

Characteristics of candidates for allergen immunotherapy

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ABSTRACT

Allergic rhinitis (AR) may be cured by allergen immunotherapy (AIT). However, patient characteristics for prescribing AIT are not well defined. This study aimed at evaluating the patient's profile to be a candidate for AIT in a cohort of patients suffering from AR, evaluated in 20 Italian Allergy or Ear, Nose, and Throat Centers. The study has been performed on 198 patients (98 men; mean age, 26.8 years) with AR (assessed by Allergic Rhinitis and Its Impact on Asthma [ARIA] criteria). The kind and the number of prescribed allergen extracts, type of diagnosis, severity of symptoms, and patient's perception of symptoms and drug use were evaluated. Patients were subdivided in AIT-treated and without AIT (as controls) subgroups. Most of the patients (69.7%) had persistent AR with moderate-severe symptoms. The mean number of sensitization was 3.4. ARIA classification and sensitization number did not affect AIT choice, but the type of allergen was relevant. AIT-treated patients had milder symptoms than controls if assessed by doctors, but AIT patients perceived more severe symptoms and larger drug use than controls. This study shows that the choice of AIT is based on patient's perception and type of allergen, but number of sensitizations, symptom severity assessed by doctors, and ARIA classification are not relevant factors. The key message might be that it is always relevant to pay attention to the complaints referred by the patient.

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Allergic rhinitis (AR) is a very frequent disorder, affecting up to 40% of general population and its prevalence is still rising.¹ Social and economic costs are substantial because of such high prevalence; daily activities, productivity, and quality of sleep are also significantly affected by AR.²

AR classification has been recently revised by the Allergic Rhinitis and Its Impact on Asthma (ARIA) group.¹ This classification includes a measurement of frequency and duration of symptoms. Intermittent AR (IAR) is defined by symptoms occurring for <4 days/wk or <4 consecutive weeks. Persistent AR (PER) is defined by symptoms occurring for >4 days/wk and >4 consecutive weeks. Additionally, a severity scale of mild-to-moderate-severe symptoms (based on the AR impact on both daily activities and quality of life) is included in the revised classification.

AR is characterized by four main symptoms, such as itching, sneezing, watery rhinorrhea, and obstruction. Moreover, it is well known that AR is frequently associated with conjunctivitis. The characteristic symptoms

of allergic conjunctivitis are itching, redness, and lacrimation.

The treatment of AR may be classified as preventive, symptomatic, and allergen immunotherapy (AIT). Preventive therapy is theoretically the simplest, but it is almost impossible to achieve. Symptomatic therapy is based on the prescription of drugs; it is usually effective, but it does not cure AR, because symptoms recur immediately after its suspension if allergen exposure persists. In contrast, AIT treats all AR symptoms, including ocular symptoms, by tackling the underlying cause of allergy. AIT is effective and exerts long-term preventive activity also after its discontinuance.

AIT is indicated in patients with AR when symptoms are surely IgE dependent. However, the patient's characteristics to be a candidate for AIT are not well defined. Several issues have to be considered before prescribing AIT, including severity of symptoms, number of sensitizations, type and response to drugs, costs, *etc.*, but standardized criteria are not well identified. Therefore, the major aim of this study was to evaluate the patient's profile to be a candidate for AIT in a cohort of patients suffering from AR.

MATERIALS AND METHODS

Study Design

The study was called RINOBIT using the Latin words "RINItis OBservatio ITALica" (in English, Italian

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Table 1 Patient distribution according the ARIA classification and the AIT treatment

ARIA Classification	No. of Patients Undergoing AIT (%)	No. of Patients Not Undergoing AIT (%)	Total (%)
Mild intermittent	3 (2.5)	2 (2.56)	5 (2.53)
Mild persistent	14 (11.7)	9 (11.5)	23 (11.6)
Moderate-to-severe intermittent	21 (17.5)	11 (14.1)	32 (16.2)
Moderate-to-severe persistent	82 (68.3)	56 (71.8)	138 (69.7)
Dichotomous score (basal)			
Severity of allergic rhinitis			
Mild	17 (14.2)	11 (14.19)	28 (14.1)
Moderate-to-severe	103 (85.8)	67 (85.9)	170 (85.9)

AIT = allergen immunotherapy; ARIA = Allergic Rhinitis and Its Impact on Allergy.

Observation on Rhinitis). The study was conducted in 20 allergy and rhinology centers, homogeneously distributed in Italy. It was designed to include samples representative of the general AR population and to have the ability to identify newly diagnosed cases. The study was approved by the Review Board of each participating center and an informed written consent was obtained from each patient.

Subjects

A total number of 198 patients (98 men; mean age, 26.8 years) with AR were prospectively and consecutively enrolled. A detailed clinical history was taken and a complete physical examination was performed. The patients were included in the study based on AR diagnosis.

Skin-prick tests were performed as stated by the European Academy of Allergy and Clinical Immunology.³ The panel consisted of house-dust mites (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*), cat, dog, grasses mix, ragweed, *Parietaria officinalis*, birch, hazel, olive tree, cypress, *Alternaria tenuis*, *Cladosporium*, and *Aspergillus* mix (Stallergenes, Milan, Italy).

The diagnosis and severity classification were made based on the concordance between history of nasal symptoms and positive skin-prick test, according to ARIA document.¹

Nasal and ocular symptoms were assessed by a physician. Four nasal and three ocular symptoms were evaluated: nasal itching, sneezing, rhinorrhea, nasal obstruction, ocular itching, ocular redness, and lacrimation. Each individual symptom was scored as follows: 0, no symptoms; 1, mild symptoms; 2, moderate symptoms; and 3, severe symptoms.⁴

Moreover, patients reported their perception of both symptom severity and drug use assessed by a visual analog scale (VAS).⁵ For symptoms, VAS must assess a global evaluation including all symptoms (for eyes, itching, tearing, and redness; for nose, itching, sneez-

ing, rhinorrhea, and obstruction). Antihistamines and intranasal corticosteroids were used by patients on demand.

Patients were further subdivided in two subgroups according to the presence (or absence) of AIT prescription, performed at the initial visit.

Statistical Analysis

Continuous and/or discrete parameters were reported as mean, SD, third quartile, and frequency. Categorical parameters were reported in contingency tables. Homogeneity of data was evaluated by χ^2 -Fisher's exact test. The significance of the values concerning the principal parameters was calculated by Student's *t*-test for paired data and by nonparametric Wilcoxon test for continuous parameters. McNemar test was used for categorical or discrete parameters. The *p* value concerning the statistical significance was set at 0.05. Statistical analysis was performed by statistical package BMDP Dynamic produced by BMDP Statistical Software, Inc. (Los Angeles, CA).

RESULTS

Number of Sensitizations

Globally, the mean number of sensitizations was 3.4. There was no difference between subgroups, because AIT-treated patients had a mean of 3.3, and patients without AIT prescription had, on average, 3.4 sensitizations.

Classification of Rhinitis

The severity of ARIA classification was considered in all patients (Table 1). Most of the patients (69.7%) had PAR with moderate-severe symptoms, 16.2% had IAR with moderate-severe symptoms, 11.6% had PAR with mild symptoms, and 2.53% had IAR with mild symptoms. Considering a dichotomous score, most patients (85.9%) had moderate-severe symptoms and 14.1% had mild symptoms. The comparison between sub-

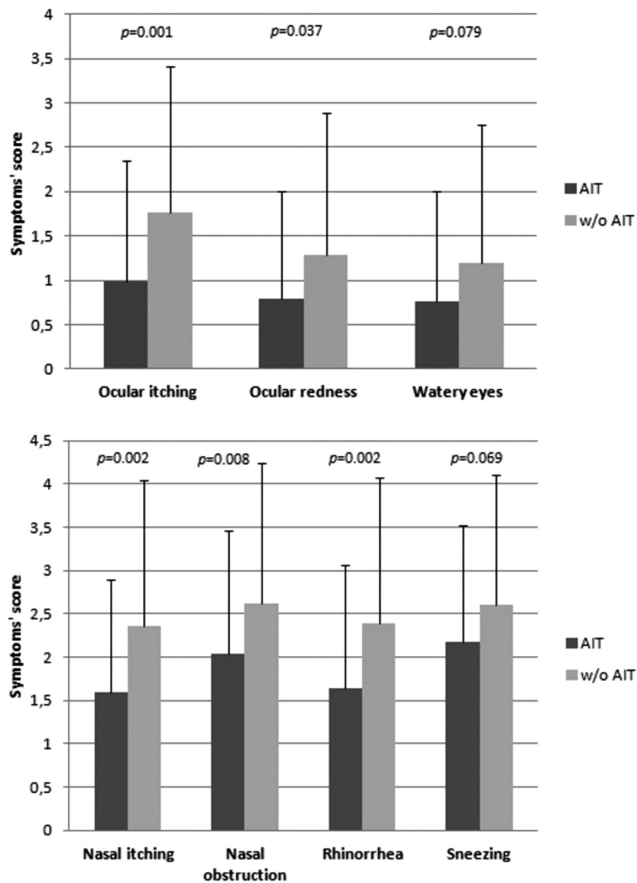


Figure 1. Nasal symptoms (upper picture) and ocular symptoms (lower picture) assessed by the doctor in patients treated with allergen immunotherapy (AIT) or not treated with AIT (w/o AIT).

groups did not show any difference for all considered items.

Severity of Symptoms

All symptoms assessed by a doctor, except sneezing and lacrimation, were significantly more severe in patients without AIT prescription than in the AIT-treated group, as reported in detail in Fig. 1.

Patient's Perception of Symptom Severity and Drug Use

The use of drugs was significantly higher in patients with AIT prescription as well as the perception of symptom severity as reported in detail in Fig. 2.

Sensitizations in AIT Patients

The most relevant allergen was house-dust mite: 73 patients were sensitized and 38 were treated with its extract (52%); the second allergen was *Parietaria*: 58 sensitized subjects and 37 treated with its extract (63%);

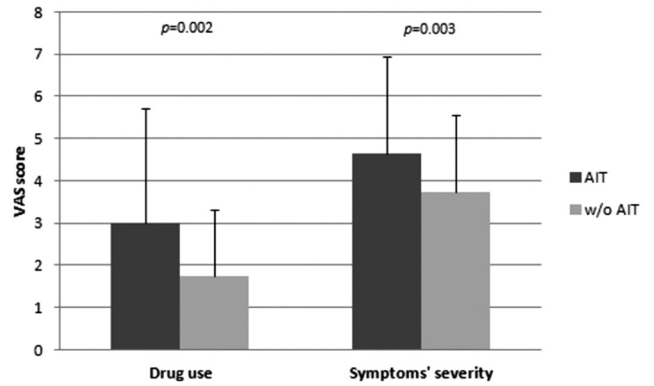


Figure 2. Drug use and symptom severity as perceived by patients treated with allergen immunotherapy (AIT) or not treated with AIT (w/o AIT).

Table 2 Distribution of positive results to skin-prick test and allergen extracts chosen for sublingual immunotherapy (expressed as absolute number and percentage)

Allergen	n	n	%
<i>Dermatophagoides</i>	73	38	58.9
Grasses	57	20	35
<i>Parietaria</i>	58	37	63
Olive	30	5	16.7
Birch	20	9	45
Cypress	23	10	43.5

the third was grass pollen: 57 sensitized patients, 20 of them (35%) treated with its extract. The other allergens are reported in Table 2.

DISCUSSION

AR is characterized by bothersome symptoms; moderate–severe AR negatively impacts quality of life and has socioeconomic burden.^{1,2} AR symptoms may be controlled by drugs, but their effect is not longstanding. Only AIT may cure AR, because it acts on the underlying immunologic mechanisms: restoring the immune tolerance toward the causal allergen. There is evidence that AIT is indicated when symptoms are severe, as recently reported by a *post hoc* analysis of regulatory studies.⁶ In fact, this analysis showed that the greatest improvement was observed in the medium and particularly the high tertiles of patients stratified for symptom severity.

On the other hand, the clinical practice indicates that there is no consensus about the prescription of AIT, mainly concerning the definition and identification of the candidate for AIT. In this regard, polysensitization is usually experienced as a possible obstacle for AIT prescription.⁷ Polysensitization is an immunologic phenomenon that is clinically significant and relevant

from an epidemiological point of view, as reported in recent surveys.⁸⁻¹⁰ The increasing number of sensitizations seems to characterize the natural history of allergic patients. Polysensitization may be associated with a different clinical picture in respect to monosensitization, especially with a more impaired quality of life.⁷ However, it has been shown that polysensitization should be not actually considered as an impediment for AIT, because AIT may be effective also in polysensitized patients.¹¹

Nevertheless, the present study aimed at evaluating the possible characteristics of a candidate for AIT in the common clinical practice in both allergy and ear, nose, and throat centers.

The analysis of the characteristics of patients showed that the majority of them (~80%) had PAR and moderate-severe symptoms. This finding may be partially explained by the relevant number of sensitizations per patient (*i.e.*, 3.4), confirming previous studies.⁷⁻¹² Second, the clinical relevance of polysensitization is confirmed by the high mean number (3.4) of sensitizations; nonetheless, AIT was prescribed in ~60% of patients. Therefore, the number of sensitizations as well as the ARIA classification severity did not influence the choice for AIT, because there was no difference between the two subgroups. In addition, a single extract was chosen in about one-half of patients, and two allergens were used in the remaining subjects. This outcome indicates that polysensitization should not constitute an impediment to sublingual immunotherapy prescription if only a few allergens are chosen.

The type of allergen may be a relevant criterion for prescribing AIT. In fact, mites and *Parietaria* were the most commonly prescribed extracts. This might depend on the duration of symptoms: both are long-standing, whereas grass and olive pollens last a few weeks or months.

A surprising finding of the present study was the inconsistency between the doctor assessment and patient's perception of symptom severity about the choice for AIT. Patients treated with AIT showed less severe symptoms when evaluated by the doctor but more severe symptoms if perceived by themselves. Instead, the use of drugs was more frequent in AIT-treated patients. The paradox of patients with higher VAS and higher medication use having lower symptom scores for ocular and nasal symptoms could be a cause and an effect. In other words, if there is more medication used because of higher disease burden, it could result in lower symptom scores.

Therefore, the present study seems to suggest some characteristics for identifying the candidate to AIT in the clinical practice: the ARIA classification and the number of sensitizations are not relevant factors; the type of causal allergen may instead influence the AIT prescription because symptom duration (mainly con-

cerning mites and *Parietaria*) or symptom severity (*e.g.*, birch and cypress) could be determinant in the decision. Notably, doctors prefer to prescribe AIT in patients with slight symptoms when assessed by themselves, but select for AIT patients perceiving more severe symptoms and larger drug consumption.

The main limitation of the present study is that it was observational, but it may reflect the genuine doctor behavior, as based on real life.

In conclusion, this study shows that the choice of AIT is based on symptom severity as perceived by the patient and on the consumption of symptomatic drugs, and number of sensitizations and ARIA classification are not relevant factors. The key message might be that it is always relevant to pay attention to the complaints referred by the patient. However, additional studies are needed to fully confirm these findings.

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