

Discrimination between moderate and severe disease may be used in patients with either treated or untreated allergic rhinitis

A. Valero^{1,13}, M. Ferrer^{2,14}, E. Baró³, J. Sastre^{4,13}, A. M. Navarro⁵, E. Martí-Guadano⁶, I. Dávila⁷, A. del Cuvillo⁸, C. Colás⁹, I. Antépara¹⁰, J. Alonso^{2,14}, O. Mola¹¹, I. Izquierdo¹¹ & J. Mullol^{12,13}

¹Unitat d'Al·lèrgia, Servei de Pneumologia i Al·lèrgia Respiratòria, Hospital Clínic, Barcelona; ²Health Services Research Unit, Institut Municipal d'Investigació Mèdica (IMIM-IMAS); ³3D Health Research, Barcelona; ⁴Servicio de Alergia, Fundación Jiménez Díaz, Madrid; ⁵Unidad de Alergia, Hospital El Tomillar, Dos Hermanas, Sevilla; ⁶Servei d'Al·lèrgia, Hospital Sant Pere Claver, Barcelona; ⁷Servicio de Alergia, Hospital Clínico. Salamanca; ⁸Clínica Dr. Lobatón, Cádiz; ⁹Servicio de Alergia, Hospital Clínico 'Lozano Blesa'. Zaragoza; ¹⁰Servicio de Alergia, Hospital de Basurto, Bilbao; ¹¹Unidad de Desarrollo Clínico, Grupo Uriach SA, Barcelona; ¹²Unitat de Rinologia i Clínica de l'Olfacte, Servei d'Otorinolaringologia, Hospital Clínic, IDIBAPS, Barcelona, Catalunya; ¹³Centro de Investigación Biomédica en red en Enfermedades Respiratorias (CIBERES); ¹⁴Centro de Investigación Biomédica en red en Epidemiología y Salud Pública (CIBERESP), Spain

To cite this article: Valero A, Ferrer M, Baró E, Sastre J, Navarro AM, Martí-Guadano E, Dávila I, del Cuvillo A, Colás C, Antépara I, Alonso J, Mola O, Izquierdo I, Mullol J. Discrimination between moderate and severe disease may be used in patients with either treated or untreated allergic rhinitis. *Allergy* 2010; DOI:10.1111/j.1398-9995.2010.02410.x.

Keywords

allergic rhinitis; ARIA; moderate; quality of life; severe; severity.

Correspondence

Antonio Valero, MD, PhD, Unidad de Alergia, Servicio de Neumología y Alergia Respiratoria, ICT, Hospital Clínic, C/Villarroel 170, 08036 Barcelona, Spain.
Tel.: (34) 932275540
Fax: (34) 932275455
E-mail: Valero@clinic.ub.es

Accepted for publication 18 April 2010

DOI:10.1111/j.1398-9995.2010.02410.x

Edited by: Wytske Fokkens

Abstract

Background: Allergic rhinitis (AR) is a common disease with major socioeconomic burden and a significant impact on quality of life.

Objective: The aim of this study was to discriminate between moderate and severe AR patients whether receiving treatment or not, using a modified criterion of allergic rhinitis and its impact on asthma (ARIA) classification.

Methods: The modified ARIA severity classification (J Allergy Clin Immunol, 120, 2007, 359) categorizes AR as mild (no items affected), moderate (1–3 items affected), and severe (all four items affected). We applied these criteria to 1666 treated and 1058 untreated AR patients and compared their symptoms total four-symptom score (T4SS) and quality of life (ESPRINT-15), according to their clinical severity.

Results: Allergic rhinitis clinical status was significantly worse ($P < 0.001$) in treated than in untreated patients. For both treated and untreated patients, T4SS and ESPRINT-15 Quality of life scores were significantly worse ($P < 0.001$) in severe than in moderate patients.

Conclusions: The modified ARIA severity classification is a useful clinical tool to discriminate moderate from severe AR among both treated and untreated patients.

Allergic rhinitis (AR) is a common and increasingly prevalent disease that generates an important socioeconomic burden and a significant impact on quality of life (QoL) (1). Allergic rhinitis has traditionally been classified as perennial or sea-

sonal depending on the allergen responsible of symptoms (2, 3). The allergic rhinitis and its impact on asthma (ARIA) document developed a new classification based on symptom duration: intermittent (IAR) and persistent (PER) rhinitis. The ARIA classification also introduced a system for assessing AR severity based on the impairment of four health-related quality of life (HRQL) items: sleep, daily activities/sport and leisure, work or school performance, and troublesome symptoms.

According to the ARIA workshop group, AR is mild when there is no impairment of any of these items, while moderate/severe when one or more of these items are impaired (1). Moreover, the large prevalence of moderate/

Abbreviations

AR, allergic rhinitis; ARIA, allergic rhinitis and its impact on asthma; ESPRINT, *ESTudio de la calidad de vida en Pacientes con RInoconjuntivitis* (Quality of Life Study in Patients with Rhinoconjunctivitis); HRQL, health-related quality of life; IAR, intermittent allergic rhinitis; PAR, persistent allergic rhinitis; RQLQ, rhinoconjunctivitis quality of life questionnaire; SCUAD, severe chronic upper airway disease; T4SS, total four-symptom score.

severe rhinitis (69–90%) (4–6) suggests an important heterogeneity in this disease severity group (7). Bousquet et al. (2) have proposed the replacement of the term ‘moderate/severe’ by ‘severe’ as a result of the high proportion of patients reporting impaired activities, while Van Hoecke et al. (8) have proposed to discriminate between moderate and severe rhinitis by reducing the number of the ARIA severity criteria in two: impact on sleep and impact on daily activities, sport and leisure, and work or school performance. Our group has recently proposed a modification of the ARIA severity classification, by maintaining the original severity items, which allows to discriminate between AR patients with different levels of severity: mild (not affected items), moderate (1–3 affected items), and severe (four affected items) (9).

Because ARIA recommends the use of its severity classification in untreated patients, the modified criterion proposed was only validated among untreated patients. However, as most AR patients attended in outpatient clinics are already treated (10, 11), recent studies have started to use the ARIA severity classification also in treated AR patients (2, 8, 12, 13).

The objective of the study was to validate the modified ARIA criterion (9) in a large sample population of patients with AR, allowing to discriminate between moderate and severe status among patients either receiving or not receiving treatment.

Methods

Study design and population

The study was performed using a pre-existing database from a cross-sectional, population-based study. The study was a survey conducted from April to June 2005 to evaluate a large representative data on adult outpatient population suffering from AR in Spain. Patient's characteristics have been published elsewhere (14). Participants were older than 18 years, with a confirmed diagnosis of AR and currently visiting their physician for AR, either under current treatment or untreated. The study investigators ($N = 539$) mainly were general practitioners (69%), ENT specialists (18.2%), or allergologists (8.4%) from primary care and hospital-based settings distributed throughout Spain (data were not available for 4.4% of the study investigators). Patients with AR ($N = 2756$) were recruited by a quota sampling procedure: 16 quotas of 170 patients each were performed to ensure representative sampling of age, gender, and ARIA classification (duration and severity) from the studied population. This study has been approved by the Ethics Committee of Hospital Clinic de Barcelona (Spain).

Patient's clinical evaluation

In addition to sociodemographic characteristics of patients (age, gender, and educational level), data about the type of AR rhinitis (persistent or intermittent, according to ARIA definition) (1) and the treatment regime were collected.

Different outcome measures were administered:

- *Allergic rhinitis severity classification.* AR severity was assessed by the four ARIA items (sleep, daily activities/sport, work/school performance, and troublesome symptoms) to classify patients on different levels of disease severity (1): mild (no affected items) and moderate/severe (one or more affected items), as well as distinguishing between moderate (1–3 affected items) and severe (four affected items), based on the modified criterion (9).
- *Total Four-Symptom Score (T4SS).* The T4SS was computed as the sum of the four main nasal symptoms of rhinitis: nasal congestion, rhinorrhea, nasal itching, and sneezing. Symptoms were scored from 0 to 3 (0, no symptoms; 1, mild; 2, moderate; and 3, severe).
- *ESPRINT-15 questionnaire.* This is an AR-specific QoL questionnaire, validated in Spain, which contains 15 items covering five domains: symptoms (five items), daily activities (three items), sleep (three items), psychological affection (three items), and wellness (one item). Items were answered using a six-point Likert scale. Both global and domain scores are computed, ranging from 0 to 6 (the worst QoL) (15, 16).

Statistical analysis

Group comparisons were performed using unpaired Student's *t*-test, nonparametric Mann–Whitney *U*-test, and Chi-square or Fisher's exact statistics, when appropriate. Chi-square statistics were also used to examine differences in the T4SS (asymptomatic, mild, moderate and severe) among different AR severity levels, in both treated and untreated patients. Comparisons of ESPRINT-15 between subjects with or without treatment and their AR severity were carried out by ANOVA test for lineal trend. Tukey's studentized range was calculated for *post hoc* comparisons if a statistical difference was found among groups. All hypothesis tests were two tailed, and statistical significance was assessed at the 0.05 levels. All statistical procedures were performed using an SPSS package version 13 for Windows (SPSS Inc, Chicago, IL, USA).

Results

The analysis included 2.724 patients with AR either treated ($N = 1666$) or untreated ($N = 1058$). Clinical severity according to T4SS, disease severity, and HRQL outcomes of AR was significantly worse ($P < 0.001$) for treated than for untreated patients (Table 1), suggesting that more severe symptoms lead patients to seek treatment. In addition, significant differences were found in the distribution of T4SS scores among the different severity groups, using both original and modified ARIA criterion classifications, for both treated ($P < 0.001$) and untreated ($P < 0.001$) patients (Table 2).

Using ARIA original severity classification, ESPRINT-15 HRQL global scores were significantly higher (worse) for moderate/severe patients than for mild patients (Figs 1A and 2A). When using the modified ARIA classification, ESPRINT-15 HRQL global scores also significantly discrimi-

Table 1 Characteristics of the allergic rhinitis (AR) study population

	Global (N = 2724)	Treated patients (N = 1666)	Untreated patients (N = 1058)	P-value
Age, years (mean $\pm$ SD)	47.5 $\pm$ 16.8	47.6 $\pm$ 16.4	47.2 $\pm$ 17.5	NS
Gender, women, N (%)	1427 (52.4)	899 (54.0)	528 (50.0)	0.041*
Type of AR duration (%)				
Persistent	49.0	55.6	38.5	<0.001*
Intermittent	51.0	44.4	61.5	
AR severity (ARIA original) (%)				
Mild	12.4	8.9	17.8	<0.001*
Moderate/severe	87.6	91.1	82.2	
AR severity (New Criterion) (%)				
Mild	12.4	8.9	17.8	<0.001*
Moderate	62.5	62.2	63.1	
Severe	25.1	28.9	19.1	
ESPRINT questionnaire, mean $\pm$ SD				
Global score	2.3 $\pm$ 1.4	2.5 $\pm$ 1.3	2.0 $\pm$ 1.4	<0.001†
Symptoms domain	2.5 $\pm$ 1.4	2.7 $\pm$ 1.3	2.2 $\pm$ 1.4	<0.001†
Daily activities domain	2.2 $\pm$ 1.5	2.4 $\pm$ 1.4	1.9 $\pm$ 1.5	<0.001†
Sleep domain	2.2 $\pm$ 1.6	2.4 $\pm$ 1.6	2.0 $\pm$ 1.6	<0.001†
Psychological impact domain	2.2 $\pm$ 1.5	2.4 $\pm$ 1.5	1.9 $\pm$ 1.5	<0.001†
ESPRINT- item 15 (%)				
Excellent	4.2	3.0	6.2	<0.001*
Very good	19.3	16.7	23.6	
Good	45.1	45.8	44.7	
Normal	26.7	29.7	22.4	
Bad	4.1	4.8	3.1	

Statistical analysis between treated and untreated AR subgroups: *Chi-square or t-test; †Mann–Whitney test. ARIA, allergic rhinitis and its impact on asthma; NS, non significant; SD, standard deviation.

Table 2 Correlation between Total 4-Symptom Score (T4SS) intensity and allergic rhinitis (AR) severity, using both the ARIA original and new criterion classifications, in treated and untreated AR patients

	Treated patients		Untreated patients	
		T4SS median, interquartile range		T4SS median, interquartile range
AR severity	N		N	
T4SS score mean by ARIA original severity classification				
Mild	142	0, 0–1	184	0, 0–1
Moderate/Severe	1449	2, 1–3	846	2, 1–2
Severity intragroup analysis	$P < 0.001$		$P < 0.001$	
(Kruskal–Wallis)				
T4SS score mean by ARIA new criterion severity classification				
Mild	142	0, 0–1	184	0, 0–1
Moderate	990	2, 1–2	648	1, 1–2
Severe	459	3, 2–3	198	2, 2–3
Severity intragroup analysis	$P < 0.001$		$P < 0.001$	
(Kruskal–Wallis)				

ARIA, allergic rhinitis and its impact on asthma.

noted between moderate and severe patients (Figs 1B and 2B). These differences were observed in both untreated (Fig. 1) and treated (Fig. 2) patients with AR.

A significant trend on global scores of ESPRINT-15 among groups of treated and untreated patients defined by different levels of disease severity (mild/moderate/severe) was demonstrated. Higher scores (worse QoL) were observed through AR severity groups. Tests for pair wise comparisons showed significant differences between mild and moderate patients and between moderate and severe patients (Figs 1 and 2).

Discussion

The main findings of this study were: *first*, the New Criterion of ARIA to discriminate between moderate and severe disease was validated in a large population of patients with AR. Severe patients showed significantly worse symptom and QoL scores than moderate patients. *Second*, the application of the modified criterion was valid not only for the untreated but also for the treated AR patient population, where differences among moderate and severe disease on symptoms and QoL were significant as well.

The excessive proportion of patients with AR classified in the moderate/severe group (69–90%) (2, 4, 6) clearly justifies the need of differentiating among moderate and severe

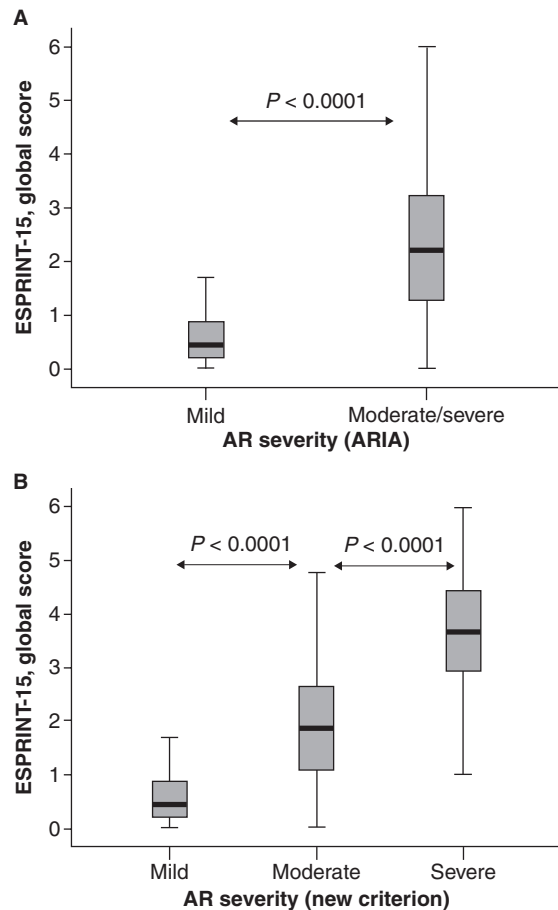


Figure 1 Distribution of patients WITHOUT treatment according to ESPRINT-15 global score, defining allergic rhinitis (AR) severity subgroups using either the allergic rhinitis and its impact on asthma original (A) or the modified criterion (B) classifications. Box plots show the 25th, 50th (median), and 75th percentile values. Whiskers show the minimum and maximum values. Kruskal–Wallis test.

rhinitis patients, if progression of disease is to be adequately monitored. This discrimination between moderate and severe patients would be useful to obtain more homogeneous populations of patients, according to their severity, to better design epidemiological studies and clinical trials, and to develop disease management strategies in both treated and untreated patients (2, 17–19).

Until present, the ARIA classification only in patients with untreated rhinitis, although most patients with AR evaluated in outpatient clinics are receiving treatment (10, 11). Following the results of this study, we are now able to classify the severity of AR also in patients with treated rhinitis and thereby monitor the response to different therapeutic strategies. Nevertheless, the development of rhinitis control tools to evaluate the response to treatment and to generate adequate therapeutic strategies should be strongly encouraged. The analysis of both control and clearly defined severity phenotypes may also help to develop new epidemiological, clinical,

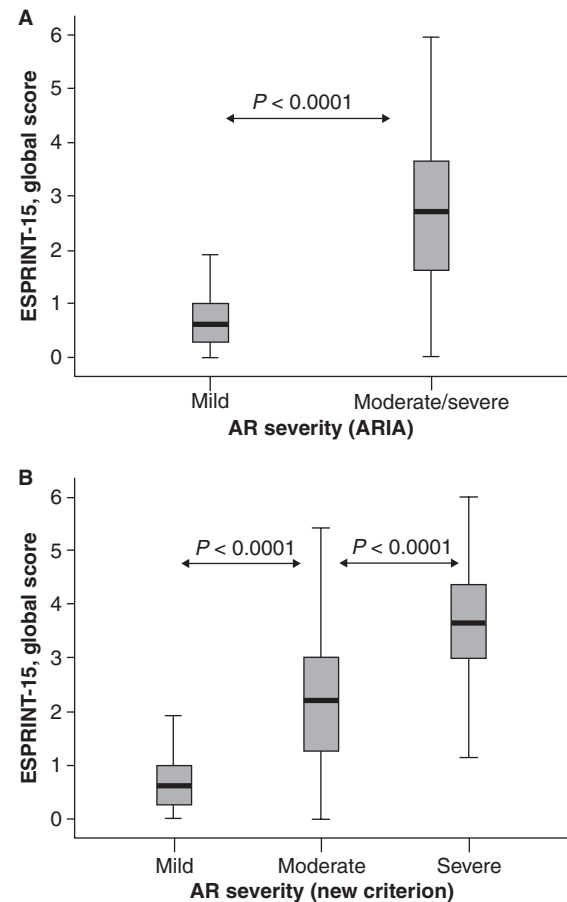


Figure 2 Distribution of patients WITH treatment according to ESPRINT-15 global score, defining allergic rhinitis (AR) severity subgroups using either the allergic rhinitis and its impact on asthma original (A) or the modified criterion (B) classifications. Box plots show the 25th, 50th (median), and 75th percentile values. Whiskers show the minimum and maximum values. Kruskal–Wallis test.

and pharmacoeconomic studies under the umbrella of the new concept of Severe Chronic Upper Airway Disease (20).

In conclusion, we have shown that modified ARIA severity classification can validly discriminate between moderate and severe AR in a large population of both treated and untreated patients with AR. Using the number of affected ARIA severity items: mild (no item affected), moderate (one to three affected items), and severe (four affected items), we have achieved a more efficient and valid grouping of patients whose symptoms and QoL are clearly different.

Acknowledgments

This study was sponsored by an unrestricted educational grant from Grupo Uriach SA, Barcelona, Spain. We also thank all the investigators participating in the different phases of the ESPRINT project.

We are extremely grateful to the 539 investigators who made this study possible.

References

1. Bousquet J, Khaltav N, Cruz AA, Denburg J, Fokkens WJ, Togias A et al. ARIA Update. *Allergy* 2008;**63**(Suppl. 86):8–160.
2. Bousquet J, Neukirch F, Bousquet PJ, Gehano P, Klossek JM, Le Gal M et al. Severity and impairment of allergic rhinitis in patients consulting in primary care. *J Allergy Clin Immunol* 2006;**117**: 158–162.
3. Ciprandi G, Cirillo I, Vizzaccaro A, Tosca M, Passalacqua G, Pallesstrini E et al. Seasonal and perennial allergic rhinitis: is this classification adherent to real life? *Allergy* 2005;**60**:882–887.
4. Bousquet J, Annesi-Maesano I, Carat F, Leger D, Rugina M, Pribil C et al. Characteristics of intermittent and persistent allergic rhinitis: DREAMS study group. *Clin Exp Allergy* 2005;**35**:728–732.
5. Bachert C, van Cauwenberge P, Olbrecht J, van Schoor J. Prevalence, classification and perception of allergic and nonallergic rhinitis in Belgium. *Allergy* 2006;**61**:693–698.
6. Pereira C, Valero A, Loureiro C, Dávila I, Martínez-Cócera C, Murio C et al. Iberian study of aeroallergens sensitization in allergic rhinitis. *Allerg Immunol (Paris)* 2006;**38**: 186–194.
7. Mullol J, Valero A, Alobid I, Bartra J, Navarro AM, Chivato T et al. Allergic Rhinitis and its Impact on Asthma Update (ARIA 2008). The perspective from Spain. *J Investig Allergol Clin Immunol* 2008;**18**: 327–334.
8. van Hoecke H, Vastesaeger N, Dewulf L, De Bacquer D, van Cauwenberge P. Is the allergic rhinitis and its impact on asthma classification useful in daily primary care practice? *J Allergy Clin Immunol* 2006;**118**:758–759.
9. Valero A, Ferrer M, Sastre J, Navarro A, Monclús L, Martí-Guadano E et al. A new criterion by which to discriminate between patients with moderate allergic rhinitis and patients with severe allergic rhinitis based on the allergic rhinitis and its impact on asthma severity items. *J Allergy Clin Immunol* 2007;**120**:359–365.
10. Schatz M. A survey of the burden of allergic rhinitis in the USA. *Allergy* 2007;**62**(Suppl. 85):9–16.
11. Canonica GW, Bousquet J, Mullol J, Scadding GK, Virchow JC. A survey of the burden of allergic rhinitis in Europe. *Allergy* 2007;**62**(Suppl. 85):17–25.
12. Todo-Bom A, Loureriro C, Almeida MM, Nunes C, Delgado L, Castel-Branco G et al. Epidemiology of rhinitis in Portugal: evaluation of the intermittent and the persistent types. *Allergy* 2007;**62**:1038–1043.
13. Bousquet PJ, Combescure C, Neukirch F, Klossek JM, Mechin H, Daures JP et al. Visual analog scales can assess the severity of rhinitis graded according to ARIA guidelines. *Allergy* 2007;**62**:367–372.
14. Valero A, Baró E, Sastre J, Navarro-Pulido AM, Izquierdo I, Martí-Guadano E et al. Population reference values of the Spanish version of the Esprint-15 questionnaire. *J Investig Allergol Clin Immunol* 2009;**19**: 396–400.
15. Valero A, Alonso J, Antépara I, Baró E, Colás C, del Cuervo A et al. Health-related quality of life in allergic rhinitis: comparing the short form Esprint-15 and the mini-RQLQ questionnaires. *Allergy* 2007;**62**:1372–1378.
16. The ESPRINT Study Group. Development and validation of a new Spanish instrument to measure health-related quality of life in patients with allergic rhinitis: the ESPRINT questionnaire. *Value Health* 2007;**10**:466–477.
17. Bousquet J, van Cauwenberge P, Ait Khaled N, Bachert C, Baena-Cagnani CE, Bouchard J et al. Pharmacologic and anti-IgE treatment of allergic rhinitis ARIA update (in collaboration with GA²LEN). *Allergy* 2006;**61**:1086–1096.
18. Prenner BM, Schenkel E. Allergic rhinitis: treatment based on patients profiles. *Am J Med* 2006;**119**:230–237.
19. Hoecke H, Vastesaeger N, Dewulf L, Sys L, van Cauwenberge P. Classification and management of allergic rhinitis patients in general practice during pollen season. *Allergy* 2006;**61**:705–711.
20. Bousquet J, Bachert C, Canonica GW, Casale TB, Cruz AA, Lockett RJ et al. Unmet needs in Severe Chronic Upper Airway Diseases (SCUAD). *J Allergy Clin Immunol* 2009;**124**:428–433.