

Original article

How representative are clinical study patients with allergic rhinitis in primary care?

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Background: Guidelines are the cornerstone of health care decision making and are based on the best available evidence, ideally large randomized controlled trials (RCTs). Although guidelines target typical patients, RCTs are often based on narrow inclusion and exclusion criteria.

Objectives: We explored to what extent typical patients, such as those consulting general practitioners for allergic rhinitis, differ from patients enrolled in RCTs.

Methods: We conducted a prospective cohort study including all the consecutive patients with allergic rhinitis cared for by general practitioners in the Languedoc-Roussillon region of France within 2 weeks during the grass pollen season. We evaluated how the characteristics of these patients differed from those of patients included in the 4 largest placebo-controlled RCTs of persistent and intermittent allergic rhinitis.

Results: Three hundred eleven patients seen by 48 general practitioners were enrolled in this study. Only 7.4% (95% CI, 4.5% to 10.3%) of the patients would have been enrolled in the RCTs. The primary reasons for this difference were as follows: diagnosis of allergy based on skin test results, serum specific IgE levels, or both (20.4%); severity of allergic rhinitis (11.5%); other chronic diseases (11.4%); history of sinusitis (10.4%); and asthma comorbidity (10.1%). A sensitivity analysis excluding contraception and the diagnosis of allergy showed that the percentage of representative patients increased to 20.2% (95% CI, 15.8% to 24.7%).

Conclusion: Only a small proportion of patients with allergic rhinitis seen in the primary care setting for allergic rhinitis would be eligible for RCTs. Thus guideline developers and health decision makers need to make careful judgments about the directness of the evidence from RCTs conducted in highly controlled settings. (*J Allergy Clin Immunol* 2011;■■■:■■■-■■■.)

Key words: Allergic rhinitis, randomized controlled trial, Allergic Rhinitis and its Impact on Asthma, Global Allergy and Asthma European Network, general practitioner, guidelines

Guidelines are the cornerstone of health care decision making and should be based on the best available evidence, ideally large randomized controlled trials (RCTs). However, RCTs are usually designed to answer specific questions, and patients' inclusion and exclusion criteria are often narrow, focusing on mechanistic rather than pragmatic issues. A critical question for guideline developers, clinical trialists, clinicians, patients, and policy makers is whether the population enrolled in RCTs is representative of the patients seen in primary care. It has previously been shown that less than 5% of patients with asthma consulting in primary care and hospital outpatient clinics are eligible for large RCTs.¹ Thus guideline developers must evaluate whether the evidence from RCTs can be applied to the patients for whom they intend to develop the guidelines. Moreover, they should evaluate whether the interventions used in RCTs are similar to those that can be used in daily practice.

Allergic rhinitis is the most common disease in developed countries, and guidelines such as those established by Allergic Rhinitis and its Impact on Asthma (ARIA),^{2,3} have been available for many years. A revision of the ARIA guidelines using the Grades of Recommendation Assessment, Development and Evaluation (GRADE) methodology⁴ is pending.

A cohort study was conducted to assess the percentage of patients with allergic rhinitis cared for in primary care that would have been eligible for inclusion in RCTs to inform the level of directness of the evidence⁵ between the population under study and the typical population being cared for in primary practice. The study was carried out in collaboration with the International Primary Care Respiratory Group in the Languedoc-Roussillon region of France.

METHODS

Study design

A cross-sectional multicenter study assessed whether patients consulting general practitioners for allergic rhinitis were representative of patients

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Abbreviations used

ARIA: Allergic Rhinitis and its Impact on Asthma
 GRADE: Grades of Recommendation Assessment, Development and Evaluation
 RCT: Randomized controlled trial
 T5SS: Total score of 5 symptoms (nasal obstruction, rhinorrhea, nasal pruritus, sneezing, and ocular symptoms)

enrolled in RCTs. The study was carried out by the group of primary care physicians of the Languedoc-Roussillon region (south of France, 2,520,000 inhabitants) who were registered as participating in training of medical doctors (the list of physicians is shown in the acknowledgments section). This group was selected because the teaching physicians are representative of the physicians in the region. The study was performed over a 2-week period (from June 8 to June 19, 2009) corresponding to the expected peak of the grass pollen season in that area. The inclusion and exclusion criteria of 3 RCTs previously carried out on patients with persistent allergic rhinitis⁶⁻⁸ or intermittent allergic rhinitis⁹ were applied.

Consecutive patients older than 18 years and consulting general practitioners for allergic rhinitis were included. All patients fulfilled the following inclusion criteria: (1) they had allergic rhinitis for at least the past 3 years and (2) the diagnosis of allergic rhinitis was based on symptoms according to criteria proposed in the International Consensus of Rhinitis.¹⁰ Moreover, some patients had a diagnosis previously confirmed by an allergist. Patients were not necessarily sent for referral to specialists after the consultation because we wanted to have a real-life study. Patients with an uncertain diagnosis of allergic rhinitis by the primary care physician were not enrolled. Patients were categorized as having intermittent or persistent rhinitis according to the ARIA classification.^{2,3} The participating physicians received no specific training.

According to French law, the observational study was exempt from the need to obtain ethics committee approval. Patients were informed about and consented to the study and its objectives and could refuse to participate without giving any justification.

Questionnaires

Patients were interviewed by the physicians using a structured questionnaire based on the inclusion and exclusion criteria applied in the 4 largest double-blind, placebo-controlled RCTs of persistent and intermittent allergic rhinitis (Tables I^{2,3,8,9,11} and II).⁶⁻⁹ Demographic data and the diagnosis of allergic rhinitis (based on clinical history, skin test results, and serum specific IgE levels¹²) were also collected. The questionnaires were scanned with specific software (Data-scan; Neoptec, Montpellier, France).

The questions relating to diagnosis assessed whether the diagnosis was made on the basis of clinical symptoms alone or by combining symptoms with skin prick test results, serum specific IgE levels, or both, as requested in RCTs. The severity of allergic rhinitis was assessed by measuring 5 symptoms (nasal obstruction, rhinorrhea, nasal pruritus, sneezing, and ocular pruritus) scored from 0 (no symptom) to 3 (very bothersome) according to the protocol of the RCTs.⁶⁻⁹ A total score of 5 symptoms (T5SS; nasal obstruction, rhinorrhea, nasal pruritus, sneezing, and ocular symptoms) was established. In RCTs a minimal T5SS of 6 is required for inclusion.

Questions specific to the inclusion/exclusion criteria in RCTs considered concomitant upper and lower airway diseases (eg, asthma, nasal abnormalities, and sinusitis), as well as antiallergic treatment (immunotherapy started within the past 3 months and use of inhaled corticosteroids). Further information was gathered concerning comorbidities, drug and alcohol abuse, and compliance with treatment. Additional consideration was given to female patients aged 18 to 50 years (childbearing age), assessing contraception, pregnancy, and breastfeeding. This group was considered because women are excluded from RCTs if unable to guarantee effective contraception. Finally, the use of antibiotics or oral corticosteroids within the last 12 weeks was recorded.

Several criteria were not included in the present study because they did not pertain to patients consulting in primary care and were only applicable to RCTs (Table II). According to French law, patients without affiliation to the

national health insurance system should be excluded from RCTs. Criteria on follow-up were not considered.

Pollen counts were assessed in Perpignan, Montpellier, and Nîmes, the 3 main cities of the region, by the Réseau National de Surveillance Aérobiologique (rnsa@rnsa.fr).

Study size

The objective of the present study was to assess the prevalence of patients (with sufficient precision; ie, $\pm 5\%$ CI under normal approximation) seen in general practice who would have been eligible for inclusion in RCTs. No study previously assessed such prevalence, and therefore a theoretical prevalence of 50% was considered for the sample size. This prevalence was used in a conservative way. Thus a sample size of 384 subjects was needed to be enrolled to observe a prevalence of 50% (95% CI, 45% to 55%).

Statistical methods

The patients studied were described by using frequencies and proportions (categorical data) or medians and 25th to 75th percentiles (quantitative data). For each inclusion/noninclusion criterion, the proportion of patients who did not fulfill the eligibility criteria was evaluated. The prevalence and 95% CI of patients compliant with all eligibility criteria were assessed. A sensitivity analysis assessed the prevalence without taking the contraception criterion into account because this is considered a compulsory exclusion criterion in RCTs. The same analysis was performed without considering the allergy diagnosis and by using objective tests (skin prick tests or serum specific IgE measurements) because seasonal allergic rhinitis in primary care is often diagnosed based on symptoms.

For the representation of data, the Pareto chart was used because it is commonly used to graphically summarize and display the relative importance of the differences between groups of data.¹³ It makes it possible to arrange the information in such a way that priorities for process improvement could be established.

Statistical analyses were performed with SAS version 9.2 software (SAS Institute, Inc, Cary, NC).

Role of the funding source

The Centre Hospitalier Universitaire of Nîmes provided unrestricted funding. Physicians did not receive compensation for participation in the study.

RESULTS**Participants**

The questionnaires were sent to 130 general practitioners, of whom 48 (37%) responded. The median age was 52.5 years (25th-75th percentile, 48.7-57.0 years). Eleven (23%) were working in rural areas, 26 (54%) in semirural areas, and 11 (23%) in urban areas.

Each practitioner recruited between 2 and 19 patients (median, 5.5; 25th-75th percentile, 4.5-7.1). All of the patients fulfilling the inclusion criteria accepted participation in the study. A total of 354 patients aged between 4 and 89 years were recruited. Forty-five were excluded from the analysis because they were younger than 18 years or had been presenting symptoms for less than 3 years (ineligible for RCTs, see Fig E1 in this article's Online Repository at www.jacionline.org). The analysis was therefore carried out on 311 (87.9%) patients.

Descriptive data

The median age of the enrolled participants was 48.0 years (25th-75th percentile, 35.0-62.0 years). Approximately two thirds (188 [60.5%]) were women, and 104 (55.3%) were of childbearing age (Table III). The diagnosis of allergic rhinitis was made mainly by general practitioners (228 [73.3%], without reference to specialists in 166 [53.4%]), followed by allergists (108

TABLE I. Questions used in the study

Question	
Inclusion criteria	
1	Subjects must be 12 years of age or older. ● Age range ● Mean age
2	Subjects can be of either sex. ● Male ● Female
3	The diagnosis of intermittent or persistent allergic rhinitis is based on the ARIA classification. ^{2,3}
4	Subjects must have a positive skin prick test result at screening to 1 or more allergens in the Global Allergy and Asthma European Network's (or the usually used local) panel of seasonal and perennial allergens. ¹¹ Subjects must demonstrate an antigen-induced skin prick test wheal response at least 3 mm in diameter greater than that elicited by the diluent control. The positive test results must include the allergen or allergens prevalent during the study. ● Skin tests ● Serum allergen-specific IgE measurements ● Total
5	At the run-in visit, subjects must be sufficiently symptomatic, with a T5SS 12-hour reflective symptoms severity score of at least 6 of a total of 15. ● Sneezing ● Rhinorrhea ● Nasal obstruction ● Nasal pruritus ● Ocular symptoms ● RTSS 5 > 6
6	Subjects must be free of any clinically significant disease, other than allergic rhinitis, which would interfere with the study evaluations.
7	In female subjects of childbearing potential, the urine pregnancy test (human chorionic gonadotropin) result must be negative at the screening visit. Nonsterile or premenopausal female subjects must be using a medically accepted method of birth control (ie, oral contraceptive, hormonal implant, medically prescribed intrauterine device, or depot injection during the entire study). A female subject who is not currently sexually active must agree and consent to use one of the above-mentioned methods while participating in the study. A female subject who is not of childbearing potential must have a medical record of being surgically sterile (eg, hysterectomy or tubal ligation) or must be at least 1 year after menopause.
Exclusion criteria	
8	Subjects with a history of anaphylaxis, severe local reactions(s), or both to skin testing with allergens
9	Subjects who have had an upper respiratory tract or sinus infection that required antibiotic therapy and who have not had at least a 14-day washout before the run-in period or who have had a viral upper respiratory tract infection within 7 days before screening
10	Subjects with asthma who require chronic use of inhaled or systemic corticosteroids
11	Subjects with a current history of frequent, clinically significant sinusitis or chronic purulent postnasal drip
12	Subjects receiving immunotherapy (desensitization therapy) unless on a regular maintenance schedule
13	Female subjects who are pregnant or nursing
14	Subjects with a history of hypersensitivity to the study drug or to their excipients or known to not tolerate any antihistamine
15	Subjects with current evidence of clinically significant hematopoietic, cardiovascular, hepatic, renal, neurologic, psychiatric, autoimmune disease, or any other type of disease that precludes participation in the study
16	Subjects with rhinitis medicamentosa
17	Subjects who, in the opinion of the investigator or designee, have clinically significant nasal structural abnormalities, including large nasal polyps or marked septal deviation, that significantly interfere with nasal air flow

Patients with a diagnosis of allergy based on serum allergen-specific IgE levels or skin prick test results were included because, although they are not identical, both methods can be used to make an allergy diagnosis. The questions listed above are from the AERIUS Control: Clinical Evaluation Profile of Treatment-1 and 2 studies.^{8,9} RTSS 5, Rhinitis total score of 5 symptoms (T5SS).

[34.7%]). The diagnosis was based on symptoms alone for 149 (47.9%) patients and on symptoms and serum specific IgE levels, skin prick test results, or both for 136 (43.7%) patients.

In the present study the vast majority of patients had moderate-to-severe persistent allergic rhinitis. The symptom score (T5SS) was 6 or less for 84 (27.0%) patients.

The pollen season was measured in 3 centers representing the Languedoc-Roussillon region and showed that pollen counts were low by comparison with previous years.

Main results

In our study population 7.4% (95% CI, 4.5% to 10.3%) of the patients consulting general practitioners for allergic rhinitis met the precise inclusion and exclusion criteria used in the 4 previously performed RCTs.

All of the RCTs excluded women of childbearing age unless they could guarantee effective contraception for ethical reasons. Excluding the latter criterion from the analysis would lead to a prevalence of 7.7% (95% CI, 4.8% to 10.7%). Moreover, the confirmation of diagnosis of allergic rhinitis by means of skin prick test results or serum specific IgE levels is not routinely performed in primary care, and deleting this item would increase the prevalence of representative patients to 19.0% (95% CI, 14.6% to 23.3%). Finally, excluding both criteria would lead to a prevalence of 20.2% (95% CI, 15.8% to 24.7%).

Pareto chart

The Pareto chart reported that 4 major criteria affected the results: diagnosis of allergy based on skin test results, serum

TABLE II. Questions not considered for the study

- For a subject to qualify at the baseline visit, the sum of the daily averages of the diary recordings of the 12-hour AM-PRIOR + PM-PRIOR (reflective) T5SS collected during days -4 to -1 and the AM-PRIOR T5SS on the morning of the baseline visit (day 1) must be 30 or greater.
- Subjects, parents, or legal guardians must provide written informed consent. Subjects must be able to adhere to dose and visit schedules and must meet study requirements.
- Subjects with intolerable symptoms that would make participating in the study unbearable
- Subjects who have used any drug or device in an investigational protocol in the 30 days before visit 1
- Subject is a member of the investigational study staff (currently involved with this study) or a member of the staff's family.
- Subjects whose ability to provide informed consent is compromised
- Subjects who have not observed the medication washout times outlined in the protocol before visit 2

specific IgE levels, or both (20.4% of errors); severity of allergic rhinitis (11.5%); other chronic diseases (11.4%); and asthma comorbidity with inhaled corticosteroid use (10.1%; [Fig 1](#) and [Table IV](#)). These 4 criteria represented approximately two thirds of the exclusions according to previously set criteria.

DISCUSSION

Key results

The present study shows that only 7.4% (95% CI, 4.5% to 10.3%) of patients consulting in primary care in the south of France would have met the narrow inclusion criteria used in the 4 RCTs for allergic rhinitis. However, the criteria used are stringent, and by removing the requirement for contraception along with an accurate diagnosis of allergic rhinitis based on skin test results, serum specific IgE levels, or both, the level increases to 20.2% (95% CI, 15.8% to 24.7%). This study shows that to inform guidelines adequately, broader inclusion criteria are needed to expand the findings from the narrow populations included in the RCTs to the "real-life" populations encountered in daily clinical practice, as has been proposed for asthma.¹⁴ Because current guidelines are based on such exclusive RCTs, it might be difficult to accept that recommendations are applicable. The GRADE approach, which ranks the relevance of recommendations to everyday clinical practice, is a welcome addition to guideline interpretation.^{15,16} The GRADE methodology is applied to allergic rhinitis.⁴

Limitations

Our study does have some limitations. First, we did not conduct this study in the context of an actual RCT. Thus our study might overestimate the patient population that would have participated in an RCT because not all patients who meet the eligibility criteria for a trial wish to participate. We also aimed for a slightly larger number of participants than those enrolled. However, the lower enrollment had little influence on the precision of our estimates.

Another limitation was the selection and number of participating primary care physicians. However, their location is representative of all primary care physicians of the region, and it is unlikely that patients select to visit these physicians because they are teaching. Only 48 (37%) of 130 participated. Thus only the physicians with the greatest interest in the study participated. However, these considerations are unlikely to result in a selection bias for patients.

Furthermore, many patients with allergic rhinitis either do not recognize that they have this problem or self-medicate. Thus those presenting for medical help are effectively a self-selected group, which might further bias our findings.¹⁷

TABLE III. Demographic characteristics of the patients

Sex (female)	188 (60.5%)
Female patient of childbearing age	104/188 (55.3%)
Age (25th-75th percentile; y)	48.0 (35.0-62.0)
Diagnosis based on:	
Symptoms	285 (91.6%)
Symptoms alone	149 (47.9%)
Skin prick test	135 (43.4%)
Serum specific IgE	61 (19.6%)
Diagnosis performed by:	
General practitioner	228 (73.3%)
General practitioner alone	166 (53.4%)
Allergist	108 (34.7%)
Pneumologist	35 (11.3%)
Ear, nose, and throat physician	17 (5.5%)
Duration of symptoms (25th-75th percentile; y)	11 (5-20)
ARIA classification	
Mild intermittent	12 (3.9%)
Moderate-to-severe intermittent	82 (26.4%)
Mild persistent	13 (4.2%)
Moderate-to-severe persistent	199 (64%)

Values are presented as numbers (percentages), except where shown.

The population of patients was representative of the population of the Languedoc-Roussillon region, and the vast majority of patients with allergic rhinitis had moderate-to-severe persistent allergic rhinitis. This population is similar to a population of patients consulting for the same disease in general practices¹² and specialist practices¹⁸ in France. In the present study the severity of the disease was assessed by using the ARIA classification, symptom scores, and a visual analog scale.^{19,20} The age range of the population studied was limited by the age range of RCTs, and younger or older patients were not considered in the study.

The study was carried out in patients with suspected allergy to grass pollens because this type of rhinitis is the easiest to diagnose. Patients with grass pollen allergy might have intermittent or persistent rhinitis.¹ Thus the results observed can be extended to all patients with allergic rhinitis.

The inclusion/exclusion criteria were drawn from 4 large studies of persistent and intermittent allergic rhinitis.⁶⁻⁹ Other large RCTs have been carried out only in patients with seasonal or perennial allergic rhinitis, thus differing from those of the ARIA classification.^{2,3} The ARIA classification was preferred because it is closer to the patients' views than the previous classification (seasonal and perennial allergic rhinitis); it is used worldwide and has been translated into more than 50 languages. The treatment of the patients was not recorded because this would have even further reduced the number of patients who could have been included in RCTs.

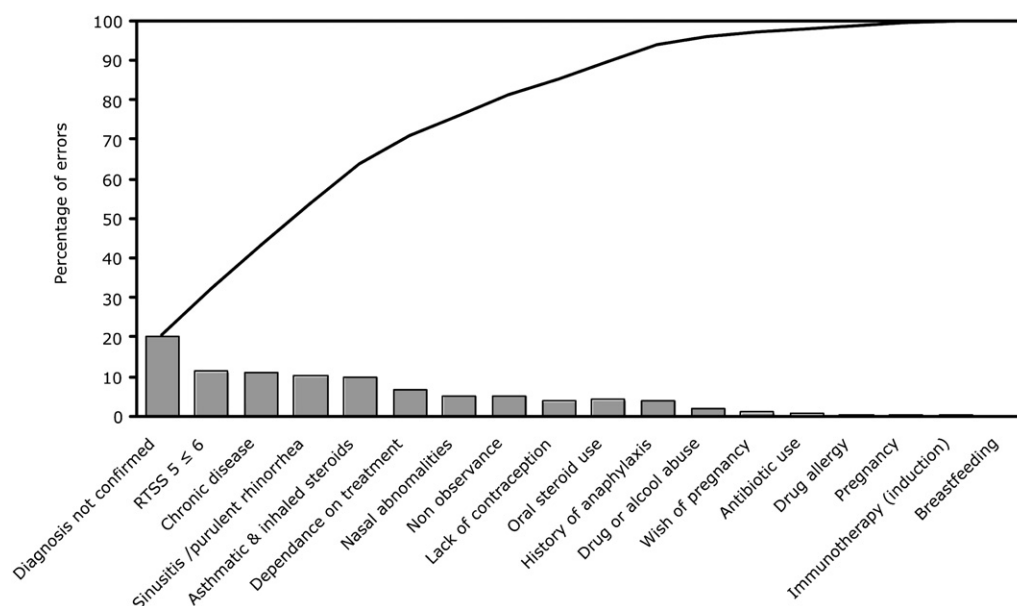


FIG 1. Pareto chart reporting the effect of inclusion/exclusion criteria of RCTs on patients seen in primary care daily practice. RTSS 5, Rhinitis total score of 5 symptoms (T5SS).

Smoking habit was not considered in this study. It has inconsistent effects on symptoms of allergic rhinitis. Smokers are not generally excluded from RCTs in this disease area.

Interpretation

The study population consisted of 3 groups of patients who consulted their physician during the grass pollen season: (1) patients previously given diagnoses by an allergist and returning for care of symptoms, (2) patients previously given diagnoses of allergic rhinitis and returning during the current season, and (3) patients with new diagnoses during the current season and now given diagnoses on the basis of a past history over the previous 3 years. However, because these criteria are not used in RCTs, the relative repartition cannot be provided.

Major exclusion criteria (for entry into allergic rhinitis RCTs) include a precise diagnosis of allergy based on skin test results, serum specific IgE levels, or both; contraception; asthma comorbidity; and the severity of allergic rhinitis. For the diagnosis of grass pollen allergy in primary care, a diagnosis of allergy confirmed by means of skin prick tests or specific IgE measurement might not be necessary because symptoms are relatively obvious and contemporaneous with the pollen season. Although structured allergy history has been found to be insufficient for the diagnosis of allergy to most allergens, including grass pollens,²¹ most patients consulting in primary care do not have an allergy diagnosis made based on skin test results, IgE levels, or both.²²

For severe cases of allergic rhinitis or in patients resistant to current treatment, it would seem appropriate to have an allergy diagnosis.²³ On the other hand, it might be very difficult to obtain a rapid allergy evaluation by specialists or even primary care–based allergy clinics for all patients given the numbers of patients involved. One might therefore consider whether the analysis of the present study should include patients with a clinical history of allergic rhinitis but with no confirmation of allergy diagnosis based on skin prick test results or serum specific IgE levels.

Moreover, contraception is a key exclusion criterion for RCTs, but in primary care this is not usually considered for the prescription of rhinitis drugs. The exclusion of such criteria would increase the prevalence to 20.2% (95% CI, 15.8% to 24.7%).

For safety and efficacy reasons, asthma comorbidity is always excluded from allergic rhinitis RCTs in patients requiring long-term treatment. To some extent, this is a legitimate exclusion. Conversely, treatment with inhaled corticosteroids might induce a systemic activity affecting efficacy. Both of these scenarios could confound trial results.

Most RCTs are carried out on patients with symptoms severe enough to warrant treatment and to show a significant difference between placebo and verum. However, this study shows that patients with milder symptoms are frequently seen in general practice and seek help. One would hope that RCTs might begin to include these patients who are more representative of the typical consulting patient.

As previously done in several RCTs,⁶⁻⁹ methodology to capture average symptoms over a few days needs to be developed to compensate for the day-to-day variability experienced by patients with rhinitis. In our study patients with mild symptoms are also included. These patients might not have had the worst symptoms on the day of consultation. Our criteria might therefore be too strict.

Between-population differences might be significant enough to cause either effect modification or differences in baseline risk for outcomes. Thus our data support widening inclusion criteria and conducting pragmatic trials.²⁴

Generalizability

The majority of patients with allergic rhinitis are seen in primary care.^{25,26} It is therefore of paramount importance to determine whether trials adequately inform guidelines and general practice.²⁷ This is the first study to address this issue for patients with allergic rhinitis, the most common disease in developed

TABLE IV. Effect of inclusion/exclusion criteria for RCTs on patients seen in primary care daily practice

Questions on diagnosis		
Diagnosis not confirmed by skin prick test result/IgE level	149 (47.9%)	
RTSS $5 \leq 6$	84 (27.0%)	
Patient presenting ≥ 1 exclusion criterion	191 (61.4% [56.0% to 66.8%])	
Questions related to allergy		
Immunotherapy (induction)	3 (1%)	
Dependence on allergic treatment	51 (16.4%)	
Nasal abnormalities (eg, polyposis and septal deviation)	39 (12.5%)	
Asthmatic with inhaled corticosteroids	74 (23.8%)	
History of sinusitis or purulent rhinorrhea	76 (24.4%)	
History of anaphylaxis during skin prick tests	30 (9.6%)	
Drug allergy	5 (1.6%)	
Patient presenting ≥ 1 exclusion criterion	160 (51.4% [45.9% to 57.0%])	
Questions on health status and other diseases		
Noncompliant patient	38 (12.2%)	
Chronic disease	83 (26.7%)	
Drug or alcohol abuse	16 (5.1%)	
Patient presenting ≥ 1 exclusion criterion	118 (37.9% [32.5% to 43.3%])	
Questions on women's health		
Pregnancy	5 (1.6%)	
Desire of pregnancy	9 (2.9%)	
Lack of contraception	29 (9.3%)	
Breast-feeding	1 (0.3%)	
Patient presenting ≥ 1 exclusion criterion	34 (10.9% [7.5% to 14.4%])	
Questions on treatment		
Antibiotic use	6 (1.9%)	
Steroid use within past 12 wk	32 (10.3%)	
Patient presenting ≥ 1 exclusion criterion	33 (10.6% [7.2% to 14.0%])	
Summary		
Patient without any exclusion criteria	23 (7.4% [4.5% to 10.3%])	
Patient without any exclusion criteria and not considering contraception	24 (7.7% [4.8% to 10.7%])	
Patient without any exclusion criteria and not considering diagnostic confirmation	59 (19.0% [14.6% to 23.3%])	
Patient without any exclusion criteria and not considering contraception and diagnosis confirmation	63 (20.2% [15.8% to 24.7%])	

Results are expressed as frequencies and percentages. The summary results also include 95% CIs. RTSS, Rhinitis total score of 5 symptoms (T5SS).

countries. Our results indicate that inclusion criteria in RCTs are too narrow and not representative of real life. In the context of an actual RCT, potential subjects would undergo skin prick tests or serum specific IgE measurements to confirm allergy diagnosis, and potential female subjects would be offered access to contraception. Thus in an actual clinical trial many subjects considered ineligible here would, in fact, have been eligible for these clinical trials. Beyond this, it is unclear how one could possibly conduct a scientifically valid study without the confirmed allergy diagnosis or an ethical trial given potential risks to the fetus without the contraception requirement. In contrast, asthma comorbidity and allergic rhinitis severity are indeed substantial limitations of the generalizability of the clinical trial populations. The exclusion of asthma comorbidity is justified by the potential safety concerns, and the focus on subjects with more severe allergic rhinitis is justified by both the patient's need for treatment and considerations of statistical power.

Thus guideline developers must carefully examine the relevance of trial populations, and we must call for pragmatic trials to be more representative of the population cared for in general practitioner offices. It appears that evidence from current trials is only partially applicable to clinical practice. The application of guidelines that are based on the best available evidence and ideally directly relevant to the patient population of interest are capable of improving patients' outcomes. Two cluster randomized trials attempted to study the effect of guideline-based treatment in patients with pollen-induced allergic rhinitis consulting

in primary care or with specialists.^{18,28} These 2 studies showed that guideline-based treatment was more effective than free treatment choice administered by the physician. Both symptom scores and quality-of-life measurements were significantly improved in the guideline-based treatment group.

Randomized controlled trial results should be pertinent to the group to which they are to be applied.²⁹ This relatively new way of thinking has implications for current guidelines drawn on evidence that is ranked according to specific criteria.³⁰ The GRADE approach helps to retrospectively address the missing dimension of generalizability and facilitates the true practice of evidence-based medicine.³¹

One of the criteria for evaluation in the category of relevance relates to the care setting in the countries where the guidelines will be applied. A multinational study is proposed, and the current protocol will be used by a joint Global Allergy and Asthma European Network and International Primary Care Respiratory Group study group.

Most large RCTs are designed for getting drug approval from regulatory agencies, and thus the inclusion and exclusion criteria are often based on regulatory requirements. However, it has recently been proposed to design pragmatic randomized trials to support decision making.²⁹ Pragmatic trials are more real-life trials with broader inclusion criteria than RCTs, which allow normal factors to occur. They usually use simpler outcomes, but they are less rigorous. Our study supports this proposal. Observational studies can also support the decision, but they present many

problems, including the lack of randomization, group comparability, and matching of cases and controls. This concept extends to other therapy areas¹ and is thus of broader significance and relevance than the area of rhinitis.³²

Conclusions

Although the nonrepresentativeness of clinical trial populations is common knowledge, the data presented in this study quantify the huge magnitude of the differences between clinical trial participants and the general population. Of the population included in RCTs for rhinitis, only 7.4% (95% CI, 4.5% to 10.3%) of patients with allergic rhinitis seen in primary care are representative of the population seen in primary care. These results are similar to those found for asthma and chronic obstructive pulmonary disease.¹ Taking into account 2 common exclusion criteria (allergy tests and contraception), up to 20.2% (95% CI, 15.8% to 24.7) of patients consulting in primary care are similar to those enrolled in RCTs. Patients consulting with clear-cut symptoms during a defined allergen exposure (eg, grass pollen) might be treated according to guidelines developed in RCTs because cluster randomized trials have confirmed the efficacy of the guidelines, but the proportion of patients similar to those enrolled in RCTs is still low. To our knowledge, there is no other study assessing the representativeness of patients seen in primary care in allergic rhinitis. Studies designed for and carried out in primary care are essential and need to be performed.

The protocol of this study is part of a joint Global Allergy and Asthma European Network and International Primary Care Respiratory Group study group. The following investigators participated in the study: L. Aigle, M. Amouyal, F. Baylé, H. Boulard, G. Bourrel, M. Brouillet, J. M. Cabot, M. Calone, R. Cazalis, A. M. Chiffre, J. F. Clapet, B. Clary, T. Cornille, M. Cukier, M. David, P. Dutilleul, E. de Roffignac, D. Durand, H. Fanton, B. Gabbaï, M. Garcia, L. Garcin, F. Giu, F. Komac, G. Havard-Fourage, P. Heuze, I. Lafont, P. Lambert, J. Levin, B. Lognos, M. T. Matera, B. Meric, P. Munc, A. Noraz, P. Olombel, J. Rambaud, J. P. Sastourné, C. Sauget, M. Segura, P. Serayet, T. Stefanaggi, and D. Wible.

Clinical implications: Guidelines in allergic rhinitis are based on RCTs conducted in highly controlled settings. Many patients might have a disease that differs from that seen in patients enrolled in these trials.

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**FIG E1.** Flow chart.