

Safety and efficacy of rush allergen-specific immunotherapy in Chinese allergic rhinitis patients

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Abstract

The purpose of this prospective, open-IV clinical trial was to assess the safety and efficacy differences between Rush immunotherapy (RIT) and conventional immunotherapy in Chinese allergic rhinitis (AR) patients. The trial involved 174 patients with AR. They were divided into two groups according to their preference of therapy: RIT or conventional immunotherapy. A total of 162 patients completed a 1-year treatment course. For safety and effectiveness evaluation, the local and systemic adverse reactions were recorded throughout the initial phase of both groups. Weeks 0, 2, 5, and 17 were set as observation time points for immunoglobulin G (IgG) and IgG4. Besides that, another observation time point (Week 11) was added in for a visual analog scale (VAS) and a weekly drug dosage scale. In the RIT group, systemic adverse events of AR were similar to those of the conventional therapy group. LTB4 was descended. The VAS of the RIT group did not show a downward trend clearly, instead Week 5 was higher compared with Week 0. The weekly drug dosage scale did not indicate a significant decline, but there was a clear rise in IgG4 in the RIT group. The safety and efficacy of RIT for AR is positive, but further study is needed for improvement.

Keywords

allergic rhinitis, conventional immunotherapy, rush immunotherapy

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Introduction

Allergic rhinitis (AR) is a common and prevalent disease in the ENT department. Epidemiological studies conducted in 11 cities in the mainland of China revealed a self-reported prevalence of AR as high as 8.0–21.4%.¹

Allergen-specific immunotherapy (AIT), administered subcutaneously, is an effective therapy for AR.² It is currently known as the only available treatment that can modulate the immune response to modify the natural course of the disease and prevent the development of new sensitizations, with therapeutic gains persisting even after discontinuation of treatment.^{3,4}

AIT can be divided into two phases, the build-up and maintenance phases. The immunotherapy build-up schedule is further grouped as conventional and

accelerated schedules based on the duration for build-up. The latter may be administered using

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cluster and rush immunotherapy schedules (RIT). RIT offers the shortest time for build-up and can shorten the treatment from 4 months in conventional schedules to less than 1 week. Therefore, it can improve patient medication adherence and reduce their dropout rates.⁵ RIT with honey bee venom and pollen for AR has been carried out in Europe.⁶ However, in China, house dust mites and common floor mites are the leading triggers of AR and currently no RIT with standardized house dust mite antigen has been established. Therefore, to explore a safe, effective, and standardized RIT protocol suitable for China will greatly promote the use of AIT and benefit the AR patients in China. In this study, the safety and efficacy of RIT with standardized house dust mites in patients with moderate-to-severe AR was observed using a prospective study, with a conventional schedule as the control.

Materials and methods

The clinical data

The AR patients from the Department of Otolaryngology of Guangdong General Hospital and Union Hospital of Huazhong University of Science and Technology were enrolled according to World Health Organization (WHO) recommendations and European Academy of Allergology and Clinical Immunology (EAACI) guidelines.^{7,8} Skin prick test (SPT) was performed using histamine (positive control) and standardized allergen extracts (ALK-Abelló, Hørsholm, Denmark). The standardized allergen extracts include house dust mites, common floor mites, tropical fowl mites, artemisia, ragweed, mixed mold group I and group IV mixed with fungal American cockroach, German cockroach, cat fur, dog fur, mixed grass-pollen (*Corylus heterophylla*, *Betula*, and *Alnus cremastogyne*) were detected. The patients were divided into two groups also according to the preference of the patients: one group underwent RIT and another group was subjected to conventional immunotherapy. Patients in the RIT group were hospitalized during the build-up phase. The study groups were comparable in terms of gender, age, race, and region as well as history of asthma. The peripheral total IgE concentrations in both groups were detected to compare the similarity of the allergy between the two groups before treatment.

From 30 June 2011 to 30 June 2012, 104 patients underwent RIT (referred to as the RIT

group) and 70 cases were treated with conventional immunotherapy (referred to as the conventional immunotherapy group). This study was conducted in accordance with the Declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Guangdong General Hospital. Written informed consent was obtained from all participants.

Immunotherapy schedule

All patients were treated with AIT using standardized house dust mite (HDM) vaccine (Alutard SQ, ALK-Abelló). The highest concentration of vaccines had an allergenic activity of 100,000 SQ/mL (equivalent to 9.8 µg/mL). The maximum dose of 100,000 SQ/m was administered on the day 6 of RIT and in week 15 of the conventional immunotherapy. The highest concentration of 100,000 SQ/mL was given again in week 5 of the RIT, and week 17 of the conventional immunotherapy. After that, the interval between each administration extended to 6 weeks, until the end of treatment.

For safety concerns, all patients were hospitalized for 6 days and orally given antihistamines and glucocorticoids during RIT. The dosages for adults were as follows: loratadine tablets (Schering-Plough, Kenilworth, NJ, USA) 10 mg/day, methylprednisolone tablets 8 mg/day; the dosage for children was half of the adult dose. Pulmonary function tests were performed in the RIT group to determine whether patients had complications with asthma. In addition, peak expiratory flow (PEF) was measured three times both before and after RIT using a peak flow meter. If the average value of PEF is no more than 80% of the predicted normal value, the patients should be given symptomatic treatment and injections were given under close observation. If the mean value of PEF is no more than 70% of predicted value, patients should cease injections and were given appropriate treatment. The injection could be continued only after PEF value returned to normal. On the seventh day of the two treatment regimens, peripheral blood samples were taken for serological test. In order to match the two groups, the patients in the conventional treatment group were also treated with oral administration of antihistamines and glucocorticoids for 1 week. All patients were observed at least for 30 min after the injection. The detailed information about regimen was listed in Table 1.

Table 1. Rush and conventional ASIT schedule.

Conventional schedule					Rush schedule				
Visit time	Injection no.	Vial no.	Volume (mL)	Dose (SQ-U)	Visit time	Injection no.	Vial no.	Volume (mL)	Dose (SQ-U)
WID1	1	1	0.2	20	WID1	1 (9:00)	1	0.1	10
						2 (11:00)	2	0.1	100
						3 (15:00)	3	0.1	1000
					WID2	4 (9:00)	3	0.2	2000
						5 (11:00)	3	0.4	4000
						6 (15:00)	3	0.6	6000
					WID3	7 (9:00)	3	0.8	8000
						8 (11:00)	4	0.1	10,000
						9 (15:00)	4	0.2	20,000
					WID4	10 (9:00)	4	0.3	30,000
						11 (15:00)	4	0.4	40,000
					WID5	12 (9:00)	4	0.5	50,000
						13 (15:00)	4	0.5	50,000
					WID6	14 (9:00)	4	1.0	100,000
W2	2	1	0.4	40					
W3	3	1	0.8	80					
W4	4	2	0.2	200					
W5	5	2	0.4	400	W5	15	4	1.0	100,000
W6	6	2	0.8	800					
W7	7	3	0.2	2000					
W8	8	3	0.4	4000					
W9	9	3	0.8	8000					
W10	10	4	0	10,000					
W11	11	4	0.2	20,000	W11	16	4	1.0	100,000
W12	12	4	0.4	40,000					
W13	13	4	0.6	60,000					
W14	14	4	0.8	80,000					
W15	15	4	1.0	100,000					
W17	16	4	1.0	100,000	W17	17	4	1.0	100,000

Observation time points and serological indicators

Six time points in the questionnaire were set to conduct visual analogue scale (VAS) and weekly medication score in both study groups. They were week 0 (before treatment, W0), week 2 (1 week after the dose build-up phase of RIT, W2), week 5 (the first injection of dose maintenance phase of RIT, W5), week 11 (after the first 6-week interval of RIT, W11), week 17 (initial dose maintenance phase of conventional immunotherapy, injection time of the two group overlapped, W17), and week 52 (1 year AIT finished). Furthermore, peripheral blood samples were collected for serological tests at five time points of W0, W2 (the 7th day), W5, W17, and 52, such as immunoglobulin G4 (IgG4) and leukotriene B4 (LT-B4).

In this study, the safety was evaluated by local and systemic adverse reaction rates as well as

LT-B4. The effectiveness was evaluated by VAS, weekly medication scores, and serum levels of IgG4.

Assessment of adverse reactions

The degree of local adverse reactions was expressed as wheal diameters at the injection site. The immediate-phase adverse reactions with wheals <5 cm in diameter and late-phase adverse reactions displaying wheals <10 cm in diameter irrelevant to clinical manifestation was excluded.⁹ Systemic adverse reactions were evaluated according to guidelines of EAACI.⁸ The adverse reactions (local and systemic) occurring in the two treatment groups must be documented with details, including batch number and doses of allergen, allergic time, relived time, severity, and the corresponding management.

Serological tests

Collection and preservation of samples. In order to ensure the accuracy of the test of the cytokines, all the blood samples were stored at room temperature for 2 h or at 4°C overnight, and were centrifuged at 3000 rpm for 10 min. The resulting serum was stored in a refrigerator at -20°C.

Reagents, instruments, and test methods

Human immunoglobulin E (IgE) enzyme-linked immunosorbent assay (ELISA) kit, human dust mites IgG4 (Der p IgG4) ELISA kit, and human LT-B4 ELISA kit were used in this study. All kits were purchased from Cayman Chemical (USA). Synergy HT Multi-Mode Microplate reader (Biotek, USA) and carbon dioxide incubator (Binder, Germany) were utilized. IgE and LT-B4 were tested using ELISA, and IgG4 was tested with double-antibody sandwich technique.

Clinical questionnaires

VAS. In this study, the overall treatment efficacy was assessed using the VAS. The VAS was a horizontal line of 10 cm long, without marks or signs. An endpoint descriptor representing “best” (a score of 0) is marked at the left end, and “worst” (a score of 10) is marked at the right end. The patient was asked to indicate a point along the line to evaluate the overall efficacy of the therapy for 1 recent week.

Weekly medication scores

Daily dosage of the drug was documented and scored by patients. The weekly medication scores were the mean value of the daily medication scores.

In order to ensure the absolute safety of the RIT, all patients enrolled in this group were orally given loratadine and methylprednisolone from week 1 of intervention, while the patients in the conventional immunotherapy group underwent the same medications. Therefore, in week 1 of the treatment, the scores of the medication mentioned above were not included in the study scores, but other medication scores were documented.

Statistical analysis

The statistical analysis was conducted using SAS 9.1.3 software. Generalized linear mixed model (GLIMMIX) was used to compare differences in

VAS, weekly medication scores, IgG4, IgE as well as LT-B4 at different time points between different groups. $P < 0.05$ was statistically significant.

The following variables were analyzed using SPSS13.0 software, χ^2 test was utilized to compare the differences in gender, ethnic groups, regions, other allergic histories, drop-out rates, and the incidence of systemic adverse reactions between groups. Mann-Whitney U test was employed to compare differences between ages. When $P < 0.05$, the results were statistically significant.

Results

Basic information of the patients

From 30 June 2011 to 30 June 2012, 104 patients with AR receiving RIT were recruited in our study, in which 98 patients completed the study while two patients dropped out due to studying abroad (in week 5), three patients dropped out due to pregnancy (in week 12), and one patient dropped out due to traffic problems. Seventy patients were enrolled in the conventional immunotherapy group, in which 64 patients completed the treatment, while two patients dropped out of the study due to traffic issues (one in week 12, another in week 16), three patients claimed the treatment was ineffective and abandoned the treatment (in week 9), and one patient dropped out due to pregnancy.

Safety

Adverse reactions. During the build-up phase, the local adverse reaction rate was 32.45% in the RIT group and 30.86% in the conventional immunotherapy group. All local adverse reactions occurring in the two groups were immediate and unrelated to disease (with wheal diameters < 5 cm). In the RIT group, 18 times the systemic adverse reactions (16 times for grade I, 2 times for grade II, accounting for 1.3% of the injections) were observed in 12 patients (accounting for 12.2% of all patients); in the conventional immunotherapy group, 10 times the systemic adverse reactions (all grade I, accounting for 1.1% of the injections) were seen in eight patients (accounting for 12.5% of all patients) (Table 2).

LT-B4

Inter-group comparison: from week 2 to week 52, the mean of LT-B4 in both groups showed

Table 2. The systemic adverse reactions in both groups.

	Conventional group		Rush group	
	Times	Patients	Times	Patients
Build-up phase	8 (1.1%)	10 (12.5%)	18 (1.3%)	12 (12.2%)
Grade I	10		16	
Grade II	0		2	

The systemic adverse reactions in both groups showed no statistically significant differences ($P > 0.05$).

Table 3. VAS profile at different time points and groups.

VAS	Conventional group	Rush group	Difference	P
Week 2–Week 0	−2.37 (−2.93~−1.81)	−3.30 (−3.75~−2.84)	0.93 (0.21~1.65)	0.012
Week 5–Week 0	−2.13 (−2.69~−1.56)	−2.52 (−2.97~−2.07)	0.40 (−0.33~1.16)	0.282
Week 11–Week 0	−3.11 (−3.67~−2.55)	−2.61 (−3.06~−2.15)	−0.50 (−1.23~0.22)	0.174
Week 17–Week 0	−2.87 (−3.44~−2.30)	−2.45 (−2.91~−1.99)	−0.42 (−1.15~0.32)	0.254
Week 52–Week 0	−3.79 (−4.45~−3.13)	−3.79 (−4.45~−3.13)	−0.72 (−1.57~0.13)	0.095

no statistically significant differences ($P > 0.05$). Intra-group comparison: the mean of LT-B4 showed a downward trend in both groups; the difference between week 0 and the other time points in the conventional immunotherapy group was statistically significant; there was a statistically significant difference between week 0 and the other time points in the RIT group ($P < 0.05$).

Clinical efficacy

VAS. Inter-group comparison: at week 2, the mean of VAS was lower in the RIT group than the conventional immunotherapy group, with statistical significance ($P < 0.05$), but the other time points were not statistically significant between the two groups ($P > 0.05$). Intra-group comparison: the mean of VAS showed a downward trend in both groups; the difference between week 0 and the other time points in both groups was statistically significant ($P < 0.05$) (Table 3).

Weekly medication scores

Inter-group comparison: the mean of weekly medication score at week 2 in the RIT group was lower than that in the conventional immunotherapy group, and the difference was statistically significant ($P < 0.05$); no significant difference was found between other time points. Intra-group comparison: the mean of the weekly medication score at week 2 went up in contrast to week 0, the difference between week 0 and week

2 in the conventional immunotherapy group was statistically significant; no significant difference was found between other time points. The RIT group showed no statistically significant differences in the mean of the weekly medication score between week 0 and the other time points ($P > 0.05$).

Immunoglobulin G4 (IgG4)

Inter-group comparison: the means of IgG4 at week 5 in the RIT group were higher than that in the conventional immunotherapy group, and the difference was statistically significant ($P < 0.05$); there was no significant difference between other time points ($P > 0.05$). Intra-group comparison: the mean of IgG4 in both groups demonstrated an upward trend; there was a significant difference between week 0 and other time points in both groups ($P > 0.05$) except from week 2.

Discussion

The safety in AIT is the premise for immunotherapy application. Adverse reactions during immunotherapy are likely caused by patients' sensitivity to allergens, patients' physical conditions, vaccine formulation and dose, as well as injection time schedule and modality.¹⁰ Some literature seemed to indicate that a shortened build-up phase increased systemic adverse reactions.^{11,12} However, some research indicated that premedication or adjusted doses greatly improved the safety of RIT.^{13,14}

In this study, adverse reactions at the build-up phase were examined and compared between RIT and conventional immunotherapy. It was demonstrated that the RIT group and the conventional immunotherapy group had a lower incidence of adverse reactions and a downward trend of leukotriene levels (LT-B₄, etc., a pro-inflammatory mediator for asthma). It implies that the two groups have a similar safety. This conclusion is similar to that of previous studies.^{13,14}

In our study, VAS, weekly administration scores, and IgG4 (a marker of ASIT induced immune tolerance) levels in peripheral serum at difference time points between the two groups were compared to evaluate their efficacy. The results demonstrated that VAS in the RIT group was lower at week 2 while the IgG4 levels were higher in the early stage of treatment, and at the point after RIT dose build-up finished 1 week later, weekly medication scores were higher in the conventional immunotherapy group. It implies that RIT can exert an effect earlier than conventional immunotherapy. Our result is similar to that of the study by Lai et al.¹⁵

To conclude, the safety and efficacy of RIT applied in Chinese patients with AR under pre-meditation is similar to that of conventional immunotherapy.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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