

Ranking in importance of allergen extract characteristics for sublingual immunotherapy by Italian specialists

Giorgio Walter Canonica, M.D.,¹ Giovanni Passalacqua, M.D.,¹ Cristoforo Incorvaia, M.D.,² Gianni Cadario, M.D.,³ Alessandro Fiocchi, M.D.,⁴ Gianenrico Senna, M.D.,⁵ Oliviero Rossi, M.D.,⁶ Antonino Romano, M.D.,⁷ Enrico Scala, M.D.,⁸ Catello Romano, M.D.,⁹ Antonino Ingrassia, M.D.,¹⁰ Marcello Zambito, M.D.,¹¹ Ilaria Dell'Albani, B.S.,¹² and Franco Frati, M.D.¹²

ABSTRACT

The efficacy of allergen immunotherapy (AIT) is well supported by evidence from trials and meta-analyses. However, its actual performance in daily practice may be diminished by several pitfalls, including inappropriate patient selection, and, especially, the use of allergen extracts of insufficient quality. We performed a survey, the Allergen Immunotherapy Decision Analysis, to evaluate which criteria specialists use to choose products for sublingual immunotherapy (SLIT) in adult patients suffering from allergic respiratory disease. We surveyed a total of 169 Italian allergists randomly chosen from a database belonging to a market research company (Lexis Ricerche, Milan, Italy). The survey was performed between October and November 2012 under the aegis of the European Center for Allergy Research Foundation and consisted of a questionnaire-based electronic survey prepared by a scientific board of 12 AIT experts. The questionnaire comprised two parts, the first of which contained 14 items to be ranked by each participant according to the importance assigned to each when choosing SLIT products. The physicians' rankings assigned major importance to the level of evidence-based validation of efficacy and safety, standardization of the product, efficacy based on personal experience, and defined content(s) of the major allergen(s) in micrograms. The results of this survey show that Italian allergists rank the quality-related characteristics of allergen extracts as highly important when choosing products for AIT. The allergists' preference for high-quality products should be addressed by regulatory agencies and by producers.

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Over the century-long history of allergen immunotherapy (AIT), the quality of the allergen extracts used for treatment has continually improved. The raw pollen extracts used in the earliest studies, for which no information concerning the allergenic content or potency was available,¹ have been progressively replaced by extracts containing measured amounts of protein² and, subsequently, by extracts for which the allergen content was assessed by *in vivo* or *in vitro* assays of the biological potency and labeled in units of potency that differ among

the various producers.³ The evolution of AIT through the first landmark studies was recently reviewed by Larenas-Linneman.⁴ More recent developments have led to the concept of standardization.^{5,6} Such standardization depends on a number of requirements, *viz.*, adequate quality of the source material, batch-to-batch reproducibility of the extract, defined content(s) of the major allergen(s) in micrograms, and validation of the clinical efficacy of the extract according to the criteria of evidence-based medicine (EBM). The use of products with such characteristics is currently considered a prerequisite for achieving significant clinical results from either subcutaneous immunotherapy (SCIT) or sublingual immunotherapy (SLIT).⁷ However, although these characteristics are of obvious importance in clinical trials, there is little information concerning the attitudes of allergists toward these qualities when choosing immunotherapy products.

We performed a survey, the Allergen Immunotherapy Decision Analysis (AIDA), to evaluate the importance that different specialists assign to various criteria when choosing products for SLIT in adult patients with respiratory allergies.⁸ Here, we present the data collected from the allergists surveyed.

METHODS

The survey was administered to Italian allergists chosen randomly from a database belonging to a market research company (Lexis Ricerche, Milan, Italy)

From ¹Allergy and Respiratory Diseases, Department of Internal Medicine, University of Genoa, Genoa, Italy, ²Allergy/Pulmonary Rehabilitation Unit, Istituti Clinici di Perfezionamento Hospital, Milan, Italy, ³Allergy and Clinical Immunology Unit, Città della Salute Hospital, Turin, Italy, ⁴Division of Allergy, Pediatric Hospital Bambino Gesù, Rome, Vatican City, Italy, ⁵Allergy Unit, Verona General Hospital, Verona, Italy, ⁶Department of Biomedicine, Azienda Ospedaliero-Universitaria Careggi, University of Florence, Florence, Italy, ⁷Department of Internal Medicine and Geriatrics, Università Cattolica del Sacro Cuore, Allergy Unit, C.I. Columbus, Rome, Italy, ⁸Experimental Allergy Unit, Istituto Dermatologico Italiano-Istituto di Ricovero e Cura a Carattere Scientifico, Rome, Italy, ⁹Allergy Unit, Azienda Sanitaria Locale Napoli 3 Sud, Naples, Italy, ¹⁰Allergology Department, Azienda Sanitaria Provinciale Trapani, Trapani, Italy, ¹¹Allergy Unit, Azienda Unità Sanitaria Locale 6 Palermo, Palermo, Italy, and ¹²Medical and Scientific Department, Stallergenes, Milan, Italy. F Frati and I Dell'Albani are employees of Stallergenes Italy. C Incorvaia and G Passalacqua are scientific consultants for Stallergenes Italy. The remaining authors have no conflicts of interest to declare pertaining to this article.

Address correspondence to Franco Frati, M.D., Medical and Scientific Department, Stallergenes Italy, Viale Certosa 2, Milan 20155, Italy

E-mail address: ffrati@stallergenes.it

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Table 1 Demographic data from allergists participating to the survey

Gender	Age Range (%)
75 Male subjects	Up to 34 yr (5.9)
60 Female subjects	35–64 yr (89.7)
	>64 yr (5.2)

that routinely surveys Italian physicians. It was a questionnaire-based electronic survey prepared and agreed on by a scientific board of 12 AIT experts. The questionnaire was comprised of two parts. The first contained 14 items to be ranked by each participant according to the importance assigned when choosing SLIT products (ranking: 1, meaning “the most important,” to 14, meaning “the least important”). The second part concerned the respondent’s demographic characteristics. The 14 items identified by the scientific board were 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.*, installments), dose personalization, patient preference, ease of product storage, reimbursement, and availability of a helpline or online assistance from the manufacturer. The mean score obtained for each item was subjected to analysis: the best possible score was 1 (ranked first by all allergists) and the worst was 14 (ranked last by all allergists).

The survey was performed between October and November 2012 under the aegis of the European Center for Allergy Research Foundation. Participants received an E-mail message from Lexis Ricerche indicating that they had been randomly selected to participate in a survey investigating the factors considered in the selection of SLIT products for adult patients. These communications included a link to the online survey and an opportunity to opt out.

The data were analyzed through SurveyMonkey System, the primary provider for the assessment of electronic surveys worldwide.⁹ The sample provides a degree of accuracy of $\pm 7.5\%$ (considering a confidence interval of 95%) with respect to the entire population of Italian AIT experts, which is estimated to comprise ~2000 individuals.

RESULTS

Of the 169 allergists who were invited to participate in the survey, 135 (79.9%) responded. Table 1 shows their demographic data. The geographical distribution of the respondents was roughly consistent with that of

all Italian allergy specialists, with some regions, such as Lazio, Lombardy, Piedmont, Puglia, and Veneto, better represented. All of the respondents reported that they usually prescribed AIT products in their clinical practice: 27.4% used only SLIT, whereas 74.1% used both SCIT and SLIT.

The rankings, expressed as the mean values, that the allergists assigned to each of the 14 items were, first, the level of EBM validation of efficacy (3.44); second, the level of EBM validation of safety (4.31); and third, the standardization of the product (5.25), followed thereafter by efficacy based on personal experience (5.76), defined content(s) of the major allergen(s) in micrograms (5.99), scientific evidence for each single allergen (6.18), safety based on personal experience (6.25), ease of administration protocol (8.16), cost and terms of payment (*e.g.*, installments) (9.11), dose personalization (9.13), patient preference (9.27), ease of product storage (9.99), reimbursement (10.40), and availability of a helpline or online assistance from the manufacturer (11.89) (Fig. 1).

DISCUSSION

Since the introduction of AIT, the aim has been to reduce the symptoms experienced by patients with allergies during exposure to specific allergen(s). However, improvements in our understanding of the mechanisms of the immunologic response to allergens and of the factors that determine the safety of the treatment have led to progressive and profound changes in the allergen extracts used. When high-quality extracts are used, AIT shows clear advantages over drug therapy, especially in terms of its capacity to achieve better control of symptoms and to continue to work even after its discontinuation.^{10–12} Concerning the first advantage, Frew *et al.* showed that patients whose symptoms are not controlled by drug therapy may achieve good control with SCIT.¹³ As for the persistence of efficacy after discontinuation of treatment, symptoms are known to return shortly after the withdrawal of even the most effective drugs, *i.e.*, corticosteroids, even after prolonged treatment.¹⁴ However, the efficacy of AIT persists after its discontinuation because it works by modifying the immunologic response to the administered allergen(s).¹⁵ This makes both SCIT¹⁶ and SLIT¹⁷ ultimately more cost-effective than drug therapy.

The need for high-quality, well-characterized, and clinically documented extracts is a crucial issue in the AIT field. The current availability of allergen extracts lacking these characteristics negatively influences both the perception and the actual results of AIT and may be one reason why specialists other than allergists often overlook this treatment option.¹⁸ Importantly, because SLIT induces an immunologic response similar to that

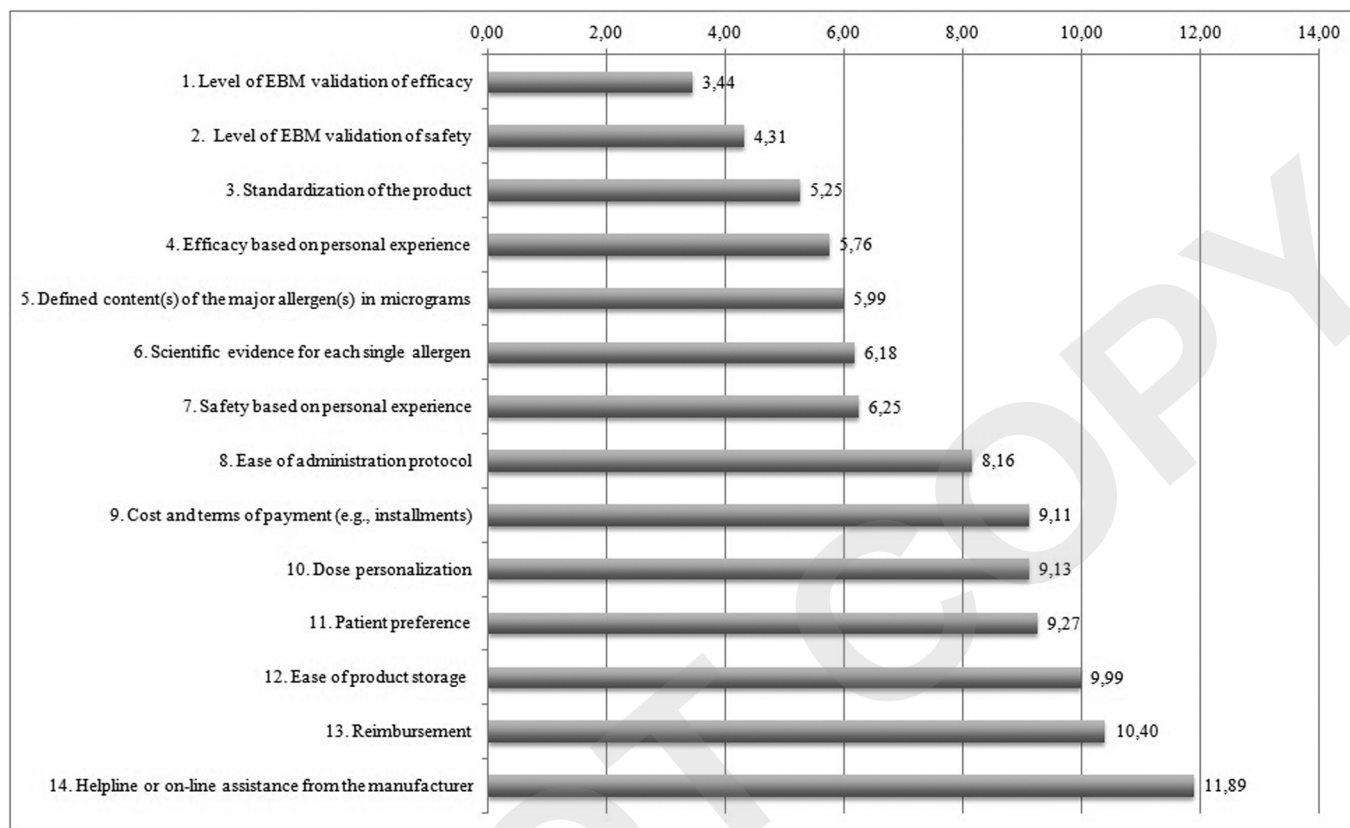


Figure 1. Final rankings attributed to 14 items by Italian allergists (1 = the most important; 14 = the least important).

of SCIT,¹⁹ the quality of the immunotherapy product is the most important determinant of clinical efficacy for both forms.²⁰ A new impetus to improve the quality of allergen extracts was provided by the development of preparations in tablet form for SLIT, which were required to meet a series of requirements imposed by regulatory agencies to be certified as pharmaceutical grade.^{21,22} SLIT is now more widely used than SCIT in a number of European countries, including Italy, and is currently under consideration for clinical use in the United States after controlled trials of grass pollen tablets in American patients.^{23–25}

The ongoing importance of SLIT was the rationale for focusing the AIDA survey on this form of immunotherapy. Our aim was to assess the criteria that specialists use to choose products for SLIT in adult patients with respiratory allergies. The results show good agreement between the requirements identified by the guidelines and practice parameters^{10–12} and allergists' expectations of products to be used for SLIT. In particular, among the factors ranked by the allergists as most important were the levels of EBM validation of efficacy and safety, standardization of the products, and defined content(s) of major allergen(s) in micrograms of the extracts. This shows that allergists are aware of the pivotal importance of extract quality for immunotherapy. Still, considerations such as the effi-

cacy based on personal experience also ranked high: this is contrary to the EBM criteria, which assign the lowest strength of evidence to personal experience.²⁶ Moreover, the important issue of patient preference, which is of central importance in the Grading of Recommendation Assessment, Development, and Evaluation approach to treatments,²⁷ was ranked only 11th. Finally, allergists did not perceive the cost of the treatment as very important, but this also is not in line with the EBM criteria or, as one may easily imagine, with the patient's point of view.

In conclusion, the results of this survey show that the priorities of Italian allergists when choosing products for AIT generally agree well with the criteria in the guidelines and consensus documents. Still, there is room for further improvement in some aspects. In any case, the allergists' tendency toward high-quality products needs to be satisfied by regulatory agencies and by producers.

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