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Factors influencing the prescription of allergen immunotherapy: the Allergen Immunotherapy Decision Analysis (AIDA) study

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Key words

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Summary

The evidence of efficacy of allergen immunotherapy (AIT) for respiratory allergy has been demonstrated by a number of meta-analyses. However, the daily practice of AIT is quite different from controlled trials, facing challenges in terms of selection of patients, practical performance, and, of particular importance, use of allergen extracts of inadequate quality. We here performed a survey, named the Allergen Immunotherapy Decision Analysis (AIDA), to evaluate which criteria are used by specialists to choose a product for sublingual immunotherapy (SLIT) in patients with respiratory allergy. A questionnaire composed of 14 items to be ranked by each participant according to the importance attributed when choosing SLIT products was submitted to 444 Italian specialists. The responses of the 169 (38.1%) physicians, who answered all questions, were analysed. Most of the respondents were allergists (79%), followed by pulmonologists (10.8%), both allergists and pulmonologists (4.8%), and otorhinolaryngologists (3%); 59.8% of the respondents were males and 40.2% were females. The age distribution showed that 89.9% of the respondents were aged between 35 and 64 years. All respondents usually prescribed AIT products in their clinical practice: 31.4% used only SLIT, whereas 69.2% used both subcutaneous and sublingual administration. The rankings, expressed as means, attributed by physicians for each of the 14 items were as follows: level of evidence-based medicine (EBM) validation of efficacy (3.44), level of EBM validation of safety (4.30), standardization of the product (5.37), efficacy based on personal experience (5.82), defined content(s) of the major allergen(s) in micro-

grams (5.96), scientific evidence for each single allergen (6.17), safety based on personal experience (6.32), ease of administration protocol (8.08), cost and terms of payment (e.g. instalments) (9.17), dose personalization (9.24), patient preference (9.25), ease of product storage (9.93), reimbursement (10.12), and availability of a helpline or on-line assistance from the manufacturer (11.89). These attitudes need to be taken into consideration by regulatory agencies as well as by producers.

Introduction

The clinical efficacy of allergen immunotherapy (AIT) for respiratory allergy has the highest level of scientific evidence, as showed by a number of meta-analyses concerning both subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) (1). However, allergen extracts of adequate quality must be used to obtain such efficacy (2,3). During the long history of AIT, the quality of the extracts used continuously improved: initially, raw pollen extracts were used in the first studies, with no information available on the content; followed by extracts measured according to the quantity of protein; and then extracts in which the allergen content was assessed by determining their biological potency using *in vivo* or *in vitro* methods, labelling such potency in units, even though different units are used by various producers (4).

The concept of standardization, which requires that the source material has adequate quality, that there is lot-to-lot reproducibility of the extract, that the major allergens contained in the extract are measured in microgram amounts, and that the clinical efficacy of the extract is validated by the criteria of evidence-based medicine (EBM), is currently required to establish measurable quality criteria (5,6). The use of products with such characteristics enables the prescribing physician to expect significant clinical results from AIT in the two forms of administration suggested by consensus documents (2,3,7), viz. SCIT and SLIT. Such a concept is of paramount importance, but the attitude of specialists in considering this when choosing the AIT products has rarely been investigated.

This survey, named the Allergen Immunotherapy Decision Analysis (AIDA), was aimed at determining which criteria are used by specialists to choose a product for SLIT in adult patients with respiratory allergy.

Materials and methods

The survey included a total number of 444 Italian specialists. It was performed as an electronic survey by Lexis Ricerche (Milan, Italy) by using a questionnaire, which was previously validated by a scientific board of 12 experts on AIT. The questionnaire was composed of two parts: the first was related to 14 items to be ranked by each participant according to the importance attributed when choosing SLIT products (from a ranking of 1 = "the most important" to a ranking of 14 = "the least important"), and the second pertaining to demographic data. The 14 items identified by the scientific board were as follows: standardization of the product, efficacy based on personal experience, level of EBM validation of efficacy, level of EBM validation of safety, defined content(s) of the major allergen(s) in micrograms, scientific evidence for each single allergen, safety based on personal experience, ease of administration protocol, cost and terms of payment (e.g. instalments), dose personalization, patient preference, ease of product storage, reimbursement, and availability of a helpline or on-line assistance from the manufacturer.

The survey was performed between October and November 2012 under the aegis of the European Centre for Allergy Research Foundation (ECARF). Participants received an e-mail message from Lexis Ricerche indicating that they had been randomly selected to participate in a survey investigating the factors taken into account in the choice of SLIT products for adult patients. These communications included a link to the online survey, an opportunity to opt out, and the possibility to give permission in order to appear as co-author of the final publication.

The data were analysed through the SurveyMonkey system, the primary worldwide provider for the assessment of electronic surveys (http://it.surveymonkey.net/mp/aboutus/). The sample analysed offers a degree of accuracy defined as ±7.5% (at a confidence interval of 95%) referring to the Italian AIT experts estimated at about 2.000 units.

Results

Of the 444 physicians who were invited to participate in the survey, 184 responded, this corresponded to a 41.4% response rate. We evaluated the responses of the 169

(38.1%) physicians who answered all questions. Most of the respondents were allergists (79%), followed by pulmonologists (10.8%), both allergists and pulmonologists (4.8%), or otorhinolaryngologists (3%) (Table 1). Fifty-five per cent of respondents were males and 44.4% females. The distribution of age showed that 89.9% of respondents were aged between 35 and 64 years (Table 2). Furthermore, the distribution of respondents was consistent with the Italian allocation of these specialists, with some regions such as Lazio, Lombardy, Piedmont, Puglia, Sicily, and Veneto better represented.

All respondents usually prescribed AIT products in their clinical practice: 31.4% used only SLIT, whereas 69.2% used both SCIT and SLIT. The rankings, expressed in terms of the mean, attributed by physicians for each of the 14 items were as follows: level of EBM validation of efficacy (3.44), level of EBM validation of safety (4.30), standardization of the product (5.37), efficacy based on personal experience (5.82), defined content(s) of the major allergen(s) in micrograms (5.96), scientific evidence for each single allergen (6.17), safety based on personal experience (6.32), ease of administration protocol (8.08), cost and terms of payment (e.g. instalments) (9.17), dose personalization (9.24), patient preference (9.25), ease of product storage (9.93), reimbursement (10.12), and availability of a helpline or on-line assistance from the manufacturer (11.89) (Figure 1). Finally, 160 respondents (94.7%) agreed to appear as co-authors of a publication of the survey.

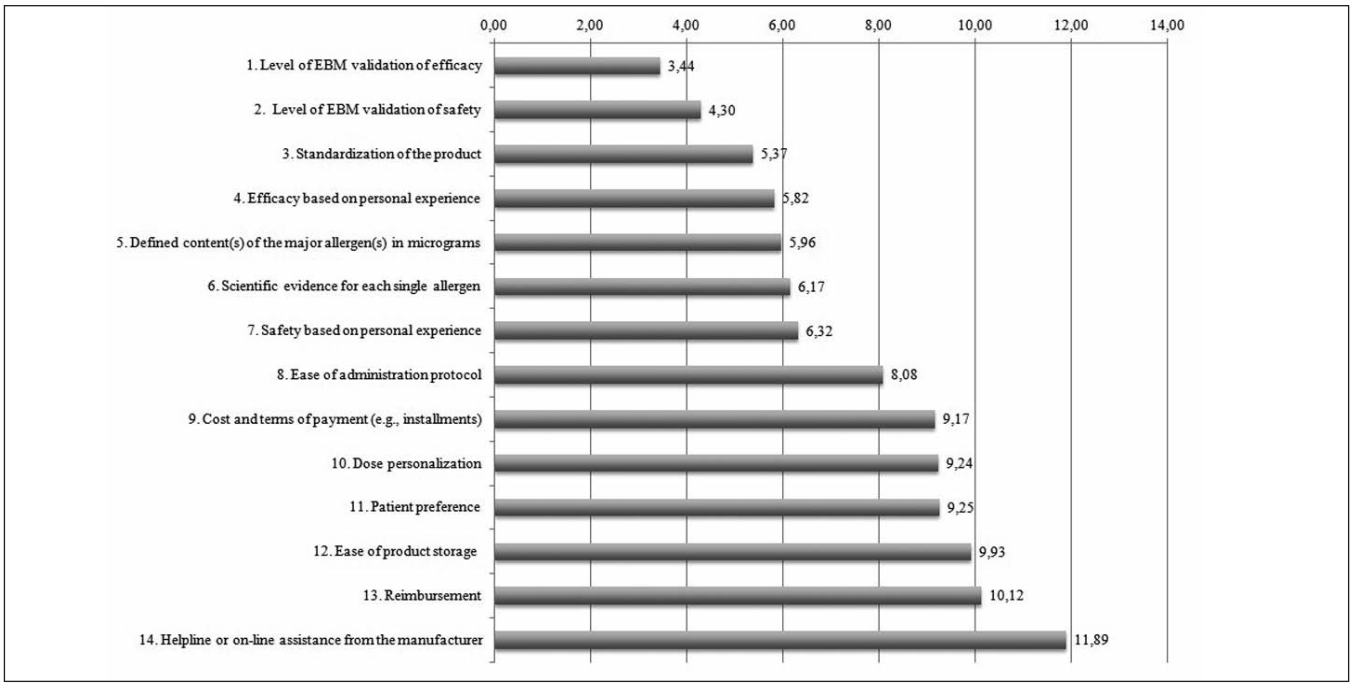
Table 1 - Distribution of respondents according to speciality

Speciality	Percentage
Allergology	79.0%
Pulmonology	10.8%
Allergology and pulmonology	4.8%
Otolaryngology	3.0%
Other	2.4%

Table 2 - Distribution of respondents according to age

Age	Percentage
Until to 34 years	5.9%
35-44 years	20.7%
45-54 years	27.8%
55-64 years	41.4%
Above 64 years	4.7%

Figure 1 - Final rankings attributed to 14 items by Italian specialists (1 = the most important, 14 = the least important)



Discussion

AIT shares with drug treatment the aim of reducing allergic symptoms, but its mode of action is completely different from those of drugs. In fact, drugs work only during their administration and once they are withdrawn, even if the most potent drugs, such as corticosteroids are used, symptoms reappear within a short interval (8). In addition, it has been shown that with drugs, good clinical control of the disease is reached in less than 50% of patients with respiratory allergy (9). Of note, Frew et al. have demonstrated that patients with symptoms uncontrolled by drug treatment achieve good control with SCIT (10).
This clearly different outcome is supported by the mechanisms of action of AIT, which modifies the immunological response to the administered allergens (11). In particular, successful AIT in respiratory allergy is associated with immunodeviation of the typical Th2 response to a more protective allergen-specific Th1 cell pattern, and with the induction of IL-10/TGF-β-producing Treg cells; similar changes are induced by SCIT and SLIT (13). Such a mechanism of action is also related to the persistence of the efficacy of AIT after its discontinuation, which in turn produces significant advantages over drug treatment in terms of cost-effectiveness for both forms of AIT (14), and particularly for SLIT (15).
Considering these important characteristics, one may think that AIT would currently be recognized as playing a central role in the management of respiratory allergy, but the available data indicate that AIT is actually used only as a second-line treatment (16). The initiative concerning the European declaration on immunotherapy signed by the EAACI stated that "When used properly, following careful diagnosis, and with good quality, well-characterized, and clinically documented extracts, immunotherapy can transform the life of people living with allergic diseases" (7) and called upon European policy-makers to coordinate actions promoting immunotherapy awareness, prioritizing funding for immunotherapy research, monitoring the health economic parameters of allergy, and streamlining medical disciplines and specialties (17).
The need to use good quality, well-characterized and clinically documented extracts is a crucial issue. The current availability of allergen extracts of insufficient quality has a negative influence and may be a cause of the low regard for AIT by specialists other than allergists, who are less informed about the requirements for developing an adequate allergen extract (18). Other issues are represented by the poor awareness of AIT among the general population and general practitioners, and by the absence of reimbursement for this type of treatment in most countries.
Given this background, we felt it would be useful to perform the AIDA survey, with the aim of assessing the criteria used by specialists when choosing a product for SLIT in adult patients with respiratory allergy. The results showed that there is a good agreement between the needs identified by the experts (2,3) and the expectations of the specialists using AIT from the products to be used for the treatment. In particular, the first issues that the specialists felt as most important were the level of EBM validation of efficacy and safety, the standardization of the product, the efficacy based on personal experience, and the defined content(s) of the major allergen(s) in micrograms in the extract. Instead, other issues were perceived as less important, including cost and reimbursement (ranked 9th and 13^{th,} respectively) and patient preference (ranked 11th). The latter seems to suggest that the Grading of Recommendation Assessment, Development and Evaluation (GRADE) approach to medical treatments, which suggests that the patient preference is an issue of central importance (19), is not yet acknowledged sufficiently. A new observation from this study was the interest of the specialists participating in a study in appearing as co-authors of a publication, which was indicated by almost all the physicians involved.
The results of our study may be compared with an international survey focused on the "Current real-life management and drivers of product choice for respiratory allergic patients". This survey was conducted through a validated web-based methodology among 394 allergy specialists in seven countries (Italy, Spain, Turkey, Slovakia, Czech Republic, Austria, and Netherlands) by a market research group (Stethos, based in Sèvres Cedex, France) exclusively dedicated to the healthcare field. The results showed that, without differences among countries, the three most important factors of product choice for allergic patients are the efficacy, as documented by rigorous double-blind placebo-controlled (DBPC) trials (95.4%, 376/394), the safety and tolerability (92,6%, 365/394), and the ease of use of the product by the patients (58,9%, 232/394).
In conclusion, the results of the AIDA survey showed that Italian specialists prescribing AIT are concerned about the quality of the allergen extract when choosing the products to use for AIT, although the perception of some requirements may be further improved. Globally, the specialists' increasing requirement for high quality products needs to be fulfilled by both regulatory agencies and producers.

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Conflicts of interest

Franco Frati and Ilaria Dell'Albani are employees of Stallergenes Italy. Cristoforo Incorvaia and Giovanni Passalacqua are scientific consultants for Stallergenes Italy. The other authors don't have any conflicts of interest that are directly relevant to the content of the study.

References

1. Compalati E, Penagos M, Tarantini F, Passalacqua G, Canonica GW. Specific immunotherapy for respiratory allergy: state of the art according to current meta-analyses. Ann Allergy Asthma Immunol 2009; 102(1): 22-28.
2. Bousquet J, Lockey R, Malling HJ. Allergen immunotherapy: therapeutic vaccines for allergic diseases. A WHO position paper. J Allergy Clin Immunol 1998; 102(4 Pt 1)**:** 558-562.
3. Canonica GW, Bousquet J, Casale T (eds). Sub-lingual immunotherapy: World Allergy Organization Position Paper 2009. Allergy 2009; 64(Suppl 91)**:** 1-59.
4. Incorvaia C, Frati F. One century of allergen-specific immunotherapy for respiratory allergy. Immunotherapy 2011; 3(5): 629-635.
5. van Ree R, Chapman MD, Ferreira F, Vieths S, Bryan D, Cromwell O, et al. The CREATE project: development of certified reference materials for allergenic products and validation of methods for their quantification. Allergy 2008; 63(3): 310-26.
6. Seppala U, Dauly C, Robinson S, Hornshaw M, Larsen JN, Ipsen H. Absolute quantification of allergens from complex mixtures: a new sensitive tool for standardization of allergen extracts for specific immunotherapy. J Proteome Res 2011; 10(4): 2113.22.
7. Calderon MA, Demoly P, Gerth van Wijk R, Bousquet J, Sheikh A, Frew A, et al. EAACI: A European declaration on immunotherapy. Designing the future of allergen specific immunotherapy. Clin Transl Allergy 2012; 2(1): 20.
8. Guilbert TW, Morgan WJ, Zeiger RS, Mauger DT, Boehmer SJ, Szefler SJ, et al. Long-term inhaled corticosteroids in preschool children at high risk for asthma. N Engl J Med 2006; 354(19): 1985-1997.
9. White P, Smith H, Baker N, Davis W, Frew A. Symptom control in patients with hay fever in UK general practice: how well are we doing and is there a need for allergen immunotherapy? Clin Exp Allergy 1998; 28(3)**:** 266-270.
10. Frew AJ, Powell RJ, Corrigan CJ, Durham SR; UK Immunotherapy Study Group. Efficacy and safety of specific immunotherapy with SQ allergen extract in treatment-resistant seasonal allergic rhinoconjunctivitis. J Allergy Clin Immunol. 2006; 117(2): 319-325.
11. Jutel M, Akdis CA. Immunological mechanisms of allergen-specific immunotherapy. Allergy 2011; 66(6): 725-82.
12. Marcucci F, Sensi L, Allocca G, Chiarello F, Palleri P, Ugolini E, et al. Sublingual immunotherapy: from safety to mechanism of action. Eur Ann Allergy Clin Immunol 2007; 39(3): 101-103.
13. Maggi E, Vultaggio A, Matucci A. T-cell responses during allergen-specific immunotherapy. Curr Opin Allergy Clin Immunol 2012; 12(1): 1-6.
14. Berto P, Frati F, Incorvaia C. Economic studies of immunotherapy: a review. Curr Opin Allergy Clin Immunol 2008; 8(6): 585-9.
15. Canonica GW, Passalacqua G. Disease-modifying effect and economic implications of sublingual immunotherapy. J Allergy Clin Immunol 2011; 127(1): 44-5.
16. Burks AW, Calderon M, Casale T, Cox L, Demoly P, Jutel M, et el. Update on allergy immunotherapy: American Academy of Allergy, Asthma and Immunology/European Academy of Allergy and Clinical Immunology/Practall consensus report. J Allergy Clin Immunol 2013; 131(5): 1288-1296.
17. Akdis C, Papadopoulos N, Cardona V. Fighting allergies beyond symptoms: the European Declaration on Immunotherapy. Eur J Immunol 2011; 41(10): 2802-2804.
18. Frati F, Scurati S, Puccinelli P, David M, Hilaire C, Marcucci F, et al. Development of a sublingual allergy vaccine for grass pollinosis. Drug Des Devel Ther 2010; 4: 99-105.
19. Terracciano L, Brozek J, Compalati E, Schünemann H. GRADE system: new paradigm. Curr Opin Allergy Clin Immunol 2010; 10(4): 377-83.

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