

Implementation of Guidelines for Allergic Rhinitis in Specialist Practices

A Randomized Pragmatic Controlled Trial

Jean Bousquet^a Thierry Bodez^b Pierre Gehano^{c,†} Jean Michel Klossek^d
François Liard^e Françoise Neukirch^f Martine Le Gal^g Nicole Janin^h
Bashar Allafiⁱ

^aUniversity Hospital and INSERM U780, Montpellier, ^bParis, ^cAPHP Bichat-Claude-Bernard, Paris,

^dUniversity Hospital La Milettrie, Poitiers, ^eTours, ^fINSERM U 408, Paris, ^gCRO, MAPI SA, Lyon, ^hParis, and

ⁱAlmirall SAS, Paris, France

Key Words

Allergic rhinitis • ARIA • Pragmatic trial • Guidelines

Abstract

Background: Guidelines for allergic rhinitis are more effective than free-treatment choice in the control of seasonal allergic rhinitis. **Objective:** To validate the ARIA (Allergic Rhinitis and its Impact on Asthma) guidelines in the treatment of intermittent and persistent allergic rhinitis induced by pollens. **Design:** A multicenter, open-label, parallel, pragmatic randomized study compared two therapeutic strategies during a 2-week treatment course. In the first strategy ('guidelines group'), 417 patients were treated according to ARIA with ebastine as oral antihistamine. In the second strategy ('free-choice treatment group'), investigators had a free choice for the treatment of 422 patients. **Main Outcome Measures:** Quality of life measured using the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ), work productivity and daily symptom medication scores. **Results:** 94.2% patients returned the baseline visit questionnaires and 88.6% returned the posttreatment period questionnaires. RQLQ scores were similar in the two groups at baseline. After treatment, there were improvements in the overall score and in all domains in both treatment groups. According to pragmatic methodology, the improvements show that the guide-

lines group (-1.70 ± 1.20) is more effective than the free-choice treatment group (-1.52 ± 1.22) with a γ risk of 2%. Individual RQLQ scores, work productivity, and daily symptom scores were significantly improved in the guidelines group by comparison to the free-choice treatment group. **Conclusion:** A treatment based on ARIA guidelines offers patients a significant improvement in comparison to the use of a nonstandardized treatment regimen.

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Introduction

Allergic rhinitis is a major health problem and in many countries its prevalence is well over 20% of the population. It comprises more than the classic symptoms of sneezing, rhinorrhea and nasal obstruction. It is associated with impairments in day-to-day life at home, at work and in school [1–3] and during sleep [4]. The Allergic Rhinitis and its Impact on Asthma (ARIA) recommendations written in collaboration with the WHO devised a new classification for allergic rhinitis (intermittent and persistent rhinitis) [2, 5, 6]. The ARIA guidelines also proposed a new grading of severity (mild and moderate/severe) and stepwise therapeutic recommendations based on classification and severity.

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Correspondence to: Prof. Jean Bousquet
Clinique des Maladies Respiratoires, Hôpital Arnaud de Villeneuve
Centre Hospitalier Universitaire, 371, Avenue du Doyen Gaston Giraud
FR-34295 Montpellier Cedex 5 (France)
Tel. +33 467 33 61 05, Fax +33 467 04 27 08, E-Mail jean.bousquet@wanadoo.fr

Table 1. Treatment of the guidelines group according to ARIA

	Intermittent allergic rhinitis	Persistent allergic rhinitis
Mild	ebastine 10 mg OD	ebastine 10 mg OD
Moderate/severe	ebastine 10 mg × 2 OD	ebastine 10 mg × 2 OD intranasal corticosteroid
OD = Once daily.		

The treatment of allergic rhinitis is now well established [5, 7]. In the ARIA guidelines, oral antihistamines are the first-line therapy for patients with intermittent and mild persistent rhinitis. Moreover, they are used as second-line treatment for patients with moderate/severe persistent rhinitis. Of other oral H1-antihistamines, ebastine is of interest to be studied since its doses can be modulated, 10 mg for patients with mild symptoms and 20 mg for those with more severe ones [8, 9].

Clinical trials are often accused of being remote from the real world as they present the results of trials conducted on highly selected patients in ideal circumstances. A recent observational study carried out in general practices has shown that patients of physicians following the International Consensus on Rhinitis [1] were significantly more improved than those of physicians using a free-choice treatment [10]. Both quality-of-life and symptom scores were improved. This study confirmed the importance of guidelines in the optimization of treatment for allergic rhinitis, but the ARIA guidelines have not been implemented yet.

Schwartz and Lellouch [11] proposed in 1967 to differentiate between pragmatic and explanatory clinical trials. Although the pragmatic approach has been the object of some criticism, many authors have asked to perform pragmatic clinical trials, especially in issues requiring a therapeutic decision [12, 13].

The aim of this pragmatic randomized study was to assess the benefit of implementing a simple strategy based on the ARIA guidelines in the treatment of patients with allergic rhinitis due to pollens. The study was conducted according to a recently published protocol [10]. The primary outcome parameter was the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) global score measured after 14 days of treatment and the analysis was made according to Schwartz and Lellouch [11]. Secondary outcome parameters included individual RQLQ scores, work productivity and daily symptom scores.

Methods

Patients

Patients were included in the study after written informed consent was obtained and the protocol was approved by the Ethics Committee of Montpellier, France. All patients fulfilled the following inclusion criteria: (1) a history of allergic rhinitis during the grass pollen season, (2) a diagnosis of grass pollen allergy using skin prick tests and/or serum grass pollen-specific IgE (Pharmacia CAP System) and (3) no concomitant treatment.

Objectives of the Study

The aim of this pragmatic randomized study was to assess the benefit of implementing a simple strategy based on the ARIA guidelines [5] in the treatment of patients with allergic rhinitis due to pollens.

Design of the Study

This investigator-randomized, multicenter, multinational, open-label parallel study compared two therapeutic strategies in allergic rhinitis during a 2-week treatment. Allergy, ear, nose and throat and chest specialists were randomized into two groups and were to enrol 2 patients only between March 8 and July 15, 2002. Each physician recruited the first 2 patients who presented with allergic rhinitis due to pollen allergy at the time of the grass pollen season. Physicians in the first group ('guidelines group', $n = 195$) enrolled 417 patients and followed a simple strategy based on the ARIA guidelines [2]. Physicians in the second group ('free-choice treatment group', $n = 201$) enrolled 422 patients whom they treated as they usually do in normal practice. Only depot corticosteroids were not allowed. Investigators in both groups did not know the alternative strategy and physicians within a practice used only 1 of the 2 strategies.

Assessment of Baseline Classification and Severity of Rhinitis

Patients were categorized as having intermittent or persistent rhinitis according to the ARIA classification [5]. Several signs and symptoms may be used to assess the severity of rhinitis. Since there is no validated objective measure in the assessment of rhinitis severity, patients were categorized into different levels of severity at baseline using visual analogue scales (VAS; scale 0–100 mm with 0 = no symptoms and 100 = severe) for all combined nasal symptoms since it was found to be reliable in previous studies [5, 14, 15] and in the study implementing the International Consensus on Rhinitis [10]. Patients scoring 50 mm or more on the VAS were categorized as having moderate/severe rhinitis. Patients scoring less than 50 mm were categorized as having mild rhinitis. This VAS score was recently validated in ARIA in a study of 3,052 patients.

Patients were put into four groups: mild intermittent, moderate/severe intermittent, mild persistent and moderate/severe persistent. The treatment of patients in the guidelines group was based on the ARIA guidelines (table 1) [5] and we took advantage of the two labeled doses of ebastine.

Although in ARIA guidelines it is proposed that patients with moderate/severe persistent rhinitis should be first treated with intranasal corticosteroids which are the most effective drug [16], we proposed to immediately treat patients with ebastine and intranasal corticosteroids for two reasons. First, we wanted to have the maximal effect on nasal and ocular symptoms which are very common in the patient population studied and second, the study

had the goal to immediately give maximum treatment to the patients. Physicians had the option of intranasal corticosteroids.

The investigators assigned to the free-choice treatment group were not instructed to use the results of the VAS.

Outcome Measures

The primary outcome was the disease-specific RQLQ total score [17]. The RQLQ provides an overall score and individual scores in seven domains: limitations of activities, sleep, non-hay fever symptoms, practical problems, nasal symptoms, eye symptoms and emotions (7-point severity scale from 0 to 6). A clinically significant difference is achieved when there is a difference within groups of 0.5 or more in mean overall score (minimal important difference) [18].

Secondary efficacy end points included individual RQLQ scores, Allergy-Specific Work Productivity and Impairment (WPAI-AS) scores [19] as well as individual nasal symptom scores and conjunctivitis score (3-point severity scale from 0 to 3). Safety and tolerability of treatment regimens were evaluated by the reporting of adverse events.

Patients were asked to fill in the RQLQ and WPAI-AS questionnaires at baseline and after 14 days of treatment, and to send them back by mail to the central monitoring office. At the end of the treatment period, patients were asked to answer two questions to estimate the compliance with prescribed treatment. Symptom scores and eventual side effects were monitored by the physicians at the end of the treatment period using MeDRA (Medical Dictionary for Drug Regulatory Activities; www.meddrasso.com).

Statistical Analysis

All patients were studied in the intent to treat population for efficacy and safety analyses. A centralized randomization was balanced in blocks of 2 physicians (interactive voice response system). For RQLQ, all patients with an evaluable questionnaire (over 50% of the 28 questions filled in correctly) at the two visits were included in the analysis. A psychometric analysis of RQLQ was made [4]. The methodology of the study was based on a pragmatic approach [11] and no statistical test can be provided with such an approach for the primary outcome. A sample size estimate of 558 patients/group was based on published data and would allow the detection of a difference of 0.2 in the overall quality of life score from RQLQ used as the primary end point assuming a standard deviation of 1.24 with at least 90% power. In order to make decisions ('pragmatic' study), the risks were: $\alpha = 100\%$, $\beta = 0\%$ and $\gamma = 1\%$. The γ risk was calculated according to the following formula [11]:

$$\varepsilon_{1-\gamma} = \sqrt{k} \frac{\Delta}{\sigma} \text{ where } k = \frac{1}{(1/n_1) + (1/n_2)}$$

with n_1 , n_2 = number of patients in each strategy, $\varepsilon_{1-\gamma}$ = unit normal deviate, Δ = expected difference between the two strategies, $\alpha = 100\%$, $\beta = 0\%$.

Although some of the variables are normally distributed, others are not. We therefore chose to use nonparametric statistics for all quantitative variables and reported the data in medians and 25–75 percentiles. However, means and SD were used for the assessment of the γ risk as proposed by the authors [11]. For the secondary outcomes, we used the χ^2 test for qualitative variables and the Mann-Whitney U test with Simes's procedure [20] to account for multiple comparisons for quantitative variables.

Table 2. Baseline characteristics of patients according to treatment strategy

	Free-choice group, n	Guidelines group, n
Age ¹ , years	35.2 (18–62)	36.1 (18–69)
Gender (men/women), %	45.7/54.3	43.2/56.8
Associated asthma	91 (21.6%)	88 (21.1%)
<i>Rhinitis symptoms</i>		
Sneezing		
Absent or mild	103 (24.4%)	86 (20.6%)
Moderate/severe	319 (75.6%)	331 (79.4%)
Stiffness		
Absent or mild	102 (24.2%)	105 (25.2%)
Moderate/severe	320 (75.8%)	312 (74.8%)
Nasal discharge		
Absent or mild	75 (17.8%)	93 (22.3%)
Moderate/severe	347 (82.2%)	324 (77.7%)
Nasal pruritus		
Absent or mild	195 (46.2%)	197 (47.2%)
Moderate/severe	227 (53.7%)	220 (52.8%)
Eye symptoms	283 (67.1%)	268 (64.3%)
<i>ARIA classes</i>		
Intermittent/mild	31 (7.3%)	41 (9.8%)
Intermittent/moderate to severe	77 (18.2%)	82 (19.7%)
Persistent/mild	52 (12.3%)	49 (11.8%)
Persistent/moderate to severe	259 (61.4%)	245 (58.8%)
VAS median score ¹	6.5 (5–8)	6.7 (5–8)
<i>RQLQ¹</i>		
Median global score (25–75 percentiles)	2.82 (2–4)	2.82 (2–4)
Median individual domain scores (25–75 percentiles)		
Limitation of activities	4.0 (3–5)	4.0 (3–5)
Sleep problems	2.0 (1–3)	2.0 (1–4)
Non-hay fever symptoms	2.0 (1–3)	2.1 (1–3)
Practical problems	4.17 (3–5)	4.33 (3–5)
Nasal symptoms	3.75 (3–5)	3.50 (3–5)
Eye symptoms	2.25 (1–4)	1.75 (1–4)
Emotions	2.75 (2–4)	2.50 (1–4)

¹ Values in parentheses represent range.

Results

Baseline Characteristics of Patients and Drop-Out Rates

The baseline characteristics of the patients were similar and nonsignificantly different in the two groups and the patients were well matched between both arms in the four ARIA categories (table 2).

Nineteen physicians enrolled only 1 patient, 16 three patients and 386 two patients. Of the 839 randomized pa-

Table 3. Treatment in the two treatment strategies according to ARIA classes

Treatment	Allergic rhinitis classification according to ARIA			
	intermittent/ mild	intermittent/ moderate to severe	persistent/ mild	persistent/ moderate to severe
Free-choice group				
Oral anti-H1	21 (67.7%)	51 (66.2%)	35 (67.3%)	143 (55.2%)
Oral anti-H1 + intranasal corticosteroid	9 (29%)	26 (33.8%)	16 (30.8%)	113 (43.6%)
Oral corticosteroid	1 (3.2%)	0	1 (1.9%)	3 (1.2%)
Guidelines group				
Ebastine 10 mg OD	39 (95.1%)	9 (11%)	40 (81.6%)	10 (4.1%)
Ebastine 10 mg × 2 OD	2 (4.9%)	25 (30.5%)	0	15 (6.1%)
Ebastine 10 mg × 2 OD + intranasal corticosteroid	0	48 (58.5%)	9 (18.4%)	220 (89.8%)

OD = Once daily.

tients, 94.2% returned the baseline-visit questionnaires and 88.6% returned the posttreatment period questionnaires. Of 674 who filled in the RQLQ correctly and were considered for analysis of efficacy, there were 337 patients in the guidelines group and 337 in the free-choice treatment group. Six hundred and eighty-one patients correctly filled in the WPAI-AS questionnaires.

Compliance

Compliance was assessed by query at the end of the posttreatment period questionnaire. Of the 839 patients considered for analysis of efficacy, 164 (19.5%) failed to answer the questionnaire, 82 in each treatment group. Among the responders, 639 patients (76.2%) declared they were compliant (312 in the guidelines group and 327 in the free-choice group) and 36 (4.3%) declared they were not compliant (23 and 13 in each group, respectively).

Study Medications

Medications received by the patients according to their baseline symptom severity category and treatment strategy are shown in table 3. In the free-choice treatment group there was an overtreatment for mild intermittent rhinitis since oral H1-antihistamines plus intranasal corticosteroids were given in 29% of patients. Five patients received intranasal corticosteroid without oral H1-antihistamine. In the guidelines group, physicians correctly followed the recommendations except for moderate/severe intermittent rhinitis.

Quality of Life

Overall and individual domain scores in the RQLQ were similar in the two treatment groups at baseline (table 2). During the treatment period, there were improvements in the overall score and in all domains in both treatment groups (table 4). However, the improvement in overall score in the guidelines group (-1.70 ± 1.20) was greater than in the free-choice treatment group (-1.52 ± 1.22). The difference between the two arms was 0.18 ± 1.21 and argued for the guidelines group, with a γ risk of 2%. For all individual domains the within-group improvements in RQLQ scores were greater than 0.9 and the improvement was significantly better in the guidelines group than in the free-choice treatment group for 5 domains (table 4).

WPAI-AS Questionnaire

The WPAI-AS scores were similar in the two treatment groups at baseline. During the treatment period, there were significant improvements in the scores in both treatment groups (table 5). However, the improvements in overall scores in the guidelines group were significantly greater than in the free-choice treatment group for 3 domains.

Total and Individual Symptom Scores

At randomization patients had similar severity of rhinitis and conjunctivitis assessed by clinical symptoms and VAS (table 2). During the treatment period, there were significant improvements in the scores in both treatment groups (table 6). However, the improvements in the guidelines group were significantly greater than in the

Table 4. Mean individual domain scores on the RQLQ

Score	Free-choice group (n = 337)	Guidelines group (n = 337)	p value ^b
Limitation of activities			
Baseline	4 (3/5) ^a	4 (3/5) ^a	NS
After 15 days' treatment	1.67 (1/3) ^a	1.0 (0/2) ^a	<0.0001
Variation	-2.0 (-4/-1)	-2.33 (-3/-1)	0.008
Sleep problems			
Baseline	2.00 (1/3) ^a	2.33 (1/4) ^a	NS
After 15 days' treatment	0.50 (0/1) ^a	0.33 (0/1) ^a	NS
Variation	-1.00 (-2/0)	-1.33 (-3/0)	0.02
Non-hay fever symptoms			
Baseline	2.00 (1/3) ^a	2.14 (1/3) ^a	NS
After 15 days' treatment	0.86 (0/2) ^a	0.57 (0/1) ^a	0.03
Variation	-0.86 (-2/0)	-1.00 (-2/0)	NS
Practical problems			
Baseline	4.33 (3/5) ^a	4.33 (3/5) ^a	NS
After 15 days' treatment	1.33 (1/3) ^a	1.00 (0/2) ^a	0.0002
Variation	-2.33 (-3/-1)	-2.67 (-4/-1)	0.02
Nasal symptoms			
Baseline	3.75 (3/5) ^a	3.50 (3/5) ^a	NS
After 15 days' treatment	1.25 (1/2) ^a	0.75 (0/2) ^a	0.0003
Variation	-2.00 (-3/-1)	-2.50 (-4/-1)	0.025
Eye symptoms			
Baseline	2.25 (1/4) ^a	1.75 (1/4) ^a	NS
After 15 days' treatment	0.25 (0/1) ^a	0.25 (0/1) ^a	0.01
Variation	-1.25 (-3/0)	-1.00 (-3/0)	NS
Emotions			
Baseline	2.50 (2/4) ^a	2.75 (2/4) ^a	NS
After 15 days' treatment	0.75 (0/2) ^a	0.50 (0/2) ^a	0.006
Variation	-1.25 (-2/0)	-1.50 (-3/-1)	0.05
Results expressed in medians and 25–75 percentiles. The RQLQ scores range from 0 (best) to 7 (worst).			
^a p value (Wilcoxon test) between score at V1 and V2 <0.001 (intragroup test).			
^b p value (Wilcoxon test) between free-choice and guidelines groups (intergroup test).			

free-choice treatment group for sneezing, stuffiness and nasal discharge scores, but not for nasal pruritus or eye symptoms (table 6).

The global judgement on efficacy was excellent or good for 78.4% patients in the guidelines group and 69.2% in the free-choice group ($p < 0.01$).

Safety

There were no serious side effects attributed to medications during the study. Ninety-eight patients reported adverse events, 60 (14.4%) in the guidelines group and 38 (9%) in the free-choice treatment group ($p < 0.05$). These adverse events were more frequent when intranasal corticosteroids were used. Only 6.3% patients ($n = 53$) had an adverse event possibly or probably related to the treatment, 7.7% ($n = 32$) and 5.0% ($n = 21$) in the guidelines

group and free-choice treatment group, respectively (nonsignificant). Only 9 patients dropped out of the study due to an adverse event, 5 and 4, respectively, in the 2 groups. Tolerance was considered to be excellent or good by the physicians in 90.9 and 90.3% (guidelines and free-treatment choice) and by the patients in 90.8 and 88.9%.

Discussion

In the present study carried out in patients with pollen-induced rhinitis, it was found that treatment following guidelines is more effective than free-treatment choice even when patients are seen by allergy and ear, nose and throat specialists. Moreover, many patients with mild or intermittent disease are overtreated.

Table 5. Evolution of work productivity (WPAI-AS) after treatment

Score	Free-choice group (n = 342)	Guidelines group (n = 339)	p value ^b
Missed hours of work			
Baseline	0.00 (0/0) ^a	0.00 (0/0) ^a	NS
After 15 days' treatment	0.00 (0/0) ^a	0.00 (0/0) ^a	NS
Variation	0.00 (0/0)	0.00 (0/0)	NS
Missed productivity at work			
Baseline	30.00 (10/50) ^a	30.00 (20/50) ^a	NS
After 15 days' treatment	10.00 (0/30) ^a	10.00 (0/20) ^a	0.02
Variation	-10.00 (-30/0)	-20.00 (-35/0)	0.02
Missed global productivity at work			
Baseline	30.00 (10/50) ^a	30.00 (20/50) ^a	NS
After 15 days' treatment	10.00 (0/30) ^a	10.00 (0/20) ^a	0.03
Variation	-10.00 (-30/0)	-20.00 (-40/0)	0.05
Missed time school			
Baseline	0.00 (0/0) ^a	0.00 (0/0) ^a	NS
After 15 days' treatment	0.00 (0/0) ^a	0.00 (0/0) ^a	NS
Variation	0.00 (0/0)	0.00 (0/0)	NS
Missed productivity at school			
Baseline	40.00 (20/60) ^a	30.00 (10/60) ^a	NS
After 15 days' treatment	10.00 (0/40) ^a	10.00 (0/30) ^a	NS
Variation	-20.00 (-40/0)	-10.00 (-35/0)	NS
Missed global productivity at school			
Baseline	50.00 (40/70) ^a	40.00 (20/60) ^a	NS
After 15 days' treatment	10.00 (10/40) ^a	10.00 (0/30) ^a	NS
Variation	-20.00 (-40/-2)	-20.00 (-34/0)	NS
Missed daily activities			
Baseline	40.00 (30/60) ^a	40.00 (30/60) ^a	NS
After 15 days' treatment	20.00 (10/30) ^a	10.00 (5/25) ^a	0.04
Variation	-20.00 (-40/0)	-20.00 (-40/-10)	0.03
Results are given in medians and 25–75 percentiles for the last 7 days.			
^a p value (Wilcoxon test) between score at V1 and V2 <0.001 (intragroup test).			
^b p value (Wilcoxon test) between free-choice and guidelines groups (intergroup test).			

Clinical trials are often accused of being remote from the real world as they present the results of trials conducted on highly selected patients in ideal circumstances. An important paper by Schwartz and Lellouch [11] has drawn distinctions between explanatory and pragmatic attitudes to clinical trials [13]. Between 1976 and 2002, 95 original articles on clinical trials conducted following a pragmatic design were found in the literature. Only 4 strictly followed the approach developed by Schwartz and Lellouch [11] and Vallée [12]. In a pragmatic clinical trial, it is usually not possible to blind the interventions and for this reason randomization is imperfect. However, in the present study, we randomized the physicians and not the patients, a strategy already used for the validation of the International Consensus of Rhinitis [10]. We therefore

propose a new methodology of pragmatic studies which allows randomization.

The ARIA guidelines classify patients with allergic rhinitis into four categories [5]. Although the severity of rhinitis was not exactly based on the ARIA criteria, we proposed a simpler methodology for a study in such a large number of patients. VAS have been extensively used to assess the severity of rhinitis [10, 15, 21–23] as well as the efficacy of therapeutic interventions [10, 14, 24, 25]. The use of VAS has also been recently proposed by the Joint Task Force on Practice Parameters for the symptom severity assessment of allergic rhinitis [26]. The VAS has recently been validated against the ARIA criteria in 3,052 patients. The patients were well matched in the four ARIA categories. In the present study, most of the patients had

Table 6. Symptoms after 15 days of treatment according to treatment strategy

	Free-choice group (n = 403)	Guidelines group (n = 407)	p value
Sneezing			
Absent or mild	336 (83.4%)	363 (89.2%)	0.016
Moderate or severe	67 (16.6%)	44 (10.8%)	
Stiffness			
Absent or mild	298 (73.9%)	326 (80.1%)	0.037
Moderate or severe	105 (26.1%)	81 (19.9%)	
Nasal discharge			
Absent or mild	326 (80.9%)	357 (87.7%)	0.008
Moderate or severe	77 (19.1%)	50 (12.3%)	
Nasal pruritus			
Absent or mild	358 (88.8%)	374 (91.9%)	0.14
Moderate or severe	45 (11.2%)	33 (8.1%)	
Eye symptoms	152 (36.0%)	145 (34.8%)	0.537

moderate/severe persistent rhinitis, but this was expected since the study was carried out in specialist offices. It is likely that many patients were also allergic to indoor allergens. However, the assessment of these was not necessary due to the new ARIA classification in 'intermittent' and 'persistent' rhinitis.

In the study, there was some deviation since 16 physicians enrolled 3 patients, 19 physicians enrolled 1 patient and 386 three patients. However, these were considered as minor deviations from the protocol. The number of expected enrolled patients was calculated to be 558 per group. However, only 75% of the patients could be enrolled. Since the study is significant and the number of patients quite important, it does not appear to induce a bias in the study.

This study used a very simple method based on VAS for the evaluation of the severity of nasal and ocular symptoms, and this method can easily be used by physicians in primary care. Using the results of this evaluation in conjunction with a simple therapeutic scheme based on the ARIA guidelines, we found that patients with pollen-induced allergic rhinitis exhibited a significant improvement in comparison to those receiving a nonstandardized treatment. There were improvements in patients assigned to the latter group, but these were significantly less than those in the group treated according to the guideline-based scheme. These differences, in respect of both symptom scores and disease-specific quality of life, were statistically significant for most parameters studied.

In the free-treatment choice group, patients with mild or intermittent rhinitis were often overtreated, whereas patients with moderate/severe persistent rhinitis were often undertreated. This study shows that many physicians, even specialists, do not treat patients according to guidelines which are more effective than free-treatment choice. In the guidelines group, physicians treating patients with moderate/severe intermittent rhinitis did not follow the protocol, but used recommended ARIA strategy. This study shows that intranasal corticosteroids improve the response of patients to treatment.

The improvement of health-related quality of life is an important goal in the management of patients with allergic rhinitis [27–30]. In the present study, as well as in the previous guideline validation study, we used the well-validated disease-specific RQLQ and confirmed that the improvement in RQLQ scores in the patients treated according to the guidelines strategy was significantly greater than that observed in patients treated according to the free-choice treatment strategy. The minimal important difference has been defined as a within-group increase of 0.5 in the RQLQ global score. It is 'the smallest difference which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient's management' [17]. In the present study the within-group differences were 1.52 and 1.70, respectively, and 0.18 between groups. The between-group differences were smaller in the present study than in the previous one, but this was expected since more physicians use optimal treatment than 6 years ago and the study was carried out in specialist offices.

In the present study, many patients still experienced severe nasal symptoms although the optimal treatment was administered. This finding was already observed in our previous study [10], suggesting that not all patients can be effectively controlled using medications at the recommended dose. In the present study, this does not appear to be associated with a low compliance. Moreover, eye symptoms were not improved significantly by treatment. It is therefore possible that using topical drugs may have improved patients. However, in the previous study on guideline validation, and even though patients received ocular nedocromil sodium [10], eye symptoms were not well controlled. There is a need for other treatments, such as allergen immunotherapy which was shown to improve nasal and ocular symptoms induced by pollen allergy.

In the present study, we used a new approach to assess pragmatic trials in order to compare two therapeutic strategies. In one of the most common diseases in the

world, we found that the use of a simple method for the evaluation of severity of allergic rhinitis and a simple therapeutic scheme based on ARIA offer patients an improvement in comparison to the use of a nonstandardized treatment regimen. It is not known whether the study can be extended to other countries, but a previous study using a similar design in general practices gave similar results in the three European Union countries where it was carried out.

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