

Original article

Implementation of guidelines for seasonal allergic rhinitis: a randomized controlled trial

Background: Allergic rhinitis is a common disease altering quality of life. Its treatment is well established and guidelines have been proposed. However, their efficacy has never been tested. The aim of the study was to validate the guidelines of the International Consensus on Rhinitis in the treatment of seasonal allergic rhinitis.

Methods: A multicenter, multinational, open label, parallel, randomized study compared two therapeutic strategies in seasonal allergic rhinitis during a 3-week treatment. General practitioners were randomized into two groups. In the first group of 224 patients, doctors followed guidelines from the International Consensus on Rhinitis. Depending on the severity of nasal and ocular symptoms defined using visual analogue scales, patients received ebastine (an oral anti-histamine), triamcinolone acetonide (a topical corticosteroid) and/or ophthalmic nedocromil sodium (a topical ocular cromone). In the second group of 241 patients, general practitioners had a free choice of treatment. The primary efficacy end points were quality of life measured using the standardized rhinoconjunctivitis quality of life questionnaire (RQLQ) and the symptom-medication scores assessed daily with an electronic diary system.

Results: Adjusted mean total symptom scores over 21 days were 4.93 in the guidelines strategy group compared with 7.48 in the free-choice treatment group ($P = 0.0001$). Mean total scores in the RQLQ decreased by 2.19 in the guidelines group compared with a decrease of 1.79 in the free-choice treatment group ($P = 0.0001$). At 21 days, the least square mean difference in improvement in overall scores for RQLQ in the guidelines group compared with the free-choice treatment group was 0.53, which was greater than the minimal important difference.

Conclusions: Patients with seasonal allergic rhinitis often present severe symptoms which are not well recognized or controlled by physicians using their own criteria of severity and treatment. Using a simple method for the evaluation of the severity and a simple therapeutic scheme based on International Guidelines, patients with seasonal allergic rhinitis presented a significant improvement by comparison with those receiving a non-standardized treatment.

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Seasonal allergic rhinitis (1), a common disease worldwide, is not usually a severe disease but it alters the social life of patients and affects school and work performance (2). Many patients suffering from seasonal allergic rhinitis present also with conjunctivitis.

The treatment of seasonal allergic rhinitis is now well established. Oral antihistamines (3) and intranasal corticosteroids are the two major pharmacological treatments. Although a recent meta-analysis showed that corticosteroids were more effective than antihistamines (4), it seems that, depending on the severity of the disease, these drugs may be used sequentially or in combination (5, 6). However, in a recent study carried out in general practices, it was found that many patients are using treatment

inappropriately leading to insufficient control of symptoms (7), highlighting that current guidelines need to be better applied. In another survey of randomly selected households only 26% believed their symptoms were well controlled (8). Thus, either the treatment of seasonal allergic rhinitis is not appropriate or its administration by physicians is not optimal, possibly because they cannot assess the severity of the disease accurately enough.

National and international guidelines for the treatment of seasonal allergic rhinitis have been published (5, 6) but their implementation at the patient's level has never been established. Moreover, the validation of these guidelines is still pending largely because the assessment of the severity of allergic rhinitis is difficult. For asthma, a

Table 1. Guidelines group – allocation of treatments according to baseline symptom severity

		Rhinitis symptoms	
		Mild rhinitis	Moderate/severe rhinitis
Conjunctivitis symptoms	No/mild conjunctivitis	Oral antihistamine	Oral antihistamine + intranasal corticosteroid
	Moderate/severe conjunctivitis	Oral antihistamine + Topical ophthalmic chromone	Oral antihistamine + intranasal corticosteroid + topical ophthalmic chromone

disease often linked to rhinitis (9), there are objective measures of severity such as pulmonary function tests and well-defined criteria for symptom severity (10), whereas such measures are not available for rhinitis, and particularly so at the general practitioner level. Visual analog scales (VAS) are generally used to assess the severity of diseases with a subjective symptom such as pain (11, 12) and they have been used to establish efficacy of treatment in patients with rhinitis (13, 14) and rhinosinusitis (15). Their use to assess the global severity of seasonal allergic rhinitis may therefore be relevant.

The aim of this randomized study was to assess the benefit of implementing a simplified strategy based on the guidelines of the International Consensus on Rhinitis (5) in the treatment of seasonal allergic rhinitis.

Materials and methods

Patients

Patients were included in the study after informed consent was obtained and approval of the protocol by the Ethics Committee. All patients fulfilled the following inclusion criteria: (1) Patients had a history of seasonal allergic rhinitis for at least the past 3 years. (2) The diagnosis of grass pollen allergy was made with respect to previous years using either skin prick tests or serum grass pollen-specific IgE. (3) Patients should not have received specific immunotherapy within 1 year, nor been treated with antihistamines during the last week or corticosteroids during the previous 2 weeks. None of the patients had received depot corticosteroids for the past 2 months.

Design

This investigator randomized, multicenter, multinational, open label parallel study, compared two therapeutic strategies in seasonal allergic rhinitis during a 3-week treatment. General practitioners were randomized into two groups and were to enroll a maximum of two patients only. Physicians in the first group (guidelines group, $n = 124$) enrolled 225 patients and followed a simple strategy based on the guidelines of the International Consensus on Rhinitis (5). Physicians from the second group (free-choice treatment group, $n = 134$) enrolled 244 patients whom they treated as in normal practice. Only depot corticosteroids were disallowed. Investigators in both groups did not know the alternative strategy and physicians within a practice used only one of the two strategies. All questionnaires were administered in the patient's mother tongue, i.e. English (UK), French (France and Belgium) or Flemish (Belgium).

Assessment of baseline severity using visual analog scale

Patients were categorized into different levels of severity at baseline using VAS (scale 0–100 mm with 0 = no symptoms and 100 = severe) for the severity of symptoms of nasal discharge, nasal stuffiness and sneezing for rhinitis, and of eye symptoms for conjunctivitis. Patients scoring 50 mm or more on the VAS in any one of the rhinitis symptoms were categorized as having moderate/severe rhinitis. Patients scoring less than 50 mm in the three rhinitis symptoms were categorized as having mild rhinitis. Similarly, for conjunctivitis symptoms, those patients scoring less than 50 mm were categorized as having no/mild conjunctivitis and those scoring 50 mm or more were categorized as having moderate/severe conjunctivitis.

In the first group (guidelines group) these categories of severity were used to implement the guidelines. Depending on the results of the VAS, patients received an oral antihistamine (ebastine 20 mg OD) (16, 17) and/or an intranasal corticosteroid (triamcinolone acetonide 220 µg OD) (18–20). Those with moderate/severe conjunctivitis received in addition a cromone (nedocromil sodium 2 percent eye drops b.i.d.) (21) (Table 1).

The investigators assigned to the free-choice treatment group were not instructed to use the results of the VAS. Furthermore, as one drug (ebastine) was not available commercially, patients in the guidelines group were provided with the drugs whereas those in the free-choice treatment group bought them from a pharmacy. This did not bias the study outcome as the costs of drugs were reimbursed to the patients and, following measures of compliance, only patients who took the treatments for 3 days or more were included in the intent to treat (ITT) population.

Outcome measures

The primary outcomes were the total of daytime and night-time symptom score measured by an electronic diary over 21 days and rhinoconjunctivitis specific quality of life. Secondary efficacy end points included individual rhinitis symptom scores assessed daily by the electronic diary and generic quality of life. Safety and tolerability of treatment regimens were evaluated by the reporting of adverse events.

Assessment of symptoms and drug intake using the electronic diary. At inclusion, each patient was provided with an electronic diary (Minidoc®, Stockholm, Sweden) and was asked to record daily (morning and evening) rhinitis and conjunctivitis using the following scale: 0 = symptom absent; 1 = mild, present but not annoying to patient; 2 = moderate, present and annoying to patient but does not interfere with sleep or daily activities; 3 = severe, interferes with/or unable to sleep or carry out daily activities. Drug intake was also recorded.

Adverse events. Patients recorded adverse events or unusual health-related events on the electronic diary and were asked about the occurrence of any such events at the scheduled visits.

Assessment of quality of life. Patients' quality of life was assessed using the electronic diary at day 1 (baseline), days 7 and 21 (end of treatment) through the disease-specific rhinoconjunctivitis quality of life questionnaire (RQLQ) (21). In this questionnaire patients rate the degree of impairment during the preceding week by responding to each of 28 items using a 7-point scale on which a score of 0 indicates no impairment and a score of 6 maximal impairment. The questionnaire provides an overall score and scores in seven domains: limitations of activities, sleep, non-hay fever symptoms, practical problems, nasal symptoms, eye symptoms and emotions. A clinically significant difference is achieved when there is a difference between groups of 0.5 or more in mean overall score (minimal important difference) (23). Patients also completed the generic SF-36 questionnaire (24).

Pollen counts. Each participating country was divided into geographical regions where it was possible to record the pollen count. Only investigators who were located in these areas were recruited and randomized. Pollen counts differed between locations but during the study period grass pollen counts were measurable in all regions.

Statistical analysis

A sample size estimate of 220 patients/group was based on published data and would allow the detection of a difference of 0.5 in the overall quality of life score from RQLQ assuming a standard deviation of 1.4 with at least 90% power.

Each RQLQ domain was analyzed using a repeated measures analysis of covariance with country, strategy, country $\times$ strategy as factors and the visit 1 score as a covariate with day 7/day 21 as the repeated measure. The interaction with country was dropped from the model as it was not statistically significant ($P > 0.05$). Least square means adjusted for country and covariate were presented together with 95% confidence intervals for the difference between strategies within each time.

For diary card symptoms individually and in total, the mean over the treatment period was calculated and the two strategies were compared using a two-way analysis of variance with strategy, country and strategy $\times$ country as factors. The interaction term was not significant ($P > 0.05$) and it was dropped from the model. Least square means adjusted for country were presented together with 95% confidence intervals for the difference between strategies.

All tests were two-tailed at a 5% significance level. All analyses were performed on the ITT population. The primary variables were also analyzed using a per-protocol population with similar results to the ITT population discussed here. The validity of the model was checked through examination of the residuals from the model.

Results

Baseline characteristics of patients

Of the 469 enrolled patients, five provided no on-treatment data and 431 were considered for ITT analysis of efficacy. The main reason for exclusion from the ITT population was a lack of usable on-treatment data. There were 207 patients in the guidelines group and 224

in the free-choice treatment group (Fig. 1). Patients in the two groups had similar demographic characteristics (Table 2).

Adverse effects and dropouts

There were no significant differences in the incidence of adverse events between the two treatment groups. The most frequently reported adverse events were headache, asthenia and somnolence. Five patients withdrew because of adverse events: three from the guidelines group and two from the free-choice treatment group. There was one serious adverse event in each treatment group, of which only one (acute abdominal syndrome in the guidelines group) was considered to be possibly related to treatment. Twenty-six patients withdrew prematurely from the study, six in the guidelines group for reasons which included adverse events and treatment ineffectiveness, and 26 in the free-choice treatment group for reasons which included treatment ineffectiveness, lack of symptoms and adverse events.

Compliance

Mean compliance assessed using the electronic diary as percent days on which medication was taken was 88.7% in the guidelines group and 79.7% in the free-choice treatment group. In the guidelines group 69.1% of patients had compliance over 90% compared with only 50.4% of patients in the free-choice treatment group.

Study medications

Medications received by patients according to baseline symptom severity category and treatment strategy are shown in Table 3. Of patients in the guidelines group, 84% received the correct medications according to the study protocol. Of patients in the free-choice treatment group, 93% received at least a systemic antihistamine which was usually a non-sedating second generation antihistamine, although in 9% of patients this included a first generation sedating antihistamine. The proportion who received a nasal corticosteroid either alone or in combination was only 32%, compared with 84% in the guidelines group. Only 45 patients (20%) of free-choice group received treatment which followed the guidelines strategy.

Quality of life

Overall and individual domain scores in the RQLQ were similar in the two treatment groups at baseline (Table 4). During the treatment period there were significant improvements in all domains in both treatment groups. After 7 days of treatment mean scores had decreased by 1.63 in the guidelines group and by 1.22 in the free-choice

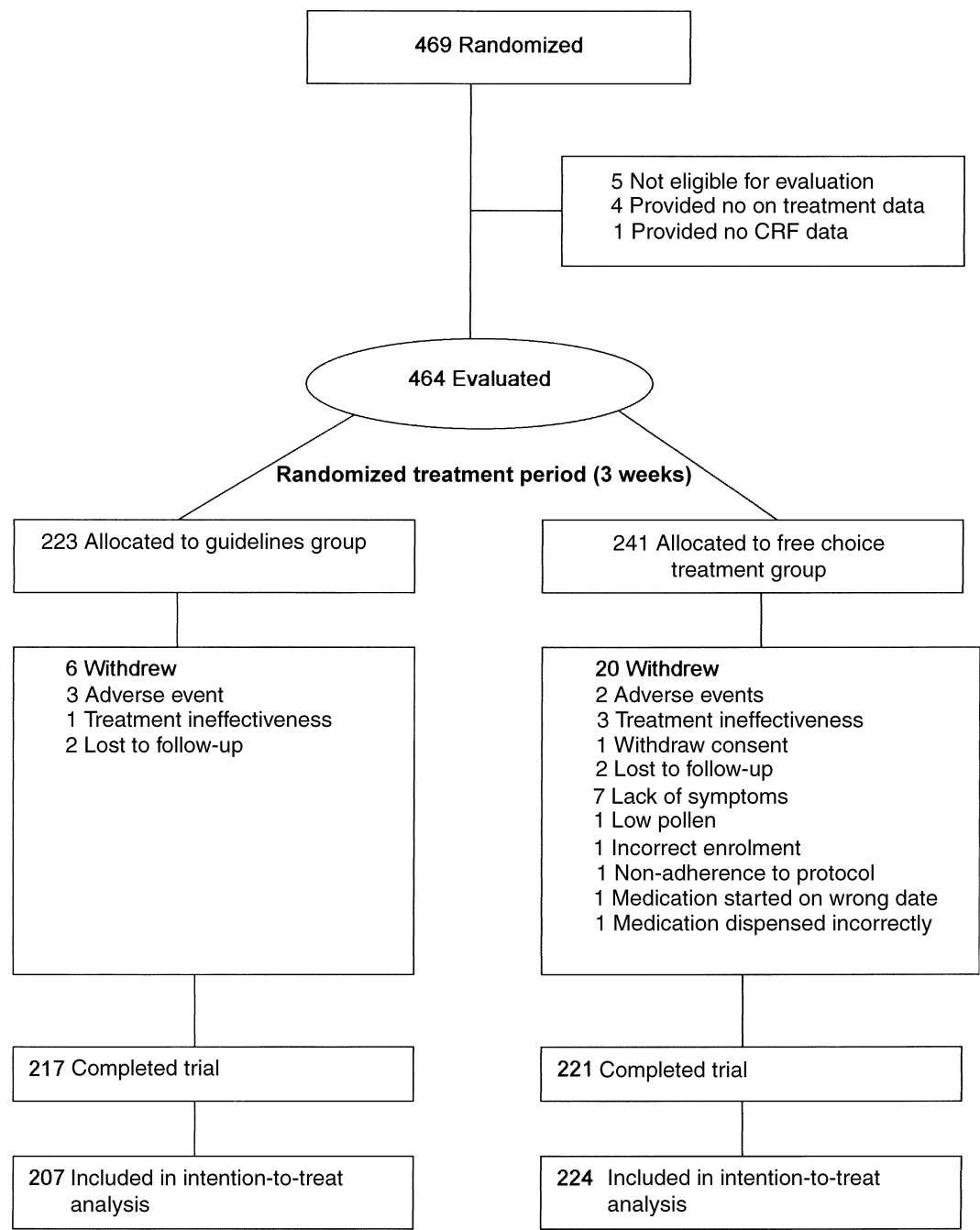


Figure 1. Trial profile.

treatment group and after 21 days had decreased by 2.19 and 1.79, respectively. The improvements in overall scores in the guidelines group at both time points were significantly greater than in the free-choice treatment group ($P = 0.0001$). The results were similar for each of the seven domains covered by the questionnaire. At 21 days the difference in improvement for overall scores in the guidelines group compared with the free-choice treatment group was 0.53.

Quality of life was also assessed using the generic SF-36 questionnaire. Although both treatment groups improved with time, there were no significant differences between the groups for any of the variables (data not shown).

Total and individual symptom scores

At randomization patients had similar severity of rhinitis and conjunctivitis assessed VAS (Table 2). For total and

Table 2. Baseline characteristics of the 431 patients (ITT population) according to treatment strategy

Characteristic	Guidelines group (<i>n</i> = 207)	Free-choice treatment group (<i>n</i> = 224)
Age (years)	33.1 ± 10.0	31.7 ± 9.0
Male sex (%)	52	48
Duration of seasonal allergic rhinitis (years)	13.4 ± 8.8	12.4 ± 7.5
Concomitant medical conditions (%)		
Perennial allergic rhinitis	23	26
Asthma	16	14
Rhinitis and conjunctivitis severity at baseline based on VAS score		
Nasal discharge		
Mild rhinitis	20.0 ± 12.3 (<i>n</i> = 35)	16.7 ± 12.0 (<i>n</i> = 29)
Moderate/severe rhinitis	59.3 ± 23.9 (<i>n</i> = 172)	59.2 ± 22.8 (<i>n</i> = 195)
Nasal stuffiness		
Mild rhinitis	20.5 ± 12.6 (<i>n</i> = 35)	19.0 ± 12.9 (<i>n</i> = 29)
Moderate/severe rhinitis	59.2 ± 23.5 (<i>n</i> = 172)	61.3 ± 21.8 (<i>n</i> = 195)
Sneezing		
Mild rhinitis	21.6 ± 15.8 (<i>n</i> = 35)	15.2 ± 12.5 (<i>n</i> = 29)
Moderate/severe rhinitis	62.3 ± 23.3 (<i>n</i> = 172)	63.2 ± 23.2 (<i>n</i> = 195)
Eye symptoms		
No/mild conjunctivitis	19.0 ± 15.3 (<i>n</i> = 63)	22.3 ± 13.0 (<i>n</i> = 68)
Moderate/severe conjunctivitis	69.1 ± 14.4 (<i>n</i> = 144)	70.1 ± 13.1 (<i>n</i> = 156)
Categorization of patients at baseline		
Mild rhinitis + no/mild conjunctivitis	12%	10%
Mild rhinitis + severe conjunctivitis	5%	3%
Severe rhinitis + no/mild conjunctivitis	18%	20%
Severe rhinitis + severe conjunctivitis	65%	67%

Plus-minus values are mean ± SD.

Table 3. Study medication of 431 patients according to symptom severity

Medications	Mild rhinitis				Moderate/severe rhinitis			
	No/mild conjunctivitis		Moderate/severe conjunctivitis		No/mild conjunctivitis		Moderate/severe conjunctivitis	
	A* <i>n</i> = 25	B† <i>n</i> = 23	A <i>n</i> = 10	B <i>n</i> = 6	A <i>n</i> = 38	B <i>n</i> = 45	A <i>n</i> = 134	B <i>n</i> = 150
OA	17 (68)	11 (48)	1 (10)	1 (17)	1 (3)	16 (36)		54 (36)
OA + NC	2 (8)	5 (22)		2 (33)	27 (71)	10 (22)	8 (6)	19 (13)
OA + NC + TE	5 (20)	1 (4)		1 (17)	10 (26)	3 (7)	121 (90)	24 (16)
OA + TE	1 (4)	3 (13)	9 (90)			1 (2)	5 (4)	15 (10)
OA + TN		2 (9)				7 (16)		8 (5)
OA + TE + TN				1 (17)		3 (6)		13 (9)
NC						3 (7)		4 (3)
OC								1 (1)
Other therapy		1 (4)		1 (17)		2 (4)		12 (8)

OA = Oral antihistamine, NC = intranasal corticosteroid, TE = topical antiallergic eye, TN = topical antiallergic nose (e.g. sodium cromoglycate), OC = oral corticosteroid.

* Strategy group A – guidelines group.

† Strategy group B – free-choice treatment group.

individual daily scores over each 7-day period of the study and over the 21-day study period there were highly significant differences ($P = 0.0001$) in favor of the guidelines group (Figs 2 and 3).

Discussion

Unlike conventional double-blind placebo-controlled studies this randomized study used a novel design in

Table 4. Mean scores on the rhinoconjunctivitis quality of life questionnaire for 431 patients

Score	Guidelines group (<i>n</i> = 207)	Free-choice treatment group (<i>n</i> = 224)	<i>P</i> -value	Difference between the two groups LSM (95% ci)
Overall				
Baseline	2.86 ± 1.08	3.01 ± 0.98		
Decrease at day 7	1.63	1.22	0.0001	−0.48 (−0.68 to −0.28)
Decrease at day 21	2.19	1.79	0.0001	−0.53 (−0.72 to −0.34)
Limitations of activities				
Baseline	3.48 ± 1.42	3.66 ± 1.39		
Decrease at day 7	2.04	1.57	0.0001	−0.64 (−0.93 to −0.35)
Decrease at day 21	2.75	2.41	0.0001	−0.54 (−0.78 to −0.30)
Sleep problems				
Baseline	2.08 ± 1.59	2.33 ± 1.68		
Decrease at day 7	1.17	0.96	0.0096	−0.33 (−0.58 to −0.08)
Decrease at day 21	1.62	1.17	0.0001	−0.61 (−0.87 to −0.35)
Non-hayfever symptoms				
Baseline	2.06 ± 1.22	2.15 ± 1.24		
Decrease at day 7	0.90	0.73	0.0191	−0.24 (−0.44 to −0.04)
Decrease at day 21	1.43	1.10	0.0004	−0.36 (−0.56 to −0.16)
Practical problems				
Baseline	3.86 ± 1.57	4.14 ± 1.49		
Decrease at day 7	2.28	1.72	0.0001	−0.74 (−1.04 to −0.44)
Decrease at day 21	3.14	2.52	0.0001	−0.78 (−1.05 to −0.51)
Nasal symptoms				
Baseline	3.41 ± 1.44	3.68 ± 1.27		
Decrease at day 7	2.00	1.50	0.0001	−0.65 (−0.90 to −0.41)
Decrease at day 21	2.65	2.18	0.0001	−0.63 (−0.88 to −0.38)
Eye symptoms				
Baseline	2.89 ± 1.73	2.96 ± 1.68		
Decrease at day 7	1.86	1.37	0.0003	−0.47 (−0.72 to −0.22)
Decrease at day 21	2.24	1.98	0.0004	−0.43 (−0.67 to −0.19)
Emotions				
Baseline	2.28 ± 1.20	2.16 ± 1.24		
Decrease at day 7	1.19	0.69	0.0001	−0.47 (−0.67 to −0.27)
Decrease at day 21	1.59	1.16	0.0002	−0.38 (−0.57 to −0.19)

Plus-minus values are mean ± SD. The scores can range from 1 to 6, with higher scores indicating greater impairment in rhinoconjunctivitis-specific quality of life. *P* values are for comparisons between the two treatment groups. Least Square means (LSM) are for differences between treatment groups and are adjusted for country and covariate (baseline score).

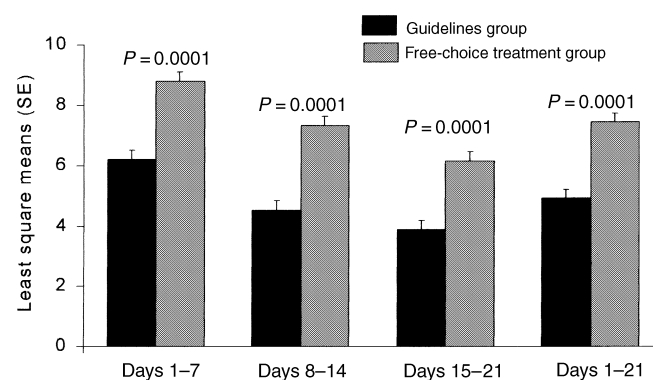


Figure 2. Mean total symptom scores (scale 0–30: sum of nasal discharge, stuffiness, sneezing, itching and eye symptoms) over each 7-day period and over 21 days. Values depicted are least square means adjusted for country. Error bars represent SEM. *P* values are for comparisons, guidelines group vs free-choice treatment group.

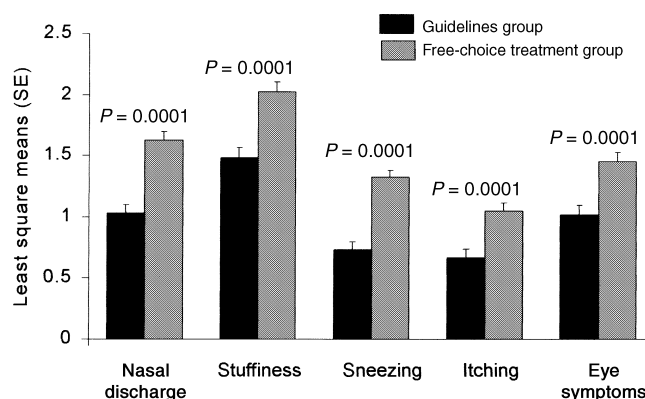


Figure 3. Mean 24 h individual symptom scores (scale 0–6) over 21 days. Values depicted are least square means adjusted for country. Error bars represent SEM. *P* values are for comparisons, guidelines group vs free-choice treatment group.

which the randomization applied not to the patients, but to the physicians treating them. A further novel feature is that instead of the selection of patients on the basis of explicit exclusion and inclusion criteria with a highly selected group of patients in an artificial setting, each physician recruited the first two patients to present with seasonal allergic rhinitis after the onset of the pollen season. Finally, very simple methodology was used for assessment of severity at baseline. The study was thus carried out in a natural setting, and was of much wider applicability to the everyday clinical world than conventional studies. The data were however reliable and robust because an electronic diary was used, eliminating the possibility of retrospective data. The study was therefore of the highest methodological quality and was ideally suited to the comparison of two different therapeutic options.

In this study, we found that patients with seasonal allergic rhinitis often present with moderate/severe symptoms which are not well recognized or controlled by physicians using their own criteria of severity and treatment. We used a very simple method based on VAS for the evaluation of the severity of nasal and ocular symptoms which general practitioners were easily able to apply. Using the results of this evaluation in conjunction with a simple therapeutic scheme based on International Guidelines (5), we found that patients with seasonal allergic rhinitis exhibited a significant improvement in comparison with those receiving a non-standardized 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 guidelines-based scheme, who received the recommended optimal treatment according to their symptom severity. These differences, in respect of both symptom scores and disease-specific quality of life, were statistically significant after only 7 days of treatment and were maintained over 21 days.

The study used three drugs which are representative of their class and is the first to evaluate in a precisely defined and controlled manner how such drugs may best be used sequentially or in combination. Ebastine (16, 17, 25), which is now available in Europe, has been shown to be at least as effective as cetirizine (25) and superior in efficacy to loratadine (26). Triamcinolone acetonide nasal spray (17–19, 27) is used worldwide and has been found to have an efficacy similar to other topical corticosteroids in the treatment of seasonal allergic rhinitis (28). Nedocromil sodium is widely used in Europe for the topical treatment of allergic conjunctivitis and has been shown to be at least as effective as sodium cromoglycate (29) and levocabastine (30) ophthalmic solutions. However, as for other ocular drugs, there is a lack of high potency drugs for the treatment of allergic conjunctivitis (31). This is possibly the reason why eye symptoms were only moderately improved using the RQLQ, although the difference between both groups was significant. From the

compliance data we found that some patients will stop taking the eye medication when they feel they are better or use them as required.

Clinical guidelines are systematically developed statements designed to help practitioners and patients in making decisions about appropriate health care for specific circumstances (32). Guidelines have existed in various countries for decades and thousands have been published for many diseases (33) including allergic rhinitis (5, 6, 34–36). Recent years have highlighted interest in guidelines as a tool for implementing health care based on proof of effectiveness. Clinicians are being inundated by a tidal wave of guidelines; so it is vital that they should be informative, simple and easy to use as the goal of guidelines is their wide dissemination within the medical community in order to improve patient care. Unfortunately, guidelines for rhinitis have not been tested and nonspecialists may find them difficult to implement. The present study validates rhinitis guidelines and shows that a simple assessment can help doctors.

It is now recognized that the improvement of health-related quality of life is an important goal in the management of patients with seasonal allergic rhinitis. In our study we used the well validated disease-specific RQLQ (22) and found 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 originators of this questionnaire have defined the minimal important difference as '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' (37). They further showed that for the RQLQ, as with other disease-specific questionnaires, the size of this difference for the overall mean score was approximately 0.5 (23). In our study the differences between two treatment strategies for this parameter after 7 and 21 days of treatment were 0.48 and 0.53, respectively. The study thus demonstrates that not only was the difference between the two strategies statistically significant but that this difference was also clinically relevant.

We also used a generic measure of quality of life, the SF-36. Generic instruments allow a comparison of the burden of illness across different disorders but may not be responsive enough to detect changes in general health status in spite of important changes in disease-related problems (38). In our study the SF-36 was able to detect improvements over time but was not sufficiently sensitive to detect any differences between the two treatment strategies. Our results are consistent with a previous study which compared the addition of intranasal corticosteroids with placebo in seasonal allergic rhinitis: the SF-36 did not distinguish between the two treatment regimens whereas the RQLQ demonstrated significant

improvements in the group receiving corticosteroids (39).

Our study suggests therefore that doctors are not able to assess adequately the severity of seasonal allergic rhinitis and/or to administer the appropriate treatment without guidelines. The benefit of applying a simple strategy based on the 1994 International Consensus Report on the Diagnosis and Treatment of Rhinitis has been clearly demonstrated and the treatment of seasonal allergic rhinitis according to guidelines has therefore been validated.

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