Long-term efficacy and safety of dust mite subcutaneous immunotherapy in monosensitized and polysensitized children with allergic rhinitis

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Abstract

Objective: The long-term efficacy of single-allergen-specific immunotherapy in polysensitized allergic rhinitis (AR) subjects remains uncertain. This study aimed to evaluate the long-term efficacy and safety of dust mite subcutaneous immunotherapy (SLIT) in monosensitized and polysensitized children with AR. **Methods:** This prospective study recruited 130 children with AR, divided into a monosensitization group and a polysensitization group. Patients received standardized dust mite SLIT for 3 years and were followed up for 5 years. Total nasal symptom score (TNSS), symptom and medication score (SMS), visual analogue scale (VAS) and rhinoconjunctivitis quality of life questionnaire (RQLQ) were assessed and compared between the two groups at T0 (before treatment), T1 (1 year of SLIT), T2 (2 years of SLIT), T3 (end of SLIT) and T5 (2 years after the end of SCIT). Safety was assessed through adverse events (AEs). **Results:** 51 monosensitized and 50 polysensitized children completed this study. At the end of SCIT, 47 monosensitized and 46 polysensitized children were effectively treated, respectively, with no significant difference ($P > 0.05$). TNSS, SMS, VAS and RQLQ were significantly lower in T1, T2, T3 and T5 in the two groups compared with T0 ($P < 0.05$). The differences in TNSS, SMS, VAS and RQLQ between the two groups were not statistically significant at T1, T2, T3 and T4 ($P > 0.05$), while the differences were significant at T5 ($P < 0.05$). No serious AEs were reported. **Conclusion:** Standardized dust mite SCIT has similarly beneficial long-term efficacy and safety in monosensitized and polysensitized children. Monosensitization children appear to receive more durable benefits.

Long-term efficacy and safety of dust mite subcutaneous immunotherapy in monosensitized and polysensitized children withallergic rhinitis

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Keywords allergic rhinitis; long-term efficacy; monosensitized; polysensitized; subcutaneous immunotherapy.

Running title: Efficacy and safety of SCIT in AR children

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Objective: The long-term efficacy of single-allergen-specific immunotherapy in polysensitized allergic rhinitis (AR) subjects remains uncertain. This study aimed to evaluate the long-term efficacy and safety of dust mite subcutaneous immunotherapy (SLIT) in monosensitized and polysensitized children with AR.

Methods: This prospective study recruited 130 children with AR, divided into a monosensitization group and a polysensitization group. Patients received standardized dust mite SLIT for 3 years and were followed up for 5 years. Total nasal symptom score (TNSS), symptom and medication score (SMS), visual analogue scale (VAS) and rhinoconjunctivitis quality of life questionnaire (RQLQ) were assessed and compared between the two groups at T0 (before treatment), T1 (1 year of SLIT), T2 (2 years of SLIT), T3 (end of SLIT) and T5 (2 years after the end of SCIT). Safety was assessed through adverse events (AEs).

Results: 51 monosensitized and 50 polysensitized children completed this study. At the end of SCIT, 47 monosensitized and 46 polysensitized children were effectively treated, respectively, with no significant difference ($P > 0.05$). TNSS, SMS, VAS and RQLQ were significantly lower in T1, T2, T3 and T5 in the two groups compared with T0 ($P < 0.05$). The differences in TNSS, SMS, VAS and RQLQ between the two groups were not statistically significant at T1, T2, T3 and T4 ($P > 0.05$), while the differences were significant at T5 ($P < 0.05$). No serious AEs were reported.

Conclusion: Standardized dust mite SCIT has similarly beneficial long-term efficacy and safety in monosensitized and polysensitized children. Monosensitization children appear to receive more durable benefits.

Keywords allergic rhinitis; long-term efficacy; monosensitized; polysensitized; subcutaneous immunotherapy.

Key message: The long-term efficacy and safety of single-allergen-specific immunotherapy in polysensitized children with allergic rhinitis is unknown. In particular, there is great interest in its efficacy and safety compared to monosensitized children. We conducted a five-year prospective cohort study in Chinese children and found that standardized dust mite subcutaneous immunotherapy had positive and non-statistically different efficacy and safety in both monosensitized and polysensitized children, and it appeared that monosensitized children had more durable long-term treatment benefits.

1. Introduction

Allergic rhinitis (AR) is one of the most common chronic inflammatory diseases of the upper respiratory tract[1]. Its clinical manifestations are itchy nose, sneezing, nasal congestion, and runny nose caused by inhalation of allergens, which may be accompanied by itchy eyes, itchy throat, cough, and chest tightness[1, 2]. According to epidemiological surveys, AR affects about 10-40% of adults and 2-25% of children worldwide[3, 4]. Real-world data also show that the prevalence of AR is still on the rise across China in recent years[5, 6]. The allergens that can trigger AR vary, among which dust mites as the main aeroallergen in AR patients of Central China, the dust mite sensitization rate of AR is over 90%[7]. And in reality, most AR subjects are polysensitized, meaning that they have positive reactions to 2 or more inhaled allergens[8].

Allergen immunotherapy (AIT) is the only treatment that can alter the natural course of AR from its etiology[9]. The World Allergy Organization recommends that AIT be considered as an initial treatment strategy for AR and that failure of drug therapy is not a necessary prerequisite for the use of AIT[10]. AIT mainly consists of subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT)[9]. SCIT is recommended as a priority treatment for AR patients sensitized to dust mites[11]. Especially for children with AR, the short-term efficacy of SCIT has been widely demonstrated in clinical practice, but there are fewer studies on its long-term efficacy[12, 13]. There is also a lack of clinical trials exploring the difference in the long-term efficacy of single-allergen-specific SCIT between monosensitized and polysensitized children with AR. Previous studies have also shown that children with AR are more likely to have more and stronger adverse effects (AEs) to SCIT[14].

To clarify this aspect, we conducted a prospective study to investigate the long-term efficacy and evaluate the safety of standardized dust mite SCIT in monosensitized and polysensitized children with AR. In order to provide more evidence of efficacy and safety analysis for SCIT in children with AR of different clinical characteristics.

2. Materials and methods

2.1 Study design, setting, and participants

This study is a prospective cohort study. We consecutively recruited 130 children with AR who were diagnosed with dust mite allergy and underwent standardized dust mite SCIT at Xiangya Hospital of Central South University from June 2017 to September 2017. The patients were divided into 2 groups: monosensitized to only dust mites and polysensitized to at least 1 additional allergen beyond dust mites. General demographic data such as gender, age, body mass index (BMI), duration of disease, family history of AR, asthma, urticaria, allergic conjunctivitis and food allergy, as well as clinical characteristics such as severity of symptoms, number of allergens, long-term efficacy and AEs were collected from patients. The Medical Ethics Committee of Xiangya Hospital of Central South University approved this study. All children's guardians provided informed consent before the children were recruited.

Inclusion criteria: (1) conforming to the guidelines for diagnosis and treatment of AR[15], positive skin test results of Dermatophagoides farina (*Der f*) and/or Dermatophagoides pteronyssinus (*Der p*) ([?] ++) and/or sIgE level for *Der f*or *Der p* >0.35 IU/ml; (2) 5 years [?] age [?] 13 years; (3) complete clinical data; (4) uninterrupted 3 years of standardized dust mite SCIT; (5) complete follow-up for 2 years after the end of SCIT; (6) patient's guardian gave informed consent and signed the informed consent form. Exclusion criteria: (1) patients who did not cooperate with follow-up or missed follow-up; (2) patients with tumor or psychiatric abnormalities; (3) severe uncontrollable asthma or cardiopulmonary disease; (4) patients who fell off or interrupted treatment several times; (5) patients who were taking β-blockers.

2.2 Immunotherapy

SCIT was conducted as previously described[16]. All AR patients received Novo-Helisen Depot (NHD) allergen extracts (Allergopharma, Reinbek, Germany) from *Der f* and *Der p* at a 1 : 1 ratio. According to the manufacturer's instructions, SCIT consists of two phases: initial treatment phase and maintenance treatment phase. The initial treatment phase started with the minimum dose of low concentration NHD NO.1 and gradually increased to the maximum dose of high concentration NHD NO.3. The injection interval was generally 7-14 days. For NO.1 and NO.2, the doses were increased from 0.1, 0.2, 0.4, to 0.8 ml. For NO.3, the dose was increased from 0.1, 0.2, 0.4, 0.6, 0.8, to 1.0 ml. In the maintenance treatment phase, patients were injected with 1.0 ml of NO.3 with an injection interval of 4 to 6 weeks. SCIT was conducted in the outpatient department under the guidance of allergy experts, and all patients were observed for >30 minutes before leaving. To achieve long-term efficacy, a treatment course of 3 years is recommended[17].

2.3 Clinical efficacy assessment

For a total of 5 years of follow-up, all AR patients were scored monthly for symptoms and medication use using the widely accepted total nasal symptom score (TNSS), symptom and medication score (SMS),

rhinoconjunctivitis quality of life questionnaire (RQLQ) and visual analogue score (VAS). In this study, TNSS, SMS, RQLQ and VAS were counted at different periods including T0 (before SCIT), T1 (1 year of SLIT), T2 (2 years of SLIT), T3 (end of SLIT) and T5 (2 years after the end of SCIT). The primary efficacy endpoint was SMS. Key secondary efficacy endpoints included TNSS, RQLQ and VAS. The main criterion for effective treatment of SCIT was the reduction of SMS score by more than 30% before and after treatment, otherwise SCIT was considered ineffective[18].

2.3.1 TNSS and symptom severity grading

The TNSS includes four nasal symptoms, including itchy nose, nasal congestion, sneezing and runny nose, and is scored by a "four-point scale", with each symptom being assigned a score of 0 to 3 depending on its severity. The TNSS counts the sum of the 4 symptom scores, with a total score of 0-12.

The severity of symptoms was evaluated based on the total TNSS score, where a TNSS score >0 and [?]4 was considered mild AR, and a score >4 and [?]12 was considered moderate-severe AR[19].

2.3.2 SMS

The SMS was defined as the sum of TNSS and the medication score (MS). MS was recorded according to the recommendations of the World Allergy Organization: 1, 2, and 3 points for oral or intranasal antihistamines, intranasal glucocorticoids, and oral glucocorticoids, respectively.

2.3.3 RQLQ

The RQLQ consists of 28 questions in the following 7 domains: sleep problems, general symptoms, practical problems, nose symptoms, eye symptoms, activity limitation and emotional function, which are given a score from 0 to 6 according to the severity.

2.3.4 VAS

VAS: A horizontal line of 10 cm in length was drawn, and a marker was made for each cm to mark the number. 0 at one end of the horizontal line indicated no symptoms; 10 at the other end indicated the most severe symptoms, and 1-9 was marked in the middle.

2.4 AEs

All patients were observed for at least 30 minutes after vaccine injection for the occurrence of AEs, and appropriate treatment was taken to alleviate the AEs under the guidance of the physician. According to the international SCIT AEs classification[19], the type, occurrence phases, grading, duration and treatment measures of patients' AEs were recorded.

2.5 Statistical analysis

All statistical analyses were performed with SPSS version 22.0 (IBM, Chicago, IL, USA). Categorical variables are expressed as numbers and percentages and compared utilizing the chi-squared test. Quantitative variables with normal distribution are shown as mean ± standard deviation and compared with the student's t-test between the two groups. Those data without normal distribution are presented as median and interquartile ranges (IQRs), and the Mann-Whitney U test is utilized in the comparison between the two groups. Statistical significance is regarded as a two-tailed $P < 0.05$.

3 Results

3.1 Demographic data and clinical characteristics of the included children with AR

An initial cohort with 130 children with AR was enrolled, and 29 subjects were excluded based on the exclusion criteria (Figure 1). A total of 101 children eventually completed this study, including 72 males and 29 females with a mean age of 10.0 years, 51 patients with monosensitization and 50 patients with polysensitization. According to the SMS efficacy determination criteria, 93 (92.1%) children were effectively

treated after 3 years of SCIT. The specific baseline characteristics and clinical data of the study subjects are shown in Table 1.

3.2 Comparison of clinical data of monosensitized and polysensitized children with AR

The children with AR were further divided into the monosensitized group and the polysensitized group, and the clinical characteristics and long-term efficacy of SCIT were compared between the two groups. As shown in Table 2, there was a significant difference in food allergy between the two groups ($P < 0.05$). After 3 years of SCIT, both groups of children with AR achieved positive outcomes, while there was no statistical difference in the 3-year outcomes of SCIT and other clinical characteristics between the two groups ($P > 0.05$).

3.3 Changes in different scale scores of monosensitized and polysensitized children with AR

Then the changes in the different scale scores of monosensitized and polysensitized children before and after SCIT were compared separately. As shown in Table 3, TNSS, SMS, RQLQ and VAS had statistically significant decreases ($P < 0.05$) at different times (T1, T2, T3 and T5) after treatment in both monosensitized and polysensitized children compared to pre-treatment (T0).

Further, the difference in the scores of different scales between monosensitized and polysensitized children was compared at different time points of SCIT. As shown in Figure 2, there was no significant distinction in TNSS, SMS, RQLQ and VAS between the two groups at T1, T2 and T3 time points ($P > 0.05$). While at T5, there was a statistical difference between the two groups in TNSS, SMS, RQLQ and VAS ($P < 0.05$).

3.4 Statistical analysis of the AEs of SCIT

As shown in Table 4, 101 patients received altogether 5567 injections during SCIT, of which 2809 injections were monosensitized and 2758 injections were polysensitized. 108 (1.9%) local AEs occurred in children with AR during SCIT and 101 (93.5%) of them occurred within 30 minutes of injection, mainly during the maintenance treatment phase. The local AEs included localized redness and swelling or wind mass diameter at the injection site of 5-20 mm, which could be relieved by local ice and/or oral antihistamines. A total of 31 (0.6%) systemic AEs occurred, of which 30 (96.8%) occurred within 30 minutes of injection, mainly during the maintenance treatment phase, and were mostly grade 1, which could be relieved by oral antihistamines and/or inhalation of rapid-acting β-agonists, and no serious adverse events occurred. There was no statistical difference between the monosensitized group and the polysensitized group in the type, occurrence phases and grading of AEs.

4 Discussion

In recent years, the incidence of AR has been increasing year by year, and not only the disease itself can bring discomfort, but AR is also considered an independent risk factor for diseases such as asthma, allergic conjunctivitis and atopic dermatitis[20]. While seriously affecting the health and quality of life of patients, AR also imposes a heavy burden on society and has become a health issue of global concern[21]. AR can be divided into seasonal AR and perennial AR[3]. Dust mites, as the most common type of inhaled allergens in perennial AR, are ubiquitous in daily life and difficult to avoid, and repeated and prolonged allergic reaction is more likely to bring more discomfort to AR patients[22].

Real-world clinical data suggest that polysensitization is very common, with approximately 3/4 of AR patients being sensitized to more allergens and polysensitized AR patients accounting for the majority of all AR patients[23]. In addition, previous studies have shown that polysensitized AR patients have more severe symptoms and poorer quality of life compared to monosensitized AR patients[23, 24]. It has been observed that polysensitized AR patients also have asthma associated with them more frequently than monosensitized AR patients[8, 25]. Standardized dust mite AIT has been used for hundreds of years, but evidence for the efficacy of AIT in polysensitized patients is still scarce and focused on short-term efficacy[26]. For example, a retrospective cohort study showed that a 1-year SLIT with standardized *Der f* drops had similar efficacy for both monosensitized and polysensitized AR patients[26]. Another 2-year observational study showed that

SCIT with house dust mite vaccine was an effective treatment for both monosensitized and polysensitized AR patients, and there was no difference in efficacy between the two groups[27]. In contrast, the long-term efficacy of AIT for polysensitized patients remains an unsolved mystery in this regard, and there are few studies on this issue.

In the present study, we included a sufficient number of samples to design the prospective cohort study exploring the long-term efficacy of SCIT for both monosensitized and polysensitized children. We found that both groups of children improved various clinical symptoms without significant differences, improved quality of life, and reduced medication use after standardized dust mite SCIT over 3 years. This study provides strong evidence for the exact long-term efficacy of standardized dust mite SCIT for monosensitized and polysensitized children. Interestingly, monosensitized children had a longer-lasting benefit after 3 years of SCIT compared to polysensitized children.

Routine SCIT is divided into an initial treatment phase and a maintenance treatment phase, with the initial treatment phase starting with a small dose and gradually increasing so that the organism's immune response decreases when the patient is re-exposed to the allergen, eventually inducing the initial formation of the organism's immune tolerance[17, 28]. In both phases of SCIT, AR patients receive repeated allergenic vaccine stimulation, which can still trigger AEs even at small doses[14]. Therefore, except for the efficacy of SCIT, the various AEs that may occur during SCIT treatment have been a major concern for rhinologists[29]. Previous studies have shown that children with AR seem to be more prone to AEs and that they may be more severe and have more adverse medical events[14, 30]. Thus, it is essential to explore the safety analysis of standardized dust mite SCIT in children with AR over a long course of treatment. In this study, the type and grade of various AEs, as well as the time of occurrence and management measures, occurred during the SCIT course in monosensitized and polysensitized children were recorded in detail. The results showed that the safety of children receiving SCIT is reliable, and there was no significant difference in the occurrence of AEs between monosensitized and polysensitized patients. This study provides definitive evidence for the safety of SCIT in children with AR and provides real-life clinical experience in the prevention and management of AEs.

Our study has several limitations. First, the study subjects included in this study were from a single medical center, which may increase the risk of selection bias. Second, as a prospective cohort study, only the relevant variables included at the beginning of the study design were observed, and there may be other possible factors associated with the long-term outcome of SCIT in children with AR that were not included. In addition, only changes in scale scores before and after SCIT were recorded, and changes in relevant immune indicators were not observed, making it difficult to further explore the mechanisms of SCIT efficacy in AR patients in depth based on this study.

5 Conclusion

This prospective cohort study has suggested that standardized dust mite SCIT for 3 years has similar positive long-term efficacy and safety in both monosensitized and polysensitized children, but monosensitized children appear to receive a more durable benefit.

Authorship contribution

XY analyzed the results and wrote the manuscript. SX HZ, JZ and RF collaborated in the acquisition, analysis, or interpretation of data. JW and ZX collaborated in the final approval of the article before submission.

Conflict of interest

There are no patents, products in development or marketed products to declare. Authors on this manuscript have no relevant financial or other relationships to disclose.

Disclosure Statement

The authors have nothing to disclose.

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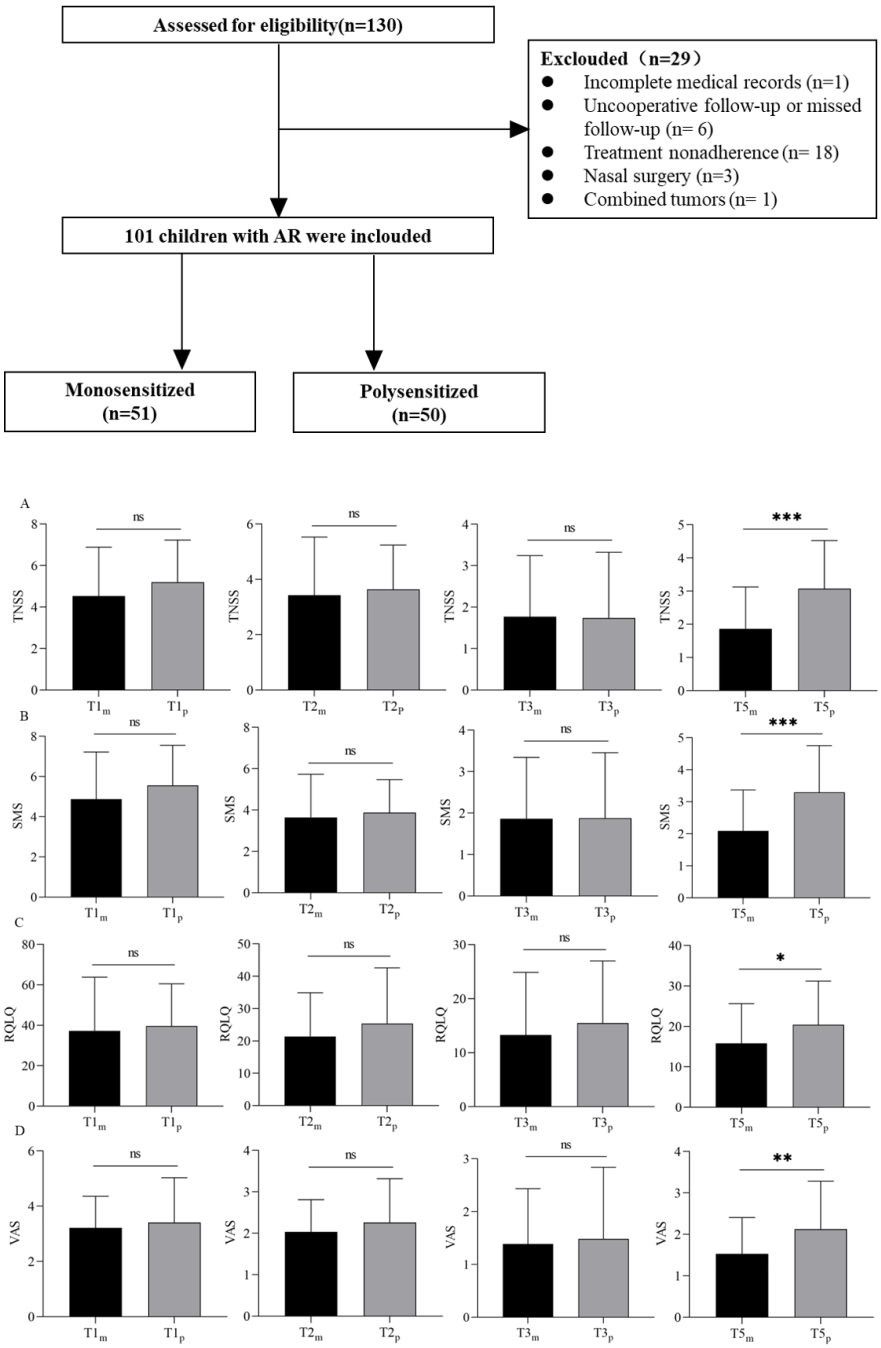
Figure legend

Figure 1. Flowchart classification of the AR cohort.

AR, allergic rhinitis.

Figure 2. Comparisons of different scale scores between monosensitized and polysensitized children at different time periods of SCIT (A) TNSS; (B) SMS; (C) RQLQ; (D) VAS. ns: $P>0.05$, *$P<0.05$, ***$P<0.001$.

m, monosensitized; p, polysensitized.



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