Allergol Immunopathol (Madr). 2017;xxx(xx):xxx-xxx

Allergologia et immunopathologia

Sociedad Española de Inmunología Clínica, Alergología y Asma Pediátrica

www.elsevier.es/ai

ORIGINAL ARTICLE

The safety profile of subcutaneous allergen immunotherapy in children with asthma in Hangzhou, East China

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Received 19 February 2017; accepted 6 April 2017

KEYWORDS
Asthma;
Children;
Subcutaneous allergen immunotherapy;
Systemic reactions;
Dermatophagoides pteronyssinus

Abstract
Background: The aim of the current study is to evaluate the prevalence, severity and possible risk factors of systemic reactions (SRs) to subcutaneous allergen immunotherapy (SCIT) in children and adolescents with asthma in Hangzhou, east China's Zhejiang province.
Methods: From January 2011 to December 2016, this survey analysed the SCIT-related SRs involving 429 patients (265 children and 134 adolescents) affected by allergic asthma. Recorded data included demographics, diagnosis, patient statuses, pulmonary function testing results before and after each injection, allergen dosage, and details of SRs.
Results: All patients finished the initial phase and six patients withdrew during the maintenance phase. There were 2.59% (328/12,655) SRs in all injections (3.28% in children and 1.47% in adolescents); 15.62% (67/429) patients experienced SRs (18.49% children and 10.98% adolescents). There were 54.57% SRs of grade 1; 42.37% SRs of grade 2; 3.05% SRs of grade 3; and no grades 4 or grade 5 SRs occurred in patients. Most reactions were mild, and were readily controlled by immediate emergency treatment. There was no need for hospitalisation. The occurrence of SRs was significantly higher in children than that in adolescents ($p < 0.01$). A higher ratio of SRs was found among patients with moderate asthma.
Conclusion: This retrospective survey showed that properly-conducted SCIT was a safe treatment for children and adolescents with asthma in Hangzhou, East China. Children and patients with moderate asthma may be prone to develop SRs.

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http://dx.doi.org/10.1016/j.aller.2017.04.002
0301-0546/

Introduction

Asthma is one of the most prevalent respiratory conditions, representing some of the most common and costliest conditions in the world. The prevalence of allergic asthma has increased in the last decades.[1,2] In subtropical latitudes, most individuals with allergy are sensitised to house dust mites (HDMs).[3] HDMs constitute a major, persistent source of indoor aeroallergens and constitute the leading cause of respiratory allergies such as allergic rhinitis (AR) and allergic asthma. These conditions affect more than 500 million people worldwide.[4]

To date, allergic asthma treatment includes allergen avoidance, pharmacotherapy and allergen specific immunotherapy (AIT). Drugs, such as inhaled corticosteroids, long-acting beta agonists and montelukast, can powerfully control the inflammation, alleviate symptoms and restore respiratory functions. However, pharmacotherapy only treats the symptoms or inflammation and cannot modify the natural history of disease.[5]

AIT is currently a key part of the allergic asthma management prevention strategy of the Global Initiative for Asthma (GINA). It is effective in reducing the clinical symptoms associated with allergic asthma and the only available treatment method that addresses the causes of asthma.[1] Subcutaneous immunotherapy (SCIT) and sublingual immunotherapy are the two most prescribed routes for administering AIT. SCIT is now widely used in the management of allergic diseases, including allergic asthma. In the meta-analysis carried out by Ross et al.,[6] 24 prospective, randomised studies involving 962 asthmatic patients were evaluated. They reported significant amelioration in symptoms and drug intake related with asthma as well as in pulmonary function in the SCIT group in comparison to the placebo. It was deduced that immunotherapy was beneficial in 17 (71%) studies, ineffectual in four (17%) studies, and equivocal in three (12%) studies. Similar to the previous meta-analyses, the authors concluded that SCIT is effective in patients suffering from allergic asthma.[7]

However, SCIT is associated with a risk of systemic reaction (SRs), which may be severe or even life threatening. Risk factors for SRs that have been identified include type of extract, treatment regimen, patients, administration errors, and seasonal exacerbation of symptoms.[8–10] SCIT has been applied for more than 50 years in China; however, there were few reports on the safety of SCIT in children and adolescents. In China, dust mite allergen vaccine (Alutard SQ, Horsholm, Denmark) is the only available standardised product. In this retrospective study, we evaluated the prevalence of SRs of standardised SCIT with the vaccine based on the European house-dust mite (*Dermatophagoides pteronyssinus*, Dp; Alutard) in Hangzhou east China's Zhejiang province.

Materials and methods

Paediatric patients were children (5–11 years old) and adolescents (12–17 years old). They were recruited from the outpatient allergy clinic of The Children's Hospital Zhejiang University School of Medicine. Patients enrolled in this study were those who: were diagnosed with allergy asthma according to the GINA guidelines; showed positive skin prick test to Dp; and serum Dp-specific IgE levels ≥class 2 had allergic symptoms that could be attributable to mites. All patients met all the three criteria.

Skin tests for 19 kinds of inhalant allergens were performed, including dust mites (Dp and *Dermatophagoides farina*), cockroach, mulberry silk, animal dander (cat, dog, sheep, and horse), tree pollens (Sabina, Platanus, Populus, and cryptomeria), weed pollens (Artemisia, Ambrosia, and Humulus), and fungi (Alternaria, Cladosporium, Aspergillus, and Paecilomyces) (Macro-Union Pharmaceutical, Beijing, China). Histamine (10 mg/mL) and diluent were used as positive and negative controls. Serum specific IgEs were measured by ImmunoCAP (Phadia, Thermo Fisher Scientific, Uppsala, Sweden).

An asthma severity score was used to classify the patients' asthma as mild, moderate, or severe based on the criteria of Zureik and Ronchetti et al.[11,12] Briefly, scores took into account the patient's FEV1 values (mild: >80%, moderate: 70–80%, or severe: <70% predicted), the number of asthma attacks in the past year (2, 3–6, or >6), the number of hospital admissions for respiratory problems in the past year (0, 1–2, or >2), and whether inhaled or oral corticosteroids were taken in the past year. Each criterion was scored as 1, 2, or 3 based on increasing severity with the exception of corticosteroid use, which was scored as either 1 or 2 (Table 1). Scores for all four criteria were combined to produce a severity score ranging from 4 to 11, with severity levels being mild (score 4 or 5), moderate (6), or severe (> or equal to 7). Severe patients (whether asthma was well controlled or not) were all excluded in this study.

All patients were treated by standardised SCIT with Alutard Dp vaccine. The treatment regime was set up according to the manufacturer's product insert (Table 2), and no cluster schedule administered to any patient. During the initial

Table 1 Asthma severity scoring system.

Variables	Score levels		
	1	2	3
FEV_1 (%predicted)	>80	70–80	<70
Asthma attacks in the preceding year	2	3–6	>6
Hospitalisations in the preceding year	0	1–2	>2
Inhaled or oral corticosteroids taken in the preceding year	Inhaled corticosteroids	Oral corticosteroids	–

Each criterion was scored as 1, 2, or 3 with the exception of corticosteroid use, with a cumulative asthma severity score ranging from 4 t o11. Severity levels were defined as mild (4–5), moderate (6), or severe (>7). FEV_1, forced expiratory volume in one second.

Please cite this article in press as: Liu J-L, et al. The safety profile of subcutaneous allergen immunotherapy in children with asthma in Hangzhou, East China. Allergol Immunopathol (Madr). 2017. http://dx.doi.org/10.1016/j.aller.2017.04.002