

# A prospective multicenter study of systemic reactions in standardized specific immunotherapy for allergic rhinitis in China

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## ABSTRACT

**Background:** Standardized allergen-specific immunotherapy (SIT) has been used in China for years. However, there is no extensive study of the safety of standardized SIT in Chinese patients until now. The aim of the current study is to perform a prospective and multicenter study to evaluate the systemic reactions (SRs) of standardized SIT in Chinese patients.

**Methods:** The study was performed in 13 allergy centers in China, using the same vaccine and practice procedure. The length of observation period was 2 years. SRs were recorded and analyzed.

**Results:** There were 666 patients included (261 children and 405 adults). All patients finished the initial phase and 47 patients withdrew during the maintenance phase. There were 0.47% (94/19,963) SRs in all injections (0.72% in children and 0.31% in adults); 8.26% (55/666) patients experienced SRs (12.26% children and 5.68% adults). The occurrence of SRs was significantly higher in children than that in adults ( $p < 0.01$ ). A higher ratio of SRs was found among patients accompanied with asthma. There were 74.47% SRs of grade I, 15.96% SRs of grade II, 7.45% SRs of grade III, and 2.13% SRs of grade IV. There were 90.43% of SRs associated with the discomfort of lower respiratory tract.

**Conclusion:** This multicenter study showed that properly conducted standardized SIT was a safe treatment for allergic rhinitis in China. The incidence of SRs was higher in children than that in adults.

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Allergen-specific immunotherapy (SIT) is currently the only logical treatment for allergic rhinitis (AR). The clinical efficacy of SIT is well documented. SIT is also the only method that can modify the natural course of allergy. SIT is considered safe, but there is some risk of side-effects during application.<sup>1,2</sup>

SIT has been used for decades in mainland China, but most vaccines are nonstandardized.<sup>3</sup> In recent years, standardized products for SIT have been accepted by most physicians, because the quantity and reactivity of the major proteins of these standardized vaccines can be guaranteed. The stability of standardized products is also better than that of nonstandardized products. The standardized vac-

cine products used in China include Alutard (ALK, Hørsholm, Denmark) and Novo-Helisen-Depot (Allergopharma, Berlin, Germany). Some reports have confirmed the efficacy of standardized SIT for asthma and AR in China.<sup>4–6</sup> However, today, an extensive study of the safety of standardized SIT in the Chinese population has not been performed.

In this prospective and multicenter study, we evaluated the prevalence of systemic reactions (SRs) of standardized SIT with a vaccine based on the European house-dust mite (*Dermatophagoides pteronyssinus*; Alutard) in a Chinese population.

## MATERIALS AND METHODS

J. Chen, B. Li, Y. Zhao, and Q. Zhang contributed equally to this work. The study protocol was approved by the Ethics Committee of Huazhong University of Science and Technology (Wuhan, China). Informed consent was obtained from every patient (or guardian if the patient was  $\leq 14$  years old) before the start of SIT.

## Patients

Patients with AR who agreed to undergo standardized SIT from 13 Allergy Centers were included in the study. The recruitment period was from January 2008 to January 2009. The recruitment criteria were moderate-severe persistent rhinitis according to guidelines set by the Allergic Rhinitis and Its Impact on Asthma and clinical history of AR with/without asthma, major sensitization to *D. pteronyssinus* of  $\geq 1$ -year duration based on positive skin-prick tests and/or serum-specific IgE (class 2 or higher; UniCAP Pharmacia, Uppsala, Sweden). Patients were grouped as children ( $\leq 14$  years old) and adults ( $> 14$  years old). All patients were treated by standardized SIT with Alutard *D. pteronyssinus* vaccine. The observation period for each patient was 2 years. The reasons why patients did not complete 2 years of SIT were recorded. The diagnoses of AR and asthma were according to

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Table 1 Treatment schedule of standardized immunotherapy

| Time of Injection | Vial | Concentration (SQ-U/mL) | Injection Dose (mL) |
|-------------------|------|-------------------------|---------------------|
| Build-up phase    |      |                         |                     |
| Week 1            | 1    | 100                     | 0.2                 |
| Week 2            | 1    | 100                     | 0.4                 |
| Week 3            | 1    | 100                     | 0.8                 |
| Week 4            | 2    | 1000                    | 0.2                 |
| Week 5            | 2    | 1000                    | 0.4                 |
| Week 6            | 2    | 1000                    | 0.8                 |
| Week 7            | 3    | 10,000                  | 0.2                 |
| Week 8            | 3    | 10,000                  | 0.4                 |
| Week 9            | 3    | 10,000                  | 0.8                 |
| Week 10           | 4    | 100,000                 | 0.1                 |
| Week 11           | 4    | 100,000                 | 0.2                 |
| Week 12           | 4    | 100,000                 | 0.4                 |
| Week 13           | 4    | 100,000                 | 0.6                 |
| Week 14           | 4    | 100,000                 | 0.8                 |
| Week 15           | 4    | 100,000                 | 1.0                 |
| Maintenance phase |      |                         |                     |
| Week 17           | 4    | 100,000                 | 1.0                 |
| Week 21           | 4    | 100,000                 | 1.0                 |
| Week 27           | 4    | 100,000                 | 1.0                 |
| Week 33           | 4    | 100,000                 | 1.0                 |
| Every 6 wk        | 4    | 100,000                 | 1.0                 |

SQ = standardized quality.

guidelines set by Allergic Rhinitis and Its Impact on Asthma guideline and the Global Initiative for Asthma, respectively.

## Standardized Immunotherapy

The treatment schedule was standardized among all centers before the study. The same record sheet and data management software were adopted. All physicians and nurses were trained together before the project. The treatment regime was set up according to the manufacturer's product insert (Table 1) and recommendations of the European Academy of Allergy and Clinical Immunology (EAACI).<sup>7</sup>

During the initial phase of SIT, weekly injections were administered to reach an optimal dose. Subsequently, the patient followed maintenance injections every 6 weeks for  $\geq 2$  years. The maintenance dose was usually predefined by the manufacturer, but some patients could not reach the maintenance dose. We accepted the criterion, set by the World Health Organization, that the optimal dose was the one that induced a clinically relevant effect without leading to unacceptable adverse effects.

Before each injection, patients had to have (i) physical examination, (ii) peak expiratory flow (PEF) test (only patients whose PEF was  $>80\%$  of the predicted value were allowed to take the injection), and (iii) assessment of local and SRs after a previous injection for dose adjustment. The dose was reduced in the case of SRs, unpleasant appreciable delayed local reactions, and exceeding the intervals between two series of injections. Doses were repeated if the diameter of the immediate local reaction was  $>5$  cm in children or  $>8$  cm in adults.

An antihistamine was given *via* the oral route before each injection (loratadine or cetirizine; 10 mg for patients aged  $\geq 12$  years and 5 mg for patients who are  $<12$  years old). Patients were observed by nurses and physicians in the clinic for at least 30 minutes after each injection. Patients presenting with SRs were observed and rescue treatments were instituted by physicians. The SRs were classified based on symptoms and the patients' responses to rescue treatments. If the SRs occurred after the patients had left the clinic, the physicians and patients would follow-up by telephone to ensure optimal treatments.

Table 2 Basic information of patients

|                                     | Children        | Adults           | Total             |
|-------------------------------------|-----------------|------------------|-------------------|
| No.                                 | 261             | 405              | 666               |
| Average age (yr)                    | 9.62 $\pm$ 2.71 | 28.31 $\pm$ 10.3 | 20.07 $\pm$ 12.16 |
| Male % (n)                          | 62.45 (163)     | 47.9 (194)       | 53.6 (357)        |
| AR with asthma,* % (n)              | 25.67 (67)      | 15.56 (63)       | 19.52 (130)       |
| AR with atopic dermatitis,# % (n)   | 17.62 (46)      | 19.01 (77)       | 18.47 (123)       |
| Injections during build-up phase    | 4005            | 6106             | 10,111            |
| Injections during maintenance phase | 3886            | 5966             | 9852              |

\*Asthma was diagnosed by a physician and occurred recently.

#Atopic dermatitis was diagnosed by a physician and occurred recently.

AR = allergic rhinitis.

Table 3 Reasons for study withdrawal

| Reason                                  | Child Group % (n) | Adult Group % (n) |
|-----------------------------------------|-------------------|-------------------|
| Too expensive                           | 6.25 (1)          | 9.68 (3)          |
| Lacks confidence in the efficacy of SIT | 31.25 (5)         | 51.61 (16)        |
| Unable to participate                   | 25 (4)            | 16.13 (5)         |
| SR                                      | 18.75 (3)         | 6.45 (2)          |
| Other reasons                           | 18.75 (3)         | 16.13 (5)         |
| Total                                   | 100 (16)          | 100 (31)          |

SIT = specific immunotherapy; SR = systemic reaction.

## Grading of SRs

SRs were classified according to the Immunotherapy Position Paper of the EAACI<sup>8</sup>:

Grade 0—indicates no symptoms or nonspecific symptoms.

Grade I—mild SRs (localized urticaria, rhinitis, or mild asthma; PEF  $< 20\%$  decrease from baseline).

Grade II—moderate SRs (slow onset of  $<15$  minutes) of generalized urticaria, moderate asthma, or both (PEF  $< 40\%$  decrease from baseline).

Grade III—severe (non-life-threatening) SRs (rapid onset of  $<15$  minutes) of generalized urticaria, angioedema, or severe asthma (PEF  $\geq 40\%$  decrease from baseline).

Grade IV—anaphylactic shock (immediate evoked reaction of itching, flushing, erythema, generalized urticaria, stridor, angioedema, immediate asthma, hypotension, etc.).

As for the time of the appearance of SRs after the administration of SIT, SRs was classified as "early" ( $\leq 30$  minutes after SIT) or "late" ( $>30$  minutes after SIT) according to the classification of the EAACI guideline.<sup>8</sup>

## Data Recording

For all patients, sex, date of birth, date of treatment commencement, diagnosis, and phase of treatment (initial or maintenance) were recorded. Adverse reactions were recorded on a form designed according to two aspects: description of reactions (local or systemic, grade, and adverse event) and rescue treatments (epinephrine; inhaled  $\beta$ -agonists; antihistamines; systemic corticosteroids; oxygen; and invasive measures such as endotracheal intubation, mechanical

Table 4 Prevalence of SRs in children and adults

| Phase       | Percentage of Injections with SRs |                 | <i>p</i> Value | Percentage of Patients with SRs |                | <i>p</i> Value |
|-------------|-----------------------------------|-----------------|----------------|---------------------------------|----------------|----------------|
|             | Children % (n/N*)                 | Adults % (n/N*) |                | Children % (n/N*)               | Adult % (n/N*) |                |
| Build-up    | 0.75 (30/4005)                    | 0.25 (15/6106)  | <0.01          | 7.28 (19/261)                   | 2.72 (11/405)  | <0.01          |
| Maintenance | 0.69 (27/3886)                    | 0.37 (22/5966)  | <0.05          | 5.75 (15/261)                   | 4.2 (17/405)   | >0.05          |
| Total       | 0.72 (57/7891)                    | 0.31 (37/12072) | <0.01          | 12.26 (32/261)                  | 5.68 (23/405)  | <0.01          |

\*N is the total number of patients who had entered the treatment phase.

SR = systemic reaction.

Table 5 Prevalence of SRs in patients with or without asthma/atopic dermatitis

|                                   | Accompanied with Asthma or Not |                   | <i>p</i> Value | Accompanied with Atopic Dermatitis or Not |                   | <i>p</i> Value |
|-----------------------------------|--------------------------------|-------------------|----------------|-------------------------------------------|-------------------|----------------|
|                                   | With, % (n/N*)                 | Without, % (n/N*) |                | With, % (n/N*)                            | Without, % (n/N*) |                |
| Percentage of patients with SRs   |                                |                   |                |                                           |                   |                |
| Children, % (n/N)                 | 23.88 (16/67)                  | 9.28 (18/194)     | <0.01          | 10.87 (5/46)                              | 13.49 (29/215)    | >0.05          |
| Adults, % (n/N)                   | 12.70 (8/63)                   | 4.39 (15/342)     | <0.05          | 6.49 (5/77)                               | 5.49 (18/328)     | >0.05          |
| Percentage of injections with SRs |                                |                   |                |                                           |                   |                |
| Children, % (n/N)                 | 1.32 (27/2045)                 | 0.49 (30/6078)    | <0.01          | 0.62 (9/1453)                             | 0.72 (48/6670)    | >0.05          |
| Adults, % (n/N)                   | 0.90 (17/1882)                 | 0.19 (20/10418)   | <0.01          | 0.26 (6/2320)                             | 0.31 (31/9980)    | >0.05          |

\*N is the total number of patients who had entered the treatment phase.

SR = systemic reactions.

ventilation, and intensive hemodynamic care). In current study, we focused on SRs greater than grade 0.

## Statistical Analyses

Descriptive parameters were shown in the study as mean  $\pm$  SD. The prevalence of SRs was expressed as the number of reactions per patient and the number of reactions per dose. The Student's *t*-test was used to compare clinical characteristics between children and adults. The  $\chi^2$ -test was used to compare the prevalence of SRs between children and adults. A value of  $p < 0.05$  was considered as significant statistically. SPSS version 17.0 (SPSS, Inc., Chicago, IL) was used for all analyses.

## RESULTS

### Patients

A total of 666 patients was included in this multicenter study. The basic information of the patients is shown in Table 2. All patients completed the initial phase of SIT. From the beginning of the maintenance phase to the end of observations, 6.1% (16/261) patients withdrew in the child group and 7.7% (31/405) patients withdrew in the adult group. The reasons for withdrawal are shown in Table 3. The attending physician terminated one treatment from the child group because of SRs. Other patients withdrew of their own volition because of SRs.

### Prevalence of SRs

The prevalence of SRs was shown in Table 4. A total of 0.47% (94/19,963) SRs occurred in all injections (0.72% in children and 0.31% in adults). A total of 8.26% (55/666) patients had SRs out of all patients in the study (12.26% in children and 5.68% in adults). The prevalence of SRs was significantly greater in children than that in adults ( $p < 0.01$ ), especially during the initial phase. Eighteen children had only one SR and seven children experienced two SRs. Another seven children experienced more than two SRs. Fourteen adults had only one SR and five adults experienced two SRs. Another four adults experienced more than two SRs. The mean time of patients entering the

maintenance phase was  $\approx 15$  weeks. A total of 3.75% (25/666) patients (12 children and 13 adults) had SRs from the beginning of the maintenance phase to the end of 1 year of treatment. A total of 1.8% (12/666) patients (7 children and 5 adults) had SRs during the 2nd year of treatment; 7 patients (3 children and 4 adults) had SRs for the first time in this cohort.

The prevalence of SRs between patients who had or did not have asthma/atopic dermatitis is compared in Table 5. The prevalence of SRs in patients with asthma was higher than in those who did not have asthma. The prevalence of SRs was not significantly different in patients who had atopic dermatitis or those who did not.

### Description of SRs

The time of occurrence of SRs after injection was shown in Fig 1 *a*. There was no significant difference in the time of occurrence between children and adults ( $p = 0.50$ ). Most SRs occurred 6–30 minutes after injection. Nevertheless, overall, there was 19.2% SRs after 30 minutes.

The SRs occurring at different doses were shown in Fig. 1 *b*. Most SRs occurred if a high dosage was injected for all patients. In adults, SRs did not occur with vial 1 ( $10^2$  standardized quality [SQ]/mL) or vial 2 ( $10^3$  SQ/mL), and only one SR occurred with vial 3 ( $10^4$  SQ/mL). Eight SRs occurred with vials 1–3 in children.

The severity of SRs was shown in Fig. 1 *c*. A total of 74.47% SRs were grade I, 15.96% were grade II, 7.45% were grade III, and 2.13% were grade IV. No grade IV SRs occurred in children and two grade IV SRs occurred in adults.

The prevalence of adverse events of SRs was shown in Fig. 1 *d*. A total of 90.43% SRs were associated with discomfort in the lower respiratory tract (including cough, chest tightness, or asthma). The remaining events (AR, urticaria, or cardiovascular reactions) occurred at a lower frequency. A total of 17.02% patients (17.54% children and 16.22% adults) had two or more adverse events.

### Treatment of SRs

SRs were treated according to EAACI guidelines.<sup>6</sup> We used salbutamol (by inhalation) as well as antihistamines, corticosteroids, or epinephrine (intramuscular) and all SRs were reversed effectively. Epinephrine was used six times (three times in children and three

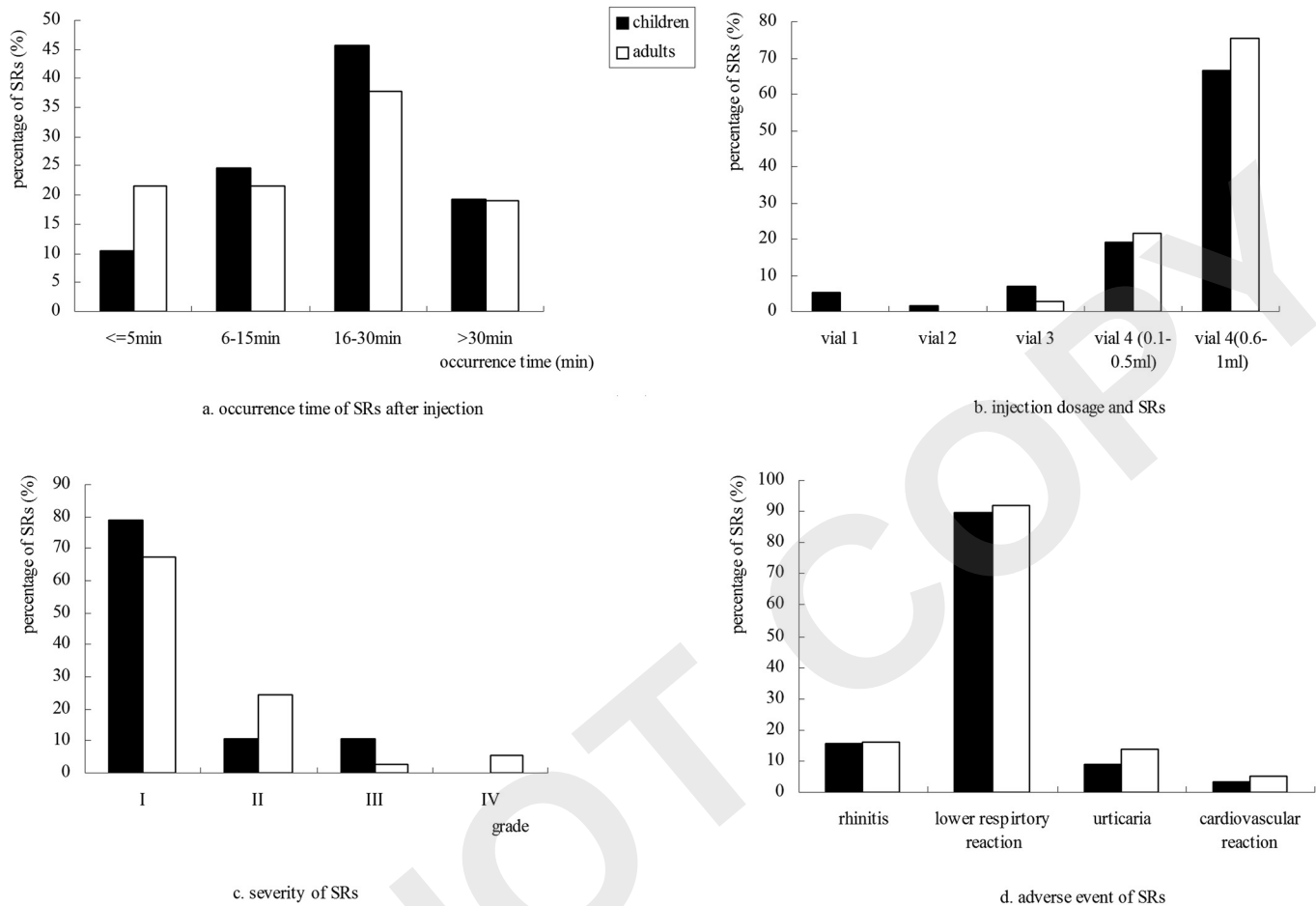


Figure 1. Description of systemic reaction (SR) pictures.

times in adults). Seventy-six SRs were relieved in 30 minutes and one SR was relieved in 1 hour.

## DISCUSSION

Common risk factors for SRs in SIT are errors in injection dose or concentration, injection of new vials, symptoms of asthma (forced expiratory volume in 1 second, <70%), using of  $\beta$ -blockers, injections during periods of exacerbation of symptoms, and ignoring previous SRs.<sup>9,10</sup> In addition, insufficient management could worsen SRs, such as observation time <30 minutes after injection, inadequate treatment of emergency conditions, or delayed rescue after SRs.<sup>11</sup>

We avoided the known risk factors as much as possible and unified the treatment schedule in all centers to make the data comparable. We found that 0.47% of SRs occurred in all injections, and 8.26% of all patients had SRs during the 2 years of SIT. Winther *et al.* reported that 1.08% of all patients occurred in all injections when using Alutard in AR patients.<sup>12</sup> Rieckenberg *et al.* stated that SRs occurred in 6.7% of 901 patients.<sup>13</sup> Businco *et al.* found that 3.7% of 1056 children aged 4–16 years had mild SRs during immunotherapy.<sup>14</sup> Comparing data concerning the safety of immunotherapy was difficult because authors applied various vaccines and had different observation times.

In the present study, children and adults had an identical treatment schedule and dose that was based on the product fact sheets. Children had more SRs than adults during SIT irrespective of the percentage of injections (0.72% in children versus 0.31% in adults) or patient number (12.26% in children versus 5.68% in adults). Children had many more SRs if injected with a low dose of vaccine (14.03% in children versus 2.7% in adults if injected with vials 1–3). Gamboa *et al.* also

reported a higher prevalence of SRs in children than in adults.<sup>15</sup> One study showed no relationship between SRs and age,<sup>16</sup> but we postulated that the dose is the most important reason for the discrepancy in the prevalence of SRs between children and adults.

Most SRs occurred in the initial phase or early period of the maintenance phase, but 1.8% (12/666) of patients had SRs during the 2nd year of treatment. Moreover, within this group, 1.05% (7/666) of patients had SRs for the first time. Rogala *et al.* also suggested that SRs could occur irrespective of the concentration of allergens in the preparation.<sup>17</sup> It had been proposed that patients should be observed carefully after each injection irrespective of whether they had had an SR or the duration of SIT.

We assessed the prevalence of SRs in those who had asthma or atopic dermatitis and those who did not. Children or adults who had asthma had a significantly higher prevalence of SRs than those who did not even though symptoms were well controlled during SIT. There was no difference in the prevalence of SRs between subjects who had atopic dermatitis and those who did not. Other reports confirmed that asthma was a significant risk factor for SRs during SIT.<sup>18,19</sup> Special consideration should be given to individuals with asthma during SIT.

Most guidelines for SIT stated that patients should be observed for 30 minutes after injection. Most SRs occurred during this period, but 19.2% occurred after 30 minutes. Ventura *et al.* reported that 45.3% of SRs were classified as “late” according to EAACI even though the severity was lower than for early SRs.<sup>20</sup> High-risk subjects (*e.g.*, those with asthma or repeated SRs) should be observed for a longer period of time.<sup>7</sup>

In our study, no SRs were fatal. A total of 90.4% of SRs were grades I–II. Grades III–IV SRs were treated effectively according to EAACI guidelines.<sup>8</sup> We undertook measures such as preventative antihistamines and careful control of hyperresponsiveness of the lower respiratory tract, but some severe SRs could not be prevented, which implied that careful observation after each injection was needed.

In conclusion, these data suggested that standardized SIT, if conducted appropriately, was safe with only a few SRs, which were mostly mild in character. The prevalence of SRs was greater in children than in adults. There were several unpredictable factors of SRs during SIT, so meticulous care must be taken during each injection.

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