THÈSE
Pour obtenir le grade de
Docteur

Délivré par **Université de Montpellier**

**Préparée au sein de l'école doctorale
Information Structures Systemes**

**Et de l'unité de recherche
Laboratoire de Biostatistique Epidémiologie et Recherche Clinique**

Spécialité: Biostatistique

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The epidemiology survey of uncontrolled allergic rhinitis and allergic rhinitis control test questionnaire-driven stepwise pharmacotherapy in Wuhan

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Soutenue le 12 Décembre 2016 devant le jury composé de

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Abbreviations List

ACT	Asthma Control Test
ACQ	Asthma Control Questionnaire
AR	Allergic Rhinitis
ARCT	Allergic Rhinitis Control Test
ARIA	Allergic Rhinitis and its Impact on Asthma
BMI	Body Mass Index
CARAT	Control of Allergic Rhinitis and Asthma Test
CS	Corticosteds
GINA	Global Initiative for Asthma
H1A	H1 antihistamine
LTRAs	Leukotriene Receptor Antagonists
NS	Numeric Scale
NCS	Nasal Corticosteds
OTC	Over-The-Counter
QoL	Quality of Life
RCAT	Rhinitis Control Assessment Test
RQLQ	Rhinoconjunctivitis Quality of Life Questionnaire
SCUAD	Severe Chronic Upper Airway Disease
SCIT	Subcutaneous Immunotherapy
SLIT	Sublingual Immunotherapy
TSS	Total Symptom Score
VAS	Visual Analog Scale
WHO	World Health Organization

Résumé

Introduction

La rhinite allergique (RA) est une maladie fréquente qui altère la qualité de vie.

Le traitement de la RA est maintenant bien établi et la plupart des patients atteints par cette maladie y répondent.

Néanmoins, il existe un pourcentage de patients qui ne sont pas contrôlés, malgré un traitement maximal, amenant au concept de SCUAD (*Severe Chronic Upper Airway Disease*), acronyme anglais pour "atteinte sévère et chronique des voies aériennes supérieures". Les patients souffrant de SCUAD ont une qualité de vie altérée et cela participe à l'augmentation du fardeau de cette maladie, au niveau individuel et sociétal.

En Chine, les données concernant la RA non contrôlée et le SCUAD sont insuffisantes.

Le consensus d'experts ARIA (*Allergic Rhinitis and its Impact on Asthma*, acronyme anglais pour *Rhinite Allergique et son Impact sur l'Asthme*) a adopté une classification de la RA compte tenu de sa sévérité et durée et recommande une pharmacothérapie par paliers, guidée par la sévérité (initiale, et de plus en plus selon le niveau de contrôle). Le test de contrôle de la rhinite allergique (*Allergic Rhinitis Control Test*, ARCT) est un outil validé pour évaluer le contrôle de la RA et identifier la RA sévère. Néanmoins, l'ARIA n'offre pas de définition claire du contrôle de la RA et, du fait de l'absence de critères uniformes, le choix de la pharmacothérapie varie dans différentes régions et populations.

Objectif

La première étude a eu pour objectif d'évaluer la prévalence et les caractéristiques des patients avec RA non contrôlée et SCUAD à Wuhan. Elle montrait que les médecins utilisaient l'échelle visuelle analogique (EVA) et l'ARCT dans la prise en charge de la RA, pour évaluer la sévérité de la RA et la réponse au traitement. A partir de cette étude préliminaire, une autre étude a été mise en oeuvre, pour évaluer le rôle de l'ARCT en tant qu'outil pour guider une pharmacothérapie par paliers, dans le but d'atteindre le contrôle de la RA.

Méthode

Dans la première étude, tous les patients consultant pour une RA ont été évalues en prospectif par EVA et ARCT, et mis sous traitement selon le guide ARIA. Au bout de 15 jours (J15), une interview téléphonique a permis de ré-évaluer la RA au moyen d'une échelle numérique et de l'ARCT. La RA non contrôlée était définie par un score ARCT < 20. Les patients souffrant de SCUAD étaient définis par un score ≥ 5 à J15.

Dans la 2ème étude prospective, un traitement pharmacologique standard a été proposé aux patients souffrant de RA. Les paliers allaient du palier 1 (antihistaminique H1 à la demande) jusqu'au palier 5 (corticoïde oral). La RA était traitée et évaluée tous les 15 jours par ARCT. Si le score ARCT était ≥20, maintenu pendant 15 jours, le patient terminait l'étude. Si l'ARCT était < 20 (RA non contrôlée), le patient recevait le prochain palier de traitement, selon une démarché prédéfinie, progressive, jusqu'au palier 5. Les différents sous-groupes de contrôle de la RA ont été comparés.

Résultats

Au total, 252 patients ont été inclus dans la 1ère étude. La RA modérée/sévère (EVA ≥ 5) était présente en 82,9% des patients, avec un impact sur le sommeil (86,9%), travail (84,9%), activités sociales (81%) et physiques (90,1%). Les patients avec RA non contrôlée à J15 (27,7%) étaient ceux avec un poids plus important (P=0,042), antécédents d'infections ORL ou de prise d'antibiotiques pour infections respiratoires dans les derniers 12 mois (62,3 vs. 45,6%, P=0,018), de tabagisme (15,9 vs. 6,7%, P=0,024) et de dysosmie (26,1 vs. 11,7%, P=0,005). Les patients avec SCUAD (24,5%) avaient plus fréquemment des antécédents d'infections ORL ou de prise d'antibiotiques pour infections respiratoires (63,9 vs. 45,7%, P=0,014) et de dysosmie (27,9 vs. 11,7%, P=0,003) et moins fréquemment de dermatite atopique (13,1 vs. 28,2%, P=0,017).

Deux cents cinquante cinq patients ont été inclus dans la 2ème étude; 5 patients ont été perdus de vue. Deux patients (0,8%) étaient contrôlés à J0, 85 (34,0%) à J15, 177 (70,8%) à J30, 222 (88,8%) à J45, 241 (96,4%) à J60 et 242 (96,8%) à J75. Seulement 8 patients (3,2%) sont restés non contrôlés à la fin de l'étude. Les patients avec une RA modérée à sévère selon ARIA, RA persistante, impact modéré à sévère sur la qualité de vie, antécédents d'asthme, rhinorrhée et toux avaient toujours besoin d'un traitement associé (corticoïde nasal et antihistaminique H1), ainsi qu'un traitement prolongé pour atteindre le contrôle. Après ajustement sur chacune des variables, le seul facteur de risque restant significatif était la présence d'un asthme (il était moins probable que ces patients soient contrôlés par les premiers paliers de traitement).

Conclusion

Les patients ayant une RA non-contrôlée ou atteints de SCUAD sont nombreux. L'EVA et l'ARCT sont des outils simples qui peuvent être utilisés dans l'évaluation globale de la sévérité et du contrôle de la RA. La plupart des patients atteints de RA peuvent être contrôlés en utilisant un traitement par paliers. L'ARCT offre un critère objectif pour guider le

traitement par paliers. L'analyse des facteurs de risque n'a pas relevé une association forte avec des caractéristiques cliniques qui permettrait un meilleur contrôle de la RA.

Mots clés：Mots clés : rhinite allergique, épidémiologie, ARIA, auto-questionnaire, sévérité, contrôle, échelle visuelle analogique, test de contrôle de la rhinite allergique, SCUAD, traitement par paliers

Abstract

Background

Allergic rhinitis (AR) is a highly prevalent disease that affects the quality of life. The treatment of AR is now well established and most patients respond well to the treatment. However, there are still some patients with uncontrolled AR despite optimal maximum treatment, leading to the concept of severe chronic upper airway disease (SCUAD). Patients with SCUAD often present impaired quality of life and they increase the health-economic burden of the individual and society. In China, there are insufficient epidemiological data regarding uncontrolled AR and SCUAD. Allergic Rhinitis and its Impact on Asthma (ARIA) has divided AR into different subgroups according to the symptom severity and duration and recommend different pharmacotherapy to step up or step down treatment according to disease severity (initially and more and more according to control) level. Allergic Rhinitis Control Test (ARCT) has been validated for assessing AR control and to identify severe AR. However, ARIA still has no clear definition of AR control, and due to the absence of uniformed criteria, pharmacotherapy adjustment regimens varies in different areas and populations.

Objective

The first study aimed to assess the prevalence and the characteristics of patients with uncontrolled AR and SCUAD in Wuhan. It also proposes that physicians in charge of AR patients use visual analogue scale (VAS) and/or ARCT as a simple and quantitative method for the global evalution of AR severity and response to treatment. On the basis of the preliminary study, a further study is designed to assess ARCT as a questionnaire driven stepwise pharmacological treatment to achieve AR control.

Methods

In the first epidemiology study, all patients consulting for AR were prospectively assessed using VAS and ARCT and put on standardized treatment based on ARIA guidelines. After 15 days, they were reevaluated by a telephone interview using a numerical scale and ARCT. A score of ARCT < 20 defined uncontrolled AR and a score ≥ 5 at day-15 defined SCUAD patients.

In the second study, a standard pharmacotherapy regimen from step 1 (oral second generation H1 antihistamine as needed) to step 5 (oral corticosteroid) was applied prospectively in a Chinese AR population. The AR patients were initiated with 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 less than 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 252 patients were included in the first study. Moderate/severe AR (VAS ≥ 5) was diagnosed in 82.9% of the patients and they had an impact on sleep (86.9%), work life (84.9%), social activities (81%) and physical activities (90.1%). Patients with uncontrolled AR (27.7%) at day-15 more frequently presented a higher weight (*P*=0.042), past history of ENT infection or antibiotics intake for respiratory infection in the last 12 months (62.3 vs. 45.6%, *P*=0.018), smoking (15.9 vs. 6.7%, *P*=0.024) and smell disturbance (26.1 vs. 11.7%, *P*=0.005). Patients with SCUAD (24.5%) more frequently presented a past history of ENT infection or antibiotics intake for respiratory infection (63.9 vs. 45.7%, *P*=0.014) and smell disturbance (27.9 vs. 11.7%, *P*=0.003), while less commonly had atopic dermatitis (13.1 vs. 28.2%, *P*=0.017).

255 patients were enrolled in the second study, 5 patients dropped out. 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. After adjustment on each of the variables, the only factor that remained significant was asthma (less likely to be in a group controlled by the first steps' therapies).

Conclusion

Uncontrolled AR and SCUAD patients are numerous. VAS and ARCT are simple and quantitative methods and self-completion questionnaire that can be used for a global evaluation of the severity and control of AR. The majority of AR can be controlled with standard stepwise treatment. ARCT offers an objective criterion for the stepwise pharmacotherapy of AR. Risk factor analysis did not reveal strong clinical characteristics that would help the physician to control AR better.

Key words：allergic rhinitis, epidemiology, ARIA, self-completion questionnaire, severity,

control, visual analogue scale, allergic rhinitis control test, severe chronic upper airway disease, stepwise pharmacotherapy

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1- Introduction

Allergic rhinitis (AR) is a common disease worldwide affecting up to 40% of the population in young adults in Europe and its prevalence is increasing (1). The early studies have shown that the prevalence of AR in 13 to 14 year-old children in Chinese mainland (2) was about 10%. A cross-sectional population-based study in 11 major cities of China showed that the prevalence of AR ranges from 8.7% to 24.1% (3). Despite the fact that approximately 50% of AR patients visit their doctor for their symptoms present at least 4 months a year (4), over half of AR of sufferers do not seek medical advice from a physician in Europe, resulting in AR being usually under-recognized and ineffectively treated (5). The direct and indirect health-care costs incurred by AR are substantial and can not be neglected by healthcare payers (6).

The main typical symptoms of AR are nasal congestion, rhinorrhea, sneezing, and nasal itching as well as ocular redness, tearing, and itching (7). 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 (8, 9, 10). AR is also a strong risk factor for other chronic respiratory diseases such as asthma and chronic rhinosinusitis (11). Nearly 40% of AR patients combine or will develop asthma (12), whereas almost 85% of asthma patients have rhinitis (13). A large epidemiological survey showed that sleep impairment is common in AR, particularly in more severe forms (14). Over 45% of adults and 41% of children with AR reported a serious impact on work or school in the previous years because of AR in Asia (15, 16). The majority of patients suffering from AR consult their general practitioner first (17, 18). In China, patients are allowed to consult directly the specialist. In order to enhance the effectiveness and quality of management for AR, a number of international guidelines and consensus statements have been developed (19).

Allergic Rhinitis and its Impact on Asthma (ARIA) workshop (organized by the World Health Organization (WHO) was the first evidenced-based guidelines. It was published in 2001 and updated in 2008 and 2010 (13, 20, 21). ARIA focuses on the assessment and treatment of AR based on quality of life (QoL). ARIA guidelines introduced AR management including allergen avoidance, pharmacotherapy, patient education, allergen immunotherapy and surgical treatment. It divided AR into different subgroups according to the symptom severity (mild vs. moderate/severe) and duration (intermittent vs. persisitent). ARIA severity classification has been validated in primary care patients in many countries (22). Several composite instruments

have been developed to objectively assess the severity of AR, including Total Symptom Score 6 (TSS6) and Visual Analog Scale (VAS) (23, 24, 25).

Although the treatment guidelines are now well established, treated patients may report poor levels of satisfaction, with a frequent search for a combination of medications to better reduce their nasal or ocular symptoms (26). Many patients with AR continue to be undertreated and are at risk for acute exacerbations, resulting in reduced productivity at work, school performance and QoL, triggering increased health-care costs and the use of oral corticosteroids. As for the management of asthma following the introduction of the Global Initiative for Asthma (GINA) guidelines (27), the generalization of the "control" is now being considered as a trend in the management of patients with AR, chronic rhinosinusitis, chronic urticaria and atopic dermatitis (28). There is currently no single definition of AR control and the definition of AR control was a missing part in the original ARIA. The determination of AR control depends on the variables taken into account by the different available tools. Therefore, the concept of AR control was being only recently understood (29). Nevertheless, rhinitis control is essentially "absence of symptoms". The fact that the level of AR control is often overestimated by both patients and physicians indicates that AR treatment guidelines alone are not enough to determinethe assessment of AR control. The overestimation of AR control can result in failure to make the necessary adjustments to medication.

A measure of AR control should be used to evaluate treatment outcomes and simplify monitoring. Both severity and control can be measured in different ways, with both objective and subjective measurements and patient-reported vs. physician-reported outcomes. Till now, several questionnaires of AR control have been developed and validated in clinical practice (30, 31, 32). Most of the control questionnaires focus on measurements of daily or nocturnal symptoms, symptom magnitude (i.e., the patients' perception of how bothersome their symptoms are) and impairment in every day activities. 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 VAS has also been validated to assess AR control.

In case of poor control of symptoms despite optimal maximum guideline-directed treatment, one needs to consider the presence of severe chronic upper airway disease (SCUAD) (33). In the national French survey validating the ARCT instrument, 14.9% of the 902 AR patients were not controlled after 15 days of treatment (32). Poor disease control may be related to

suboptimal treatment, poor treatment compliance (34), a co-morbid condition not taken into account including psychosocial factors and treatment-resistant AR (35, 36). Patients with SCUAD often present uncontrolled nasal and/or ocular symptoms and impaired quality of life. In a randomized European trial, it was found that 10% to 20% of patients with AR consulting a specialist have SCUAD (37). In China, there are insufficient epidemiological data regarding uncontrolled AR and SCUAD.

ARIA guidelines (21) have recommended different pharmacotherapy to step up according to 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. An accessible and effective tool should be used to monitor the 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.

In this series of studies, the criteria utilized for the assessment of AR severity and control as well as the existing validated instruments were reviewed. Specifically, we provide insight into their use in clinical practice. More importantly, a prospective cohort study was designed to investigate the prevalence of uncontrolled AR and SCUAD in the allergy department of Tongji university hospital of Wuhan, China, and to describe their characteristics. This was done in partnership between the allergy unit of the University Hospital of Montpellier and that of the Tongji Hospital. Moreover, this study indicated that VAS and ARCT are simple and quantitative methods and self-completion questionnaire that can be used for a global evaluation of the severity and control of AR. Based on the first study, another prospective cohort study was designed and carried out in the allergy department of Tongji hospital, Wuhan, China to further assess ARCT as a questionnaire driven stepwise pharmacological treatment to achieve AR control and to describe the characteristics of the AR patients in different subgroups.

2- Assessment of the AR severity

ARIA recommendations written in collaboration with the WHO devised a new classification for AR (intermittent and persistent rhinitis) (21). The ARIA guidelines also proposed a new grading of severity (mild and moderate/severe) and stepwise therapeutic recommendations based on this classification of severity.

2.1 ARIA classification of AR

In the early guidelines, AR was divided seasonal and perennial rhinitis (13). However, this classification is not entirely perfect. Due to many patients are sensitized to different allergens, perennial symptoms of AR are often present and they have seasonal exacerbations when exposed to seasonal allergens (such as pollens and molds). Thus, a change in the classification of AR was proposed in the ARIA guidelines with the terms "intermittent" and "persisitent" (21).

ARIA paid close attention to the impact of AR on social life, school and work and emphasized the need to assess patients' symptoms. Therefore, it has been proposed to classify the severity as "mild" and "moderate/severe" and it is very easy to implement in clinic. Patients only need to answer yes/no to the following questions: "My symptoms disturb my sleep", "My symptoms restrict my daily activities (sports, leisure, etc.)", "My symptoms restrict my participation in schoolar work" and "My symptoms are troublesome". Patients with no answers to all four questions are considered as having "mild" AR, whereas patients with a "yes" for one or more items are considered as having "moderate/severe" AR (21, 38, 39).

Objective measures of the severity of AR include symptom scores, measurements of nasal obstruction, measurements of inflammation and reactivity (such as nitric oxide measurements, provocation with histamine or allergens), measurements of the sense of smell and VAS. VAS is widely used in clinical practice as a simple and effective method to assess the severity of AR (21).

2.2 Instruments for assessing AR severity

Total Symptom Score 6 (TSS6) is a 4-point scale used to assess the severity of patients' 4 nasal symptoms (rhinorrhea, itching, sneezing and nasal congestion) and 2 nonnasal symptoms (gritty/red/itchy eyes and watery eyes) (40). Each nasal and nonnasal symptoms

are presented on a 0-3 scale: 0, no symptoms; 1, mild symptoms (obvious symptoms, but easily tolerated); 2, moderate symptoms (bothersome but tolerable symptoms) and 3, severe symptoms (symptoms hard to tolerate and/or impact the activities of daily living). (41). The TSS6 is the total scores of nasal and non-nasal symptoms ranging from 0-18. However, the cut-off level of the TSS6 discriminated the severity has not been suggested. In some studies the score of the 4 nasal symptoms is separated (*Total Nasal Symptom Score*) from that of the 2 ocular symptoms (*Total Ocular Symptom Score*).

Visual Analog Scale (VAS) is a simple and quantitative measure extensively used to assess the severity of AR in both intermittent and persistent rhinitis. Bousquet et al. (42) satated that a 0-10cm VAS soce and the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) global score were significantly correlated and that a cut-off level of 5 cm was proposed to discriminate between mild and moderate/severe patients with AR. Many studies in different languages are being carried out to confirm the possible use of this scale in different countries. Other study suggested that all symptoms of rhinitis could be assessed by VAS, but, a single scale with a simple simple question would be easier to use in primary care.

2.3 Severity assessment of AR in clinical practice

The ARIA severity classifications have been validated and implemented in primary care patients in many countries (22, 43), and the majority of physicians and specialists are aware of this tool (44). A cohort study of AR patients in Spain found patients with "moderate/severe" AR have significantly higher symptom, RQLQ and VAS score than patients with "mild" AR (45, 46). In China, among the subjects with self-reported AR in 11 major cities, 25.6% were diagnosed with persistent AR and 74.4% suffered from intermittent AR (3). Bousquet et al. (47) reported that impairments were correlated more significantly with severity than duration. "Moderate-severe" AR usually includes patients with SCUAD (48), who may have severe symptoms and need allergen immunotherapy.

Low levels of awareness and application of the ARIA severity classification do not meet the clinical needs of patient care. Demoly et al. (49) found that in France, only about 54% of the primary care physicians were aware of the ARIA classification, and over 90% of them had indeed applied the classification in clinical practice. Moreover, awareness of the ARIA classification could not influence the opinion of treatment according to the patient's symptoms severity (50).

In most developed countries, a patient with "mild" AR is likely to consult a primary care physician rather than a specialist. However, in China, patients are more likely to consult the specialist directly, because general practioners are lacking. Thus, the "mild" vs. "moderate/severe" distinction has more value for specialists. Van Hoecke et al. (51, 52) observed that 89.3% of patients consulting physicians in Belgium were classified as "moderate-severe". In the telephone survey of self-reported AR in 11 major cities in China, 74.4% had intermittent AR, 25.6% had persistent AR, and only 39.3% had presented to a clinic (3). This reflected that severity of symptoms was an important factor to drive the patients to visit hospitals (53).

3- Assessment of AR control

3.1 Allergic rhinitis control

Currently, there is not a standardized definition of AR control. The concept of disease control is only applicable in treated patients (54). Based on an analogy with GINA (55), the concept of overall AR control may be considered as the degree of symptom reduction and of achievement of the treatment's goals. From this point of view, AR control can be measured in a multitude of ways, with both objective and subjective measurements and using patient-reported vs. physician-reported outcomes. Patient-reported metrics are growing in importance in clinical research and, increasingly, in patient care (56), although there is debate as to whether it is the physician or the patient that is best placed to judge disease control (57).

Therefore, evaluation of AR control can be based on a number of criteria, including: nasal and ocular symptoms (congestion, rhinorrhea, sneezing, pruritus, post-nasal drip); a patient-reported metric of QoL and satisfaction (i.e., impairment in sleep or daily activities); objective measurements (e.g., peak nasal inspiratory flow, rhinomanometry); the necessity for increased use of rescue medication and how much. The last is also important as it has been suggested that a patient's degree of control could simply correspond to the "strength" of the medication necessary to suppress symptoms (58). Therefore, any increment in medication could indicate loss of control. Finally, presence of rhinitis comorbidities could also affect control, as 10% to 40% of rhinitis patients have comorbid asthma (59). Practical tools are also needed for patients and physicians to determine whether optimal AR care is provided or whether treatment strategies needed to be adjusted.

3.2 Instruments for assessing AR control

Several composite instruments, mainly self-administered questionnaires, have been developed over the years. The time period of assessment ranges from 1–4 weeks prior to the consultation, long enough to assess changes and short enough to avoid recall bias.

3.2.1 The Control of Allergic Rhinitis and Asthma Test (CARAT）

CARAT is a self-administered questionnaire (including 17 questions in a questionnaire with a Likert scale), initially developed by Nogueira-Silva et al. (60) for assessing control of both AR and asthma in patients with comorbid diseases, as recommended by ARIA. Subsequently, a simply 10-item version of CARAT (CARAT10) was validated in a cross-sectional study of

193 adults with AR and asthma from 15 outpatient clinics in Portugal (61). The range of possible scores for CARAT10 is 0 (absence of control) to 30 (complete control), and the reference/evaluation period is 4–6 weeks. Fonseca et al. (62) observed good correlations between CARAT10 and Asthma Control Questionnaire (ACQ), symptoms' VAS and a simple binary yes/no physician's assessment of control. CARAT10 has adequate test-retest reliability and internal validity. It can be used in clinical practice to compare groups and to guide patient management.

3.2.2 Rhinitis Control Assessment Test (RCAT)

RCAT is a 26-item instrument developed by Nathan et al. (63) for the assessment of control of nasal and ocular symptoms the previous week. It was finally refined to a 6-item self-administered questionnaire (including frequency of nasal congestion, sneezing, watery eyes, sleep interference, activity avoidance and self-assessed control) after testing the RCAT in 410 AR patients (64). RCAT questions are measured on a 5-point scale with total score ranging from 6 (poor control) to 30 (complete control). A longitudinal study in 402 patients in 9 sites of allergists and otolaryngologists showed that RCAT demonstrated adequate reliability and validity, and confirmedthe items to be relevant and easy to answer. Moreover, RCAT provided an accurate picture of the severity of the symptoms of AR and non-AR (65). Based on its sensitivity and specificity, a cut-point score of 21 or less was suggested to identify AR control (65). It is planed to be included in an e-Health tool for AR patients (66).

3.2.3 Allergic Rhinitis Control Test (ARCT)

Demoly et al. (67) developed the ARCT including 5 items by working with a multidisciplinary group associating allergists, pulmonologists, ENT physicians and methodologists. Similar to the Asthma Control Test (ACT) (68), measuring AR control with the ARCT is multidimensional. The 5 items include the impact on professional/personal activities, sleep disturbance, medication and overall assessment of the disease. A 2-week recall is used in ARCT. The questionnaire was validated by testing it in 902 patients selected by 411 primary care physicians and allergists before the treatment and 2 weeks after the treatment. It appears to be correlated to the clinical status of the AR, as well as to the evolution after treatment. A score higher than or equal to 20, as a marker of well-controlled AR, is the most efficient (sensitivity: 67%, specificity: 82%). It is incorporated into a patient support programme (69).

3.2.4 Visual Analog Scale (VAS)

Initially developed as a simple tool to measure AR severity, VAS has turned out to be a possible tool to assess AR control, with a score of 50 mm or greater as the cut-off for uncontrolled AR during treatment (70). It was estimated that 20% of patients with AR are still uncontrolled despite adequate medical treatment of AR in a retrospective analysis (54). In a post-hoc analysis assessing VAS at inclusion and after 15 days of treatment, the change of VAS greater than 30 mm was considered significant in relation to the improvement of quality of life and of symptom score (70). The exact cut-off may still need to be worked out because it was shown to be of 23 mm based on a multi-centre prospective study (71).

3.2.5 Allergy-Control-SCORE

The Allergy-Control-SCORE ^{TM} (72) is a symptom-medication scale. It was designed to assess the AR patients'allergy severity by recording nasal and non-nasal symptoms and rescue medication. The study showed that the Allergy-Control-SCORE was significantly correlated with the RQLQ score and the global assessment of allergy severity. The Allergy-Control-SCORE has been extensively used in clinical trials for many years as a "combined score" (a combination of a symptom score and a medication score) (73).

3.3 AR control instruments in clinical practice

Despite the availability of effective therapies, total control of AR is difficult to achieve for many patients. The ARIA guidelines stated that "treatment should be tailored according to the severity of the disease, comorbidities, treatment availability and affordability and patients' preference" (38). The concept of achieving control can contribute to improve the doctor-patient relationship in the treatment and management of AR.

The CARAT, RCAT and ARCT are multi-item questionnaires that require the patient to provide a fair amount of informationon his/her recent condition. It should help treatment decisions. However, since control is largely a patient-led concept, remote measurements (by phone or over the Internet) could conceivably reduce the frequency of face-to-face consultations. Applications on cellular phones (i.e., e-health technology) could help (74). Nevertheless, as noted by Glasziou et al. (75), the benefits of monitoring the response to treatment, detecting adverse effects and gauging the need to adjust treatment must be balanced against inconvenience, cost and the potential impact of false positives and false negatives of disease control. Measurements of control must therefore be reproducible, easy to perform, easy to interpret and should focus on the disease's impact in every-day life. For the patient, measures should be easily obtained and allowing patients to self-medicate. For the

physician, tools must have a low burden in a busy clinical practice (i.e., should be auto-questionnaire) and should guide clinical action following the test result.

3.4 Relationship between severity and control of AR

Recent papers developed under the aegis of ARIA indicate that disease control is being considered for future initiatives and that, methods for measuring severity and control in respiratory allergic diseases must be uniformed (76). Severity, control and responsiveness to treatment are different concept, but they are not opposite to each other (73). AR severity is not equivalent to the level of control. The severity is defined as the clinical grade experienced by each patient in the disease process. The control can be defined as significantly less disease syptoms or relapse.

Some cases of severe disease might respond well to treatment (i.e., good control), whereas some cases of mild disease might not (i.e., poor control). Likewise, a totally controlled patient taking an H1 antihistamine (H1A) combined to a nasal corticosteroid (NCS) and relapsing every time will probably have a severe underlying disease (77). Furthermore, poor disease control may also be related to poor treatment compliance and psychosocial factors rather than high disease severity (29). Mild disease may be a problem for some patients but not for others. Conversely, severe disease may bother some patients far less than others.

Severity can be measured in treatment-naïve patients as proposed by ARIA guidelines (21), but, by definition, the concept of disease control is only applicable in treated patients (54). Therefore, measurements of severity will be indispensable in treatment-naïve patients consulting for the first time. Measuring tools (such as VAS, ARCT and CARAT) appear to be simple and convenient for assessments of disease severity or control. However, a one dimensional scale cannot replace or encompass the complex parameters of objective measurement involved in disease control (i.e., examination of nasal mucosa and structure, respiratory function tests and exacerbations quantification).

4- Uncontrolled allergic rhinitis

4.1 The definition of SCUAD

Constantly updated ARIA guidelines provide standard diagnostic procedures and personalized treatment programs according to the patient's symptoms and impact on quality of life. The traditional goal of treatment has been to reduce the symptoms of AR, and current opinion suggests that management should be aimed at achieving long-term, stable control, corresponding to minimal or even no symptoms, no limitations indaily activity, minimal use of rescue medications and infrequent exacerbations. Current drug therapy can be effective in relieving the symptoms of AR and improving the quality of life of patients. However, in real life, a significant percentage of patients still have very bothersome symptoms that are not readily controlled after adequate medical treatment based on established ARIA guidelines. Bousquet et al. (48) defined this form of the disease as SCUAD.

4.2 The factor of SCUAD for AR

The proposed concept of SCUAD represents a therapeutic challenge for both patients and physicians. It is important to find the risk factors involved in SCUAD in clinical practice.

4.2.1   Disease-related factors of SCUAD

Allergic diseases show strong familial and intraindividual clustering and often occur with atopy (21). Genetic factors are related to the inflammatory response and immune disorders (78) as well as the presence of nasal mucosa hyperreactivity (79). Environmental factors such as exposure to cigarette smoke, allergen load, indoor and outdoor pollutants and work-related factors may have an effect on the control of allergic airway symptoms in AR patients (7). For example, it is possible that the achievement of control in patients with AR induced by grass pollen is very different from that in patients with persistent AR induced by house dust mites. This is a complex area requiring and more research is required to clarify this complex process. Hormonal factors have been related to the severe immune response (39). More severe allergic inflammation may occur during the pregnancy, puberty and the menstrual cycle (21). Steroid resistance has been reported in asthma and may be the cause of lack of control. However, The existence and mechanisms of steroid resistance in AR need to be further explored (80, 81, 82).

4.2.2   Diagnosis-related factors of SCUAD

In recent years, the prevalence of AR continues to raise and more different phenotypes have

been recognized while it remains an under-diagnosed conditions (83). In patients with SCUAD, the physician needs to reconsider the diagnosis of AR according to the treatment algorithm recommended by ARIA guideline and attempt to find out other factors that may be overlooked or an incorrect diagnosis. A study found that only about 56% of the otolaryngologists preferred the management pathway of starting treatment and then discharging AR patients to general practitioners for further follow-up (84). Several subgroups of AR such as isolated nasal hyperreactivity and local AR present with mild symptoms that are often ignored and not adequately addressed (85). The diagnosis of AR needs to combine a typical history of symptoms and diagnostic tests. *In vivo* and *in vitro* test (e.g., positive skin prick testing or serum-specific IgE) are often used to diagnose allergic diseases. In patients with nasal hyperreactivity or occupational rhinitis, nasal or ocular challenge tests with allergens are important (86). Nasal obstruction and increased nasal secretions can be observed in AR patients with nasal polyps, septal deviation and nasal valve dysfunction (87). ARIA recommends that all patients with persistent AR should undergo nasal examination and nasal endoscopy is the next step which is useful in patients with treatment failure (21).

4.2.3   Treatment and management-related factors of SCUAD

Many patients with AR do not recognize the signs and symptoms suggestive of moderate/severe rhinitis or do not consider doctors can do anything and do not timely consult a physician. Most of them commonly use over-the-counter (OTC) drugs or complementary medicines, seeking self-treatment for the relief of symptoms (20). It is therefore particularly important to improve the management of AR. In the longer treatment period, comprehensive and meticulous medical management is necessary for the long-term follow-up of AR. However, in the majority of developing countries, abundant medical resources tend to be concentrated in large cities, thus the difficulty of follow-up is increased for patients with AR in the city with poor medical service. Uneven distribution of medical resources result in poor doctor-patient communication and treatment failure (26). Efficient and optimal treatment of AR should take many factors into account, including safety, efficacy, patient's preference, cost-effectiveness of medications, severity and control of the disease and presence of co-morbidities. The expected efficacy of different treatment options may differ between patients. The route of administration (e.g., intranasal or oral) of medication has an impact on the efficacy (88). Additionally, ocular and ear symptoms should not be neglected (89).

4.2.4   Patient-related factors of SCUAD

Noncompliance to the prescribed therapeutic regimen and incorrect medication use should be considered when treating uncontrolled AR. Low compliance to treatment is a problem of daily practice especially in long-term regimes, and the consequences are poor health outcomes. Mahesh et al. (90) found 60% of the patients with AR and/or asthma were compliant to subcutaneous immunotherapy (SCIT). Chang et al. (91) reported a discontinuation of sublingual immunotherapy (SLIT) in 30% of patients with AR for house dust mites within 6 months of treatment. A study of a novel antihistamine demonstrated high compliance rates of 90% and 83% after 6 and 12 months of treatment, respectively (92). Other studies on intranasal glucocorticosteroids stated compliance rates of 65% and 85% (93). Ideally, clinical efficacy, cost, fear for side effects are considered the major issues influencing patient's compliance (94). The perceived knowledge, preferences, beliefs and expectations of the patient are perceived as important drivers in treatment outcome (95, 96). The most outstanding influences on under-treatment of AR in Europe are patients' perception about therapy (97). A survey found that patients consulting for AR have high expectations of anti-allergic treatment, prefer a nasal spray above oral treatment, prefer combined treatment rather than monotherapy, and fear adverse events of treatment (98).

The use of the nasal route for drug delivery has had some new developments and strategies. The correct use of nasal sprays is believed to be the key issue in the efficacy of treatment. Optimal effect of treatment will not be obtained in case of inappropriate use of intranasal spray and bad positioning of the nasal spray at the time of nebulization of the molecule. Therefore, an appropriate patient–physician relationship, family and community interactions are the major factors in improving compliance.

5- Prevalence of uncontrolled allergic rhinitis in Wuhan, China: A prospective cohort study

5.1 Objectives

The main aim of this prospective cohort study was to investigate the prevalence of uncontrolled AR and SCUAD consulting in the allergy department of Tongji Hospital, Wuhan, China (N.B. this is a partial prevalence, described in the sub-population of patients consulting in the allergy department of Tongji Hospital, Wuhan). The second aim was to describe the clinical characteristics of these patients. The results of this study can help doctors and patients understand the clinical features and control of AR in Wuhan City. We suggest that physicians in charge of AR patients use VAS and/or ARCT as a simple and quantitative method for the global evaluation of AR severity and response to treatment.

5.2 Materials and Methods

5.2.1   Patients

Patients consulting for AR were consecutively enrolled in the allergy department of Tongji Hospital, Wuhan, China during 1 year (August 2011 to July 2012).

The inclusion criteria were as follows:

(1) Patients aged 18–75 years, male or female;

(2) Patients presented at least 2 clinical symptoms of AR (rhinorrhea, nasal congestion, sneezing, nasal itching) at inclusion;

(3) Patients had a history of AR for at least the past 2 years;

(4) Patients had a positive skin prick tests to aeroallergens and/or serum specific IgE level (sIgE ≥ 0.35KU/L, Phadia CAP System);

 (5) Patients had a history of AR symptoms when exposed to allergens;

 (6) Patients volunteer to participate in the study, and have the ability to read, understand and sign an informed consent form.

The exclusion criteria were as follows:

(1) Aged < 18 years or > 75 years;

(2) Patients presented less than 2 clinical symptoms of AR (rhinorrhea, nasal congestion, sneezing, nasal itching) at inclusion;

(3) Patient had a negative skin prick tests to aeroallergens and/or serum specific IgE levels (sIgE ≥ 0.35KU/L, Phadia CAP System);

(4) Patients had received allergen immunotherapy,or been treated with antihistamines during the last week;

(5) Patients had an infection of the upper airway and have finished necessary antibiotics intake in more than 14 days or a viral infection more than 7 day;

(6) Patients had chronic sinusitis and purulent discharge;

(7) Patients had a history of drug allergy;

(8) Patients had drug-induced rhinitis;

(9) Pregnant or breast-feeding women;

(10) Patients suffering from neurological or psychiatric diseases;

(11) Patients can not provide contact information.

5.2.2 Sudy Design

5.2.2.1 Sample Size Estimation

Based on published data (3), we expected a prevalence of AR in Wuhan of around 20%. Considering a sampling error of 5% and a confidence interval of 95%, a sample of at least 246 participants was required.

5.2.2.2 Study period

The subjects were included during the following three periods:

(1) August 1, 2011 - October 15, 2011, Pollen concentration of Artemisia, Ambrosia and Humulus is higher during this period;

(2) October 30, 2011 - February 28, 2012, dust mites and mold are bleeding due to the temperature, humidity and other climatic factors change more apparent. Although patients allergic to dust mites may have symptoms throughout the year, this period is a peak. season;

(3) March 1, 2012 - June 1, 2012, Pollen concentration of Cypress and Platanusis higher during this period.

5.2.2.3 Questionnaire of AR

The main contents of the questionnaire include: general information (patient number, the time included and contact information); inclusion and exclusion criteria (see the section of patients); history; ARIA severity classification; AR symptom severity assessed by the score of VAS at inclusion and a Numeric Scale (NS) after 15 days; score of ARCT; AR treatment.

(1) General conditions of patients

The general conditions of patients include: age, sex, education (postgraduate, undergraduate and bachelor), residential area (city, suburbs and mountainous area), height, weight and Body Mass Index (BMI).

(2)   Diagnostic history and concomitant diagnosed pathologies

Diagnostic history includes: duration of the rhinitis and smoking. Concomitant diagnosed pathologies include: history of atopic dermatitis, history of asthma, history of ENT infection or antibiotics intake for respiratory infection in the last 12 months, recurrent rhinosinusitis, nasal deformities, allergic conjunctivitis and smell disturbance. If AR patients had both history of atopic dermatitis and history of asthma, they were considered as having "multimorbidity".

(3)   ARIA classification

Intermittent: < 4 days per week, or < 4 weeks per year;

Persistent: ≥ 4 days per week, and ≥ 4 weeks per year;

Mild: normal sleep, no impairment of daily activities, sport and leisure, normal work and school, no troublesome symptom;

Moderate-severe (one or more items): abnormal sleep, impairment of daily activities, sport and leisure, abnormal work and school, troublesome symptom.

(4)   Score of VAS at baseline

VAS is a scale from 0-10 cm, with 0 cm representing no symptoms and 10 cm representing maximal imaginable symptoms (42). Patients were asked to mark the line at that location that they found appropriate to best describe the severity of the symptoms they experienced at baseline. In this study, the severity of all combined symptoms (nasal and ocular symptom) and impact of AR (impact of sleep and work, social activities, physical activities and overall discomfort) was assessed using a VAS.

(5)   NS at day 15

Patients were also asked to rate the severity of their symptoms by a telephone interview using a NS ranging from "0" (no symptoms) to "10" (maximum imaginable symptoms) after 15 days of treatment.

(6)   ARCT

ARCT is a self-completion questionnaire on the control of AR validated by Demoly et al. (67), It is made up of five questions ranging from 1 to 5, and these scores were then added up to

obtain a score ranging from 5 to 25 (best score). A Chinese version of ARCT was obtained after a translation-back translation process (99).

(7)   AR treatment

The standardized treatment based on ARIA guidelines was put on: oral H1A, nasal H1A, ocular H1A, oral or nasal corticosteroid (CS), Leukotriene Receptor Antagonists, (LTRAs) and other treatment.

5.2.2.4   Initial Assessment

At the first visit (D0), patients were consecutively included in the study by physicians after written informed consent was obtained according to inclusion and exclusion criteria. Physicians completed a general questionnaire. For each patient, symptoms of AR and their impacts were scored by VAS levels and AR control by treatment measured by ARCT (32). Patients with a baseline VAS level < 5 cm were considered as having "mild" AR, whereas a VAS level ≥ 5 cm were equated with "moderate to severe" AR (42). Physicians followed a simple treatment based on the ARIA guidelines using a VAS score to assess severity.(21). Oral or nasal H1A was used for the patients with "mild" AR (VAS < 5). Oral or nasal H1A plus NCS and/or LTRAs were used for the patients with "moderate to severe" AR (VAS ≥ 5). Ocular H1A was used for the patients with ocular symptom.

5.2.2.5   Re-assessment

ARIA recommend the symptoms of patients with AR need to be re-assessed after 2-4 weeks treatment period (100). In this study, after 15 days, patients were reevaluated by a telephone interview using a NS and ARCT after 15±2 days (D15).

5.2.2.6   Data Entry

After the investigation was completed, all questionnaires were collected, reviewed, numbered and archived. The data was entered into the database and checked for accuracy.

5.2.3   Outcome measures

5.2.3.1   SCUAD

Currently, SCUAD does not have a precise definition. SCUAD defines those patients who have poor control of symptoms despite adequate guideline-directed pharmacotherapy (48, 54). For this study, patients presented a NS score at day 15 ≥ 5 were considered SCUAD patients.

5.2.3.2   Uncontrolled AR

Uncontrolled AR was defined by the score of ARCT after 15 days of treatment: patients with a score of ARCT < 20 were considered as having uncontrolled AR at day 15 (32).

5.2.3.3 Significant improvement in symptoms

A change between VAS (day 0) and NS (day 15) $\geq$ 2.5 was considered as a significant improvement in symptoms (71). Patients whose initial VAS score was $\leq$ 2 were considered as having a significant improvement in symptoms if they had a NS score equal to 0 at day 15.

5.2.4 Statistical analysis

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 for the qualitative data such as patient characteristics were carried out between groups by using 2. Comparisons of quantitative variables were made by using nonparametric Mann-Whitney U test and Wilcoxon test. Correlations between ARCT and VAS were examined using Spearman's rank test. A binary logistic regression was performed to evaluate possible risk factors for SCUAD, uncontrolled AR and insignificant improvement in symptoms. Only factors associated ($P < 0.15$) with the outcome were included in this model. The analysis was performed with SPSS 11.5 software with the significance level set at 5% (0.05).

5.3 Ethics

This study was approved by Ethics Committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, China (N° 20110702). Informed consent was obtained from each participant after a full explanation of the study.

5.4 Results

Two hundred fifty-two patients were recruited by 8 allergists from the allergy department of Tongji Hospital during 1 year (August 2011 - June 2012). 80 patients were included during August 1, 2011 to October 15, 93 patients were included during October 30, 2011 - February 28, 2012 and 79 patients were included during March 1, 2012 - June 1, 2012. Three patients could not be contacted by telephone after 15 days and therefore 249 patients were analysed at day-15.

5.4.1 Patient characteristics

Of 249 patients, the mean (SD) age was 32 ± (18) years, 103 (41%) were men and the mean (SD) age was 30 ± (10.9) years. Mean weight, height and BMI were respectively 58 ± (13) kg, 164 ± (10) cm and 21.3 ± (3.1) kg/m^2. 20 patients (7.9%) were postgraduate, 95 patients (37.7%) were bachelor and 137 patients (54.4%) were under bachelor. Among them, 191 (75.8%) lived in the city, 47 (18.7%) in suburbs and 14 (5.6%) in a mountainous area. Twenty-four patients (9.5%) were smokers. All patients had a diagnosis of sensitization to aeroallergens determined by skin-prick tests (96% of patients with a documented diagnosis) and/or serum allergen-specific IgE (53.6% of patients with a documented diagnosis). The first symptoms of their rhinitis appeared at a mean of 17 years before the consultation. 38.1% presented a family history of atopy, rhinitis for 27.8%, asthma for 11.5%, atopic dermatitis for 5.2%. Similarly, 43.7% had personal history of atopic dermatitis (24.6%) and asthma (24.2%). Half of them (50%) had a past history of ENT infection or antibiotics intake for respiratory infection in the last 12 months. Sneezing (99.2%), rhinorrhea (98.9%), nasal itching (96.8%), nasal congestion (92.9%), itchy eyes (88.9%) were commonly presented. Ocular symptoms were also commonly presented by most patients (65.9%), followed by nasal deformity (31.7%), rhinosinusitis (21.4%), smell disturbance (15.9%).

5.4.2   ARIA classification

According to ARIA, mild intermittent rhinitis was diagnosed in 6 patients (2.4%), mild persistent rhinitis in 7 (2.8%), moderate/severe intermittent rhinitis in 35 (13.9%) and moderate/severe persistent rhinitis in 204 (81%).

5.4.3   AR treatment

On the consultation day, all 249 patients were receiving H1A (87.6% of cases were oral administration, 1.6% nasal administration and 10.8% both routes of administration), 210 patients (84.3%) were receiving corticosteroids (97.6% nasal and 2.4% oral), 156 patients (62.7%) were being treated with ocular antihistamines, 74 patients (29.7%) with an anti-leucotrienes, and 28 patients (11.2%) with other treatments (Figure 5-1).
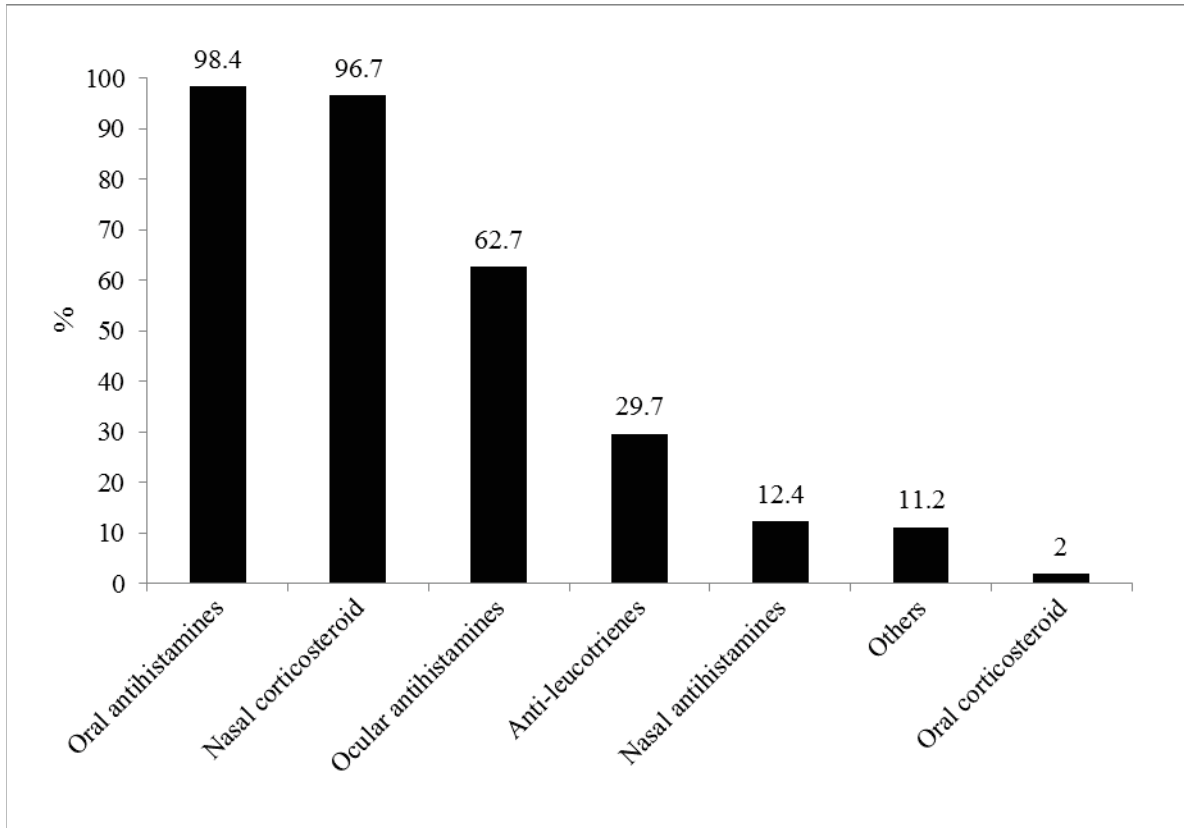
Figure 5-1 The initial treatment (%)

5.4.4 Improvement of symptoms and impact of AR
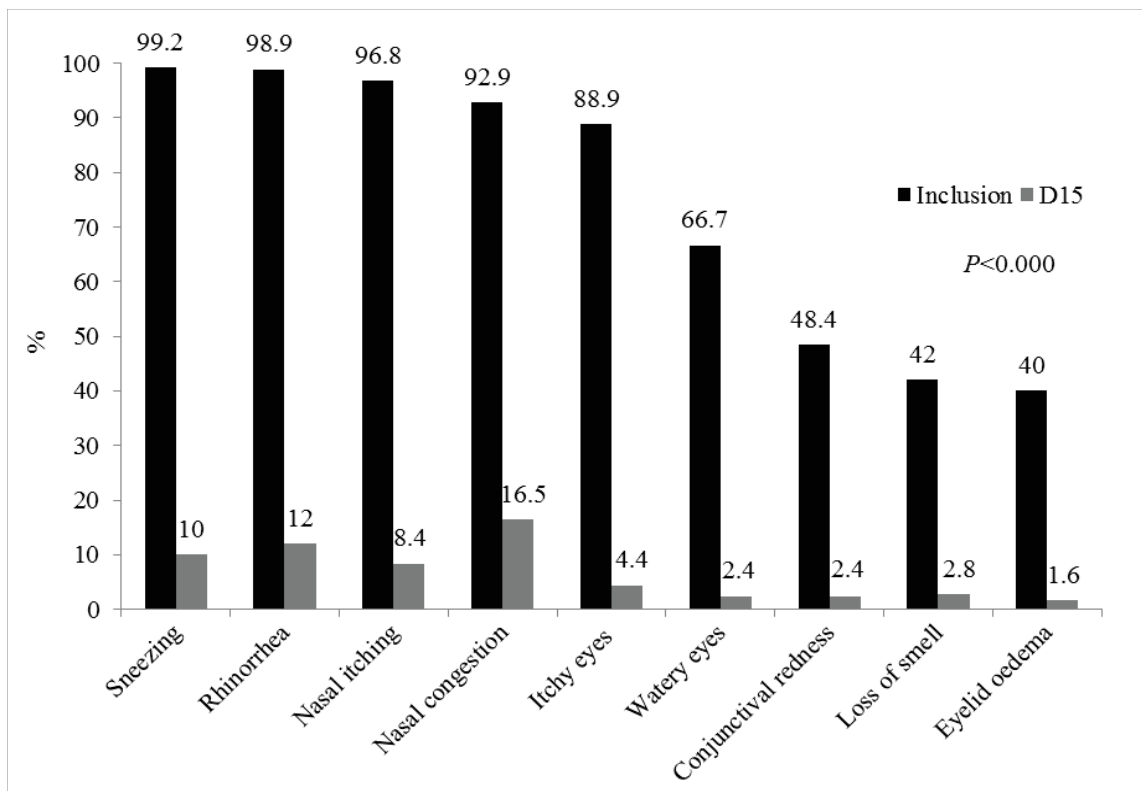
Figure 5-2 Improvement of nasal and ocular symptoms (%)

We compared the symptoms of AR patients at inclusion and on the 15th day, nasal and ocular symptoms reduced significantly ($P < 0.0001$) (Figure 5-2). This reduction in symptomatology was accompanied by a very important improvement of impact of AR on sleep, work life, social and physical activities (Figure 5-3), as well as on the overall discomfort (Figure 5-4).
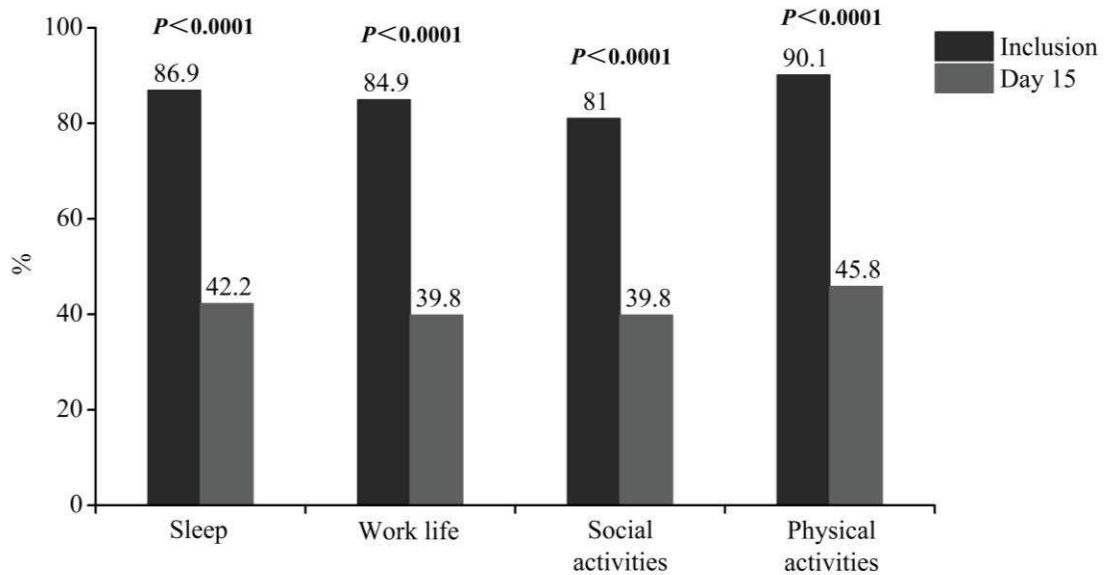
Figure 5-3 Improvement of impact of allergic rhinitis on sleep, work life, and social and physical activities
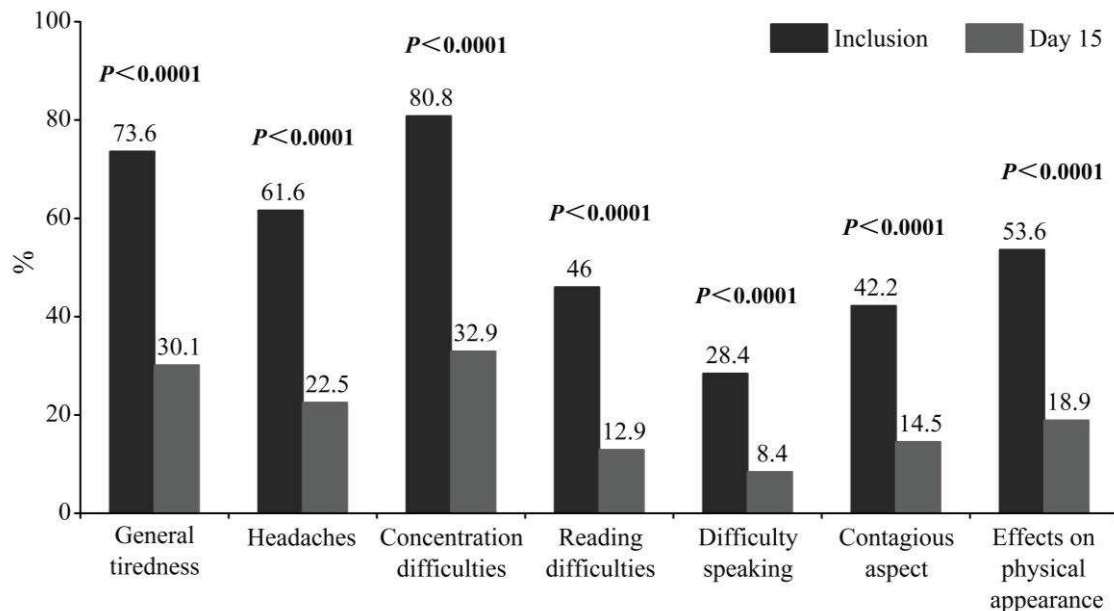
Figure 5-4 Improvement of impact of allergic rhinitis on overall discomfort

5.4.5 Improvement of the score of VAS and ARCT
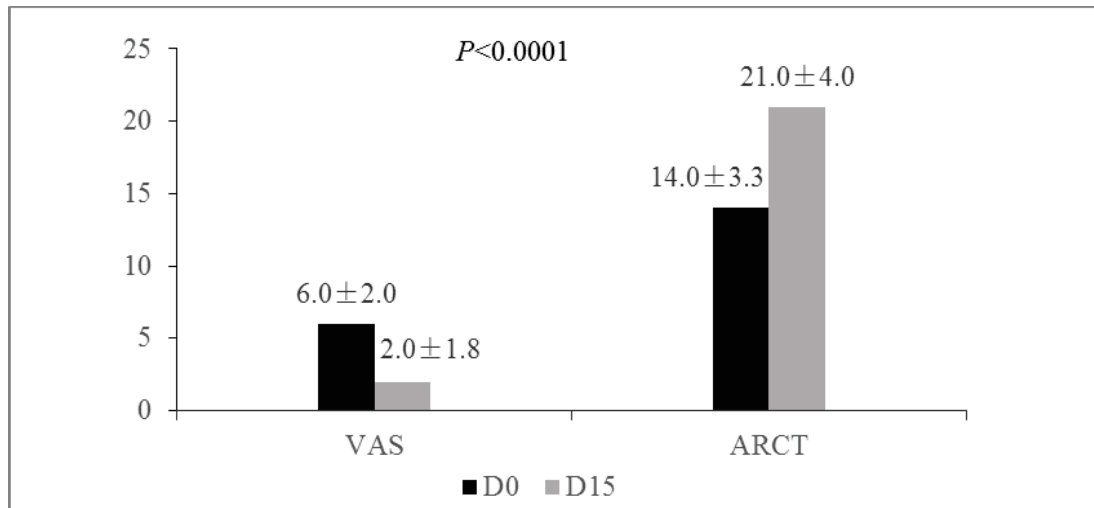
Figure 5-5 Improvement of overall score of VAS and ARCT

The improvement of overall score of VAS and ARCT is showed in Figure 5-5. The score of VAS decreased significantly and the average difference between the NS and the VAS was 3.0 ± 2.8. Compared to the score of ARCT at inclusion and on the 15th day, the score of ARCT improved markedly and the average difference was 6.9 ± 3.3. These changes showed the significant improvement in overall symptoms of AR patients.

Assessed on VAS at inclusion and NS on the 15th day, all nasal and ocular symptoms reduced dramatically ($P < 0.0001$) (Figure 5-6).
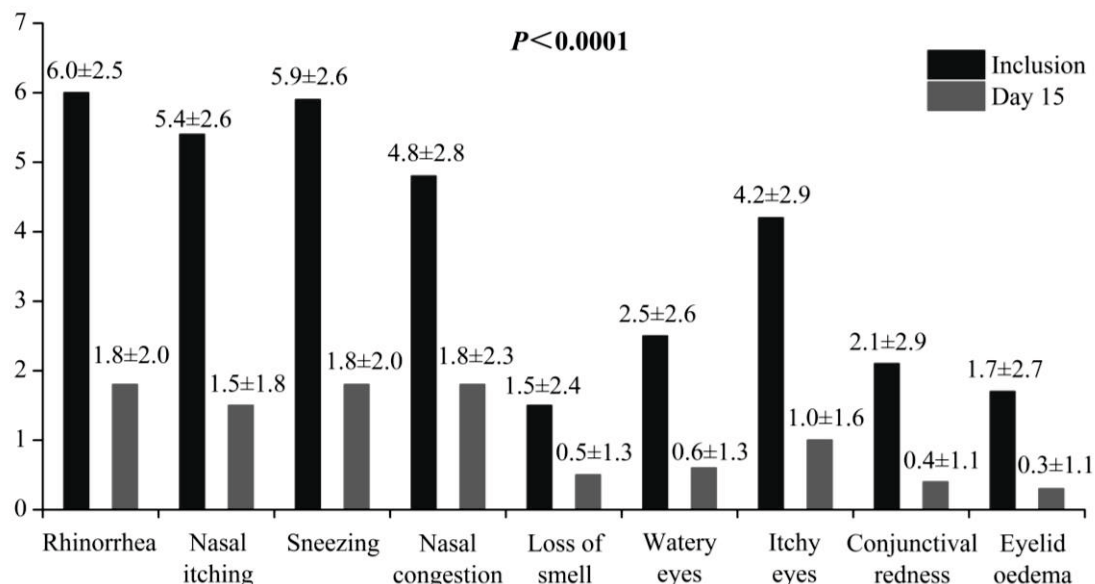
Figure 5-6 Improvement of nasal and ocular symptoms (mean ± SD)

5.4.6　Comparison of patients with mild vs. moderate/severe AR according to VAS

At inclusion, the comparisons of patients with mild (VAS < 5) and moderate to severe (VAS ≥ 5) AR are presented in Table 5-1.

5.4.6.1 General information

209 patients (82.9%) had moderate/severe rhinitis and 43 patients (17.1%) had mild rhinitis. No difference was found for age, gender, height, weight, education, residential area or smoking ($P > 0.05$). Patients with moderate/severe AR more frequently presented allergic conjunctivitis (70.8% vs 41.9%, $P < 0.001$).

5.4.6.2 ARIA classification and the impact of AR

There were more moderate/severe persistent AR according to ARIA in the moderate/severe (VAS ≥ 5) group (87.6% vs. 48.8%, $P < 0.001$) and, in this group, there were more impacts of AR, such as sleep, work life, social activities and physical activities were significantly more common ($P < 0.001$).

5.4.6.3 Treatment and AR control

Treatment with NS was more frequent and the number of SCUAD was significantly greater in patients with moderate/severe AR at inclusion ($P < 0.001$). Patients receiving nasal antihistamines were more common in mild (VAS < 5) group (46.3 vs. 5.8%, $P < 0.001$). At inclusion, there were more AR patients with the score ARCT ≥ 20 in mild (VAS<5) AR group (90.2% vs. 68.8%, $P < 0.05$).

Table 5-1 Characteristics of patients with mild and moderate/severe AR (as defined by VAS) at inclusion

	Mild AR (VAS < 5)	Moderate/severe AR (VAS ≥ 5)	P Value[1]
Number	43 (17.1)	209 (82.9)	-
Age (year)	30±16.0	32±18.0	0.729
Duration of the rhinitis (years)	14±11.0	16±10.0	0.183
Height (cm)	163±10.0	164±10.0	0.863
Weight (kg)	58.5±10.1	58±13.0	0.834
BMI (kg/m^2)	21.3±2.5	21.4±3.0	0.821
Male gender	21 (48.8)	82 (39.2)	0.243

Education:			
Postgraduate	4 (9.3)	16 (7.7)	0.957
Bachelor	15 (34.9)	80 (38.3)	0.676
Under bachelor	24 (55.8)	113 (54.1)	0.834
Residential area:			
City	33 (76.7)	158 (75.6)	0.873
Suburbs	7 (16.3)	40 (19.1)	0.661
Mountainous area	3 (7.0)	11 (5.3)	0.935
Smoking	6 (14.0)	18 (8.6)	0.423
History of atopic dermatitis	12 (27.9)	50 (23.9)	0.581
Family history of allergic diseases	14 (32.6)	82 (39.2)	0.412
History of asthma	12 (27.9)	49 (23.4)	0.534
Past history of ENT infection or antibiotics intake for respiratory infection in the last 12 months	20 (46.5)	106 (50.7)	0.615
Recurrent rhinosinusitis	12 (27.9)	42 (20.1)	0.256
Nasal deformities	9 (20.9)	71 (34)	0.094
Allergic conjunctivitis	18 (41.9)	148 (70.8)	<0.001
Smell disturbance	4 (9.3)	36 (17.2)	0.195
Rhinitis graded according to ARIA:			
Mild intermittent	5 (11.6)	1 (0.5)	<0.001
Mild persistent	6 (14.0)	1 (0.5)	<0.001
Moderate/severe intermittent	11 (25.6)	24 (11.5)	0.015
Moderate/severe persistent	21 (48.8)	183 (87.6)	<0.001
Impact of AR on sleep	25 (58.1)	194 (92.8)	<0.001
Impact of AR on work life	22 (51.2)	192 (91.9)	<0.001
Impact of AR on social activities	25 (58.1)	179 (85.6)	<0.001

Impact of AR on physical activities	32(74.4)	195 (93.3)	<0.001
Optimal treatment [2*]	36 (87.8)	194 (93.3)	0.377
Treatment at inclusion [*]:			
Oral antihistamines	41 (100)	204 (98.1)	1.000
Nasal corticosteroid	5 (12.2)	200 (96.2)	<0.001
Ocular antihistamines	20 (48.8)	136 (65.4)	0.045
Anti-leucotrienes	14 (34.1)	60 (28.8)	0.497
Nasal antihistamines	19 (46.3)	12 (5.8)	<0.001
Oral corticosteroid	0 (0)	5 (2.4)	0.595
Others	1 (2.4)	27 (13.0)	0.092
Controlled at inclusion (D0):			
According to ARCT	9 (20.9)	3 (1.4)	<0.001
Controlled at D15 [*]:			
According to ARCT	37 (90.2)	143 (68.8)	0.005
SCUAD [*]	1 (2.4)	60 (28.8)	<0.001

Data are presented as number (percentage) or means ± SD, unless otherwise specified.

[1]$\chi2$ and Wilcoxon-Mann-Whitney test were used for qualitative and quantitative variables.

[2]The treatment was considered as "optimal" if mild AR (VAS D0 < 5) received treatment with oral antihistamines and moderate to severe AR (VAS D0 ≥ 5) received treatment with oral antihistamines and nasal corticosteroid.

[*]Three patients were lost for follow-up and therefore 249 patients were analysed at D15.

5.4.7 Prevalence and characteristics of SCUAD patients

5.4.7.1 Prevalence and characteristics of SCUAD patients

The comparisons of the patients in different groups at day 15 (SCUAD vs non-SCUAD) are presented in Table 5-2. 24.5% of the patients had SCUAD (n = 61/249).

A past history of ENT infection or antibiotics intake for respiratory infection in the last 12 months, smell disturbance and impact of AR on sleep, work life, social activities and physical activities were more frequently present in patients with SCUAD, whereas history of atopic dermatitis was less common (*P* < 0.05; Table 5-2).

Patients with SCUAD were less frequently treated with anti-leucotrienes (4.9 vs. 37.8%, $P < 0.001$) and nasal antihistamines (4.9% vs 15.4%, $P = 0.033$), while nasal corticosteroid and other drugs were more frequently received (93.4 vs. 78.7%, $P = 0.009$). Almost all of them had uncontrolled AR according to ARCT at day-15.

Table 5-2 Characteristics of the patients in the different group at day 15
(SCUAD vs. non-SCUAD)

	SCUAD	Non-SCUAD	P value[1]
Number	61 (24.5)	188 (75.5)	-
Age (year)	32±19.0	32±18.0	0.664
Duration of the rhinitis (years)	16±10.5	16±10.0	0.778
Height (cm)	165.4±7.9	163.5±10.0	0.813
Weight (kg)	60±19.0	57.8±14.0	0.248
BMI (kg/m^2)	21.6±3.4	21.4±2.7	0.435
Male gender	25 (41.0)	77 (41.0)	0.997
Education:			
Postgraduate	8 (13.1)	12 (6.4)	0.159
Bachelor	20 (32.8)	74 (39.4)	0.357
Under bachelor	33 (54.1)	102 (54.3)	0.983
Residential area:			
City	44 (72.1)	145 (77.1)	0.428
Suburbs	14 (23.0)	32 (17.0)	0.300
Mountainous area	3 (4.9)	11 (5.9)	1.000
Smoking	7 (11.5)	16 (8.5)	0.487
History of atopic dermatitis	8 (13.1)	53 (28.2)	0.017
Family history of allergic diseases	28 (45.9)	67 (35.6)	0.152
History of asthma	14 (23.0)	45 (23.9)	0.875
Multimorbidity (asthma&atopic dermatitis)	2 (3.2)	16 (8.5)	0.170
Past history of ENT infection or antibiotics intake for respiratory infection in the last 12 months	39 (63.9)	86 (45.7)	0.014
Recurrent rhinosinusitis	15 (24.6)	38 (20.2)	0.468

Nasal deformities	25 (41.0)	54 (28.7)	0.074
Allergic conjunctivitis	42 (68.9)	123 (65.4)	0.623
Smell disturbance	17 (27.9)	22 (11.7)	0.003
Rhinitis graded according to ARIA:			
Mild intermittent	0 (0)	6 (3.2)	0.351
Mild persistent	0 (0)	7 (3.7)	0.279
Moderate/severe intermittent	4 (6.6)	31 (16.5)	0.052
Moderate/severe persistent	57 (93.4)	144 (76.6)	0.004
Impact of AR on sleep	58 (95.1)	158 (84.0)	0.027
Impact of AR on work life	61 (100)	150 (79.8)	<0.001
Impact of AR on social activities	56 (91.8)	145 (77.1)	0.012
Impact of AR on physical activities	60 (98.4)	164 (87.2)	0.012
Optimal treatment	55 (90.2)	175 (93.1)	0.639
Treatment at inclusion :			
Oral antihistamines	60 (98.4)	185 (98.4)	1.000
Nasal corticosteroid	57 (93.4)	148 (78.7)	0.009
Ocular antihistamines	43 (70.5)	113 (60.1)	0.145
Anti-leucotrienes	3 (4.9)	71 (37.8)	<0.001
Nasal antihistamines	3 (4.9)	29 (15.4)	0.033
Oral corticosteroid	3 (4.9)	2 (1.1)	0.096
Others	18 (29.5)	10 (5.3)	<0.001
Controlled at inclusion (D0):			
According to ARCT	0 (0)	12 (6.4)	0.093
Controlled at D15:			
According to ARCT	3 (4.9)	177 (94.1)	<0.001

Data are presented as number (percentage) or means $\pm$ SD, unless otherwise specified.

[1] $\chi 2$ and Wilcoxon-Mann-Whitney tests were used for qualitative and quantitative variables.

5.4.7.2 The risk factors for SCUAD at day 15

A binary logistic regression was performed to evaluate possible risk factors for SCUAD. Only

factors associated ($P < 0.15$) with the outcome were included in this model. The variables with significance level less than 0.05 ($P < 0.05$) were presented in Table 5-3. Treatment with oral corticosteroid, treatment with "others" and smell disturbance were positively associated with SCUAD (OR=32.167, 6.264, 2.922, $P < 0.05$).

Table 5-3 Risk factors for SCUAD at day 15

Patient's Characteristics	SCUAD			
	ß	OR	95% CI	P Value
History of atopic dermatitis	-1.359	0.257	0.096-0.688	0.007
Smell disturbance	1.072	2.922	1.129-7.562	0.027
Treatment with oral corticosteroid	3.471	32.167	1.847-560.199	0.017
Treatment with anti-leucotrienes	-3.751	0.023	0.003-0.197	0.001
Treatment with "others"	1.835	6.264	2.142-18.324	0.001

Hosmer and Lemeshow Test $P = 0.508$

5.4.7.3 Comparison of score of VAS and ARCT in different groups (SCUAD vs. non-SCUAD)

At inclusion, patients with SCUAD had slightly but significantly greater VAS scores and lower ARCT scores than non-SCUAD patients ($P < 0.0001$). The same result was found at day 15 ($P < 0.0001$) (Figure 5-7). Therefore, the assessment results of VAS and ARCT were consistent.
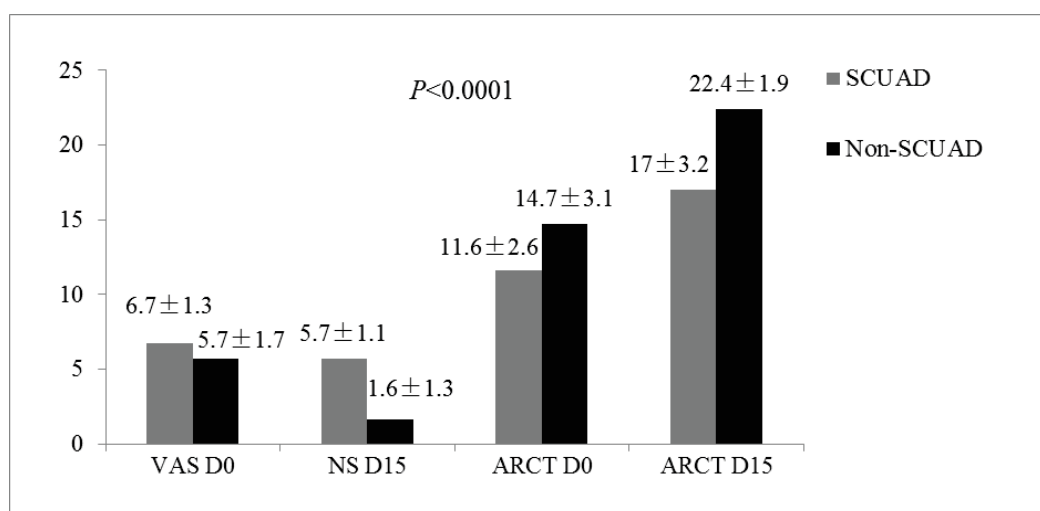
Figure 5-7 Comparison of score of VAS and ARCT (SCUAD vs. non-SCUAD)

The change of symptom severity score (NS-VAS) and ARCT (D15-D0) in the SCUAD patients is significantly lower than in non-SCUAD patients ($P < 0.0001$) (Figure 5-8).
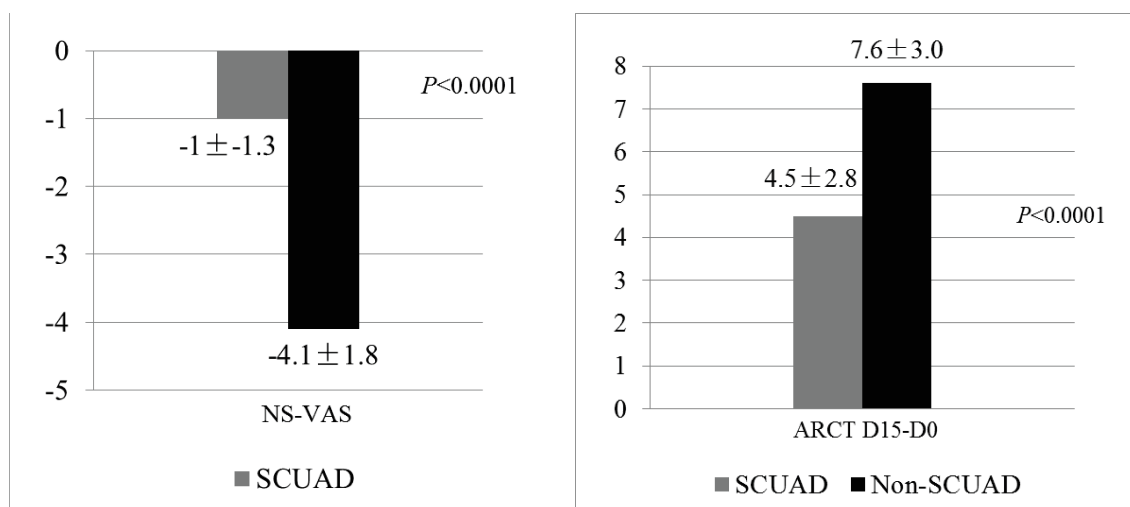
Figure 5-8 Change of the score of VAS and ARCT (SCUAD vs. non-SCUAD)

5.4.8 Characteristics of patients according to clinically significant vs insignificant improvement of symptoms

5.4.8.1 Characteristics of patients with insignificant improvement of symptoms

34.5% of the patients had insignificant improvement in symptoms at day 15. Most of them had postgraduate degrees (12.8 vs. 5.54%, $P = 0.045$), whereas less of them had bachelor degrees (29.1 vs. 42.3%, $P = 0.040$). Moreover, they frequently presented a smell disturbance (22.1 vs. 12.3%, $P = 0.043$) and were more frequently treated with other drugs (20.9 vs. 6.1%, $P < 0.001$), while less of them received anti-leucotrienes (4.7 vs. 42.9%, $P < 0.001$). The number of controlled AR at day-15 was significantly less (32.6 vs. 93.3%, $P < 0.001$) (Table 5-4).

Table 5-4 Characteristics of the patients in the different group at day 15 (significant improvement in symptoms vs. insignificant improvement in symptoms)

Number	Significant improvement in symptoms	Insignificant improvement in symptoms	P value [1]
	163 (65.5)	86 (34.5)	-
Age (year)	32.0±17.0	32.0±17.0	0.660
Duration of the rhinitis (years)	16.0±9.0	15.5±10.0	0.842
Height (cm)	164±10.0	164.5±12.0	0.443

Weight (kg)	58.0±13.0	58.0±17.0	0.657
BMI (kg/m^2)	21.4±2.8	21.5±3.1	0.418
Male gender	68 (41.7)	34 (39.5)	0.739
Education:			
Postgraduate	9 (5.5)	11 (12.8)	0.045
Bachelor	69(42.3)	25 (29.1)	0.040
Under bachelor	85 (52.1)	50 (58.1)	0.367
Residential area:			
City	124 (76.1)	65 (75.6)	0.931
Suburbs	29 (17.8)	17 (19.8)	0.702
Mountainous area	10 (6.1)	4 (4.7)	0.846
Smoking	13 (8.0)	10 (11.6)	0.344
History of atopic dermatitis	42 (25.8)	19 (22.1)	0.522
Family history of allergic diseases	56 (34.4)	39 (45.3)	0.090
History of asthma	39 (23.9)	20 (23.3)	0.906
Multimorbidity (asthma&atopic)	13 (7.9)	5 (5.8)	0.531
Past history of ENT infection or antibiotics intake for respiratory infection in the last 12 months	78 (47.9)	47 (54.7)	0.308
Recurrent rhinosinusitis	32 (19.6)	21 (24.4)	0.380
Nasal deformities	52 (31.9)	27 (31.4)	0.935
Allergic conjunctivitis	108 (66.3)	57 (66.3)	0.997
Smell disturbance	20 (12.3)	19 (22.1)	0.043
Rhinitis graded according to ARIA:			
Mild intermittent	4 (2.5)	2 (2.3)	1.000
Mild persistent	5 (3.1)	2 (2.3)	1.000
Moderate/severe intermittent	27 (16.6)	8 (9.3)	0.117
Moderate/severe persistent	127 (77.9)	74 (86.0)	0.122
Impact of AR on sleep	141 (86.5)	75 (87.2)	0.876
Impact of AR on work life	134 (82.2)	77 (89.5)	0.126

Impact of AR on social activities	130 (79.8)	71 (82.6)	0.594
Impact of AR on physical activities	145 (89.0)	79 (91.9)	0.469
Optimal treatment	150 (92.0)	80(93.0)	0.778
Treatment at inclusion :			
Oral antihistamines	160 (98.2)	85 (98.8)	1.000
Nasal corticosteroid	141 (86.5)	64 (74.4)	0.017
Ocular antihistamines	105 (64.4)	51 (59.3)	0.428
Anti-leucotrienes	70 (42.9)	4 (4.7)	<0.001
Nasal antihistamines	21 (12.9)	11 (12.8)	0.983
Oral corticosteroid	5 (3.1)	0 (0)	0.167
Others	10 (6.1)	18 (20.9)	<0.001
Controlled at inclusion (D0):			
According to ARCT	10(6.1)	2(2.3)	0.306
Controlled at D15::			
According to ARCT	152 (93.3)	28 (32.6)	<0.001

Data are presented as number (percentage) or means ± SD, unless otherwise specified

[1]χ2 and Wilcoxon-Mann-Whitney tests were used for qualitative and quantitative variables.

5.4.8.2 The risk factors for insignificant improvement of symptoms at day 15

A binary logistic regression was performed to evaluate possible risk factors for insignificant improvement of symptoms. Only factors associated ($P < 0.15$) with the outcome were included in this model. The variables with significance level less than 0.05 ($P < 0.05$) were presented in Table 5-5.

Treatment with "others" presented the strong association with patients had significant improvement in symptoms (OR = 4.348 [1.66-11.38], $P = 0.003$).

Table 5-5 Risk factors for insignificant improvement of symptoms at day 15

Patient's Characteristics	Insignificant improvement of symptoms			
	ß	OR	95% CI	P Value
Treatment with nasal corticosteroid	-1.387	0.250	0.104-0.600	0.002
Treatment with anti-leucotrienes	-2.706	0.067	0.023-0.197	0.000

| Treatment with "others" | 1.470 | 4.348 | 1.661-11.383 | 0.003 |

<div align="right">Hosmer and Lemeshow Test $P = 0.740$</div>

5.4.8.3 Comparison of patients with insignificant improvement in symptoms versus significant improvement in symptoms according to score of VAS and ARCT

At inclusion, the score of VAS in the two groups (significant improvement of symptoms vs. insignificant improvement of symptoms) were respectively 6.0 ± 2.0 and 6.0 ± 2.0 ($P = 0.129$). Patients with significant improvement of symptoms had significantly greater ARCT score than patients with insignificant improvement of symptoms ($P < 0.0001$).
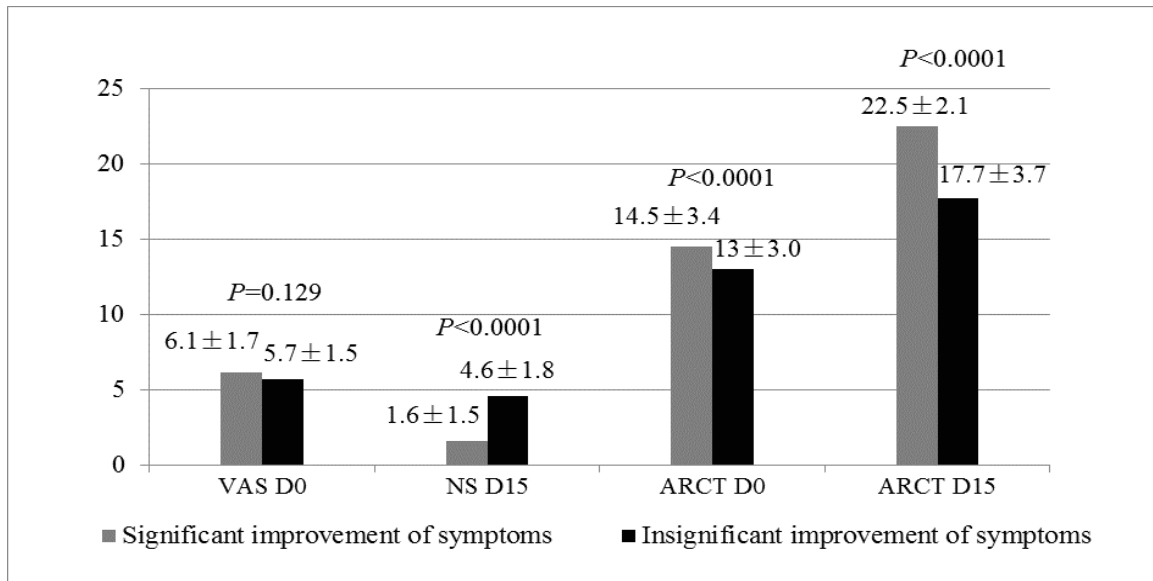
Figure 5-9 Comparison of score of VAS and ARCT (significant improvement of symptoms vs. insignificant improvement of symptoms)
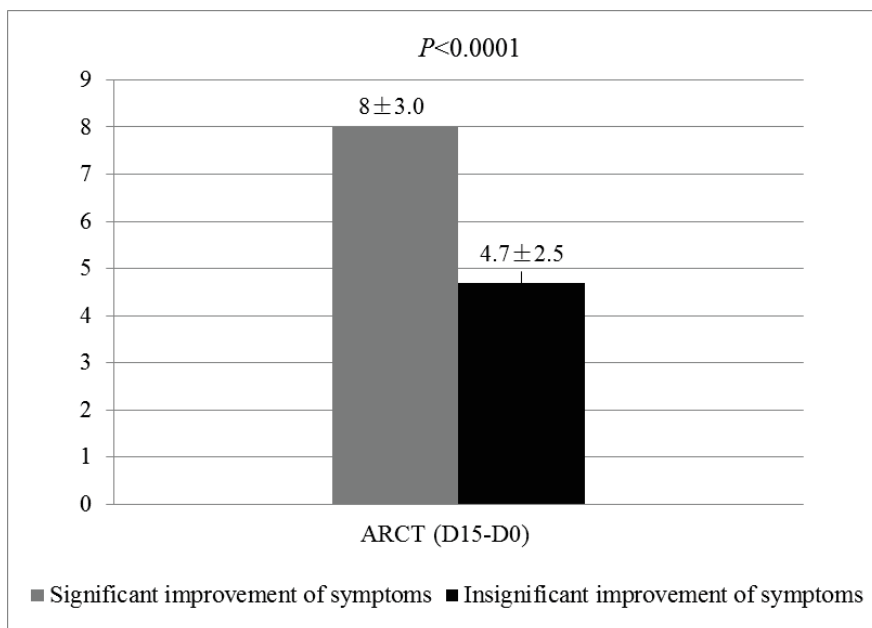
Figure 5-10 Change of the score of ARCT (significant improvement of symptoms vs. insignificant improvement of symptoms)

Patients with significant improvement of symptoms had markedly lower NS level and greater ARCT level than patients with insignificant improvement of symptoms ($P < 0.0001$) (Figure 5-9).

The change of ARCT score (D15-D0) in two groups (significant improvement of symptoms vs. insignificant improvement of symptoms) were respectively 8.0 ± 4.0 and 5.0 ± 3.0, ($P < 0.0001$) (Figure 5-10).

5.4.9 Comparison of patients with uncontrolled AR (ARCT < 20) and controlled AR (ARCT ≥ 20）

5.4.9.1 Characteristics of patients according to ARCT

The mean ARCTs were 14 ± 3.3 and 21 ± 4.0 at day-0 and day-15 respectively. ARCT ≥ 20 patients at inclusion were 4.8% and 72.3% after 15 days of treatment. At day-15, patients with uncontrolled AR (ARCT < 20) had higher weight ($P = 0.042$) and were more often smokers (15.9% vs. 7.0%, $P = 0.024$); they frequently presented a smell disturbance, moderate/severe persistent rhinitis according to ARIA, past history of ENT infection or antibiotics intake for respiratory infection in the last 12 months and impact of their AR on sleep, work life, social activities and physical activities ($P < 0.05$, Table 5-6). Patients with uncontrolled AR more frequently received other drugs (27.5 vs. 5.0%, $P < 0.001$), but less of them were being treated with anti-leucotrienes than patients with controlled AR (7.2 vs. 38.3%, $P < 0.001$). The

number of SCUAD was significantly greater in patients with uncontrolled AR (84.1 vs. 1.7%, $P < 0.001$) (Table 5-6).

5.4.9.2 Risk factors for uncontrolled AR at day 15

A binary logistic regression was performed to evaluate possible risk factors for uncontrolled AR. Only factors associated ($P < 0.15$) with the outcome were included in this model. The variables with significance level less than 0.05 ($P < 0.05$) are presented in Table 5-6.

Impact of AR on work life (OR = 9.409), treatment with oral corticosteroid (OR = 15.772) and treatment with "others" (OR = 6.826) were significant risk factors for uncontrolled AR (Table 5-7).

Table 5-6 Comparison of characteristics of the patients with uncontrolled AR and controlled AR at day 15

	Controlled AR (ARCT ≥ 20)	Uncontrolled AR (ARCT < 20)	P Value [1]
Number	180 (72.3)	69 (27.7)	-
Age (year)	32±17.0	32±18.0	0.799
Duration of the rhinitis (years)	16±10.0	16±10.5	0.863
Height (cm)	163±10.0	165±11.5	0.403
Weight (kg)	57±13.8	60±17.0	0.042
BMI (kg/m^2)	21.3±2.7	21.7±3.4	0.093
Male gender	71 (39.4)	31 (44.9)	0.431
Education:			
Postgraduate	11(6.1)	9 (13.0)	0.072
Bachelor	70 (38.9)	24 (34.8)	0.550
Under bachelor	99 (55.0)	36 (52.2)	0.689
Residential area:			
City	141 (78.3)	48 (69.6)	0.148
Suburbs	28 (15.6)	18 (26.1)	0.055
Mountainous area	11 (6.1)	3 (4.3)	0.816
Smoking	12 (6.7)	11 (15.9)	0.024

History of atopic dermatitis	48 (26.7)	13 (18.8)	0.199
Family history of allergic diseases	66 (36.7)	29 (42.0)	0.436
History of asthma	46 (25.6)	13 (18.8)	0.265
Past history of ENT infection or antibiotics intake for respiratory infection in the last 12 months	82 (45.6)	43 (62.3)	0.018
Recurrent rhinosinusitis	39 (21.7)	14 (20.3)	0.812
Nasal deformities	55 (30.6)	24 (34.8)	0.521
Allergic conjunctivitis	119 (66.1)	46 (66.7)	0.934
Smell disturbance	21 (11.7)	18 (26.1)	0.005
Rhinitis graded according to ARIA:			
Mild intermittent	6 (3.3)	0(0)	0.191
Mild persistent	7 (3.9)	0(0)	0.217
Moderate/severe intermittent	30 (16.7)	5 (7.2)	0.056
Moderate/severe persistent	137 (76.1)	64 (92.8)	0.003
Impact of AR on sleep	151 (83.9)	65 (94.2)	0.032
Impact of AR on work life	143 (79.4)	68 (98.6)	<0.001
Impact of AR on social activities	138 (76.7)	63 (91.3)	0.009
Impact of AR on physical activities	156 (86.7)	68 (98.6)	0.005
Optimal treatment	167 (92.8)	63 (91.3)	0.695
Treatment at inclusion:			
Oral antihistamines	177 (98.3)	68 (98.6)	1.000
Nasal corticosteroid	143 (79.4)	62 (89.9)	0.054
Ocular antihistamines	110 (61.1)	46 (66.7)	0.417
Anti-leucotrienes	69 (38.3)	5 (7.2)	<0.001
Nasal antihistamines	27 (15.0)	5 (7.2)	0.102
Oral corticosteroid	2 (1.1)	3 (4.3)	0.132
Others	9 (5.0)	19 (27.5)	<0.001
SCUAD	3 (1.7)	58 (84.1)	<0.001

Data are presented as number (percentage) or means±SD, unless otherwise specified

[1]χ2 and Wilcoxon-Mann-Whitney tests were used for qualitative and quantitative variables.

Table 5-7 Risk factors for uncontrolled AR at day 15

Patient's Characteristics	Uncontrolled AR			
	ß	OR	95% CI	P Value
Treatment with oral corticosteroid	2.758	15.772	1.594-156.040	0.018
Treatment with anti-leucotrienes	-2.523	0.080	0.022-0.298	0.000
Treatment with "others"	1.921	6.826	2.336-19.948	0.000
Impact of AR on work life	2.242	9.409	1.049-84.427	0.045

Hosmer and Lemeshow Test $P = 0.173$

5.4.10 Correlation between ARCT and VAS

Correlations between ARCT and VAS were poor on the consultation day (day 0) (r = -0.482, $P < 0.001$) but significantly stronger after 15 days of treatment (r = -0.884, $P < 0.001$). Similar findings were observed for the change between consultation day and day-15 (r = 0.588, $P < 0.001$) (Table 5-8).

Table 5-8 Correlations between symptoms, impact of AR, VAS and ARCT

	VAS (total)			ARCT		
	D0	D15	Change (D15-D0)	D0	D15	Change (D15-D0)
Nasal symptoms	0.749	0.817	0.634	-0.512	-0.816	0.428
	$P<0.0001$	$P<0.0001$	$P<0.0001$	$P<0.0001$	$P<0.0001$	$P<0.0001$
Ocular symtoms	0.415	0.551	0.279	-0.496	-0.557	0.393
	$P<0.0001$	$P<0.0001$	$P<0.0001$	$P<0.0001$	$P<0.0001$	$P<0.0001$
Impact of sleep	0.504	0.698	0.395	-0.734	-0.708	0.630
	$P<0.0001$	$P<0.0001$	$P<0.0001$	$P<0.0001$	$P<0.0001$	$P<0.0001$
Impact of work	0.559	0.661	0.343	-0.698	-0.668	0.560
	$P<0.0001$	$P<0.0001$	$P<0.0001$	$P<0.0001$	$P<0.0001$	$P<0.0001$
Social activities	0.482	0.597	0.350	-0.642	-0.628	0.522
	$P<0.0001$	$P<0.0001$	$P<0.0001$	$P<0.0001$	$P<0.0001$	$P<0.0001$

Physical activities	0.479	0.667	0.374	-0.669	-0.679	0.509
	P<0.0001	*P<0.0001*	*P<0.0001*	*P<0.0001*	*P<0.0001*	*P<0.0001*
Overall	0.339	0.593	0.202	-0.562	-0.637	0.422
discomfort	*P<0.0001*	*P<0.0001*	*P<0.0001*	*P<0.0001*	*P<0.0001*	*P<0.0001*
VAS (total)	-	-	-	-0.482	-0.884	-0.588
	-	-	-	*P<0.0001*	*P<0.0001*	*P<0.0001*

<div align="right">Spearman's rank test</div>

5.5 Discussion

5.5.1 Epidemiology of AR

The prevalence of AR has increased in recent years worldwide. There are many epidemiological studies of the prevalence of AR in other countries. Bauchau et al. (101) reported that among 9646 subjects, 19% self-identified as having AR numbered 19%, and of this group, 70% reported having a doctor diagnosis of AR. Klossek et al. (102) found that the overall prevalence of AR was 31%. China is vast in territory, it is relatively difficult to implement a large-scale epidemiological survey. Therefore, there are not enough epidemiological data of AR in China. Zhang et al. (3) reported the self-reported prevalence of AR (16-65 year old general population) in 11 major cities in China was 8.7%-24.1%, among of them, prevalence of AR in Wuhan was 19.3%. Kong et al. (103) reported the prevalence of AR in 3-6 year old children in Wuhan was 24.1%, and 10.8% were confirmed by skin tests. Moreover, the prevalence of positive nasal symptoms was 29.4% after 5-year follow-up (104). As a major industrial city of China with more than 8 million inhabitants, Wuhan has a high prevalence of AR and its impact on patient quality of life should be substantial but has never been evaluated. The results of prevalence of AR are different due to the different countries, regions, race, climate, environment and living habits and so on.

In recent years, the clinical research of AR is not only confined to the prevalence survey, but focus more on the severity of AR, the quality of life and treatment effect, so as to explore a simple, accurate and effective management or self-management method improved the quality of life of patients. As for the management of asthma, the control is now being considered as a goal of AR treatment. Therefore invertigating the prevalence of uncontrolled AR and proposing the simple and quantitative methods to evaluation the severity and control of AR are the aims of this study.

5.5.2 Assessment of the severity of AR

ARIA introduced a classification based on the symptom duration ("intermittent" vs. "persistent") and symptom severity impacting daily quality of life ("mild" vs. "moderate/severe") (38). VAS has long allowed the assessment of subjective symptoms such as pain VAS (105), and it is considered to be a sensitive, robust and reproducible method of expressing severity in AR (58). Bousquet et al. (42) found that a 0 to 10 cm VAS score and the RQLQ score were significantly correlated. VAS can also be used to assess the symptom severity of AR and the impact of quality of life (106, 107), but total VAS score is often used in practice due to its simple implement. VAS $\geq$ 5 is an easy way to distinguish mild and moderate/severe AR at inclusion of patients, and our study showed that 82.9% of the patients with moderate/severe AR had allergic conjunctivitis, moderate/severe persistent AR according to ARIA classification and symptoms usually with an impact on sleep, work life social activities and physical activities. In the telephone survey of Zhang et al. (3) including patients with self-reported AR in 11 major cities in China, 74.4% had intermittent AR, 25.6% had persistent AR and only 39.3% had presented to a clinic. This reflected that the impairments were correlated more strongly with severity than duration, and severity of symptoms was an important factor to drive the patients to the hospital allergy clinic.

5.5.3 Prevalence and characteristics of SCUAD patients

For different types of AR, ARIA recommends different treatment regiments, which makes it easy to apply in clinical practice (21). However, some patients still have very severe symptoms after adequate treatment according to ARIA guidelines. Bousquet et al (54) defined this form of the disease as SCUAD, and addressed attention to the control of AR patients using simple clinical tools. In this study, patients were reevaluated by a telephone interview using NS, thereby obtaining the prevalence of SCUAD.

The prevalence of SCUAD in our cohort was 24.5%, which was higher than that in France: 18.9% (54) and 22% (71). However, our cohort has very few mild intermittent/persistent AR patients (5.2%) compared to that of Bousquet et al. (20.2%), which implied that the prevalence of SCUAD might be overestimated in our cohort or reflect the reality in Wuhan. Both studies being run with different methodologies in different countries, it is not possible to draw any conclusion.

There are many risk factors associated with SCUAD, such as environment (allergen exposure, direct or indirect smoking, air pollution, etc.) (108), genetic factors (78, 79),

glucocorticoid-resistance (80), diagnosis and treatment-related factors and patient's own factor (psychological factor) (109). In this study, compared with non-SCUAD patients, SCUAD patients had less history of atopic dermatitis but more smell disturbance problem, more history of ENT infection or antibiotics administration in the last 12 months and more significant impact on quality of life. This may reflect either a higher susceptibility of these patients with upper respiratory infections or some participation of non-allergic components. Thus, bacterial infection of the upper airways may play an important role in SCUAD. The history of asthma and recurrent sinusitis were not significantly more prevalent in SCUAD compared to non-SCUAD patients, and more data is needed to better understand SCUAD pathophysiology.

5.5.4 Clinical response of patient with AR to drug treatment

Currently, there are many methods to assess the therapeutic effect in AR, but most have not yet been confirmed or implemented in real life (21). RQLQ and TSS6 are two methods commonly used, but their sensitivity are poor (110). VAS combines AR symptoms and the impact on quality of life of patients to assess the effect of treatment, and has been used in several clinical trials (106, 110, 111, 112). In a randomized cluster trial assessing VAS at baseline and after 15 days of treatment, the optimal cut-off in VAS was 30 mm (70). Other study reported changes in VAS greater than 23 mm may reflect the responsiveness to treatment (71). The patients in the first study were included to receive treatment according to the ARIA or to the free-choice treatment. The cut-off in the latter study was calculated on the basis of RQLQ and TSS score and the patients at baseline included a majority of severe AR. In this study, we chose the latter as the reference standard, but for easy implementation, a change in VAS $\geq$ 2.5 was considered as a significant improvement in symptoms.

The result showed that the percentage of patients with insignificant improvement was 34.5%. It was slightly higher than in the study of Zhang et al. (3) reporting that 27.2% of the patients received treatment in clinic, and amongst them, 71.1% were satisfied. To obtain the control of AR, it is probably necessary to better phenotype severe AR patients and patients with no response to current treatment and treat according to phenotype and not according to severity only, as it is the case nowadays.

5.5.5 The control of AR

Demoly et al. (67) demonstrated that similar to the asthma control questionnaire (113), ARCT is a sensitive self-questionnaire to distinguish poor and well-controlled rhinitis and is

correlated to VAS for symptoms and symptom impacts. According to WHO recommendations (39), the general course of treatment for patients with AR is 2-4 weeks. In our study, patients were assessed after 2 weeks after the start of treatment. We found that 27.7% of our patients had uncontrolled AR. This study validates the Chinese translation of ARCT. We also found weight, smoking, past history of ENT infection or antibiotics administration in the last 12 months and smell disturbance had impacts on AR control, and especially on work life (OR = 9.4), however, we do not know through which exact mechanisms. 27.7% of the patients with uncontrolled AR (ARCT < 20) presented higher prevalence of SCUAD, which also suggested that ARCT had a strong correlation with VAS and could be used as a surrogate indicator in future AR survey.

5.5.6 Clinical significance of study results

Based on our results, we propose a simple and effective practical method for the management of AR. First, a careful history, a nasal examination (using a nasal speculum/otoscope) and allergy tests (skin tests, *in vitro* tests or even nasal challenge) to confirm or exclude an allergic etiology are recommended to confirm the diagnosis of AR (38). Second, a VAS is used to evaluate the severity of AR and the threshold of 5 is satisfied to distinguish mild (VAS < 5) and moderate/severe (VAS ≥ 5) AR. The first-line treatment based on the ARIA guidelines is followed according to the assessment of severity using VAS score. Third, a reevaluation (possibly self-assessment) should be practiced after 15 days of treatment using a NS or ARCT.

When dealing with SCUAD or uncontrolled AR, the first question one should ask is about patient's compliance in correct medication use and adherence to the prescribed therapy. Correct utilization of the prescribed medication is a key factor for obtaining control by medical treatment beyond several weeks (114). Second, a co-morbidity should be looked for. For the AR patients with polyp, nasal valve dysfunction and/or malformations (e.g., septal deviation), a consensus has to be made by allergist and otolaryngologist. Li et al. (115) reported 68.9% of patients with AR had skin-prick tests positivity to more than one allergen in China. Therefore, allergen avoidance is important for the patients with positive skin prick testing and/or serum-specific IgE with symptoms when exposed to the positive allergens. It is likely that allergen immunotherapy can improve severe symptoms that are uncontrolled by medications, but more studies are required. Novel treatments are also needed.

5.5.7 Deficiencies and prospects

There are some limitations in this trial. First, patients were selected from one hospital

consultation, but because we included response to treatment, there is no real other way in China to include and follow treated patients, private medicine being very limited. Second, the reevaluated data of rhinitis severity was acquired by telephone interview but not by a rescheduled follow-up visit to assure patients' compliance; however, the scores filled out by patient in a print scale directly under the doctors' guide were considered to be reliable. Third, similar to other trials, few patients may have had poor compliance, which may have had an influence on the final outcome.

5.6 Conclusions

Our study provides the prevalence and demographic characteristics of uncontrolled AR and SCUAD in Wuhan allergy clinic. We suggest that physicians in charge of AR patients use VAS and/or ARCT as a simple and quantitative method for the global evaluation of AR severity and response to treatment.

6- Allergic Rhinitis Control Test questionnaire-driven stepwise strategy to improve allergic rhinitis control

6.1 Objectives

ARCT has been validated for assessing AR control and to identify severe AR. The present study was designed to further assess ARCT as a questionnaire driven stepwise pharmacological treatment to achieve AR control. ARCT offers an objective criterion for the stepwise pharmacotherapy of AR.

6.2 Materials and Methods

6.2.1   Patients

Patients consulting for AR were consecutively seen at the allergy department of Tongji Hospital, Wuhan, China during 1 year (September 2013 to August 2014).

The inclusion criteria were as follows:

(1)   Over 5 years of age, male or female;

(2)   With the diagnosis of AR according to ARIA and presenting clinical symptoms;

(3)   Over one year history of AR;

(4)   With positive skin prick tests result and serum specific IgE (sIgE $\geq$ 0.35KU/L, Phadia ImmunoCAP) to at least one relevant common aeroallergen;

(5)   All patients or their guardians had signed a written informed consent for anonymous data collection.

The exclusion criteria were as follows:

(1)   Receiving allergen immunotherapy;

(2)   With upper respiratory infection or chronic rhinosinusitis;

(3)   With a history of drug allergy;

(4)   Pregnancy or breast-feeding;

(5)   Who have had neurological or psychiatric system diseases.

Patients were classified as intermittent, persistent, mild, or moderate-to-severe AR according to ARIA classification (21).

6.2.2 Sudy 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.

6.2.2.1 Questionnaire of ARCT-driven stepwise strategy included

(1) Social, demographic and environmental data

The social, demographic and environmental information include: age, sex, occupation, residential area, smoking, living condition, contact with animal allergens and duration of the rhinitis.

(2) Rhinitis graded according to ARIA

Intermittent: < 4 days per week, or < 4 weeks per year;

Persistent: ≥ 4 days per week, and ≥ 4 weeks per year;

Mild: normal sleep , no impairment of daily activities, sport and leisure, normal work and school, no troublesome symptom;

Moderate-severe(one or more items): abnormal sleep, impairment of daily activities, sport and leisure, abnormal work and school, troublesome symptom.

(3) Impact of AR on quality of life (0-3 scale)

Patients were asked to rate the severity of impact of AR on quality of life using a scale including "0" (no impact), "1" (mild), "2" (moderate) and "3" (severe).

(4) Concomitant diagnosed pathologies

Diagnostic history include: history of asthma, history of sinus surgery and history of deviated septum surgery.

(5) Nasal examinations

Nasal examinations include: nasal mucosa, nasal structure and nasal secretions.

(6) Symptoms of AR

The symptoms of AR include: rhinorrhea, sneezing, nasal congestion, nasal itching, itchy eyes, watery eyes, cough and dysosmia.

(7) Test of allergens

16 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 (Populus, Cypress, Platanus, Artemisia, Ambrosia and Humulus) and moulds (Alternaria, Cladosporium, Aspergillus, Paecilomyces).

(8) Stepwise treatment

The study was designed as an open-labelled stepwise pragmatic 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 (32). 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 non sedative 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); Step 5: oral CS (0.5 mg/kg once daily), for 15 days. The endpoint of the patient was ARCT ≥ 20 and maintained for 15 days or received step 5 treatment for 15 days.Once the treatment was initiated, the patients were assessed with ARCT every 15 days until study completed.

6.2.3 Outcome measures

6.2.3.1 Allergic rhinitis control test

Allergic rhinitis control test (ARCT): ARCT is a self-completion questionnaire assessing the control of AR (32). 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 (32). The Chinese version has been validated (53).

6.2.3.2 Grading of AR control

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 every day 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); ARC5: when AR was not controlled by any treatment at the end of the study.

6.2.4 Statistical analysis

Taking into account the fact that about 10% of the patients suffering from AR in Wuhan would be uncontrolled (53), we estimated a prevalence of controlled AR at the end of the study of 90%. We calculated a sampling error of 4% with a confidence level of 95%. A sample of at least 216 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 for the qualitative data such as patient characteristics were carried out between groups using χ2 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 a posteriori in 3 groups that were: 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 by 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. Non-parametric 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 (survival)) and Schoenfeld residuals. Numerical variables were introduced in classes. Data were analysed using SPSS version 11.5 (SPSS, Inc., Chicago, IL) software and SAS (SAS® Studio, SAS® University edition, SAS Institute Inc.) with a final level of statistical significance of $P<0.05$.

6.3 Ethics

The study was approved by the Independent Ethics Committee (IEC) of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, China ((Nº 20130907). All the participators or his/her statutory guardians had signed the informed consent to participate in the study.

6.4 Results

6.4.1   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 year-old) and the mean duration of AR was 6.6 ± 5.7 years. According to 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.

16 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 of them, patients had positive skin-prick tests to 8 aeroallergens including *Dermatophagoides farina* (90.8%), *Dermatophagoides pteronyssinus* (90.0%), cockroach (15.6%), *Platanus* (8.0%), *Artemisia* (8.0%), *Alternaria* (3.2%), cat (1.6%) and dog (1.2%).

6.4.2 The treatment and control status of AR according to ARCT

6.4.3 Initial Assessment

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.

6.4.2.1 Overall situation of control and treatment at inclusion

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 (Figure 6-1). AR control rate increased with follow-up and treatment step up. 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.

6.4.2.2   The step up treatment and control status of AR

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); 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 H1A plus NCS [145 (67.4%) were controlled]; 2 (0.8%) patients finished the follow-up (because they had been controlled for 2 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, 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, 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, 7 (2.8%) patients were not controlled by any treatment and finished the follow-up passively (right-censored patients) (Table 6-1).
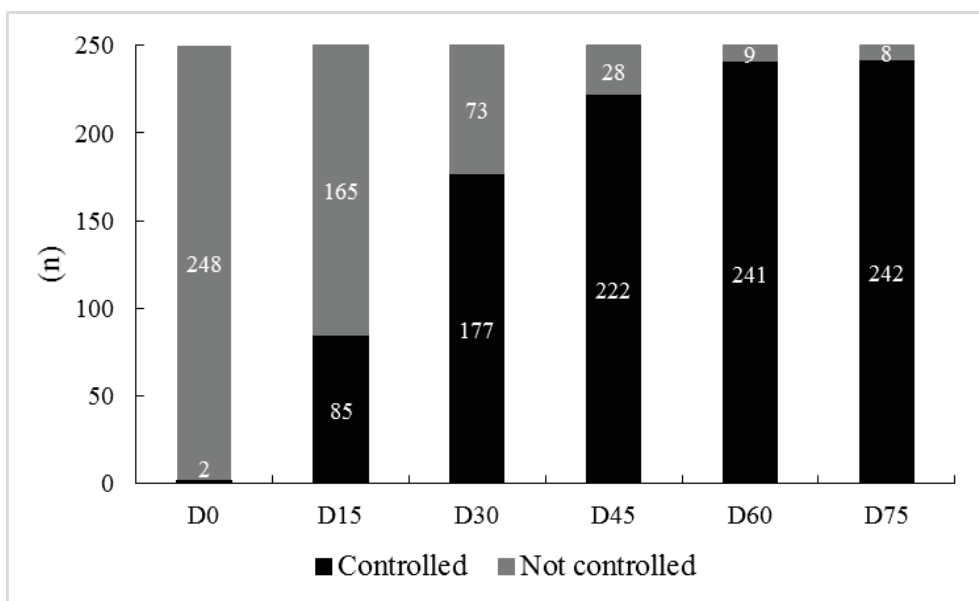
Figure 6-1 The control status of AR

Table 6-1. 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; NCS = Nasal corticosteroid;

LOCF=Last Observation Carried Forward;

N = not controlled; Y = controlled.

6.4.4 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 6-.

According to 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 subgroup 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 ($P < 0.01$).

Table 6-2. Comparison of characteristics of different AR subgroups

	Number	ARC1	ARC2	ARC3	ARC4	ARC5	P
	(%)	2 (0.8)	29 (11.6)	205 (82)	6 (2.4)	8 (3.2)	
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
Mold	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*
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
Platanus acerifolia	20(8.0)	-	3(15.0)	16(80.0)	0	1(5.0)	0.766
Artemisia sieversiana	20(8.0)	3(15.0)	15(75.0)	-	2(10.0)	-	0.340
Alternaria alternate	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

ARC = Allergic Rhinitis Control;

Dp = Dermatophagoides pteronyssinus; Df = Dermatophagoides farinae.

Qualitative data: 2test; Quantitative variables: Kruskal-Wallis H test;

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

* Sensitization to both *Dp* and *Df* was considered as monosensitization

6.4.5   Risk factor analysis

Ten variables ($P < 0.20$, Table 6-2) were kept in the multivariate model. After adjustment on each of the variables, the only factor that remained significant was asthma. Thus, compared to non-asthmatics, 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 ($P > 0.05$).

6.4.6   Predictors of achieving control

Twenty five per cent of the patients achieved control by D30 and three quarters by two months (D60) (Figure 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 at 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).
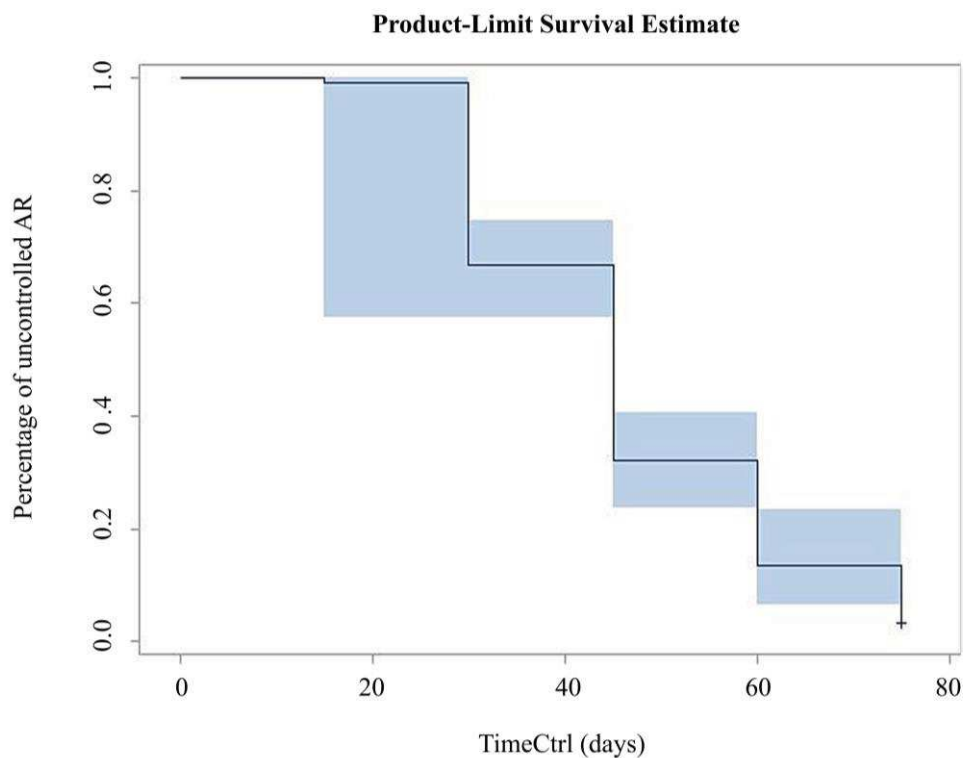
Figure 6-2 Graph of the survival analysis for the event "*controlled AR*" (probability to be uncontrolled at different time points)

Table 6-3 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 farina

6.5 Discussion

6.5.1   AR control status

Allergic rhinitis affects at least 600 million people worldwide and some studies suggest that its incidence is increasing (116). AR not only substantially affects patients' health-related quality of life but also causes reduced productivity at work and alters school performances (117). ARIA guidelines classify AR into 4 subgroups according to 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 (118). 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.

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 regimens varies in different areas and populations (119). 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 (120). Our preliminary study (53) 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 (32, 53). In this study, we further assessed ARCT as a questionnaire driven stepwise pharmacotherapy for AR.

6.5.2   ARCT driven treatmentcould achieve AR well control

Our study showed a slightly higher control rate of AR compared to the treatment regimen determined by AR severity classification in ARIA (32, 41). Previous published data showed that, using ARCT (32) or a visual analog scale (41), 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. In published real life studies (32, 41), the choice of treatment was left to the physician. With our prolonged and pre-defined stepped up treatment, the AR control rate elevated gradually up to 96.8% at day 75. This demonstrates that ARCT driven treatment could achieve AR well control in the majority of the patients in a step-wise 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 2-4 weeks interval. Two weeks is the duration chosen to validate the sensitivity to change of patient related outcomes in AR (32, 41). Only two patients' symptoms relapsed when controlled after only 2 weeks in conditions of high level allergen exposure (house dust mite), concomitant respiratory infection, non-compliance and other cofactors, which probably led to the overestimation of long term AR control level in our study (data not shown).

6.5.3   The demographic and clinical characteristics impacted AR treatment.

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 (121). Patients with moderate/severe persistent AR have a greater bronchial hyperreactivity and may be more likely to suffer from asthma than those with mild intermittent AR (122). ARIA recommend oral H1A and NCS to be used to control the symptoms of moderate/severe AR (20). We also observed that AR associated with asthma needed more medications, confirming previous studies in which comorbidities may affect the

control level of AR (123)

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 AR controlled, and we supposed that cough might be a manifestation of asthma or airway hyperreactivity (124). However, after adjustment on other variables, cough as a symptom in itself become non-significant, probably owing to the multiple mechanisms eliciting cough in AR patients (association of asthma, presence of posterior nasal drip…).

6.5.4 Deficiencies and prospects

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 (125). 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 VAS 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 if 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 (126). However, the placebo effects were less than 60% in majority studies (127). 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 was derived from the ARCT driven stepwise pharmacotherapy but not to a placebo effect.

6.6 Conclusion

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 2 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.

7- General discussion

7.1 New information brought

The prevalence of AR has increased in recent years worldwide. However, little epidemiological data have been published for AR in China. In this series of studies, the prevalence and demographic characteristics of uncontrolled AR and SCUAD in the Wuhan Allergy Clinic were provided. Specifically, this study indicated that VAS and ARCT are simple and quantitative methods and self-completion questionnaire that can be used for a global evaluation of the severity and control of AR. Moreover, the criteria utilized for the assessment of AR severity and control as well as the existing validated instruments were reviewed and we provide insight into their use in clinical practice. Our further study showed 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. The study result suggested that the majority of AR patients can be controlled with ARCT driven stepwise standard treatment.

7.2 Strength and limitations

This series of studies were prospective cohort studies. Patients consulting for AR were consecutively enrolled in the allergy department of Tongji Hospital, Wuhan, China during 1 year. All patients were prospectively assessed using questionnaire (VAS and ARCT). Standardized treatment based on ARIA guidelines was put on. Patients were reevaluated by a telephone interview using a numerical scale and ARCT. The second study is on the basis of the preliminary study and was designed to assess ARCT as a questionnaire driven stepwise pharmacological treatment to achieve AR control. Therefore, in methodology and operability, they are reliable, objective and easy to draw practical conclusions from.

There are some limitations in the first trial. First, patients were selected from one hospital consultation, but because we included response to treatment, there is no real other way in China to include and follow treated patients, private medicine being very limited. Second, the reevaluated data of rhinitis severity was acquired by telephone interview but not by a rescheduled follow-up visit to assure patients' compliance; however, the scores filled out by patient in a print scale directly under the doctors' guide were considered to be reliable. Third, similar to other trials, few patients may have had poor compliance, which may have had an influence on the final outcome.

A few limitations may hamper the results of the second study. 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. 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, 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 VAS or RCAT. 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 and the high efficacy was derived from the ARCT driven stepwise pharmacotherapy but not to a placebo effect.

7.3 Perspectives

According to our results, we suggest that physicians in charge of AR patients use VAS and/or ARCT as a simple and quantitative method for the global evaluation of AR severity and response to treatment. It should help the physician to control AR better. As shown in recent years, remote measurements (by phone or over the Internet) could conceivably reduce the frequency of face-to-face consultations. Applications on cellular phones (i.e., e-health technology) could help patients to manage their AR. Our study also 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. Another study would need to be designed to assess ARCT as a questionnaire driven step-down (and not up) pharmacological treatment to achieve AR control.

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Annexe 1 Allergic Rhinitis Control Questionnaire

Part 1 Initial Assessment Questionnaire

Number	└┴┴┴┘	
Date:	└┴┴┴┘	
TEL:		

Inclusion criteria

1. Aged 18–75 years	₁ Yes	₂ No
2. Presented at least 2 clinical symptoms of AR (rhinorrhea, nasal congestion, sneezing, nasal itching)	₁ Yes	₂ No
3. Had a history of AR for at least the past 2 years	₁ Yes	₂ No
4. Had a positive skin prick tests to aeroallergens and/or serum serum specific IgE level(sIgE ≥ 0.35KU/L, Phadia CAP) System	₁ Yes	₂ No
5. Had a history of AR symptoms when exposed to allergens	₁ Yes	₂ No
6. Volunteer to participate in the study, and have the ability to read, understand and sign an informed consent form.	₁ Yes	₂ No

Exclusion criteria	₁ Yes	₂ No
1. Receiving allergen immunotherapy	₁ Yes	₂ No
2. Had an infection of the upper airway and have finished necessary antibiotics intake in more than 14 days or a viral infection more than 7 day	₁ Yes	₂ No
3. Had chronic sinusitis and purulent discharge	₁ Yes	₂ No
4. Had a history of drug allergy	₁ Yes	₂ No
5. Had drug-induced rhinitis	₁ Yes	₂ No
6. Pregnant or breastfeeding women	₁ Yes	₂ No
7. Suffering from neurological or psychiatric disorders	₁ Yes	₂ No

8. Can not to provide contact information	₁ Yes	₂ No

General information

Age (year) |�___|

Sex ₁ Male ₂ Female

Height (cm) |___|___|___|

Weight (kg) |___|___|___| ⌟

BMI (kg/m^2) |___|___|___| ⌟

Education:

Postgraduate	₁ Yes	₂ No
Bachelor	₁ Yes	₂ No
Under bachelor	₁ Yes	₂ No

Residential area:

City	₁ Yes	₂ No
Suburbs	₁ Yes	₂ No
Mountainous area	₁ Yes	₂ No

History

Duration of the rhinitis (years): |___|___| ⌟

Smoking	₁ Yes	₂ No
History of atopic dermatitis	₁ Yes	₂ 否
Family history of allergic diseases	₁ Yes	₂ No
History of asthma	₁ Yes	₂ No
Past history of ENT infection or antibiotics intake for respiratory infection in the last 12 months	₁ Yes	₂ No
Recurrent rhinosinusitis (> 3times /year)	₁ Yes	₂ No

Nasal deformities	1 Yes	2 No
Allergic conjunctivitis	1 Yes	2 No
Smell disturbance	1 Yes	2 No

Rhinitis graded according to ARIA

Symptoms of AR : <4 days per week, or <4 weeks per year	1 Yes	2 No
Symptoms of AR ≥4 days per week, and ≥4 weeks per year	1 Yes	2 No
Impact of AR on sleep	1 Yes	2 No
Impact of AR on work life	1 Yes	2 No
Impact of AR on social activities	1 Yes	2 No
Impact of AR on physical activities	1 Yes	2 No

Assessment of AR according to VAS

Please place the cursor at the position that best defines the severity of your AR symptoms. The left end (0cm) correspond to no symptoms and the right end (10cm) to maximal imaginable symptoms.

0   1   2   3   4   5   6   7   8   9   10

No symptoms   Maximal imaginable symptoms
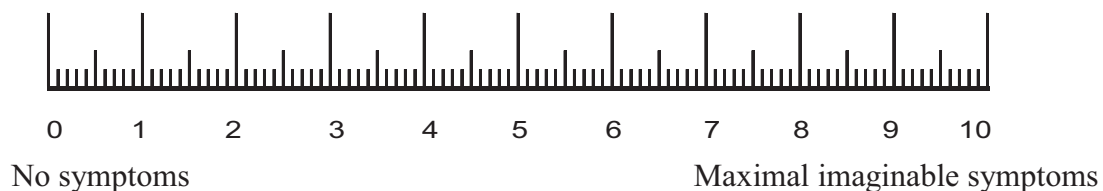
Please place the cursor at the position that best defines the severity of your AR symptoms and mark the score in the followlling table:

1. Sneezing

2. Rhinorrhea

3. Nasal congestion

4. Nasal itching

5. Itchy eyes

⌐_|__|_

6. Conjunctival redness

⌐_|__|_

7. Watery eyes

⌐_|__|_

8. Loss of smell

⌐_|__|_

9. Eyelid oedema

⌐_|__|_

Please place the cursor at the position that best defines the severity of impact of AR on quality of life and mark the score in the followlling table.

1. Impact of AR on sleep

_|__|_

2. mpact of AR on work life

_|__|_

3. Impact of AR on social activities

_|__|_

4. Impact of AR on physical activities

_|__|_

Please place the cursor at the position that best defines the severity of impact of AR on overall discomfort and mark the score in the followlling table.

1. General tiredness

_|__|_

2. Headaches

_|__|_

3. Concentration difficulties

_|__|_

4. Reading difficulties

5. Difficulty speaking

6. Contagious aspect

7. Effects on physical appearance

Allergic Rhinitis Control Test（ARCT）

During the last 2 weeks, has your allergic rhinitis had an effect on your professional/personal activities?

   1 Permanently   2 Very often   3 Often   4 Not often   5 Never

During the last 2 weeks, has your allergic rhinitis made you irritable?

   1 Permanently   2 Very often   3 Often   4 Not often   5 Never

During the last 2 weeks, has your allergic rhinitis disturbed your sleep (going

to sleep, waking at night)?

   1 Permanently   2 Very often   3 Often   4 Not often   5 Never

During the last 2 weeks, have you needed to use an additional treatment not prescribed by your doctor to treat your allergic rhinitis?

1 ≥ 4nights /week	2 2-3nights/week	3 1 night/week	4 1-2times in all	5 Never

During the last 2 weeks, how would you assess your allergic rhinitis?

1 Not controlled at all	2 Very slightly controlled	3 Somewhat controlled	4 Well controlled	5 Completely controlled

Total score:

Treatment

Nasal antihistamines	1 Yes	2 No
Oral antihistamines	1 Yes	2 No
Ocular antihistamines	1 Yes	2 No
Nasal corticosteroid	1 Yes	2 No
Oral corticosteroid	1 Yes	2 No
Anti-leucotrienes	1 Yes	2 No
Others	1 Yes	2 No

Part 2 Follow-up Questionnaire

Number   └─┴─┴─┴─┘

Follow-up date   └─┴─┴─┴─┘

Assessment of AR according to NS（Telephone interview）

Please tell me the the number that best defines the severity of your AR symptoms. 0 correspond to no symptoms and 10 to maximal imaginable symptoms.

└──┴──┘

Please tell me the the number that best defines the severity of your AR symptoms. 0 correspond to no symptoms and 10 to maximal imaginable symptoms.

1. Sneezing   └──┴──┘

2. Rhinorrhea   └──┴──┘

3. Nasal congestion   └──┴──┘

4. Nasal itching   └──┴──┘

5. Itchy eyes   └──┴──┘

6. Conjunctival redness   └──┴──┘

7. Watery eyes   └──┴──┘

8. Loss of smell   └──┴──┘

9. Eyelid oedema   └──┴──┘

Please tell me the the number that best defines the severity of impact of AR on quality of life. 0 correspond to no symptoms and 10 to maximal imaginable symptoms.

1. Impact of AR on sleep   └──┴──┘

2. Impact of AR on work life   └──┴──┘

3. Impact of AR on social activities   └──┴──┘

4. Impact of AR on physical activities   └──┴──┘

Please tell me the the number that best defines the severity of impact of AR on overall

discomfort. 0 correspond to no symptoms and 10 to maximal imaginable symptoms

1. General tiredness   └──┴──┘

2. Headaches   └──┴──┘

3. Concentration difficulties   └──┴──┘

4. Reading difficulties   └──┴──┘

5. Difficulty speaking   └──┴──┘

6. Contagious aspect   └──┴──┘

7. Effects on physical appearance   └──┴──┘

Allergic Rhinitis Control Test（ARCT）

During the last 2 weeks, has your allergic rhinitis had an effect on your professional/personal activities?

$_1$ Permanently $_2$ Very often $_3$ Often $_4$ Not often $_5$ Never

During the last 2 weeks, has your allergic rhinitis made you irritable?

$_1$ Permanently $_2$ Very often $_3$ Often $_4$ Not often $_5$ Never

During the last 2 weeks, has your allergic rhinitis disturbed your sleep (going

to sleep, waking at night)?

$_1$ Permanently $_2$ Very often $_3$ Often $_4$ Not often $_5$ Never

During the last 2 weeks, have you needed to use an additional treatment not prescribed by your doctor to treat your allergic rhinitis?

$_1$ ≥ 4nights /week $_2$ 2-3nights/week $_3$ 1 night/week $_4$ 1-2times in all $_5$ Never

During the last 2 weeks, how would you assess your allergic rhinitis?

$_1$ Not controlled at all $_2$ Very slightly controlled $_3$ Somewhat controlled $_4$ Well controlled $_5$ Completely controlled

Total score: |___|___|___|

Treatment

Nasal antihistamines	1 Yes	2 No
Oral antihistamines	1 Yes	2 No
Ocular antihistamines	1 Yes	2 No
Nasal corticosteroid	1 Yes	2 No
Oral corticosteroid	1 Yes	2 No
Anti-leucotrienes	1 Yes	2 No
Others	1 Yes	2 No

Annexe 2 Questionnaire of Allergic Rhinitis Control Test-driven stepwise strategy

Part 1 Initial Assessment Questionnaire

Number	└─┴─┴─┴─┘
Date：	└─┴─┴─┴─┘

Inclusion criteria

1. Over 5 years of age   1 Yes   2 No

2. With the diagnosis of AR according to ARIA and presenting clinical symptoms   1 Yes   2 No

3. Over one year history of AR   1 Yes   2 No

4. With positive skin prick tests result and serum specific IgE (sIgE $\geq$ 0.35KU/L, Phadia ImmunoCAP) to at least one relevant common aeroallergen;   1 Yes   2 No

5. All patients or their guardians had signed a written informed consent for anonymous data collection   1 Yes   2 No

Exclusion criteria

1. Receiving allergen immunotherapy;   1 Yes   2 No
2. With upper respiratory infection or chronic rhinosinusitis;   1 Yes   2 No
3. With a history of drug allergy;   1 Yes   2 No
4. With pregnancy or breast-feeding;   1 Yes   2 No
5. Who have had neurological or psychiatric system diseases   1 Yes   2 No

Social,demographic and environmental data

Age (year)   └─┴─┘

Sex   1 Male   2 Female

Duration of the rhinitis (years):	$\lfloor$ _ $\rfloor$ _ $\rfloor$	
Occupation:	₁ Yes	₂ No
Famer	₁ Yes	₂ No
Staff	₁ Yes	₂ No
Worker	₁ Yes	₂ No
Student	₁ Yes	₂ No
Unemployed	₁ Yes	₂ No
Other careers	₁ Yes	₂ No
Residential area		
Urban	₁ Yes	₂ No
Rural	₁ Yes	₂ No
Smoking		
≥1 year	₁ Yes	₂ No
Passive smoking	₁ Yes	₂ No
No smoking	₁ Yes	₂ No
Contact with animal allergens (≥1 week)	₁ Yes	₂ No
Living condition		
Wet	₁ Yes	₂ No
Mold	₁ Yes	₂ No
Bedding used ≥ 10 years	₁ Yes	₂ No
Cockroach	₁ Yes	₂ No

Rhinitis graded according to ARIA

Symptoms of AR : <4 days per week, or <4 weeks per year	₁ Yes	₂ No
Symptoms of AR ≥4 days per week, and ≥4 weeks per year	₁ Yes	₂ No
Impact of AR on sleep	₁ Yes	₂ No

Impact of AR on work life	1 Yes	2 No
Impact of AR on social activities	1 Yes	2 No
Impact of AR on physical activities	1 Yes	2 No
Impact of AR on quality of life (0-3 scale)		
None (0)	1 Yes	2 No
Mild (1)	1 Yes	2 No
Moderate (2)	1 Yes	2 No
Severe (3)	1 Yes	2 No
History of asthma	1 Yes	2 No
Duration of asthma (year)	└──┴──┘	
History of sinus surgery	1 Yes	2 No
History of deviated septum surgery	1 Yes	2 No
Nasal examinations		
Abnormal nasal mucosa	1 Yes	2 No
Abnormal structure	1 Yes	2 No
Increased nasal secretions	1 Yes	2 No
Symptoms of AR		
Rhinorrhea	1 Yes	2 No
Sneezing	1 Yes	2 No
Nasal congestion	1 Yes	2 No
Nasal itching	1 Yes	2 No
Itchy eyes	1 Yes	2 No
Watery eyes	1 Yes	2 No
Cough	1 Yes	2 No

Dysosmia		1 Yes	2 No

Test of allergens（**To tick only when the test was performed and the result was positive**）

Allergen	Prick test	Specific IgE
Dermatophagoides pteronyssinus,	1	2
Dermatophagoides. farinae	1	2
Dog danders	1	2
Cat danders	1	2
Cockroach	1	2
Mulberry silk	1	2
Polulus	1	2
Cypress	1	2
Platanus	1	2
Artemisia	1	2
Ambrosia	1	2
Humulus	1	2
Alternaria	1	2
Cladosporium	1	2
Aspergillus	1	2
Paecilomyces	1	2

Allergic Rhinitis Control Test（**ARCT**）

During the last 2 weeks, has your allergic rhinitis had an effect on your professional/personal activities?

　　1 Permanently　　　2 Very often　　　3 Often　　　4 Not often　　　5 Never

During the last 2 weeks, has your allergic rhinitis made you irritable?

　　1 Permanently　　　2 Very often　　　3 Often　　　4 Not often　　　5 Never

During the last 2 weeks, has your allergic rhinitis disturbed your sleep (going to sleep, waking at night)?

　　1 Permanently　　　2 Very often　　　3 Often　　　4 Not often　　　5 Never

During the last 2 weeks, have you needed to use an additional treatment not

prescribed by your doctor to treat your allergic rhinitis?

1 ≥ 4nights /week   2 2-3nights/week   3 1 night/week   4 1-2times in all   5 Never

During the last 2 weeks, how would you assess your allergic rhinitis?

1 Not controlled at all   2 Very slightly controlled   3 Somewhat controlled   4 Well controlled   5 Completely controlled

Total score: └──┴──┘

Treatment		
Nasal antihistamines	1 Yes	2 No
Oral antihistamines	1 Yes	2 No
Nasal corticosteroid	1 Yes	2 No
Oral corticosteroid	1 Yes	2 No
Anti-leucotrienes	1 Yes	2 No
Ocular antihistamines	1 Yes	2 No
No treatment	1 Yes	2 No
Change the treatment	1 Yes	2 No

Part 2 Follow-up Questionnaire

Number └──┴──┴──┴──┘

Follow-up date └──┴──┴──┴──┘

Allergic Rhinitis Control Test（ARCT）

During the last 2 weeks, has your allergic rhinitis had an effect on your professional/personal activities?

1 Permanently   2 Very often   3 Often   4 Not often   5 Never

During the last 2 weeks, has your allergic rhinitis made you irritable?

1 Permanently   2 Very often   3 Often   4 Not often   5 Never

During the last 2 weeks, has your allergic rhinitis disturbed your sleep (going to sleep, waking at night)?

1 Permanently   2 Very often   3 Often   4 Not often   5 Never

During the last 2 weeks, have you needed to use an additional treatment not prescribed by your doctor to treat your allergic rhinitis?

1 ≥ 4nights /week   2 2-3nights/week   3 1 night/week   4 1-2times in all   5 Never

During the last 2 weeks, how would you assess your allergic rhinitis?

1 Not controlled at all   2 Very slightly controlled   3 Somewhat controlled   4 Well controlled   5 Completely controlled

Total score: ⌞__⌞__⌟

Treatment		
Nasal antihistamines	1 Yes	2 No
Oral antihistamines	1 Yes	2 No
Nasal corticosteroid	1 Yes	2 No
Oral corticosteroid	1 Yes	2 No
Anti-leucotrienes	1 Yes	2 No
Ocular antihistamines	1 Yes	2 No
Change the treatment	1 Yes	2 No

Annexe 3 ARIA Clasiffication

Intermittent

. < 4 days per week

. <u>or</u> < 4 weeks

Persistent

. ≥ 4 days per week

. <u>and</u> ≥ 4 weeks

Mild

Normal sleep

& no impairment of daily activities, sport, leisure

& normal work and school

& no troublesome symptoms

Moderate-severe

One or more itms

. Abnormal sleep

. impairment of daily activities, sport, leisure

. abnormal work and school

. troublesome symptoms
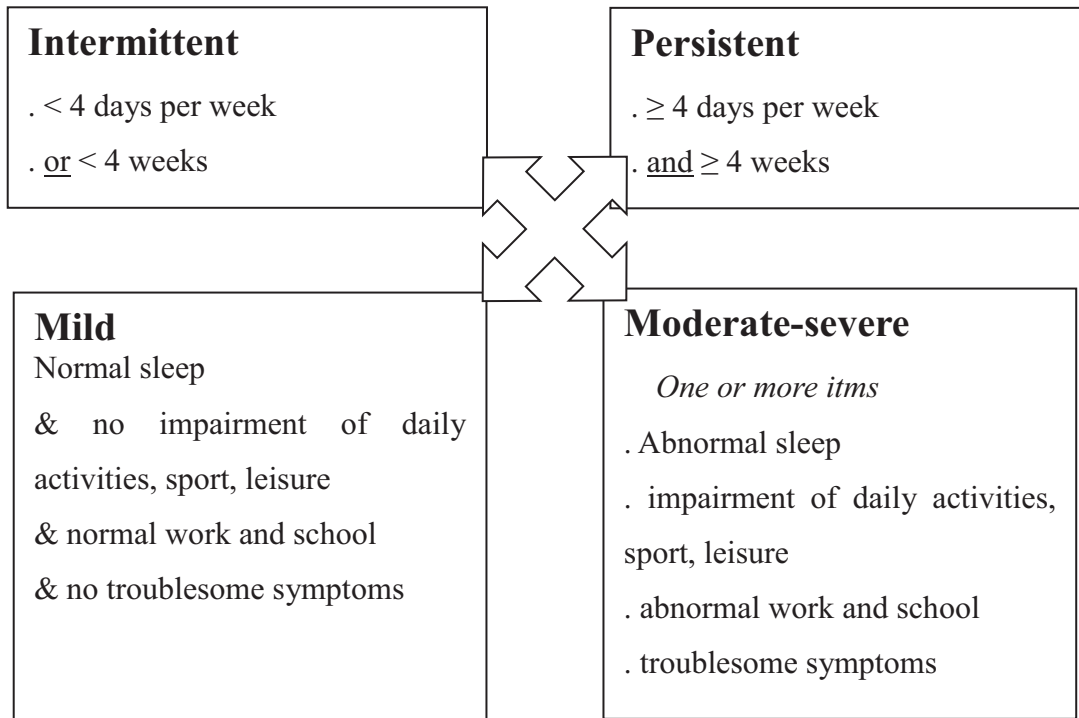
Annexe 4 Informed Consent Form

Prevalence of uncontrolled allergic rhinitisin Wuhan, China:A prospective cohort study

Research background

Your case will be reported by Professor Zhu and Doctor Wang of the allergy department of Tongji Hospital, Wuhan.

This study was approved by the Ethics Committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, China.(N^0 20110702). This form gives you important information about the study. It describes the purpose, process and method of the study, and please take time to review this information carefully. If you decide to take part in the study, you will be asked to sign this form.

Research purposes

Allergic rhinitis (AR) is a common disease worldwide. The main aim of this study is to investigate the prevalence of uncontrolled AR and severe chronic upper airway disease (SCUAD) consulting in the allergy department of Tongji Hospital, Wuhan, and to describe the clinical characteristics of these patients.

Research process and methods

You will be asked to complete a questionnaire include: general information, inclusion and exclusion criteria, history; severity classification; score of symptoms and AR treatment with the help of doctors. You will follow a standardized treatment of AR. After 15 days,your symptoms will be reevaluated by a telephone interview of doctors.

Research significance

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.

Privacy policy

Your privacy will be protected during the study.

Statement

Taking part in this study is completely voluntary. You do not have to participate if you don't want to.You may also leave the study at any time. If you leave the study before it is finished, there will be no penalty to you, and you will not lose any benefits to which you are

otherwise entitled.

Signature

I understand the information printed on this form. My questions so far have been answered. I agree to take part in this study.

Date: Signature:

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

Research background

Your case will be reported by Professor Zhu and Doctor Wang of the allergy department of Tongji Hospital, Wuhan.

This study was approved by the Ethics Committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, China. This form gives you important information about the study. It describes the purpose, process and method of the study, and please take time to review this information carefully. If you decide to take part in the study, you will be asked to sign this form.

Research purposes

Allergic Rhinitis Control Test (ARCT) has been validated for assessing allergic rhinitis (AR) control and to identify severe AR. The present study was designed to further assess ARCT as a questionnaire driven stepwise pharmacological treatment to achieve AR control.

Research process and methods

You will be asked to complete a simple questionnaire include: 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 with the help of doctors on the consultation day . 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. If ARCT score was equal or above 20 (controlled AR) and maintained for 15 days, you would finish the study; if ARCT score was strictly less than 20 (uncontrolled AR), you would receive higher step treatment according to a predefined open design up to step 5 (oral corticosteroid). Once the treatment was initiated, the patients were assessed with ARCT every 15 days until study completed.

Research significance

The results of this study can help doctors and patients understand the clinical features and control of AR in Wuhan City. A simple and quantitative method will be proposed for physicians to assess AR severity and response to treatment.

Privacy policy

Your privacy will be protected during the study.

Statement

Taking part in this study is completely voluntary. You do not have to participate if you don't want to.You may also leave the study at any time. If you leave the study before it is finished, there will be no penalty to you, and you will not lose any benefits to which you are otherwise entitled.

Signature

I understand the information printed on this form. My questions so far have been answered. I agree to take part in this study.

Date: Signature:

Annexe 5 Publications

[1] Youna Wang, Rongfei Zhu, Guanghui Liu, et.al. Prevalence of uncontrolled allergic rhinitis in Wuhan, China: a prospective cohort study. American Journal of Rhinology & Allergy. 2014, 28 (5):397-403.

[2] Youna Wang, Shanshan Qi, Rongfei Zhu, et al. Which Clinical Indicators for The Control of Allergic Rhinitis? Revue Francaise d'Allergologie. 2015, 3(55): 194-195.

[3] Wang Y, Chen H, Zhu R, et al. Allergic Rhinitis Control Test questionnaire-driven stepwise strategy to improve allergic rhinitis control: a prospective study. Allergy, 2016. DOI:10.1111/all.12963.

Acknowledgements

Finally I could have a delighted time after 3 years PH.D study. I write this final part with excited, cheerful and complicated mood I have taken an interesting and unforgettable experience in Montpellier. It is a really nice city with nice people.

First of all, I would like to express my gratitude to my supervisor, Professor Jean-Pierre Daurès, for his instructive suggestions and valuable comments on the writing of this thesis. I am deeply grateful of his help in the completion of this thesis.

I would like to extend my sincere gratitude to my co-supervisor, Professor Pascal Demoly, for his constant encouragement and guidance. Without his invaluable help, this thesis could not have reached its present form. I have nice experience under his advising and I learn a lot of stuff from him, including how to start a scientific project, write papers as well as interact with people.

I want to thank Professor Jean Bousquet, Professeur Jocelyne JUST et Docteur Isabella Annesi-Maesano, who have offered me valuable suggestions and expert guidance on my thesis.

At the same time, I would like to express my heartfelt gratitude to Professor Guanghui Liu and Professor Rongfei Zhu for providing me chances to study in France. They not only have spent much time reading through each draft and provided me with inspiring advice but also took care of my daily life.

Special thanks should go to my best friends in Montpellier, Anca Mirela CHIRIAC, who gave me her help and time in listening to me and helping me work out my problems during the difficult course of the thesis. Her encouragement and unwavering support has sustained me through frustration and depression.

Besides, I wish to thank the Professors, teachers and my colleagues at the Department of Allergy, Hôpital Arnaud de Villeneuve: Madame Marie pascal Demoly, Dr. Jean Luc, Bourrain, Dr. Marie Lagreula, Dr. Maria Chiara Leoni, Dr. Rik Schrijvers, who have instructed and helped me a lot in the past 3 years. I also want to thank all the members in the

Department of Allergy, Tongji Hospital for their direct and indirect help to me and providing an enjoyable work environment.

Finally, I greatly appreciate my parents and husband's support and endless love. They always been helping me out of difficulties and supporting without a word of complaint.

It is interesting life in France for these 3 years. It will affect me for the whole life. It is time to say goodbye to friends and people in Montpellier. I will miss you all.