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 efficacy and safety of sublingual immunotherapy in children and adult patients with allergic rhinitis

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Received 23 September 2016; accepted 31 October 2016

KEYWORDS
Allergic rhinitis;
Sublingual immunotherapy;
Dermatophagoides farinae;
Efficacy;
Young children

Abstract
Background: Clinical research has shown that sublingual immunotherapy (SLIT) is effective and safe in moderate-severe allergic rhinitis (AR) induced by house dust mite (HDM). However, the sample size in many studies is small. Meanwhile, the controversy on the efficacy and safety in the very young children younger than four years old still existed.
Objective: The aim of this retrospective study is to evaluate the efficacy and safety of SLIT with *Dermatophagoides farinae* (*Der.f*) extracts in children and adult patients with allergic rhinitis, particularly in the very young children.
Method: A total of 573 subjects aged 3–69 with AR received a three-year course of sublingual immunotherapy with *Der.f* extracts along with pharmacotherapy. The total nasal symptoms score (TNSS), total medication score (TMS), visual analogue score (VAS) and adverse events (AEs) were evaluated at each visit.
Result: TNSS, TMS, VAS were significantly improved during the three-year course of treatment in comparison to the baseline values ($P < 0.01$). Besides, significant improvement in nasal symptoms and reduction of medication use were also observed in young children aged 3–6 years ($P < 0.01$). No severe systemic adverse events (AEs) were reported.
Conclusion: SLIT with *Der.f* drops is clinically effective and safe in children and adult patients with HDM-induced AR, including the very young children less than four years old.

Introduction

Allergic rhinitis (AR) is one of the most common allergic respiratory diseases, which is associated with various comorbid diseases such as allergic asthma (AS) and conjunctivitis.[1]

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http://dx.doi.org/10.1016/j.aller.2016.10.016
0301-0546/

AR significantly affects more than 500 million patients worldwide in school attendance, work, sleep and quality of life,[1] bringing tremendous burdens to families and societies.[2] Available data indicated that the prevalence of AR has gradually increased in both adults and children over the last two decades, along with variations among different regions.[3] A recent study showed that the prevalence of subjects suffered from AR was 17.6% for 18 major cities in China.[4]

Allergen immunotherapy (AIT) has been used to treat allergic diseases since the early 1900s.[5] Allergen immunotherapy is the only treatment which may change the course of allergic disease through preventing development of asthma and onset of new sensitisations and reducing sensitisations to allergens.[6–8] Over the last three decades, the clinical application of sublingual immunotherapy has greatly increased because of its safety and convenience. However, the sample size in many studies is small.[9–11] Besides, the research on efficacy and safety in young children less than four years old is still rare. In this retrospective study, clinical data of 573 subjects aged 3–69 years old were collected to evaluate the efficacy and safety of sublingual immunotherapy with *Der.f* extracts.

Materials and methods

Patients and therapy

This clinical study was approved by the Ethics Committee and conducted in accordance with the Ethical Guidelines for Clinical Studies. In total, 573 subjects aged 3–69 years were involved, including 70 young children aged 3–6 (422 patients from Hainan People's Hospital, 151 patients from the Affiliated Hospital of Qingdao University; from December 2010 to March 2014). The inclusion criteria were (1) 3–69 years of age, diagnosed with moderate-to-severe/persistent AR with/without mild asthma, conjunctivitis or other diseases; (2) positive skin-prick test (SPT) for *Der.f*. Informed consent were signed by 573 patients who received sublingual immunotherapy for 36 months. Patients were also allowed to take standard medication according to the principle of the Allergic Rhinitis and its Impact on Asthma (ARIA).[1]

Sublingual immunotherapy

All patients were treated with sublingual immunotherapy by *Der.f* extracts (CHANLLERGEN, Zhejiang Wolwo Bio-Pharmaceutical Co., Ltd., Huzhou, Zhejiang, China) in this study, which were officially approved by the Chinese Food and Drug Administration in 2006. The HDM allergen extracts were labelled in concentration of total protein and used in the form of drops (No. 1, 1 μg/mL; No. 2, 10 μg/mL; No. 3, 100 μg/mL; No. 4, 333 μg/mL; No. 5, 1000 μg/mL.

According to the instructions, subjects were advised to take a dose of *Der.f* extracts once a day at the fixed time by keeping it under the tongue for one to three minutes and then swallowing it. The first dose was taken in hospital under medical supervision at least 30 min. Then patients could self-administer according to administration schedule at home daily. They were instructed to take an increasing dose from No. 1 to No. 3 during the first three weeks. 1, 2, 3, 4, 6, 8, 10 drops were given day after day in a week, respectively. Children under 14 years old took three drops of No. 4 solution daily in the maintenance therapy phase from the 4th week. Adults took three drops of No. 4 solution daily during the 4th and 5th week, then took two drops of No. 5 per day from the 6th week to the end of the treatment.

Pharmacotherapy

Along with sublingual immunotherapy, oral antihistamines, intranasal corticosteroid and β2-agonists use was allowed as standard pharmacotherapy by doctors' suggestions which rely on the principle of ARIA.

Allergen detection

In this study, skin prick test kit (standardised *Dermatophagoides farinae*; Zhejiang Wolwo Bio-Pharmaceutical Co., Ltd., Huzhou, China) was performed according to standard protocol before treatment. Histamine (positive control) and normal saline (negative control) were used for comparison. The skin wheal area was measured in 15 min after the SPT. Wheal diameters of *Der.f* $\geq$ 3 mm were determined as positive.

Adverse events

In case of adverse events (AEs), all the patients were instructed to take the first dose under the supervision of physicians in hospital and be monitored for at least 30 min. Physicians ought to record AEs in hospital or on telephone every three months, as well as providing suggestions for the management of adverse reactions.

Symptoms, medication scoring system and visual analogue scale

Before the treatment, nasal symptoms (nasal discharge, nasal obstruction, itching, sneezing), medication use and overall severity of symptoms of patients were recorded as baseline values in files. During the three-year course of treatment, patients were asked to accept follow-up visits in hospital or by telephone every three months. The total nasal symptoms score (TNSS), total medication score (TMS) and visual analogue score (VAS) of subjects were evaluated by physicians at each visit. TNSS was the sum of four nasal symptoms scores. These nasal symptoms were evaluated according to a 0- to 3-point scoring system.[12] TMS was evaluated as 0–3 point according to the medicine use.[10] VAS represents the overall severity of symptoms through a 10-cm visual analogue scale.[13] 0 point indicated ''no symptom'', 10 point indicated ''extremely severe symptom''.

Statistical analysis

The statistical analysis was performed with SPSS version 20.0 software (SPSS, Inc., Chicago, IL, USA) with a 5% significance level. Population statistics were expressed as numbers. Continuous variables were expressed as mean ± standard deviation (SD). The statistical significance of difference was determined by the non-parametric Mann–Whitney *U* test

Please cite this article in press as: Lin X, et al. The efficacy and safety of sublingual immunotherapy in children and adult patients with allergic rhinitis. Allergol Immunopathol (Madr). 2017. http://dx.doi.org/10.1016/j.aller.2016.10.016