT and sIgE detection: a large number of SPT may be disagreeable for the patient and a large number of sIgE tests can be both expensive and blood sample volume demanding. Furthermore, many patients with allergic symptoms are multi-sensitized, and it is often difficult to assess whether this multi-sensitization is due to a genuine co-sensitization or to cross-reactivity (1).

The Component Resolved Diagnostic (CRD) approach (2) has been developed when highly purified or recombinant allergen
molecules have become available (1). These molecules are the allergenic proteins toward which the specific and clinically relevant IgE immune response is directed. This development has enabled the identification of protein families and cross-reactivity patterns of importance in allergy (1,3).

So, the protein microarray technology and specifically the allergen microarray, allow simultaneous analysis and monitoring of patient-specific antibody profiles for a previously unknown variety of allergens in a single analytical step (4).

Immuno Solid-phase Allergen Chip (ISAC), ImmunoCAP ISAC®, (Thermo Fisher Scientific, Uppsala, Sweden) is the first in vitro diagnostic tool based on modern biochip technology: it is a miniaturized immunoassay platform, that allows multiplex measurement of specific IgE antibodies for many (actually 112) natural purified and recombinant allergen molecules using only 30 μl of serum or plasma (5). The method provides components spotted on a solid support (biochip). In a two-step assay, IgE antibodies from the patient’s serum bind to the allergen components. After a short washing step, allergen-bound IgE antibodies are detected by a fluorescence-labeled anti-IgE antibody. Test results are measured with a biochip scanner and evaluated using a dedicated software. ImmunoCAP ISAC® is a semiquantitative test and results are reported in ISAC Standardized Units (ISU) (5).

General consideration on CRD

Extractive allergen preparations (used for the skin prick test, for specific IgE detection and classic immunotherapy) are a mixture of several different molecules containing non-allergenic proteins, specific allergens (i.e., molecules that can be directly associated with that allergen), pan-allergens (molecules that are present not only in that mixture, but also in other mixtures of similar sources and constituted by highly homologous molecules) and, finally, cross-reacting allergens (i.e., molecules that are present in one allergen, but which also may be present in other not strictly related allergens, because of a certain degree of homology at least in the primary structure of the protein) (6). Conventionally, these molecules are defined as components, and the mixture of different components constitutes the allergen. A specific component is in general responsible for a genuine sensitization to that allergen, whereas a sensitization to pan-allergens or cross-reacting allergens cannot be considered genuine. Components are available for in vitro diagnosis in two different forms: as recombinant allergens (i.e., as allergens cloned in prokaryotic or eukaryotic cells using genetic engineering techniques) and as highly purified extractive molecules (6). Components are named using a conventional notation. Consequently, the first 3 letters (such as Phl, Bet, and so forth) correspond to the first 3 letters of the Linnaean name of the source (in this case Phleum, Betula). The fourth letter (in lower case, as dictated by living organism nomenclature) indicates the first letter of the “second” name of the source. Thus, a molecular component of Phleum pratense is defined as Phl p. Finally, a number is added to the letter, distinguishing each component from the others. Phl p 1 indicates that the first component identified (and in general cloned) is Phleum pratense. Finally, the letter “r” or “n” preceding the component name is indicative of the origin (namely, “recombinant” or “natural”). In general, an IgE repertoire directed to a specific component is suggestive of genuine sensitization. Any other IgE specificity cannot be considered genuine unless the clinical indication is so typical as to strongly associate that allergen to the patient’s history (6,7).

In the “molecular allergy era”, monosensitization seems to be extremely difficult to identify since the patient is in general sensitized to more than 1 component of the same allergen source. Thus, the sensitization to a pan-allergen is very frequently associated with a specific sensitization. In the presence of IgE directed to a large number of components belonging to the same family (such as PR-10, the Bet v1 homolog), the original sensitization should be defined. In this context, a gradient of capacities of sensitizing patients is frequently observed in poly-sensitized subjects and, in a significant number of cases, the sensitizing source can be identified as the component with the highest score (6).

Italian Board for ISAC (IBI)

IBI objectives

The Italian advisory BOARD for ISAC was formed in 2009 with the following objectives:

- to evaluate the advantages, disadvantages and placement in diagnosis of CRD studying its application in allergic patients (to evaluate if using CRD for allergic patients could add important information not directly available using standard SPT and sIgE, and if this method may play a key role in improving clinical management of poly-sensitized allergic patients, etc.);
- to facilitate the interpretation of molecular diagnostics for clinical allergists through the publication of reports and reviews, but also by introducing the new molecular method at congresses and symposia;
- to evaluate the effectiveness of CRD in improving diagnostic risk assessment and early preventive treatment of allergic diseases.

IBI fields of interest

Since the Board was established in 2009, its fields of interest (table 1), concerning the CRD, have been the evaluation of:

- the performance of CRD on multi-sensitized allergic patients with respiratory symptoms in a cross-sectional observational Italian study (1);
the study of the sensitization pattern in a population of poly-sensitized patients with respiratory allergy living in a restricted geographical area in the Northwest Italy (8);  
- the evolution of IgE repertoire directed to single allergenic components by evaluating allergic patients belonging to 6 groups stratified according to age at a molecular level (9);  
- the relevance of results obtained using allergen microarray technique for describing the IgE repertoire in allergic patients, by reviewing the main articles focused on CRD published in the last 2 years (10);  
- the need for an educational program focused on this new diagnostic tool also through the creation of an exhaustive and interactive explanation of the laboratory report molecular allergy (6);  
- the potential diagnostic added value of the microarray technology detecting IgE antibodies to specific or cross-reacting allergen components in poly-sensitized athletes (11);  
- the investigation of the performance and potential additional diagnostic values of the ISAC microarray in a real-life clinical setting, taking into account also the economic values (12).

Results of the studies of IBI

A total number of 321 sera from multi-sensitized adult Italian patients with well defined respiratory allergy and 92 control subjects with no history of allergy-like respiratory symptoms, were studied using both conventional extract based allergen-sIgE and a CRD diagnostic microarray tool in a prospective cross-sectional multicenter study (May 2009 - February 2010). The study involved 5 sites distributed all over Italy: Ancona, Bari, Cuneo, Florence and Genoa. In the context of this clinical study the primary objectives were to evaluate the technical performance of the ISAC (containing 103 different allergen components/molecules originating from 47 allergen sources) based CRD tool, the relation of ISAC results with extract based sIgE results with ImmunoCAP Allergens in the Phadia 250 system and finally the ability to detect and resolve patterns of true co-sensitization and cross-reactivity.

The results obtained clearly demonstrated that ImmunoCAP ISAC was an effective tool for allergen sIgE measurements and that the technical performance of ISAC and the correlation with “classic” sIgE assays was excellent. Important information on co-sensitization to other allergens than the expected aeroallergens was obtained. In addition, sensitization to cross-reacting components explaining some of the perceived multisensitization was detected. Elevated IgE antibodies to Profilins, CCD (Ana c 2) and calcium-binding proteins were detected, probably due to sensitization to grasses and trees in this study. The possibility of identifying the presence of IgE antibodies to Profilins in pa-

Table 1 - Italian Board for ISAC scientific production

<table>
<thead>
<tr>
<th>Title</th>
<th>Authors, Year</th>
<th>Study design</th>
<th>Journal</th>
</tr>
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<tr>
<td>The ImmunoCAP ISAC molecular allergology approach in adult multi-sensitized Italian patients with respiratory symptoms.</td>
<td>Melioli G et al., 2011</td>
<td>Cross-sectional observational study</td>
<td>Clinical Biochemistry</td>
</tr>
<tr>
<td>Sensitization profiles in poly-sensitized patients from a restricted geographical area: further lessons from multiplexed component resolved diagnosis.</td>
<td>Rossi RE et al., 2011</td>
<td>Retrospective study</td>
<td>European Annals of Allergy and Clinical Immunology</td>
</tr>
<tr>
<td>The IgE repertoire in children and adolescents resolved at component level: a cross-sectional study.</td>
<td>Melioli G et al., 2012</td>
<td>Cross-sectional observational study</td>
<td>Pediatric Allergy and Immunology</td>
</tr>
<tr>
<td>The added value of allergen microarray technique to the management of poly-sensitized allergic patients.</td>
<td>Melioli G et al., 2012</td>
<td>Review</td>
<td>Current Opinion on Allergy and Clinical Immunology</td>
</tr>
<tr>
<td>Molecular allergy diagnosis: we need to become more knowledgeable.</td>
<td>Melioli G et al., 2012</td>
<td>Guest editorial</td>
<td>Annals of Allergy and Asthma Immunology</td>
</tr>
<tr>
<td>Microarray evaluation of specific IgE to allergen components in elite athletes.</td>
<td>Bonini M et al., 2012</td>
<td>Cross-sectional observational study</td>
<td>Allergy</td>
</tr>
<tr>
<td>The additional values of microarray allergen assay in the management of poly-sensitized patients with respiratory allergy.</td>
<td>Passalacqua G et al., 2012</td>
<td>Multicentric study</td>
<td>Allergy 2013 in press</td>
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Molecular diagnosis and the Italian Board for ISAC

...tients with plant allergy is an interesting opportunity enabled by CRD, which may explain both numerous positive extract based tests, in vivo as well as in vitro, and Oral Allergy Symptoms to fruits and vegetables in the absence of IgE antibodies to PR10 proteins. Along this line, the possibility of excluding the presence of an allergy to profilins in patients with plant allergy, is an interesting added value of this technique for the evident therapeutic outcomes that it implies. Elevated IgE antibodies to Lipid Transfer Proteins were detected in 55% of the patients and Storage Proteins (seed) in 8%; these sensitizations imply an increased risk of severe systemic reactions. ImmunoCAP ISAC can offer a wider representation of the IgE repertoire of the patients, with evident advantages in patients with suspected multi-sensitization to panallergens and/or cross-reacting allergens (1). In the light of these findings, ImmunoCAP ISAC is also particularly powerful in poly-sensitized patients not only to detect the actual molecular component involved in the allergy, but also to rule out cross-reacting allergens and other components (such as LTP) that can be responsible of adverse events (1).

In a subsequent retrospective study, the sensitization profile by means of microarray dosing specific IgE towards 103 allergenic components in a population of poly-sensitized patients with respiratory allergy symptoms living in a restrict geographical area (Cuneo, Northwest Italy) was analyzed. The results showed that in this geographical area, Phl p 1 allergen was the most common sensitization, followed by Phl p 5 reflecting clearly the local flora, since in this area grasses are largely present. An interesting finding of this study is that the stronger allergens, capable of stimulating high levels of specific IgE, are in descending order Phl p 1, Phl p 5, Der f 2, Der p 2, Bet v 1, Der f 1, Der p 1, Ole e 1 and Fel d 1. This data should be taken into account by allergen extract producers in order to provide clinicians with improved products for diagnosis and immunotherapy (8).

It is well known that allergy evolves at clinical level from the birth to adulthood, and this has been clearly demonstrated also at a level of sensitization profile. Since little information is available on the evolution of the IgE repertoire directed to single allergenic components, the Authors, in a cross-sectional, observational study, analyzed the evolution of the IgE repertoire at component level by evaluating serum samples from 901 allergic patients (both respiratory and food allergy), stratified in 6 groups according to age (from early infancy to adult age) by means of ImmunoCAP ISAC (for the identification of specific IgE towards 103 different allergen components) (9). The main finding was a clear time-related modification of the IgE repertoire at component level. Along this line, the percentage of positive components (representative of the IgE repertoire) during the first period of life was relatively small (20-30% of the 103 ISAC molecules), and this percentage increased during the subsequent periods. As expected, food-related components (in particular those of milk and egg) were the most frequently recognized in the earliest ages, whereas specific IgE to plant allergens appeared invariably later. Nonetheless, IgE specific to mite components was the most represented in all age classes. Of note, specific IgE against cross-reacting allergens was virtually absent in the first years and tended to appear only after the age of 6. The modification of IgE repertoire at component level, from birth to adolescence, seems consistent with the clinical characteristics of the allergic march. This fact is sustained by the initial mono- or oligo-sensitization, followed by poly-sensitization during adolescence, the increase in IgE positive components over time, early sensitization to milk and egg components characterized by a low number of specific IgE followed, after the third year of life, by sensitization to inhalant allergens belonging to the mite family and characterized by a high concentration of specific IgE. In addition, cross-reacting components and pan-allergens were negative up to 6-10 yrs, becoming positive later on, in terms of number and ISU score of components identified by specific IgE (9).

The ISAC Board also focused its attention on a particular population, characterized by elite athletes that, as have been reported, have a very high and increasing prevalence of allergic sensitization and diseases. Furthermore over 80% of allergic athletes are poly-sensitized. Seventy-two poly-sensitized athletes according to SPT with different allergic phenotypes (asthma, rhino-conjunctivitis; food allergy and/or oral allergy syndrome; no clinical symptoms) and two different control populations (poly-sensitized sedentary subjects with respiratory allergy and 20 healthy athletes with negative SPT) were studied for detecting specific IgE both to allerger extracts (ImmunoCAP IgE) and to allergen components (ImmunoCAP ISAC), in order to evaluate the potential diagnostic added value of ImmunoCAP ISAC in detecting IgE antibodies to specific or cross-reacting allergen components (11). ImmunoCAP ISAC detected the presence of sIgE in 90% of poly-sensitized athletes and in 100% of allergic controls. The pattern of positivity towards the 103 components tested differed from a subject to another, even in those with the same sensitization to allergen extract SPT or sIgE. Based on the ISAC results, poly-sensitized athletes were classified into the following prototypical patterns, represented separately in the clinical phenotypes studied: a) One single predominant specific allergen positivity; b) sIgE to two or more non-cross-reacting allergens; c) sIgE to cross-reacting allergens; and d) sIgE to components potentially responsible for severe allergic reactions. On the basis of these results, the ImmunoCAP ISAC may represent a valuable complement for diagnosis and management of poly-sensitized athletes (11).

The IBI, also performed a large population-based (318 allergic patients and 91 controls) study involving six Italian allergy units (Ancona, Bari, Cuneo, Florence, Genoa and Rome) to inves-
tigate the performance and the potential additional diagnostic values of the ISAC microarray in poly-sensitized subjects in a real-life clinical setting, taking into account also the economic values. In this multicentre study, allergists were required to carefully record diagnosis and treatment of consecutive patients referred for asthma/rhininitis, using the standard methodology (history, SPT, IgE assay). Then, a microarray allergen assay was carried out. Clinicians were required to review their diagnosis/treatment according to microarray results. An economical analysis was also performed. The clinicians reported at least one additional information from the microarray in about 60% of patients, this resulting in therapeutic adjustments. In 66% of patients IgE to pan-allergens were detectable, being this clinically relevant in 38% of patients with poly-sensitization to pollens. The microarray assay proved to be economically advantageous, when more than 10 recombinant/purified molecules would otherwise have been required for a satisfactory diagnosis (12).

Conclusion

Diagnostics using CRD offer possibilities not available with extract based standard techniques such as SPT and allergen sIgE tests, in fact, CRD effectively helps in distinguishing between specificity and cross-reactivity in patients with suspected multi-sensitization to various allergens (1). This may have a significant impact on the patient management in terms of risk assessment, advice to avoid allergens, patient selection for immunotherapy, and immunotherapy regime (13).

ImmunoCAP ISAC is also particularly powerful in poly-sensitized patients (in which an accurate aetiological diagnosis is complex) not only to detect the actual molecular component involved in the allergy, but also to rule out cross reacting allergens and other components (such as LTP) that can be responsible for adverse events (1).

However, the current version of ImmunoCAP ISAC cannot fully substitute the use of SPT or allergen sIgE tests, for its apparent inability to detect very low concentrations of IgE antibodies. Moreover, the panel of 103 allergens does not include all known allergens, and some clinically relevant ones are still missing; for example Ambrosia and Parietaria are represented only by a single component (Amb a 1 and Par j 2, respectively) (9). Therefore, at present, a combined strategy of using SPT or allergen sIgE (complete allergens) together with CRD tools (purified or recombinant allergen components) seems to offer the most complete approach (1). Most likely the addition of missing components, will improve the performance of ISAC (9).

The fact that allergen microarray technology had offered a very large amount of information in the last years is certain. Not only is a more complete description of the IgE repertoire in different patients, ages and diseases now available, but also the impact of this novel approach to the solution of complex problems of allergy sensitization, even in terms of system biology approach, has been proposed. Nevertheless, from the allergist point of view, the position of allergen microarrays in the flowchart of allergy diagnosis should be better defined. Indeed, despite the indication that allergen microarray, thanks to its characteristics, could be used as first-line assay, other evidence, including costs and diffusion of the technology, indicates that its position is behind extract-based SPT and sIgE, in an accurately selected population of poly-sensitized patients, particularly those with a combined inhalant and food allergy (9). In particular, in poly-sensitized patients where an accurate aetiological diagnosis is complex, due to the presence of sensitizations to both genuine allergens and cross-reacting components.

Results obtained by IBI studies suggest that, at least at component level, a radical change in the IgE repertoire occurs starting from the age of 6 and this cut-off could be also important in the prognostic and therapeutic evaluation of the patient (8).

Microarray IgE assay inarguably represents an advancement in allergy diagnosis, as a third-level approach in poly-sensitized subjects, when the traditional diagnosis may be problematic. The use of the microarray leads to an improvement in the accuracy of diagnosis and appropriateness of treatment in a variable percentage ranging from 25 to 50% of patients, on the basis of the level of accuracy used for the molecular diagnosis (12).

Finally, when too many single recombinant allergens are required to define an accurate sensitization profile ISAC is preferable in terms of costs and efficiency, and particularly when 10 or more single recombinant allergens are required for diagnosis, microarray is economically superior (12).

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5. www.thermofisher.com
M. CAMINATI¹, M. S. MAGNONI², A. RIZZI³, F. BRAIDO³, A. FORESI⁴, G. BETTONCELLI⁵, A. INFANTINO⁶, C. D’ANDRIA⁷, L. ANTONICELLI⁸, P. L. PAGGIARO⁹, F. FALCONE¹⁰, G. SENNA¹

Asthma management among different specialists: results from a national Italian survey

¹ Allergy Unit, Verona University Hospital, Verona, Italy
² Medical and Scientific Department, GlaxoSmithKline, Verona, Italy
³ Allergy and Respiratory Diseases Clinic, Department of Internal Medicine and Biostatistics Unit, Department of Health Science, University of Genoa, Genoa, Italy
⁴ Division of Respiratory Medicine, A.O. Istituti Clinici di Perfezionamento, Sesto San Giovanni - Milano, Italy
⁵ Società Italiana di Medicina Generale (SIMG), Italy
⁶ Società Italiana Interdisciplinare per le Cure Primarie, Italy
⁷ Internal and Respiratory Medicine, SS Annunziata Hospital, Taranto, Italy
⁸ Allergy Unit, Department of Immuno-Allergic and Respiratory Diseases, Azienda Ospedaliero-Università Ospedali Riuniti, Ancona, Italy
⁹ Cardio-Thoracic and Vascular Department, University of Pisa, Italy
¹⁰ Past President Associazione Italiana Pneumologi Ospedalieri and Consultant Pulmonologist GVM Care & Research, Bologna, Italy

Summary
In Europe more than 50% of asthmatic treated patients have a not well-controlled asthma. The present survey aims at investigating how different specialists approach asthmatic patients. A web anonymous questionnaire was randomly administered to 604 General Practitioners (GPs), 241 Pneumologists and 131 Allergists. It concerned: epidemiology, diagnostic work-up, follow-up and risk factors, treatment and future risk. A general agreement emerges about asthma diagnostic work-up. All categories are aware of the impact of comorbidities on asthma. LABA/inhaled steroids combination is considered the first choice treatment. Surprisingly, depot steroids and long-acting beta2 agonists (LABA) alone are still prescribed by GPs. Concerning monitoring tools, Allergists rely on inflammation biomarkers, whereas reduction of rescue medication is more relevant for GPs. Asthma Control Test (ACT) is considered time consuming by more than 50% of all physicians and is not known by most of GPs. Adherence is considered a crucial problem in asthma management. All categories seem to have a good knowledge about asthma. The cultural background may account for mild differences in asthma control tools and treatment options. GPs have a pivotal role in discriminating patients who need specific assessment by specialists. It is thus important that GPs and specialists share common tools for recognizing and managing those patients.

Key words
Asthma; diagnosis; follow-up and monitoring tools; treatment

Introduction
Asthma affects more than 300 million persons worldwide and causes substantial morbidity. In developed countries its prevalence is estimated to be between 8% and 12% in adults and 10-15% in children (1). In Italy the overall estimate is 2.5 million. Despite being not associated with high mortality, asthma can cause sensitive limitations in daily life, in terms of reduced productivity at work or school and frequent inability to perform normal activities. According to recent European data, more than 50% of treated patients have not well-controlled asthma (2). As there is currently no cure for asthma, the cornerstone of
its management is the achievement and maintenance of an optimal control (3). Different specialists should contribute to this goal, such as Allergists (ALL), Pneumologists (PNE) and general practitioners (GPs), as GINA guidelines suggest. The present survey aims at investigating how Italian specialists and GPs approach patients with asthma, in order to point out pitfalls and unmet needs concerning real-life management of the disease.

Materials and methods

A board of experts belonging to AIPO (Associazione Italiana Pneumologi Ospedalieri – Italian Association of Hospital Pulmonologists) and IFIACI (Federazione delle Società Italiane di Immunologia, Allergologia ed Immunologia Clinica – Federation of Italian Societies of Allergy and Clinical Immunology) developed a questionnaire composed of 24 multiple choice questions covering epidemiological (number and type of asthma patients assisted) and clinical (presence of comorbidities or risk factors) aspects about asthma, and explored the overall management strategies (diagnosis, monitoring, treatment, counseling, treatment, adherence) adopted by the Italian physicians. Between 9th of December 2010 and 28th of January 2011, a self-administered anonymous questionnaire was e-mailed to a sample of GPs, Pneumologists and Allergists randomly selected from the national registers of Physicians. The online questionnaire could only be answered once. It was e-mailed two more times to non-responders 2 and 4 months after the first invitation. In respect to the total number of contacted physicians, 20% of GPs (n. 604), 25% of Pneumologists (n. 241) and 30% of Allergists (n. 131) belonging to all Italian regions effectively participated in the survey.

The sample (n. 976 Italian physicians) was representative of the medical population considered, with a standard error (95% confidence level) of 4.0% for GPs, 6.1% for Pulmonologists and 8.1% for Allergists.

The answers provided by the three groups were compared and analyzed. Student’s t-test was used to detect significant differences in the means of quantitative variables for independent samples. The statistical cut-off $\alpha = 0.05$ was chosen.

Results and comments

Study population

64% of GPs declare that among their patients at least 20 people have asthma. Considering that the number of patients for each GP is around 1000, the perception of at least 2% of asthmatic patients is rather far from epidemiological data on the general population, indicating that the proportion of patients with a diagnosis of asthma is around 5%. The possibility that some patients with intermittent asthma or with seasonal symptoms do not visit the GP’s office and self-administer bronchodilators on demand may explain that underestimation.

![Figure 1: Proportion of asthmatic patients manifesting symptoms exclusively during the pollen season or with symptoms also out of season.](image-url)
awakenings are relevant for all physicians as well as the role of triggers (smoke, allergens, physical exercise). Rhinorrhea is less relevant for Allergists, probably because it is not considered a specific symptom of asthma. Also phlegm is not considered suggestive for asthma, presumably because it is mainly related to acute bronchitis or COPD.

As far as diagnosis according to the survey there is a general agreement on the importance of spirometry, reversibility test, bronchial challenge with metacholine and evaluation of the atopic status (figure 2), as indicated in international guidelines. It is worth of note the discrepancy between the importance attributed to spirometry as a diagnostic tool and its use in clinical practice (only around 30% of asthmatic patients (6)). On the other hand, in the analysis of the data from a questionnaire it should be taken into account that results could be influenced by predefined answers, as well as by the tendency to give “desirable” more than “real” responding.

Concerning the role of chest X-ray, there is a significant difference between GPs and specialists: not surprisingly, GPs take into consideration chest X-ray evaluation too, since asthma symptoms are not so specific. Inflammation assessment (FeNO) seems to be important for Pneumologists and Allergists, but it is significantly quite neglected by GPs. Actually, according to published data and guidelines, the role of FeNO measurement in routine asthma diagnosis is yet unclear (7,8), even if its correlation with bronchial eosinophilic inflammation has been proven (9,10).

As far as Allergists and Pneumologists are concerned, one in three specialists reports seeing more than 20 asthmatic patients per week. This proportion is slightly higher for Allergists (36%) than Pneumologists (34%). This might depend on the different types of respiratory diseases treated by Pneumologists, which could reduce the time selectively dedicated to asthmatics. However, these data might also suggest that Allergists are today aware of the frequent involvement of lower airways in patients with allergic rhinitis, and therefore regularly assess both upper and lower airway involvement (4). According to GPs perception, patients with seasonal symptoms seem to have a higher prevalence than patients with chronic symptoms (56% vs. 44%, respectively), probably because pollen exacerbations are evaluated as a first step in a primary care setting (figure 1). Pneumologists report a higher number of asthmatic patients with chronic symptoms (presumably more severe patients), whereas Allergists refer an equal distribution of both kinds of patients.

### Diagnostic work-up

No significant differences are detectable among the three types of physicians concerning the relevance of symptoms suggestive for asthma (data not shown). However, cough and chest tightness are regarded as less important by GPs, presumably because these symptoms are shared by other diseases and are not considered asthma-specific in daily practice. Wheezing and night awakenings are relevant for all physicians as well as the role of triggers (smoke, allergens, physical exercise). Rhinorrhea is less relevant for Allergists, probably because it is not considered a specific symptom of asthma. Also phlegm is not considered suggestive for asthma, presumably because it is mainly related to acute bronchitis or COPD.
Asthma management among different specialists: results from a national Italian survey

Follow-up and risk factors for asthma severity

According to our data, one in three patients (31.6-36.6%) is followed-up at least twice yearly, without significant differences among the three categories. As shown in figure 3, there is a general agreement about the importance of spirometry, the use of rescue short acting beta2 bronchodilators, night awakenings, wheezing and exacerbations as markers for monitoring asthma, as reported by recently published data (11). In this context, it is important to note that according to international guidelines, the regular use of reliever is one of the elements defining uncontrolled asthma and that reducing or eliminating the need for reliever treatment is both an important goal and a measure of successful treatment (3). Exacerbations are less relevant for GPs: presumably, the lack of a standardized definition of exacerbation may account for this finding. Chest tightness and cough are also regarded as less important, being non-specific symptoms.

Another question addressed in the survey concerns the use of Asthma Control Test (ACT), a validated questionnaire reflecting the multidimensional nature of asthma control in the follow up of asthmatic patients. As shown in figure 4, more than 50% of GPs never use ACT and only 5% use it often. By contrast, a significant proportion of specialists (37%) report that they often use this tool in the assessment of their patients and only 17% never used it. Surprisingly, by analysing the reasons of poor/no use, more than 50% of all physicians declare that ACT is time consuming (figure 4). One in four GPs does not know this questionnaire, whereas two in ten specialists consider it not reliable or not useful in daily practice. However, ACT is a brief, simple, questionnaire for patient self-evaluation, with demonstrated effectiveness and reliability (12-14). It can be easily performed in the waiting room before the visit without waste of time for the physician, thus improving the assessment of asthma control in a busy clinical practice setting.

Consistently with international reports (15-18), all physicians are aware that risk factors such as smoking and comorbidities (rhinitis, gastro-esophageal reflux, sleep apnea, obesity) may impact on the natural history of asthma, being responsible for clinical exacerbations as well as for a reduction in treatment efficacy. Small differences are observed among categories, probably reflecting their different cultural background. GPs are particularly sensitive to smoking as a risk factor also for other morbid conditions treated in everyday practice (cardiovascular, metabolic diseases). Rhinitis is mainly taken into consideration by Allergists, as a consequence of the implementation of ARIA guidelines (4,17), based on a global approach of the respiratory tract. Gastro-esophageal reflux is a more significant risk factor for Pneumologists and sleep apnea for GPs. Despite increasing evidence of a strong link between asthma and obesity (15,16) it seems a less relevant comorbidity for all physicians, mainly related to metabolic and cardiovascular diseases.

Thus, comorbidities may contribute to identify patients with increased risk of severe asthma and susceptibility to exacerbations (different phenotypes?), needing a more careful and strict monitoring to maintain control.
Treatment and future risk

For all physicians the main goals of pharmacologic therapy are the prevention of symptoms and exacerbations with a regular treatment, the control of inflammation and the reduction in reliever use (figure 6), suggesting that the message of international guidelines seems to be at least partially accepted. Specialists are significantly more focused on the role of inflammation, whereas for GPs achieving bronchodilation is also a relatively important target.

For all physicians the combination of LABA and inhaled steroids is the first choice of the treatment for seasonal asthma (figure 7).
This choice is coherent with published data proving that combination therapy is more effective in preventing asthma exacerbations and more rapid in gaining asthma control (19). Moreover, it has been shown that repeated bronchoconstriction in asthma promotes airway remodeling even in the absence of additional inflammation. This evidence suggests that the use of combination therapy fulfills both a sustained and safe bronchoprotection and an adequate control of inflammation, in order to prevent the long-term adverse consequences of airway remodeling (20). The higher dosage of inhaled steroid used by Pneumologists suggests that they usually treat more severe asthma. Moreover, most patients are visited for worsening of symptoms, indicating the need
for a therapy at the step 3 or 4 of GINA guidelines (3). Anti-histamines are also prescribed, presumably for concomitant rhinitis. Surprisingly, depot steroid are still prescribed as well as long-acting beta2 agonists (LABA) alone, despite the recent warnings against their use without inhaled steroids (21). Pneumologists use more leukotriene antagonists, Allergists more immunotherapy.

Also in perennial asthma the combination of LABA and inhaled steroids (at medium or higher doses) is the first choice; only slight differences are observed with respect to seasonal asthma (figure 8), such as a wider use of leukotriene antagonists in all categories, probably used in association with inhaled steroids or with the combination of inhaled steroids and LABA.
International guidelines report that, in addition to clinical manifestations, asthma control should include the control of the expected future risk of the patient, such as exacerbations, accelerated decline in lung function and side effects of treatment. In this respect, all categories share key points in the management of the future risk, as the need of a chronic treatment (82% Pneumologists, 85% Allergists and 90% GPs) and the crucial role of adherence to treatment (76% Pneumologists, 76% Allergists and 67% GPs).

Like in every chronic disease, adherence to therapy is of fundamental importance to achieve and maintain asthma control (22). In this context, all physicians report that only 50% of patients are able to manage their treatment autonomously.

Two main aspects of adherence have been taken into account: treatment continuity and compliance to the therapeutic regimen, including the correct use of inhaler.

In regards to the first aspect, in patients with seasonal symptoms the type of sensitization and the pollen count of the causative allergen drive 63% of Allergists’ choice about the length of the treatment (vs. 41% of Pneumologists and 30% of GPs); 34% of GPs vs. 17% of specialists suggests a therapy of at least two months starting before the pollen season. A high proportion of all physicians (48% of Allergists, 59% of Pneumologists, 44% of GPs) declare to treat patients before the pollen season.

This perspective is intriguing. In fact, most of patients are treated with a combination therapy, as before mentioned. This choice agrees with a step 3 of severity according to GINA Guidelines (3). So, do GPs start this treatment before the beginning of pollen season in asymptomatic patients?

In the case of chronic symptoms of asthma, 40% of GPs and 30% of Pneumologists report to start a long-term treatment without clear indication about follow-up schedule. This behavior is therefore far from the step up and step down approach suggested by GINA Guidelines.

In regards to the factors or behaviors that may improve patient adherence and compliance, GPs are less prone than specialists to counseling, patient’s education, scheduling regular visits (figure 9), possibly due to a lack of time. Furthermore, the routine use of PEF or questionnaires (like ACT) is generally less accepted. Pneumologists are more interested in technical progress, considering the role of the type of device in patient adherence and compliance. Along this line, the Task Force of the European Respiratory Society has delivered a consensus statement for a first line approach, GPs have a pivotal role in discriminating not be switched to new devices without his involvement and without follow-up education on how to use the device properly. A recent study has shown that patient compliance and asthma control deteriorates if an inhaler is substituted with a different device at the prescribing or dispensing stage without involving the patient (24). In patients with persistent asthma, adherence is much more important if we consider that a regular use of treatment at a stable dose is necessary in order to prevent exacerbations (25).

Despite the importance attributed to treatment continuity, a recent population-based retrospective study conducted in Italy showed that patients with asthma received only 1.54 prescribed packages of controller medication per patient per year. Asthma guidelines suggest that the large majority of people with a diagnosis of asthma should be given an anti-inflammatory controller medication for regular use, but the small number of prescriptions of controller medications/patient/year clearly indicates that patients were not being treated on a regular basis (26).

Conclusions

According to the results of this survey, all physicians seem to have a good knowledge about asthma and share a common disease management goal from a theoretical point of view: to prevent symptoms and exacerbations and to control airway inflammation, thus reducing the future risk of disease progression. All physicians are aware that risk factors and comorbidities may identify patients with increased risk of poorly controlled asthma and susceptibility to exacerbations, needing a more careful and strict follow-up for treatment continuity. Interest and expertise may account for small differences across the physician types, such as the importance attributed to risk factors and comorbidities for asthma severity or the focus of Allergists for the immunological pathogenesis and the immunomodulator treatment (immunotherapy).

Although the combination of LABA and inhaled steroids is the first choice in the treatment of asthma, in line with published data showing that this regimen is more effective in preventing clinical manifestations and more rapid in gaining asthma control, it is concerning to find a high percentage of physicians (mainly GPs) still prescribing depot steroids or LABA monotherapy.

In regard to follow-up, there is general agreement that not many patients are able to manage their treatment autonomously. Scheduling regular visits and patient’s education may improve adherence especially for specialists. However, there is no a common acceptance of a simple tool like ACT to monitor asthma control. Finally, all physicians share the need of more time to dedicate to asthma plan management in daily practice.

Since patients are often evaluated in a primary care setting as a first line approach, GPs have a pivotal role in discriminating...
patients who need specific assessment by specialists. It is thus important that GPs and specialists share common tools for recognizing those patients.

References

The perception of allergen-specific immunotherapy among Italian general practitioners

C. Lombardi1, G. Bettoncelli2, G. W. Canonica3, G. Passalacqua3

Summary

Background. Allergen specific immunotherapy is the only causal therapy for respiratory allergies, and the only treatment that can modify the natural course of the disease. Information and education of patients is essential to successful treatment and, since the General Practitioner is the primary referral, a cooperation between him and the allergy specialists is crucial. We carried out a survey among Italian GPs to assess their knowledge about immunotherapy and their attitude towards it. Method. A 12-item questionnaire on specific immunotherapy, based on guidelines and literature, was prepared by a panel of experts and anonymously e-mailed to 200 GPs of the Italian Society of General Practitioners. Results. Out of 200 questionnaires, 156 were returned and 126 could be evaluated. The 126 respondents accounted for a population of about 300,000 patients. The overall knowledge on subcutaneous and sublingual immunotherapy resulted to be satisfactory and the attitude towards immunotherapy was generally favourable. On the other hand, only less than 50% of GPs were aware of the exact placement of immunotherapy in international guidelines and all considered a more detailed information on the treatment necessary. Conclusion. There is still room for improving the knowledge on specific immunotherapy among general practitioners. This would allow a better synergy between primary care operators and specialists.

Key words
Specific immunotherapy; general practitioner; questionnaire

Introduction

Allergy is a public health concern of pandemic proportions, affecting more than 150 million people in Europe. Taking into account the epidemiological trends, it is hypothesized that within 15 years more than half of the European population will suffer from some type of allergy (1). Allergic patients suffer from a debilitating disease, with a major impact on their quality of life (QoL) and work/school performance, and constitute a significant burden on health economics due to lost productivity and absenteeism (2). Given that allergy triggers including urbanization, pollution and climate are not expected to change significantly, the only way forward is strengthening and optimizing preventive and treatment strategies. In this context, the partnership and cooperation among the different medical subjects including specialists and general practitioners (GPs) remains essential. Allergen-specific immunotherapy (SIT) is the only causal treatment that induces a profound immunological modification and, therefore, can potentially affect the natural course of allergic diseases (3). Many clinical trials and meta-analyses (4) have convincingly shown that SIT can achieve promising results for patients and the society, improving the quality of life, reducing long-term costs and burden of allergies, and changing the course of the disease. In addition to the short-term symptoms’ relief, SIT maintains its effects for years after termination, this representing a potential added value in terms of pharmaco-economy (5). Despite this, SIT has not yet received adequate attention.
from Medical Institutions, as testified by the general underuse of this treatment. In a previous survey among Italian specialists about the modality of use of SIT (6) we found that: (a) specialists are overall familiar with SIT and most recommendations of the guidelines are observed; (b) the majority of physicians perform SIT in a hospital environment; (c) the availability of resuscitation devices and/or drugs to treat severe reaction is sometimes not optimal; (d) an informed consent for injection IT is routinely obtained by < 70% of the physicians and (e) poor attention was paid to the education of the patients. Since GPs are primarily responsible for education and information, and their cooperation with specialists in managing allergies is highly desirable, we attempted to assess the level of knowledge about SIT among GPs in Italy.

Methods

A panel of experts, including allergy specialists and GPs, prepared a 12-item questionnaire (table 1) based on the guidelines and the current literature (2,7-10). The questionnaire included Y/N and multiple-choice answers, and was subdivided into five main sections (clinical/general aspects, efficacy perception, pharmaco-economic aspects, sublingual (SLIT) vs. subcutaneous (SCIT) specific immunotherapy, SIT in guidelines). Questionnaires were e-mailed to GPs over the entire Italian territory, randomly selected from the registry “HealthSearch” of the Società Italiana di Medicina Generale (SIMG), and had to be returned anonymously. Only the fully completed questionnaires were considered for the descriptive statistics.

Results

Questionnaires were sent to 200 physicians. Of them, 156 were returned and 126 could be analyzed. Thirty GPs returned an incomplete questionnaire. The population of GPs had a mean age of 44.5 years (range 34-65 years), and 58% were male. They were homogeneously distributed over the Italian territory: Northern Italy 28%, Central Italy 35%, Southern Italy 37%. Of them, only 2 had a specialty degree in Allergy, and 3 in Respiratory Medicine. The physicians were also homogeneously distributed among the regions with SIT totally or partially reimbursed by the Healthcare National System. The 126 respondents accounted for a population of about 300,000 adult and adolescent patients. The results of the survey are summarized in table 1.

Discussion

Currently, SIT is the only treatment that addresses the cause of IgE-mediated immunopathology and modulates the natural course of the disease (2). Furthermore, SIT has been shown to prevent further progress of the disease and the onset of new sensitizations and asthma long after it is discontinued, thus representing a highly valuable therapeutic approach. The present survey was specifically designed for GPs, in order to assess their knowledge on SIT and their attitude towards it. This was done because GPs are primarily responsible for the education of patients (11) and usually they have to give advices on treatments prescribed by specialists. This is especially true in the case of allergen immunotherapy, which in Italy is always prescribed by allergists (12). According to the results, it seems that the general knowledge on SIT is overall satisfactory among GPs, and they are well aware that SIT is recommended in the most diffused guidelines (item 12). Nevertheless, a relevant proportion of physicians (40%) believe that SIT is only an adjunct to pharmacotherapy, to be used only when this latter is not totally effective. This is maybe the result of the statements reported in previous guidelines such as the GINA. Also, GPs are well aware that SIT has a disease-modifying effect in addition to the short term clinical efficacy (items 5-7), and the favorable cost to benefit ratio is also acknowledged. The main differences between SLIT and SCIT especially concerning the safety aspects are known as well, despite SLIT has been introduced in a relatively recent time (13). Importantly, the majority of GPs agree on the need to improve the cooperation with specialists, and express the auspice to get more information and education on the specific aspect of SIT, for instance in scientific meetings. This is indirectly confirmed by the fact that 50% of the GPs are not aware of the exact placement of SIT in current international guidelines.

In conclusion, our survey about the perception of IT among Italian GPs evidenced a satisfactory overall knowledge of IT and only few weak points. These results would allow to take appropriate educational actions and this questionnaire could be used to monitor over time the possible effects of divulgence and educational initiatives.

References

4. Compalati E, Penagos M, Frati F, Passalacqua G, Canonica GW. Specific immunotherapy for respiratory allergy: state of the art ac-
### Table 1 - Results of the 126 completed questionnaires

<table>
<thead>
<tr>
<th>ITEM</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. In your opinion, SIT is (multiple answers allowed)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A symptomatic treatment for respiratory allergy</td>
<td>57</td>
<td>45</td>
</tr>
<tr>
<td>An organ-specific treatment</td>
<td>17</td>
<td>13.5</td>
</tr>
<tr>
<td>Alternative to drugs</td>
<td>1</td>
<td>0.8</td>
</tr>
<tr>
<td>To be used when drugs do not work</td>
<td>51</td>
<td>40.5</td>
</tr>
<tr>
<td>2. Is SIT useful to treat allergic rhinitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Always</td>
<td>10</td>
<td>8.5</td>
</tr>
<tr>
<td>In the majority of patients</td>
<td>65</td>
<td>51.5</td>
</tr>
<tr>
<td>In a minority of patients</td>
<td>40</td>
<td>31</td>
</tr>
<tr>
<td>Never</td>
<td>11</td>
<td>9.0</td>
</tr>
<tr>
<td>3. Is SIT useful to treat allergic asthma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Always</td>
<td>18</td>
<td>14</td>
</tr>
<tr>
<td>In the majority of patients</td>
<td>69</td>
<td>55</td>
</tr>
<tr>
<td>In a minority of patients</td>
<td>34</td>
<td>27</td>
</tr>
<tr>
<td>Never</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>4. In your opinion is SIT cost/effective?</td>
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<td></td>
</tr>
<tr>
<td>Always</td>
<td>42</td>
<td>33</td>
</tr>
<tr>
<td>Only in some cases</td>
<td>59</td>
<td>47</td>
</tr>
<tr>
<td>Never</td>
<td>8</td>
<td>6.3</td>
</tr>
<tr>
<td>Don't know</td>
<td>17</td>
<td>13.7</td>
</tr>
<tr>
<td>5. SIT adds benefits to medications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Always</td>
<td>57</td>
<td>45</td>
</tr>
<tr>
<td>Only in some cases</td>
<td>56</td>
<td>44</td>
</tr>
<tr>
<td>Never</td>
<td>4</td>
<td>3.2</td>
</tr>
<tr>
<td>Don't know</td>
<td>9</td>
<td>7.8</td>
</tr>
<tr>
<td>6. Can SIT prevent the onset of new sensitizations?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Always</td>
<td>30</td>
<td>24</td>
</tr>
<tr>
<td>Only in some cases</td>
<td>50</td>
<td>39</td>
</tr>
<tr>
<td>Never</td>
<td>25</td>
<td>20</td>
</tr>
<tr>
<td>Don't know</td>
<td>21</td>
<td>17</td>
</tr>
<tr>
<td>7. Can SIT modify the natural history of the disease?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Always</td>
<td>37</td>
<td>29</td>
</tr>
<tr>
<td>Only in some cases</td>
<td>67</td>
<td>53</td>
</tr>
<tr>
<td>Never</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Don't know</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>8. According to your experience, are SLIT and SCIT equally safe?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>SCIT is safer than SLIT</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>SLIT is safer than SCIT</td>
<td>83</td>
<td>66</td>
</tr>
<tr>
<td>Don't know</td>
<td>19</td>
<td>15</td>
</tr>
<tr>
<td>9. When the allergist prescribes SIT to a patient, and the patient asks for your advice, your attitude is</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agree</td>
<td>108</td>
<td>85.5</td>
</tr>
<tr>
<td>Sceptic</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Disagree</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Indifferent</td>
<td>7</td>
<td>5.5</td>
</tr>
<tr>
<td>10. According to your experience, are SLIT and SCIT equally effective?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>46</td>
<td>36</td>
</tr>
<tr>
<td>SCIT is better than SLIT</td>
<td>29</td>
<td>23</td>
</tr>
<tr>
<td>SLIT is better than SCIT</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Don't know</td>
<td>43</td>
<td>34</td>
</tr>
<tr>
<td>11. Would you like to receive more information on SIT (meetings/journals)?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>122</td>
<td>96.8</td>
</tr>
<tr>
<td>No</td>
<td>4</td>
<td>3.2</td>
</tr>
<tr>
<td>12. Is SIT mentioned in asthma/rhinitis guidelines?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes in both</td>
<td>64</td>
<td>50</td>
</tr>
<tr>
<td>No</td>
<td>37</td>
<td>30</td>
</tr>
<tr>
<td>Only in ARIA guidelines</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>Only in GINA guidelines</td>
<td>11</td>
<td>9</td>
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Summary

Background. Specific subcutaneous immunotherapy (SCIT) is cost-effective; however its economic burden can lead to non-adherence. We aimed to identify the reported reasons, patient’s personal or socio-demographic characteristics and SCIT-related factors associated with non-adherence to SCIT. Methods. This is a cross-sectional, observational study held in a Portuguese University Hospital. All records from patients starting SCIT in the last 4 years were reviewed in July 2011. Those without registry of SCIT administration in the previous 3 months were included (n = 181). A telephonic survey was performed and 56 were confirmed as non-adherent; reasons for discontinuation were assessed. Univariate and multiple logistic regression models were developed using characteristics previously described as being associated with non-adherence. Results. Economical burden of SCIT was the most important factor leading to treatment discontinuation (40%). In the univariate analysis, presence of family history of allergic disease treated with immunotherapy was associated with decreased OR of non-adherence to SCIT (OR [95%CI] = 0.31 [0.11-0.88]). In the multiple logistic regression model, none of the factors was significantly associated with non-adherence. Conclusion. Adherence is influenced by economic factors. More attention should be given to the impact of economic changes in allergic patient’s treatment.

Key words
Allergen Immunotherapy; patient compliance; economical factors; subcutaneous immunotherapy; cost-effectiveness

Corresponding author
Diana Silva
Serviço de Imunoalergologia Centro Hospitalar São João, E.P.E. Al. Prof. Hernâni Monteiro 4200-309 Porto, Portugal E-mail: disolha@gmail.com

Introduction

Specific immunotherapy (IT) is a cost-effective treatment (1). It produces long-lasting clinical benefits even after completion of the treatment course (2, 3). However, subcutaneous IT (SCIT) is costly, implies adherence for 3 to 5 years, administrations at every 4 to 6 weeks and time-spent travelling to a healthcare center for subcutaneous treatment administration, which may have a negative impact on patients’ adherence. Adherence, defined as the extent to which patients take the medication prescribed by their physicians (4), requires patients’ commitment (2). It can be affected by multiple factors, including psychological and socio-demographic characteristics of the patient; severity and impact of the allergic disease in the patient’s quality of life; efficacy, safety and complexity of the treatment; and health system coverage (5). By knowing which are the main factors responsible for treatment discontinuation, physicians will be able to deal with them more effectively. Few studies addressed this question, as stated in a recent review (2).

The primary aim of this study was to describe reasons that led to SCIT non-adherence in patients with asthma and/or allergic rhinoconjunctivitis. Additionally, we aimed to identify patient’s personal or socio-demographic characteristics and SCIT-related factors associated with non-adherence to SCIT.

Methods

Study Design and data collection

This was a cross-sectional, observational study primarily targeting individuals with asthma and/or allergic rhinoconjunctivitis that discontinued SCIT with airborne allergens without me-
Most patients (88%) table 1 ical indication were considered as adherents. The characteristics survey, were still under SCIT and those who stopped due to med-

Table 1. Adherence by SCIT and medical indication. This study was held in the Allergy Department of a University Hospital in Porto, Portugal, in July 2011. SCIT administration records from patients starting immunotherapy in the previous four years were reviewed (n = 1256). Individuals that started SCIT with airborne allergens during the study period and with no record of SCIT administrations in the 3 months previous to data collection were included. The records specifying that SCIT was stopped due to medical indication or that SCIT was being continued in another health care unit were excluded. The selected individuals were contacted in July/August 2011 and invited to answer a telephonic survey. Calls were performed in working days; each phone number was contacted at least 3 times in different occasions before being abandoned. Individuals that refused to answer and those that could not be reached after 3 attempts were excluded. Individuals that, during the telephonic interview, were found to have ceased treatment with medical indication or to have continued in other health-care department were used for comparison. Data regarding gender, age, distance from home to the Hospital, type of allergic disease and SCIT-associated characteristics (including type, allergen(s), number of administrations, treatment duration and adverse effects) were collected from the records.

Survey

A structured questionnaire was built based on previous studies (6-9). A question to confirm if the patient had discontinued SCIT, specifying whether with or without medical indication, was performed in the beginning of the survey. Individuals that reported to have discontinued without medical indication were asked, in an open question, to appoint reasons for treatment withdrawal. Potentially important factors (including lack of treatment efficacy, difficulty in commuting or reconciling schedule with work/school, costs associated with SCIT and residency/work place changes) were also systematically questioned and registered in a dichotomous scale (Yes/No). The intention to restart SCIT was also asked. Questions regarding the number of years of school education, global improvement with SCIT (self-reported efficacy), personal history of other allergic diseases, family history of IT treatment and questions regarding SCIT efficacy (including changes in symptoms, medication need and emergency visits) were also included in the survey.

Participants

Overall, 181 individuals were selected, 67% (n = 122) completed the questionnaire and 46% (n = 56) were confirmed as non-adherent to SCIT (figure 1). Individuals that, at the time of the survey, were still under SCIT and those who stopped due to medical indication were considered as adherents. The characteristics of the participants are presented in table 1. Most patients (88%) began SCIT using a rush protocol. More than half (56%) were performing treatment with a mixtures of allergens, most (75%) with house dust mites combinations (Dermatophagoides pteronyssinus, farinae and Lepidoglyphus destructor). Mixtures of grasses were the more frequently used pollens (82% of pollens SCIT); weeds (Parietariae Officinalis [n = 23] or Plantago lanceolata [n = 6]) and tree-pollens (olive tree or birch), isolated or in combination, were also used. The SCIT characteristics were similar to those previously published in the same population(10). Moreover, no statistically significant differences were found between the interviewed and non-interviewed individuals in what refers to demographic data and SCIT-associated characteristics.

Statistical Analysis

Data analyses were performed using SPSS® version 20.0 for Windows (IBM SPSS, Chicago, IL, USA). When necessary, variables were re-coded for statistical analysis: school education in three categories (accounting for the Portuguese school system) and self-reported professional activity in four categories - unemployed, student, undifferentiated profession and differentiated profession. Analyses regarding school education were restricted to individuals aged 18 years or older. Categorical variables were described using absolute frequencies and proportions and compared using Chi-square tests. Continuous variables were described by medians with interquartile range (IQR) and compared using the Mann-Whitney test (non-normal distribution). A p-value of < 0.05 was considered as statistically significant. Univariate and multiple logistic regression models were developed using independent variables as risk factors for non-adhesion in adults; results were presented as odds ratio (OR) with 95% confidence interval (CI). Variables used in the model included gender, age, scholarship, profession, family history of allergic disease, home distance from hospital, asthma diagnosis, SCIT period (pre-seasonal vs. perennial), allergen, adverse reactions to SCIT and self-reported SCIT efficacy. The model was progressively adjusted considering its goodness-of-fit (Hosmer-Lemeshow test) and predictive power (ROC curve analysis).

Results

The main reasons for discontinuing SCIT without medical indication are presented in figure 2. Forty percent of the participants considered the cost of SCIT as the most important factor for treatment discontinuation and 19% also reported other costs associated with SCIT (including price of administrations and commuting for treatment). Almost 27% of the participants referred that the lack of improvement with SCIT was a reason to discontinue treatment and 20% reported adverse events. Systemic reactions occurred in three patients from each group; all were mild except for an asthma exacerbation in a patient from the non-adherent group. The number of large local reactions,
either with immediate or late onset, was similar between groups (33 [59%] in the non-adherent group vs. 33 [50%] in those adherent to SCIT). One patient stopped treatment due to pregnancy and two others because they were diagnosed with another medical condition and considered, without medical advice, not to be possible to perform SCIT at the same time. At least 7% of the patients frequently forgot to attend to SCIT administration and 5% assumed not to understand SCIT benefits or were unaware of the need to continue treatment after completion of the first batch of vials. Seventy three percent (n = 41) of the non-adherents reported improvement during SCIT and 77% (n = 43) considered to resume treatment.

Table 1 - Baseline characteristics of the participants and comparison between non-adherent and adherent patients

<table>
<thead>
<tr>
<th></th>
<th>Total Groups</th>
<th>Non Adherent Groups</th>
<th>Adherent Groups</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 122)</td>
<td>(n = 56)</td>
<td>(n = 66)</td>
<td></td>
</tr>
<tr>
<td><strong>Gender, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.390</td>
</tr>
<tr>
<td>Male</td>
<td>43 (35.2)</td>
<td>22 (39.3)</td>
<td>21 (31.8)</td>
<td></td>
</tr>
<tr>
<td><strong>Age, years, median [IQR]</strong></td>
<td>24 [20;32]</td>
<td>26 [21;32]</td>
<td>24 [18;33]</td>
<td>0.579</td>
</tr>
<tr>
<td><strong>Scholarship (≥ 18 years), n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.283</td>
</tr>
<tr>
<td>&lt; 9 years</td>
<td>13 (13.1)</td>
<td>4 (8.5)</td>
<td>9 (17.3)</td>
<td></td>
</tr>
<tr>
<td>9-12 years</td>
<td>58 (58.6)</td>
<td>31 (66.0)</td>
<td>27 (51.9)</td>
<td></td>
</tr>
<tr>
<td>&gt; 12 years</td>
<td>28 (28.3)</td>
<td>12 (25.5)</td>
<td>16 (30.8)</td>
<td></td>
</tr>
<tr>
<td><strong>Profession, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.119</td>
</tr>
<tr>
<td>Unemployed</td>
<td>14 (11.6)</td>
<td>5 (8.9)</td>
<td>9 (13.8)</td>
<td></td>
</tr>
<tr>
<td>Student</td>
<td>26 (21.5)</td>
<td>8 (14.3)</td>
<td>18 (27.7)</td>
<td></td>
</tr>
<tr>
<td>Undifferentiated profession</td>
<td>58 (47.9)</td>
<td>33 (58.9)</td>
<td>25 (38.5)</td>
<td></td>
</tr>
<tr>
<td>Differentiated profession</td>
<td>23 (19.0)</td>
<td>10 (17.9)</td>
<td>13 (20.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Family history of Allergic Disease n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.068</td>
</tr>
<tr>
<td>Absent</td>
<td>46 (39.0)</td>
<td>25 (45.5)</td>
<td>21 (33.3)</td>
<td></td>
</tr>
<tr>
<td>Yes, no immunotherapy</td>
<td>46 (39.0)</td>
<td>23 (41.8)</td>
<td>23 (36.5)</td>
<td></td>
</tr>
<tr>
<td>Yes, treated with immunotherapy</td>
<td>26 (19.0)</td>
<td>7 (12.7)</td>
<td>19 (30.2)</td>
<td></td>
</tr>
<tr>
<td><strong>Distance to Hospital, Km, median [IQR]</strong></td>
<td>11.5 [6.1;20.7]</td>
<td>10.1 [5.9;16.4]</td>
<td>12.6 [7.4;21.1]</td>
<td>0.201</td>
</tr>
<tr>
<td><strong>Pathology, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhinitis</td>
<td>117 (95.9)</td>
<td>55 (98.2)</td>
<td>62 (97.0)</td>
<td>0.235</td>
</tr>
<tr>
<td>Asthma</td>
<td>49 (40.2)</td>
<td>24 (42.9)</td>
<td>25 (37.9)</td>
<td>0.576</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>41 (33.6)</td>
<td>17 (30.4)</td>
<td>24 (36.4)</td>
<td>0.484</td>
</tr>
<tr>
<td><strong>SCIT period, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.589</td>
</tr>
<tr>
<td>Perennial</td>
<td>89 (84.0)</td>
<td>43 (86.0)</td>
<td>46 (82.2)</td>
<td></td>
</tr>
<tr>
<td>Pre-seasonal</td>
<td>17 (16.0)</td>
<td>7 (14.0)</td>
<td>10 (17.9)</td>
<td></td>
</tr>
<tr>
<td><strong>SCIT type, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.945</td>
</tr>
<tr>
<td>Polimerized</td>
<td>104 (86.0)</td>
<td>48 (85.7)</td>
<td>56 (86.2)</td>
<td></td>
</tr>
<tr>
<td>Depot</td>
<td>17 (14.0)</td>
<td>8 (14.3)</td>
<td>9 (13.8)</td>
<td></td>
</tr>
<tr>
<td><strong>Allergen, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.801</td>
</tr>
<tr>
<td>Mites</td>
<td>72 (59.5)</td>
<td>34 (60.7)</td>
<td>38 (58.5)</td>
<td></td>
</tr>
<tr>
<td>Pollens</td>
<td>49 (40.5)</td>
<td>22 (39.3)</td>
<td>27 (41.5)</td>
<td></td>
</tr>
<tr>
<td><strong>Administrations, number, median [IQR]</strong></td>
<td>10 [6;19]</td>
<td>11 [7;20]</td>
<td>7 [5;15.0]</td>
<td>0.092</td>
</tr>
<tr>
<td><strong>Duration of treatment, months, median [IQR]</strong></td>
<td>7 [2;16]</td>
<td>8 [3;18]</td>
<td>5 [2;14]</td>
<td>0.216</td>
</tr>
<tr>
<td><strong>Immediate reactions, number, median [IQR]</strong></td>
<td>0[0-2]</td>
<td>0 [0;3]</td>
<td>0 [0;2]</td>
<td>0.756</td>
</tr>
<tr>
<td><strong>Late reactions, number, median [IQR]</strong></td>
<td>0[0-2]</td>
<td>0 [0;2]</td>
<td>0 [0;2]</td>
<td>0.795</td>
</tr>
</tbody>
</table>

1 Participants that continued SCIT at other Health-Care Units were excluded
When comparing the patients that discontinued SCIT without medical indication with those from the adherent group, no differences were found (table 1). Improvement with the treatment was not statistically different between the non-adherent and the adherent groups (73% [n = 41] vs. 82% [n = 54], respectively; p = 0.373); both reported a decrease in symptoms of the allergic disease (77% [n = 31] in non-adherent vs. 94% [n = 51] in the adherent), medication need (63% [n = 26] vs. 61% [n = 33], respectively) and emergency department visits (12% [n = 5] vs. 26% [n = 14], respectively).

In the univariate analysis, the presence of family history of allergic disease treated with immunotherapy was associated with a decreased OR of non-adherence to SCIT (OR [95%CI] = 0.31 [0.11-0.88]). In the multiple logistic regression model, none of the tested factors were significantly associated with non-adherence (table 2); the model had good calibration (p = 0.269) and predictive power (area under the curve = 0.757).

Table 2 - Odds ratio (OR [95% confidence interval, CI]) of being non-adherent to SCIT (age ≥ 18 years; n = 149). Statistically significant factors are presented in bold

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted</th>
<th>Adjusted†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR [95%CI]</td>
<td>OR [95%CI]</td>
</tr>
<tr>
<td><strong>Gender (male)</strong></td>
<td>1.39 [0.66-2.92]</td>
<td>0.78 [0.20-3.06]</td>
</tr>
<tr>
<td><strong>Age (≥ 30 years)</strong></td>
<td>0.91 [0.44-1.91]</td>
<td>0.37 [0.08-1.73]</td>
</tr>
<tr>
<td><strong>Scholarship</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 9 years</td>
<td>0.266*</td>
<td>0.724*</td>
</tr>
<tr>
<td>9 to 12 years</td>
<td>2.58 [0.71-9.35]</td>
<td>0.97 [0.13-7.04]</td>
</tr>
<tr>
<td>&gt; 12 years</td>
<td>1.59 [0.40-6.38]</td>
<td>2.25 [0.13-39.62]</td>
</tr>
<tr>
<td><strong>Profession</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Student</td>
<td>0.80 [0.20-3.16]</td>
<td>0.79 [0.05-12.65]</td>
</tr>
<tr>
<td>Undifferentiated</td>
<td>2.38 [0.71-7.97]</td>
<td>3.31 [0.44-24.72]</td>
</tr>
<tr>
<td>Differentiated</td>
<td>1.39 [0.35-5.45]</td>
<td>2.00 [0.13-31.78]</td>
</tr>
<tr>
<td><strong>Family history of allergic disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Yes, no immunotherapy</td>
<td>0.84 [0.37-1.91]</td>
<td>1.24 [0.30-5.12]</td>
</tr>
<tr>
<td>Yes, treated with immunotherapy</td>
<td>0.31 [0.11-0.88]</td>
<td>0.38 [0.08-1.90]</td>
</tr>
<tr>
<td><strong>Distance to Hospital</strong>† (&gt; 20 km)</td>
<td>0.63 [0.25-1.57]</td>
<td>0.46 [0.11-1.87]</td>
</tr>
<tr>
<td><strong>Asthma</strong></td>
<td>1.23 [0.60-2.54]</td>
<td>0.76 [0.21-2.75]</td>
</tr>
<tr>
<td><strong>Rhinitis</strong></td>
<td>3.55 [0.39-32.71]</td>
<td>NI</td>
</tr>
<tr>
<td><strong>Conjunctivitis</strong></td>
<td>0.76 [0.36-1.63]</td>
<td>0.29 [0.08-1.02]</td>
</tr>
<tr>
<td><strong>Atopic dermatitis</strong></td>
<td>0.87 [0.30-2.52]</td>
<td>1.97 [0.36-10.78]</td>
</tr>
<tr>
<td><strong>Food allergy</strong></td>
<td>2.39 [0.42-13.54]</td>
<td>NI</td>
</tr>
<tr>
<td><strong>Drug Allergy</strong></td>
<td>0.55 [0.13-2.30]</td>
<td>0.14 [0.02-1.19]</td>
</tr>
<tr>
<td><strong>SCIT period</strong></td>
<td>0.75 [0.26-2.14]</td>
<td>0.58 [0.14-2.49]</td>
</tr>
<tr>
<td><strong>Allergen</strong></td>
<td>1.10 [0.53-2.28]</td>
<td>NI</td>
</tr>
<tr>
<td><strong>Adverse reactions to SCIT</strong></td>
<td>1.35 [0.66-2.77]</td>
<td>0.97 [0.25-3.76]</td>
</tr>
<tr>
<td><strong>Absence of self-reported SCIT efficacy</strong></td>
<td>1.65 [0.70-3.89]</td>
<td>0.79 [0.18-3.53]</td>
</tr>
</tbody>
</table>

† Sixty nine individuals were included;
* p-value for trend; † Participants that continued SCIT at other Health-Care Units were excluded; NI - not included
Costs of treatment affect compliance to specific subcutaneous immunotherapy

Figure 1 - Patient selection diagram

181 individuals selected

59 excluded:
- 43 with incorrect or unavailable phone number
- 15 did not answer after 3 attempts
- 1 was away and unavailable to answer the questionnaire

122 (67%) participants

56 (46%) discontinued SCIT without medical indication

33 (27%) continued SCIT elsewhere

33 (27%) discontinued SCIT with medical indication

NON-ADHERENT group

ADHERENT group

Figure 2 - Reasons for discontinuing immunotherapy without medical indication obtained by telephonic survey in 56 patients (%). In the survey it was initially asked to state the main reason for discontinuing subcutaneous immunotherapy, labeled as "Reported spontaneously", and latter questioned specific factors that had influenced the decision, labeled as "Positive answer to specific questions."

*Other reasons included: forgetfulness of treatment (7.2%), onset of a new disease (3.6%), difficulty in understanding the treatment (3.6%), thinking that treatment continuation was not necessary (1.8%) and pregnancy (1.8%)
Discussion

The main reason for SCIT discontinuation without medical indication was the cost associated with the treatment, which was reported by 59% of the respondents. The high proportion of patients that discontinued SCIT in spite of improvement supports the potential impact of the economical obstacle. Family history of allergic disease treated with immunotherapy was associated with lower risk of non-compliance to SCIT (univariate analysis), however in the multiple logistic regression model none of the evaluated factors/characteristics were significantly associated with non-adherence.

Strengths and limitations

This study, to our knowledge, was the first reporting reasons for non-adherence to SCIT in Portugal and one of the few studying personal and SCIT-related characteristics possibly associated with adhesion to treatment (9, 11). Considering that this study was performed at a time of major economic disturbances in Europe, it adds a recent new social reality to the published literature on this topic.

The study design limits the generalization, as it was only performed in one center and with a small sample. Across different countries, immunotherapy cost, funding, organization and real-life practices vary (1), which prevents a straightforward comparison. Moreover, the use of different definitions of non-adherence adds further difficulties. In fact, non-adherence can be defined according to the time when immunotherapy was stopped (usually 3 (8) or 6 months (9, 12) before the study) or considering the number of injections received (usually using < 50% of the target number to define non-adherence). In this study, a time cut-off of 3 months was considered. Recall bias could have been introduced as this was a retrospective telephonic survey and some reasons could have been forgotten at the time of the interview. Only SCIT with airborne allergens was evaluated, as it is the most frequently performed treatment; however, SCIT with other allergens, namely hymenoptera venom, may have different reasons for non-adherence and results cannot be extrapolated to these populations. The inclusion of patients under sublingual immunotherapy (SLIT) could also lead to other findings, as previously reported (13); nevertheless, the difficulties regarding SLIT administration monitoring and the specific characteristics of treatment adhesion restricted their inclusion. Data on economical income of the participants was not obtained, which limits our ability to accurately compare the specific impact of economic factors; however, questioning income in a telephonic survey performed by doctors from the department where the patients are followed could be uncomfortable for the participants.

Comparison with literature

Specific subcutaneous immunotherapy with airborne allergens is the most widely used immunotherapy in Portugal; at least three years of treatment are required to obtain a favorable clinical and immunological response (4). Non-adherence jeopardizes the benefits of this treatment and its cost-effectiveness (1). In this study, reasons perceived by the patients for discontinuing SCIT without medical indication were mainly driven by social and economic factors, namely SCIT acquisition and administration expenses, inconvenience associated with commuting to the hospital and difficulty in reconciling their daily life with SCIT administrations. These results differ from most previously published studies where the main reason for immunotherapy drop-out was inconvenience (7, 8, 12, 13), with proportions ranging from 35 to 65% in different settings (7, 8, 13, 14). To our knowledge, few studies reported economic expenses as the most important reason for SCIT discontinuation (15).

In 20% of our patients, adverse events influenced the decision to discontinue SCIT; however it was the primary reason for discontinuation in only 4%. This is in agreement with the previously published impact of adverse events on treatment discontinuation, which was reported as the responsible for 5% to 16% of SCIT withdrawals (8, 13, 15, 16).

Most of the patients that discontinued SCIT in this study (73%) referred an improvement and more than three-quarters would like to restart treatment. This is concordant with the main reason for discontinuing SCIT found in this study (costs related to the treatment) and supports the need of adequate cost-effectiveness and cost-utility studies of SCIT. Immunotherapy, being a long-term and expensive treatment (with a cost ranging from 200€ to 400€/year in Portugal and currently without reimbursement), may reduce other costs related to the treatment of allergic diseases. Hankin et al. demonstrated short-term cost offsets in patients with allergic rhinitis who received immunotherapy (6), however Donahue et al. found that individuals who completed immunotherapy had higher non-immunotherapy related costs (17). A recent systematic review pointed out that cost-effectiveness depends on the long-term clinical benefit and also on the break-even point of cumulative costs between immunotherapy and pharmacotherapy (1). From a clinical point of view, these results highlight the importance of informing patients, before starting immunotherapy, not only about SCIT efficacy, but also SCIT-associated costs and potential inconvenience related with the treatment. In order to reduce treatment drop-outs, the individual and social environments have to be taken into account when starting and following-up a patient under immunotherapy (18). Moreover, it seems that providing some form of funding/reimbursement or lowering the costs of immunotherapy could be essential to promote adherence to the treatment.
Non-adherence risk factors have been studied in case-control (6, 9) and cross-sectional studies (19), using multivariate logistic regression to infer which characteristics are associated with immunotherapy discontinuation. These factors vary according to different countries and settings (6). In a retrospective case-control study in India, having no family history of allergic diseases, missing doses repeatedly, maintaining similar medicine requirements, negative perception of immunotherapy or having allergic conjunctivitis were associated with non-adherence (9). With a similar study design and using a Cox proportional hazard, in the USA, Hankin et al. found variations based on race (Hispanic patients were 1.5 times more likely to discontinue immunotherapy); More et al. reported that non-compliant patients were younger and usually from the active population (8). In a large cross-sectional study in Germany, the strongest predictor for non-compliance in women was the presence of sensitization to food allergens (19). The inconsistency between studies can be due to the divergent population characteristics, study designs or the use of different methods for statistical analysis. In this study, family history of allergic disease treated with immunotherapy was the only factor significantly associated with SCIT adherence in the univariate analysis. As suggested by Mahesh et al. (9), this could be explained by patients’ better knowledge of allergic diseases and the need for a long-term treatment to achieve clinical results. In our multiple logistic regression model, this association lost statistical significance, which may be related to the loss of statistical power due to a small sample size.

Unmet needs

More evidence is needed from multicenter studies with larger sample and a prospective design, where more detailed information, focusing in all dimensions of adherence (social and economic, health system and treatment-related factors), is collected and assessed together (5). Moreover, future research should investigate the long-term economical impact of SCIT and direct and indirect costs related to the treatment (20). High quality studies exploring cost-effectiveness of treating allergic patients with immunotherapy are lacking (1, 3).

Conclusion

In this study, economic burden associated with specific subcutaneous immunotherapy was the most relevant factor leading to treatment discontinuation without medical indication. As economical changes are occurring throughout Europe, more attention should be given to their impact in the allergic patient’s treatment.

Acknowledgements

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References


C. Micucci¹, D. Amico², M. Braconi², C. Pareo², M.E. Cimarelli², S. Subiacò²

Exercise-induced anaphylaxis in a cardiopathic patient on chronic aspirin therapy

¹UOC di Broncopneumologia - Servizio di Allergologia, Ospedale “Carlo Urbani”, Jesi (Ancona) Italy
²UOC di Broncopneumologia - Ospedale “Carlo Urbani”, Jesi (Ancona) Italy

Summary
We report the case of a 73 year old man on chronic aspirin therapy who went in anaphylactic shock during his daily farm chores following a meal rich in wheat products. The serum specific IgE assay (ImmunoCAP) showed strong positive specific IgE responses to ω-5 gliadin. A two-year period avoiding wheat meals 3 hours prior to exercise, resulted in a lack of further anaphylaxis; this results aided us in making the diagnosis.

Case report
The specific Food Dependent Exercise Induced Anaphylaxis (s-FDEIA) is a form of EIA in which anaphylaxis develops only if physical activity occurs within a few hours after eating a specific food. Neither food intake nor physical activity by themselves produces anaphylaxis (1). Symptoms may include cutaneous, gastrointestinal, cardiovascular and respiratory manifestations. A recent study has shown that the large majority of s-FDEIAs in Italy are associated with LTP (Lipid Transfer Protein) (2), which represents the second cause of food allergy in Italian adults (3); however, ω-5 gliadin is still considered an important causative agent (2). Furthermore, NSAIDs have been identified as important co-factors in the development of post-prandial anaphylaxis in susceptible individuals (4).

A 73 year old man was admitted to our hospital for the rapid onset of hives, itching, abdominal pain, hypotension (60/40 mmHg) and loss of consciousness about two hours after a meal rich in wheat products and during his daily farm chores. He had a history of valvular heart disease and aortic aneurism. He had suffered three more episodes of shock in the preceding ten years. His therapy consisted of 100 mg of aspirin daily. On admission, complete blood count and tests of liver function, coagulation and kidney function were normal, as were serum levels of electrolytes, cardiac enzymes and the D-dimer test. A CT scan was performed to rule out a hemorrhagic shock due to aortic aneurysm rupture. Echocardiography and an electrocardiogram excluded the possibility of a cardiogenic shock. Symptoms were rapidly relieved by treatment with antihistamines and methylprednisolone. The day following admission, skin tests with commercial extracts (ALK-Abelló, Madrid, Spain and Lofarma Laboratories, Milan, Italy) and serum specific IgE assay - ImmunoCAP (Thermo Fisher Scientific, Uppsala, Sweden) were performed. Allergy skin tests were negative, whereas
the serum specific IgE assay (ImmunoCAP) employed to assess serum food-specific IgE concentrations, showed positive results for wheat, gluten and ω-5 gliadin. Other specific molecular targets were negative (table 1).

In s-FDEIA, patients develop anaphylaxis after eating a specific food and exercising (2). Over the years, several foods such as wheat, shellfish, tomatoes, peanuts and corn have been implicated in this disorder (5). In European countries, vegetables are the most common food allergens (5). In Italy, LTPs seem to represent the major trigger (2). Wheat is the principal food in Japan (5), but a recent report has shown that ω-5 gliadin exerts a certain role even in Italian people (2). Aspirin is a known and important co-factor in promoting the disease (4). Multiple theories have been devised to explain FDEIA. Intestinal permeability increases during exercise, allowing allergenic proteins to have greater access to the gut-associated immune system. Non-steroidal anti-inflammatory drugs and alcohol could favor the development of FDEIA by their ability to further increase intestinal permeability (6). Abnormality in the autonomic system (7), changes in processing specific allergens (8) and alteration in the balance between inflammatory and anti-inflammatory responses mediated by physical activity (9), could also account for the abnormal responses observed in the disease.

The patient examined above experienced an anaphylactic shock after the ingestion of a wheat rich meal, during his daily farm work and after his usual postprandial intake of aspirin. Despite the lack of data on serum tryptase levels, the clinical characteristics and the serum specific IgE assay (ImmunoCAP) results, together with the exclusion of any other possible causes of shock, led us to make the diagnosis of FDEIA certainly favored by aspirin intake. The occurrence of a previous crisis with the same symptoms in similar circumstances supported our hypothesis.

Once discharged, the patient was instructed to avoid wheat meals 3 hours prior to exercise and in order to avoid the coexistence of an additional trigger, to interrupt his aspirin therapy after consulting with a cardiologist. No more episodes of shock have occurred in this patient in the last two years.

References


**Table 1 - ImmunoCAP Specific IgE Blood Test (KU/L)**

<table>
<thead>
<tr>
<th>Antigen</th>
<th>IgE (KU/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rTri a 19 (ω-5 gliadin)</td>
<td>52.40</td>
</tr>
<tr>
<td>rPru p 3 (LTP)</td>
<td>0.03</td>
</tr>
<tr>
<td>nGal d 1 (Ovomucoid)</td>
<td>0.01</td>
</tr>
<tr>
<td>nAna c 2 (Bromelin)</td>
<td>0.09</td>
</tr>
<tr>
<td>nAsp o 1 (a-amylase)</td>
<td>0.03</td>
</tr>
<tr>
<td>Anisakis</td>
<td>0.95</td>
</tr>
<tr>
<td>Milk</td>
<td>0.03</td>
</tr>
<tr>
<td>Egg</td>
<td>0.02</td>
</tr>
<tr>
<td>Wheat</td>
<td>9.10</td>
</tr>
<tr>
<td>Corn</td>
<td>0.15</td>
</tr>
<tr>
<td>Gluten</td>
<td>13.30</td>
</tr>
<tr>
<td>Maize egg</td>
<td>0.04</td>
</tr>
<tr>
<td>Yeast</td>
<td>0.05</td>
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**FABBRICANTE:**

- **Rx,** farmaci montati, Italia srl

- **Via Marcelli di Genova, 2**

- **26030 Lodigiani (LO) - ITALY**

- **e-mail: info@dxs.it**

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via Spadolini, 7 - 20141 Milano
Tel. 02 88184 317 - Fax 02 93664 151
e-mail: ordini@lswr.it - www.edizioniedra.it

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via Spadolini, 7 - 20141 Milano
Tel. 02 88184 317 - Fax 02 93664 151
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