

Allergic Rhinitis Control Test questionnaire-driven stepwise strategy to improve allergic rhinitis control: a prospective study

Y. Wang^{1,2,3}, H. Chen¹, R. Zhu¹, G. Liu¹, N. Huang¹, W. Li¹, L. Yang¹, S. Zhang¹, S. Qi¹, J.-P. Daurès³, A. M. Chiriac^{2,4} & P. Demoly^{2,4}

¹Department of Allergy, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; ²Allergy Division, Pulmonology Department, Hôpital Arnaud de Villeneuve, University Hospital of Montpellier; ³Laboratory of Biostatistics, Epidemiology and Public Health (EA2415), University of Montpellier, Montpellier Cedex 5; ⁴UPMC Paris 06, UMR-S 1136 INSERM, IPLESP, Equipe EPAR, Sorbonne Universités, Paris, France

To cite this article: Wang Y, Chen H, Zhu R, Liu G, Huang N, Li W, Yang L, Zhang S, Qi S, Daurès J-P, Chiriac AM, Demoly P. Allergic Rhinitis Control Test questionnaire-driven stepwise strategy to improve allergic rhinitis control: a prospective study. *Allergy* 2016; DOI: 10.1111/all.12963.

Keywords

allergic rhinitis; allergic rhinitis and its impact on asthma; Allergic Rhinitis Control Test; classification; stepwise pharmacotherapy.

Correspondence

Prof. Pascal Demoly, Allergy Division, Pulmonology Department, Hôpital Arnaud de Villeneuve, University Hospital of Montpellier, 34295 Montpellier Cedex 5, France.
Tel.: +33 467336127
Fax: +33 467634581
E-mail: pascal.demoly@inserm.fr

The first two authors should be regarded as joint First Authors.

Accepted for publication 21 June 2016

DOI:10.1111/all.12963

Edited by: De Yun Wang

Abstract

Background: Allergic Rhinitis Control Test (ARCT) has been validated for assessing allergic rhinitis (AR) control and identifying severe AR. The aim of the study was to assess the ARCT questionnaire as a tool for stepwise pharmacotherapy.

Methods: A standard pharmacotherapy regimen from Step 1 (oral second-generation H1 antihistamine as needed) to Step 5 (oral corticosteroid) was carried out prospectively in a Chinese AR population. The AR patients were initiated with Allergic Rhinitis and its Impact on Asthma (ARIA) appropriate step treatment and assessed with ARCT every 15 days. If ARCT score was equal or above 20 (controlled AR) and maintained for 15 days, the patient would finish the study; if ARCT score was strictly <20 (uncontrolled AR), the patient would receive higher step treatment according to a predefined open design up to Step 5. The different AR control subgroups were compared.

Results: A total of 255 patients were enrolled in the study; 5 patients dropped out and 2 (0.8%) were controlled at day 0, 85 (34.0%) at day 15, 177 (70.8%) at day 30, 222 (88.8%) at day 45, 241 (96.4%) at day 60 and 242 (96.8%) at day 75. Only 8 (3.2%) patients remained uncontrolled at the endpoint of the study. Patients with ARIA moderate/severe or persistent symptoms, moderate/severe impaired quality of life, asthma history, rhinorrhea and cough symptoms always needed up to Step 4 (nasal corticosteroid plus antihistamine) and prolonged treatments to achieve disease control.

Conclusions: The majority of AR can be controlled with standard stepwise treatment. ARCT offers an objective criterion for the stepwise pharmacotherapy of AR.

Allergic rhinitis (AR) affects up to 40% of the population worldwide (1, 2). In China, a cross-sectional population-based study in 11 major cities showed that the prevalence of AR ranges from 8.7% to 24.1% (3). Although not life-

threatening, the symptoms of AR are frequently bothersome, adversely affect school performances and/or work and quality of life and impose a significant burden on both the individual and society (4–6). AR is also a strong risk factor for other chronic respiratory diseases such as asthma and chronic rhinosinusitis (7). Allergic rhinitis and its impact on asthma (ARIA) guidelines (8) have divided AR into different subgroups according to the symptom severity and duration and recommend different pharmacotherapy to step up according

Abbreviations

AR, allergic rhinitis; ARC, allergic rhinitis control; ARCT, Allergic Rhinitis Control Test; ARIA, allergic rhinitis and its impact on asthma; H1A, H1 antihistamine; NCS, nasal corticosteroid.

to the disease severity. They have been widely accepted and implemented in many countries. ARIA guidelines also suggested step-down treatment after the AR symptoms are controlled. However, the definition of AR control was a missing part in the original ARIA, the concept being only recently understood (9). Till now, several questionnaires of AR control have been developed and validated in clinical practice (10–12). They include the Control of Allergic Rhinitis and Asthma Test (CARAT), the Rhinitis Control Assessment Test (RCAT) and the Allergic Rhinitis Control Test (ARCT); a simple visual analogue scale has also been validated to assess AR control (10–12). A previous study of our group has shown that ARCT was an easy and reliable self-assessment questionnaire to evaluate the AR control status (13). The present study was designed to further assess ARCT as a questionnaire-driven stepwise pharmacological treatment to achieve AR control.

Methods

Patients

A total of 255 patients with age ranging from 5 to 75 years were consecutively included. All patients fulfilled the following inclusion criteria: (i) over 5 years of age, (ii) with the diagnosis of AR according to ARIA and presenting clinical symptoms, (iii) over 1-year history of AR, (iv) with positive skin prick tests result and serum-specific IgE (sIgE $\geq$ 0.35 KU/L, Phadia ImmunoCAP, Uppsala, Sweden) to at least one relevant common aeroallergen, and (v) all patients or their guardians had signed a written informed consent for anonymous data collection. The exclusion criteria were as follows: patients (i) receiving allergen immunotherapy, (ii) with upper respiratory infection or chronic rhinosinusitis, (iii) with a history of drug allergy, (iv) with pregnancy or breastfeeding, and (v) who have had neurological or psychiatric system diseases. Patients were classified as intermittent, persistent, mild, or moderate-to-severe AR according to the ARIA classification (8). The study had been approved by the Independent Ethical Committee (IEC) of Tongji Hospital, and all the participants or his/her statutory guardians had signed the informed consent to participate in the study.

Study design

The data were obtained from a prospective cohort study carried out in the Allergy Department of Tongji Hospital, Wuhan, China, with the aim to further assess ARCT as a questionnaire-driven stepwise pharmacological treatment for obtaining AR control and to describe the characteristics of the AR patients in different subgroups. Physicians completed a general questionnaire on the consultation day including contact information, social demographic data, allergen screening, nasal cavity signs, rhinitis symptoms, history, impact on quality of life (as assessed by a 0–3 scale, 0 for none, 1 for mild, 2 for moderate, and 3 for severe), concomitant diagnosed comorbidities (such as asthma), and previous AR treatments. Nasal and non-nasal symptoms of AR and

the discomfort caused by the AR were recorded by patients on the consultation day and scores were obtained by the ARCT, as previously described (12, 13). Once the treatment was initiated, the patients were assessed with ARCT every 15 days until study completed.

Stepwise treatment

The study was designed as an open-labelled stepwise approach for AR pharmacologic treatment derived from ARIA. Patients were evaluated and initiated with appropriate ARIA step treatment and assessed with ARCT every 15 days. Patients with a score of ARCT < 20 were considered as having uncontrolled AR (12). Patients with uncontrolled AR received step-up treatment and were then evaluated 15 days later. Steps were adapted according to ARIA as follows: Step 1: local or oral nonsedative H1 anti-histamine (H1A) as needed for 15 days; Step 2: oral H1A one tablet every day, for 15 days; Step 3: oral H1A (one tablet) plus local H1A (1 puff twice) every day, for 15 days; Step 4: oral H1A (one tablet) plus nasal corticosteroid (NCS, one puff per nostril) every day, for 15 days, repeated another 15 days if control was not achieved (30 days in total); and Step 5: oral CS (0.5 mg/kg once daily), for 15 days. The end-point of the patient was ARCT ≥ 20 and maintained for 15 days or received Step 5 treatment for 15 days.

Outcome measures

Allergic Rhinitis Control Test (ARCT)

ARCT is a self-completion questionnaire assessing the control of AR (12). It is made up of five questions scored from 1 to 5, and these individual scores are then added up to obtain a score ranging from 5 (worse score) to 25 (best score). ARCT ≥ 20 was regarded as controlled AR (12). The Chinese version has been validated (13).

Grading of AR control (ARC) level

We defined several steps of AR control. ARC1: when AR was controlled without medication or with H1A as needed (Step 1); ARC2: when AR was controlled by one of the following medications taken on an everyday basis: local or oral H1A or NCS (Steps 2 and 3); ARC3: when AR was controlled by daily NCS plus H1A (combined therapy, Step 4); ARC4: when AR was controlled by oral CS (Step 5); and ARC5: when AR was not controlled by any treatment at the end of the study.

Statistical analysis

Taking into account the prevalence of AR in Wuhan of about 20%, and the fact that 10% of them would be uncontrolled (13), we calculated a sampling error of 8% with a confidence level of 90% and a power of 90%. Adding 10% for dropouts, a sample of at least 236 patients was required.

Qualitative variables such as demographic data and symptoms were expressed in percentages and frequencies. Quantitative data were expressed as means and standard deviations.

Medians and 25th to 75th percentiles defined quantitative not normally distributed data. Comparisons of the qualitative data such as patient characteristics were made between groups using Chi-square or Fisher's exact test for small samples. Comparisons of quantitative variables were made using the Wilcoxon–Mann–Whitney or Kruskal–Wallis tests. Following descriptive analysis, certain explanatory variables were regrouped (low number in certain groups, no statistical difference between groups). Thus, the ARC levels were redefined in three groups as follows: Group 1 (AR controlled with no treatment or single-drug treatment daily or as needed, i.e. ARC1 and ARC2), Group 2 (AR controlled by means of combined therapy, ARC3) and Group 3 (AR control achieved by oral CS or uncontrolled AR, i.e. ARC4 and ARC5). A risk factor analysis was undertaken using ordered logistic regression. However, the proportional odds assumption did not hold, and therefore, a multinomial logistic model (generalized logit) was chosen. Variables with $P < 0.20$ in univariate analysis were introduced in the multivariate model.

Survival analysis was used to model factors that influenced achievement of control. The control state was defined as ARCT score ≥ 20 . Patients who were uncontrolled by any treatment at the end of the study (day 75, D75) were right-censored. Nonparametric estimation of the survival function was performed using the Kaplan–Meier estimator. The equality of survival function over strata was estimated by the log-rank test. Variables that showed differences between strata in univariate analysis ($P < 0.20$) and held the proportional hazard assumption were introduced into the multivariate Cox regression model. The proportional hazard hypothesis was verified using $\log[-\log(\text{survival})]$ and Schoenfeld residuals. Numerical variables were introduced in classes. Data were analysed using SPSS version 11.5 (SPSS, Inc., Chicago, IL, USA) software and SAS (SAS® Studio, SAS® University Edition; SAS Institute Inc., Cary, NC, USA) with a final level of statistical significance of $P < 0.05$.

Results

Patient characteristics

A total of 255 patients were recruited from the Allergy Department of Tongji Hospital, Wuhan, China, from

September 2013 to August 2014. Five patients dropped out. Therefore, 250 patients were analysed. Of the patients, 127 (50.8%) were men. The mean age was 25.2 ± 16.0 years (age ranging from 5 to 75 years), and the mean duration of AR was 6.6 ± 5.7 years. According to the ARIA classification, 14 (5.6%) had mild intermittent AR, 59 (23.6%) moderate/severe intermittent AR, 26 (10.4%) mild persistent AR and 151 (60.4%) moderate/severe persistent AR; 56 (22.4%) had asthma. None of them was currently taking any asthma medication. Sixteen common aeroallergen sources were skin tested for all the patients and they included house dust mites (*Dermatophagoides pteronyssinus*, *Dermatophagoides farina*), dog and cat danders, cockroach, mulberry silk, pollen (*Polulus*, *Cypress*, *Platanus*, *Artemisia*, *Ambrosia* and *Humulus*) and moulds (*Alternaria*, *Cladosporium*, *Aspergillus*, *Paecilomyces*). Among them, patients had positive skin prick tests to eight aeroallergens including *D. farina* (90.8%), *D. pteronyssinus* (90.0%), cockroach (15.6%), *Platanus* (8.0%), *Artemisia* (8.0%), *Alternaria* (3.2%), cat (1.6%) and dog (1.2%).

The control status of AR according to ARCT

On day 0, there were 248 (99.2%) patients with uncontrolled AR (i.e. ARCT < 20), and on day 75, 8 (3.2%) patients were uncontrolled (see Table 1 and Fig. 1). AR control rate increased with follow-up and step-up treatment. Regarding recent previous AR therapies, on day 0, 127 (50.8%) patients were not receiving any treatments (and were not controlled); 100 (40%) patients were prescribed H1A during the last 2 weeks (and only one was controlled); 4 (1.6%) patients were prescribed NCS (no one was controlled); and 19 (7.6%) patients were prescribed H1A plus NCS (only one was controlled). Absence and insufficiency of treatment and poor compliance were the top reasons causing uncontrolled AR in our study.

Upon follow-up and step-up treatment, on day 15, 138 (55.2%) patients were prescribed H1A [and 31 (22.5%) were controlled]; 2 (0.8%) patients were prescribed NCS (none of them was controlled); and 110 (44%) patients were prescribed H1A plus NCS [54 (49.1%) were controlled]. On day 30, 33 (13.2%) patients were prescribed H1A [and 30 (90.9%) were controlled]; 215 (86%) patients were prescribed

Table 1 Distribution of patients and control according to the treatment (N)

Treatment	D0		D15		D30		D45		D60		D75	
	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N
No treatment	0	127	0	0	0	0	0	0	0	0	0	0
H1A	1	99	31	107	30	3	1	0	0	0	0	0
NCS	0	4	0	2	0	0	0	0	0	0	0	0
H1A + NCS	1	18	54	56	145	70	136	27	69	5	22	1
OCS	0	0	0	0	0	0	4	0	6	2	4	0
Finished/LOCF	0	0	0	0	2	0	81	1	166	2	216	7
Total	2	248	85	165	177	73	222	28	241	9	242	8

H1A, H1 antihistamine; OCS, oral corticosteroids; LOCF, last observation carried forward; N, not controlled; NCS, nasal corticosteroid; Y, controlled.

Table 2 Comparison of characteristics of different AR subgroups

	Number (%)	ARC1 2 (0.8)	ARC2 29 (11.6)	ARC3 205 (82)	ARC4 6 (2.4)	ARC5 8 (3.2)	<i>P</i>
Male gender	127 (50.8)	1 (0.8)	11 (8.7)	109 (85.8)	3 (2.4)	3 (2.4)	0.516
Age (year)	27.9 ± 15.4	–	36.5 ± 30.4	21.6 ± 15.0	11.5 ± 0.7	32.7 ± 14.9	0.503
Duration (year)	6.6 ± 5.8	–	12.5 ± 6.4	7.0 ± 6.3	8.0 ± 2.8	8.3 ± 6.6	0.094
Occupation							0.569
Farmer	8 (3.2)	–	1 (12.5)	7 (87.5)	–	–	
Staff	55 (22.0)	1 (1.8)	6 (10.9)	45 (81.8)	1 (1.8)	2 (3.6)	
Worker	10 (4.0)	–	–	10 (100)	–	–	
Student	35 (14.0)	1 (2.9)	6 (17.1)	24 (68.6)	2 (5.7)	2 (5.7)	
Unemployed	103 (41.2)	–	8 (7.8)	89 (86.4)	3 (2.9)	3 (2.9)	
Other careers	39 (15.6)	–	8 (20.5)	30 (76.9)	0	1 (2.6)	
Residential area							0.058
Urban	223 (89.2)	1 (0.4)	27 (12.1)	184 (82.5)	6 (2.7)	5 (2.2)	
Rural	27 (10.8)	1 (3.7)	2 (7.4)	21 (77.8)	–	3 (11.1)	
Smoking							0.251
≥1 year	30 (12.0)	1 (3.3)	3 (10.0)	23 (76.7)	1 (3.3)	2 (6.7)	
Passive smoking	44 (17.6)	1 (2.3)	4 (9.1)	36 (81.8)	1 (2.3)	2 (4.5)	
No smoking	176 (70.4)	–	22 (12.5)	146 (83.0)	4 (2.3)	4 (2.3)	
Contact with animal allergens (≥1 week)	22 (8.8)	–	4 (18.2)	16 (72.7)	–	2 (9.1)	0.304
Living condition							
Wet	15 (6.0)	–	1 (6.7)	12 (80.0)	–	2 (13.3)	0.271
Mould	16 (6.4)	–	2 (12.5)	12 (75.0)	–	2 (12.5)	0.260
Bedding used ≥10 years	14 (5.6)	1 (7.1)	2 (14.3)	10 (71.4)	–	1 (7.1)	0.123
Cockroach	50 (20.0)	1 (2.0)	4 (8.0)	40 (80.0)	2 (4.0)	3 (6.0)	0.243
Rhinitis graded according to ARIA							0.000
Mild intermittent	14 (5.6)	1 (7.1)	10 (71.4)	3 (21.4)	–	–	
Moderate/severe intermittent	59 (23.6)	–	10 (16.9)	45 (76.3)	2 (3.4)	2 (3.4)	
Mild persistent	26 (10.4)	1 (3.8)	5 (19.2)	20 (76.9)	–	–	
Moderate/severe persistent	151 (60.4)	–	4 (2.6)	137 (90.7)	4 (2.6)	6 (4.0)	
Impact of AR on quality of life							0.000
Mild	37 (14.8)	2 (5.4)	14 (37.8)	20 (54.1)	1 (2.7)	–	
Moderate	133 (53.2)	–	13 (9.8)	110 (82.7)	4 (3.0)	6 (4.5)	
Severe	80 (32.0)	–	2 (2.5)	75 (93.8)	1 (1.3)	2 (2.5)	
History of asthma	56 (22.4)	1 (1.8)	2 (3.6)	45 (80.4)	2 (3.6)	6 (10.7)	0.001
Duration of asthma (year)	5.2 ± 5.1	–	6.5 ± 5.0	5.0 ± 5.1	3.0 ± 1.4	7.1 ± 7.0	0.583
History of sinus surgery	9 (3.6)	–	1 (11.1)	7 (77.8)	–	1 (11.1)	0.501
History of deviated septum surgery	7 (2.8)	–	1 (14.3)	5 (71.4)	–	1 (14.3)	0.332
Nasal examinations							
Abnormal nasal mucosa	245 (98.0)	2 (0.8)	28 (11.4)	201 (82.0)	6 (2.4)	8 (3.3)	0.633
Abnormal structure	43 (17.2)	–	4 (9.3)	37 (86.0)	1 (2.3)	1 (2.3)	0.979
Increased nasal secretions	239 (95.6)	1 (0.4)	25 (10.5)	199 (83.3)	6 (2.5)	8 (3.3)	0.018

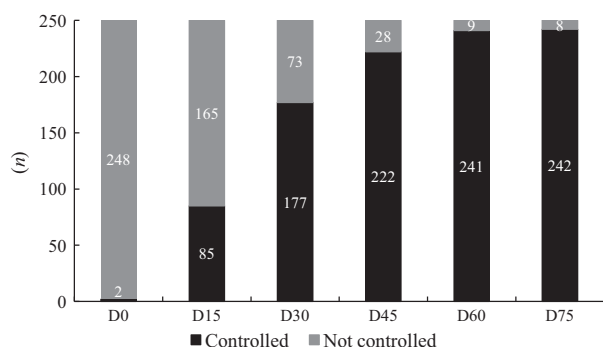
Table 2 (continued)

	Number (%)	ARC1 2 (0.8)	ARC2 29 (11.6)	ARC3 205 (82)	ARC4 6 (2.4)	ARC5 8 (3.2)	<i>P</i>
Symptoms of AR							
Rhinorrhea	249 (99.6)	1 (0.4)	29 (11.6)	205 (82.3)	6 (2.4)	8 (3.2)	0.008
Sneezing	248 (99.2)	2 (0.8)	29 (11.7)	203 (81.9)	6 (2.4)	8 (3.2)	1.000
Nasal congestion	248 (99.2)	2 (0.8)	28 (11.3)	204 (82.3)	6 (2.4)	8 (3.2)	0.328
Nasal itching	242 (96.8)	2 (0.8)	29 (12.0)	197 (81.4)	6 (2.5)	8 (3.3)	0.766
Itchy eyes	158 (63.2)	1 (0.6)	18 (11.4)	132 (83.5)	3 (1.9)	4 (2.5)	0.765
Watery eyes	133 (53.2)	1 (0.8)	17 (12.8)	107 (80.5)	3 (2.3)	5 (3.8)	0.942
Cough	94 (37.6)	1 (1.1)	4 (4.3)	82 (87.2)	2 (2.1)	5 (5.3)	0.017
Dysosmia	28 (11.2)	—	2 (7.1)	23 (82.1)	2 (7.1)	1 (3.6)	0.384
Number of positive SPT (>2)	56 (22.4)	—	2 (3.6)	50 (89.3)	1 (1.8)	3 (5.4)	0.138
Df	225 (90.0)	2 (0.9)	24 (10.7)	190 (84.4)	6 (2.7)	5 (2.2)	0.109
Dp	227 (90.8)	2 (0.9)	25 (11.0)	187 (82.4)	6 (2.6)	5 (2.2)	0.118
Cockroach	39 (15.6)	—	1 (2.6)	35 (89.7)	—	3 (7.7)	0.198
<i>Platanus acerifolia</i>	20 (8.0)	—	3 (15.0)	16 (80.0)	0	1 (5.0)	0.766
<i>Artemisia sieversiana</i>	20 (8.0)	3 (15.0)	15 (75.0)	—	2 (10.0)	—	0.340
<i>Alternaria alternate</i>	8 (3.2)	—	—	8 (100%)	—	—	0.766
Cat	4 (1.6)	—	—	3 (75.0)	1 (25.0)	—	0.221
Dog	3 (1.2)	—	—	2 (66.7)	1 (33.3)	—	0.196

Qualitative data: Chi-square test; quantitative variables: Kruskal–Wallis *H* test.

Variables in bold were introduced in the multivariate analysis ($P < 0.20$).

ARC, allergic rhinitis control; Dp, *Dermatophagoides pteronyssinus*; Df, *Dermatophagoides farinae*.

**Figure 1** Allergic rhinitis control of patients.

H1A plus NCS [145 (67.4%) were controlled]; and 2 (0.8%) patients finished the follow-up (because they had been controlled for two consecutive 15-day periods). On day 45, 1 (0.4%) patient was prescribed H1A (and controlled); 163 (65.2%) patients were prescribed H1A plus NCS [136 (83.4%) were controlled]; 4 patients (1.6%) were prescribed oral CS (and controlled after the treatment); 81 (32.4%) patients finished the follow-up; and one patient could not be controlled by any treatment and finished the follow-up passively. On day 60, 74 (29.6%) patients were prescribed H1A plus NCS [and 69 (93.2%) were controlled]; 8 (3.2%) patients were prescribed oral CS [6 (75%) were controlled]; 166 (66.4%) patients finished the follow-up; and 2 (0.8%) patients were not controlled by any treatment and finished

the follow-up passively. On day 75, 23 (9.2%) patients were prescribed H1A plus NCS [and 22 (95.7%) were controlled]; 4 (1.6%) patients were prescribed oral CS (and were controlled); 216 (86.4%) patients finished the follow-up; and 7 (2.8%) patients were not controlled by any treatment and finished the follow-up passively (right-censored patients).

Demographic and characteristics of patients in different AR control subgroups

The demographic and clinical characteristics of AR patients according to the different classification of AR control are shown in Table 2. According to the ARIA classification, most of the patients with moderate/severe intermittent, moderate/severe persistent and mild persistent AR (76.3%, 90.7% and 76.9%, respectively) were in the subgroup ARC3; 78.6% of the patients with mild intermittent AR were in subgroups ARC1 and ARC2, which indicated that patients with severe AR needed significantly higher step treatment ($P < 0.001$). Similar findings were observed in other factors such as the impact of AR on quality of life ($P < 0.001$), the duration of AR, history of concomitant asthma, increased nasal secretions and cough ($P < 0.01$).

Risk factor analysis

Ten variables ($P < 0.20$, Table 2) were kept in the multivariate model. After adjustment on each of the variables, the only factor that remained significant was asthma. Thus,

compared with nonasthmatics, asthmatics were less likely to be in a group controlled by 'softer' therapy (Group 3 vs Group 1: OR = 0.08, 95% CI 0.01–0.69; Group 3 vs Group 2: OR = 0.20, 95% CI 0.05–0.74). None of the other variables were significant ($P > 0.05$).

Predictors of achieving control

Twenty-five per cent of the patients achieved control by D30 and three quarters by 2 months (D60) (Fig. 2). After adjustment on all the potential predictors of achieving control, intermittent allergic rhinitis and low impact on QoL turned out to significantly increase the probability to achieve control within D75 from baseline (Table 3). Two other possible predictors were identified, although the proportional hazard assumption could not be confirmed for these covariables. Thus, the absence of two nasal symptoms (rhinorrhea and sneezing) was predictive (HR = 99.42, 95% CI 5.75–1717.34, $P = 0.001$ and HR = 4.23, 95% CI 1.02–17.43, $P = 0.045$, respectively).

Discussion

Allergic rhinitis affects at least 600 million people worldwide, and some studies suggest that its incidence is increasing (14). AR not only substantially affects patients' health-related quality of life but also causes reduced productivity at work and alters school performances (15). ARIA guidelines classify AR into four subgroups according to the symptom severity and duration. However, this classification cannot meet the whole needs of AR management. Generally, very few mild AR patients will visit a doctor, which is not beneficial to the prevention of AR progression and might lead to the worsening of disease process (16). Moreover, this classification does not take the patients' previous medication into consideration and most patients already receive medications before they see a doctor or go to hospital, which makes the standard treatment recommended by ARIA not applicable.

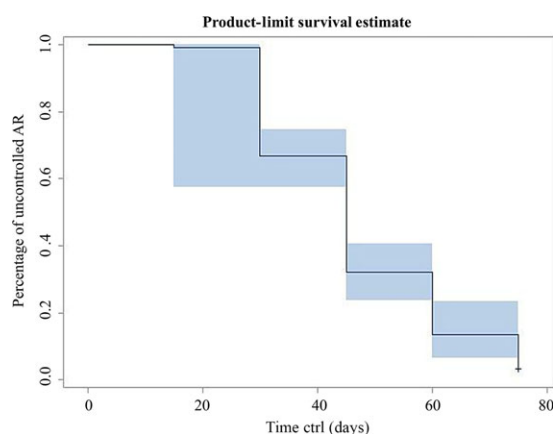


Figure 2 Graph of the survival analysis for the event 'controlled AR' (probability to be uncontrolled at different time points).

Table 3 Predictors of achieving control at D75 from baseline

Variable	P-value	Hazard ratio (95% CI)
ARIA AR classification (intermittent vs persistent)	<0.001	1.57 (1.17–2.11)
Impact on QoL (low vs moderate/severe)	<0.001	1.80 (1.24–2.61)
Nasal secretion (absent vs present)	0.14	1.59 (0.85–2.99)
Sensitization to Dp (absent vs present)	0.76	0.83 (0.33–2.26)
Sensitization to Df (absent vs present)	0.67	0.80 (0.29–2.21)

AR, allergic rhinitis; ARIA, allergic rhinitis and its impact on asthma; QoL, quality of life; Dp, *Dermatophagoides pteronyssinus*; Df, *Dermatophagoides farinae*.

According to the present study, we showed for the first time that an AR control questionnaire (namely ARCT) offers an objective criterion for the stepwise pharmacotherapy of AR. A few limitations may hamper the results. First, although opened, this study was prospective with clear predefined step-ups in case of no AR control and an imposed labelled design. We based the steps on clinical experience and published medication relative clinical impacts (17). For practicality, we did not define a step with NCS alone in our study; indeed, once a patient could not be controlled with H1A, NCS would be added but not be replaced, which could be inconsistent with ARIA. Moreover, we also found it was difficult to enrol mild intermittent AR patients, but these patients most likely do not seek for medical help. Thus, the sample size was not large enough so that the subjects in ARC1 and ARC5 were less numerous, which might lead to some other biases. Finally, we could only obtain the AR control rate according to the stepwise treatment guided by ARCT without comparison to other measurements such as visual analogue scale or RCAT. None of the available AR control tools has been used to be a criterion in AR stepwise pharmacotherapy; the first step of our study was to confirm whether ARCT is qualified for AR stepwise treatment; the next step would certainly be to focus on head-to-head comparisons of others control-based tools and ARCT. Similarly, we did not set a placebo control group in our study, because our aim was to validate the ARCT longitudinally and each patient was his/her own control. Moreover, considering the study period of our AR patients which lasted from 15 to 75 days, it would have been difficult to add a placebo group and ascertain the compliance of patients in the placebo group. It is well known that the placebo effect has a potential influence on AR studies (18). However, the placebo effects were less than 60% in majority studies (19), while in our study, 96.8% of the patients with AR were controlled with standard stepwise treatment, which was far exceeded the effect of placebo. Therefore, we can conclude that the high efficacy of the AR patients was derived from the ARCT-driven stepwise pharmacotherapy but not placebo effect.

Accurate assessment of AR control status is critical for determining whether care is optimized and for adjusting treatment strategies to achieve control. When we designed the study, ARIA still had no clear definition of AR control, and due to the absence of uniformed criteria, pharmacotherapy adjustment regimen varies in different areas and populations (20). Despite advances in knowledge about the pathophysiology of AR and the availability of effective therapy, well-controlled AR remains an elusive goal for many patients (21). Our preliminary study (13) indicated that more than one quarter of patients have uncontrolled AR. Thus, a simple tool to assess AR control was urgently needed in clinical practice. ARCT questionnaire has been validated in different populations (12, 13). In this study, we further assessed ARCT as a questionnaire-driven stepwise pharmacotherapy for AR.

Our study showed a slightly higher control rate of AR compared with the treatment regimen determined by AR severity classification in ARIA (12, 22). Using ARCT (12) or a visual analogue scale (22), 85% of the patients were controlled at day 15. According to the present study, only 34% of the patients could be controlled after 15 days of treatment. With prolonged and stepped up treatment, the AR control rate elevated gradually up to 96.8% at day 75. This demonstrates that ARCT-driven treatment could achieve well-controlled AR in the majority of the patients in a stepwise manner. ARCT offers for the first time a reliable objective indicator for AR stepwise treatment. We defined a follow-up period of 2 weeks, while ARIA guidelines recommend 2- to 4-week interval. Two weeks is the duration chosen to validate the sensitivity to change in patient-related outcomes in AR (12, 22). Only two patients' symptoms relapsed when controlled after only 2 weeks in conditions of high-level allergen exposure (house dust mite), concomitant respiratory infection, noncompliance and other cofactors, which probably led to the overestimation of long-term AR control level in our study (data not shown).

Our study showed several demographic and clinical characteristics that had impacts on AR treatment. Uncontrolled patients often needed more powerful medications (i.e. higher steps) or prolonged treatment period to achieve AR control. Persistent AR patients were more difficult to achieve AR control. Patients whose qualities of life were moderately/severely impacted at inclusion needed prolonged treatment, which was similar to the study conducted in Europe (23). Patients with moderate/severe persistent AR have a greater bronchial hyper-reactivity and may be more likely to suffer from asthma than those with mild intermittent AR (24). ARIA recommends oral H1A and NCS to be used to control the symptoms of moderate/severe AR (25). We also observed that AR associated with asthma needed more medications, confirming previous studies in which comorbidities may affect the control level of AR (26). We evaluated the role of rhinorrhea as a possible predictor of control in the Cox model, despite some inconsistency regarding the proportional hazard assumption, mostly because of its clinical importance

as a sign of rhinitis impacting the quality of life. However, as for sneezing, the results must be regarded with caution and the value of these predictors should be better assessed in studies with a different design (namely continuous survey time, in order to avoid aggregation of data in fixed time points, as in our study, where time points were chosen in advance at D15, D30, D45, D60, D75). Patients with cough were also more difficult to get controlled AR, and we supposed that cough might be a manifestation of asthma or airway hyper-reactivity (27). However, after adjustment on other variables, cough as a symptom in itself becomes non-significant, probably owing to the multiple mechanisms eliciting cough in AR patients (association of asthma, presence of posterior nasal drip...).

Conclusions

The Chinese version of the ARCT questionnaire is able to evaluate the AR control level and to guide the stepwise approach for AR treatment in a large Chinese cohort. Our study suggested that the majority of AR patients can be controlled with ARCT-driven stepwise standard treatment. ARCT was an accessible and effective tool to monitor the condition and control level of AR and to determine the adjustment needed for a stepwise treatment, which was beneficial to the control of AR and improvement of patients' quality of life. It prevented from under- and over-treatments. Independently of the usefulness of ARCT, the use of a Cox model allowed us to identify at least two predictors of achieving control, namely intermittent AR and low impact on QoL. With this in mind, practitioners dealing with patients with persistent AR and AR with moderate/severe impact on QoL could decide to adapt the stepwise treatment and in some cases skip one step when stepping up.

Author contributions

Pascal Demoly, Youna Wang, Hao Chen and Rongfei Zhu initiated this study. Guanghui Liu, Nan Huang, Wenjing Li, Lin Yang, Shucheng Zhang and Shanshan Qi were principal investigators and contributed to data collection. Youna Wang, Anca Mirela Chiriac and Jean-Pierre Daurès performed the statistical analysis. Youna Wang, Hao Chen and Rongfei Zhu wrote the initial manuscript. Pascal Demoly, Anca Mirela Chiriac and Jean-Pierre Daurès revised the manuscript. All authors participated in the design of the study, assembly of data, interpretation of the results and approved the final version.

Funding

None.

Conflicts of interest

The authors declare that they have no conflicts of interest.

References

1. Maio S, Baldacci S, Carrozzi L, Pistelli F, Angino A, Simoni M et al. Respiratory symptoms/diseases prevalence is still increasing: a 25-yr population study. *Respir Med* 2016;**110**:58–65.
2. Long A, McFadden C, DeVine D, Chew P, Kupelnick B, Lau J. Management of allergic and nonallergic rhinitis. *Evid Rep Technol Assess (Summ)* 2002;**54**:1–6.
3. Zhang L, Han D, Huang D, Wu Y, Dong Z, Xu G et al. Prevalence of self-reported allergic rhinitis in eleven major cities in China. *Int Arch Allergy Immunol* 2009;**149**:47–57.
4. Canonica GW, Bousquet J, Mullol J, Scadding GK, Virchow JC. A survey of the burden of allergic rhinitis in Europe. *Allergy* 2007;**62**:17–25.
5. Schatz M. A survey of the burden of allergic rhinitis in the USA. *Allergy* 2007;**62**(Suppl 85):9–16.
6. Schoenwetter WF, Dupclay L Jr, Appajoyula S, Botteman MF, Pashos CL. Economic impact and quality-of-life burden of allergic rhinitis. *Curr Med Res Opin* 2004;**20**:305–317.
7. Shi JB, Fu QL, Zhang H, Cheng L, Wang YJ, Zhu DD et al. Epidemiology of chronic rhinosinusitis: results from a cross-sectional survey in seven Chinese cities. *Allergy* 2015;**70**:533–539.
8. Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A et al. Allergic rhinitis and its impact on asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy* 2008;**63**:8–160.
9. Demoly P, Calderon MA, Casale T, Scadding G, Annesi-Maesano I, Braun JJ et al. Assessment of disease control in allergic rhinitis. *Clin Transl Allergy* 2013;**3**:1–7.
10. Fonseca JA, Nogueira-Silva L, Morais-Almeida M, Azevedo L, Sa-Sousa A, Branco-Ferreira M et al. Validation of a questionnaire (CARAT10) to assess rhinitis and asthma in patients with asthma. *Allergy* 2010;**65**:1042–1048.
11. Nathan RA, Dalal AA, Stanford RH, Meltzer EO, Schatz M, Derebery J et al. Qualitative development of the rhinitis control assessment test (RCAT), an instrument for evaluating rhinitis symptom control. *Patient* 2010;**3**:91–99.
12. Demoly P, Jankowski R, Chassany O, Bes-sah Y, Allaert FA. Validation of a self-questionnaire for assessing the control of allergic rhinitis. *Clin Exp Allergy* 2011;**41**:860–868.
13. Wang Y, Zhu R, Liu G, Li W, Chen H, Daurès JP et al. Prevalence of uncontrolled allergic rhinitis in Wuhan, China: a prospective cohort study. *Am J Rhinol Allergy* 2014;**28**:397–403.
14. Meltzer EO. The prevalence and medical and economic impact of allergic rhinitis in the United States. *J Allergy Clin Immunol* 1997;**99**:S805–S828.
15. Kremer B. Quality of life scales in allergic rhinitis. *Curr Opin Allergy Clin Immunol* 2004;**4**:171–176.
16. Hoyte FC, Meltzer EO, Ostrom NK, Nelson HS, Bensch GW, Spangler DL et al. Recommendations for the pharmacologic management of allergic rhinitis. *Allergy Asthma Proc* 2014;**35**:S20–S27.
17. Devillier P, Dreyfus JF, Demoly P, Calderón MA. A meta-analysis of sublingual allergen immunotherapy and pharmacotherapy in pollen-induced seasonal allergic rhinoconjunctivitis. *BMC Med* 2014;**12**:1–12.
18. Meltzer EO, Weiler JM, Widlitz MD. Comparative outdoor study of the efficacy, onset and duration of action, and safety of cetirizine, loratadine, and placebo for seasonal allergic rhinitis. *J Allergy Clin Immunol* 1996;**97**:617–626.
19. Corren J, Harris AG, Aaronson D, Beaucher W, Berkowitz R, Bronsky E et al. Efficacy and safety of loratadine plus pseudoephedrine in patients with seasonal allergic rhinitis and mild asthma. *J Allergy Clin Immunol* 1997;**100**:781–788.
20. Ramirez LF, Urbinelli R, Allaert FA, Demoly P. Combining H1-antihistamines and nasal corticosteroids to treat allergic rhinitis in general practice. *Allergy* 2011;**66**:1501–1502.
21. Nathan RA. The burden of allergic rhinitis. *Allergy Asthma Proc* 2007;**28**:3–9.
22. Demoly P, Bousquet PJ, Mesbah K, Bousquet J, Devillier P. Visual analogue scale in patients treated for allergic rhinitis: an observational prospective study in primary care: asthma and rhinitis. *Clin Exp Allergy* 2013;**43**:881–888.
23. Hellings PW, Fokkens WJ, Akdis C, Bachert C, Cingi C, Dietz de Loos D et al. Uncontrolled allergic rhinitis and chronic rhinosinusitis: where do we stand today? *Allergy* 2013;**68**:1–7.
24. Cuttitta G, Cibella F, La Grutta S, Hopps MR, Bucchieri S, Passalacqua G et al. Non-specific bronchial hyper-responsiveness in children with allergic rhinitis: relationship with the atopic status. *Pediatr Allergy Immunol* 2003;**14**:458–463.
25. Brożek JL, Bousquet J, Baena-Cagnani CE, Bonini S, Canonica GW, Casale TB et al. Allergic rhinitis and its impact on asthma (ARIA) guidelines: 2010 revision. *J Allergy Clin Immunol* 2010;**126**:466–476.
26. Cruz AA, Popov T, Pawankar R, Annesi-Maesano I, Fokkens W, Kemp J et al. Common characteristics of upper and lower airways in rhinitis and asthma: ARIA update, in collaboration with GA(2)LEN. *Allergy* 2007;**62**:1–41.
27. Naito K. Diagnosis and treatment of cough variant asthma. *Nihon Jibiinkoka Gakkai Kaiho* 2014;**117**:222–223.