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Efficacy of sublingual immunotherapy with high-dose mite extracts in asthma: A multi-center, double-blind, randomized, and placebo-controlled study in Taiwan

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Summary Sublingual immunotherapy (SLIT) has been recommended as a viable alternative to subcutaneous injection therapy in the treatment of airway allergies, though more data is needed from well-controlled studies for documenting its efficacy in different ethnic populations. Ninety-seven children (age range 6–12 years), mild-to-moderate asthma with a single sensitization to mite allergen, were enrolled from 5 medical centers in Taiwan to evaluate the efficacy and safety of SLIT with standardized mite extracts, which contain *Dermatophagoides pteronyssinus* (D.*p*.) and *Dermatophagoides farinae* (D.*f*.). Patients were double blinded and randomly assigned to either a SLIT or placebo group. Following 24 weeks of study period, symptom and medication scores, lung function tests, skin prick tests, total serum IgE, and specific IgE to D.*p*. and D.*f*. were recorded. The results showed that there was statistically significant difference between these two groups in the analysis of daily ($P = 0.011$), nighttime ($P = 0.028$), and daytime ($P = 0.009$) asthmatic scores after 24 weeks of treatment. Patients receiving SLIT improved their forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), and peak

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expiratory flow (PEF) as compared to baseline ($P = 0.042$, $P = 0.048$, and $P = 0.001$, respectively). No differences were found in skin prick test, total serum IgE and specific IgE to D.*p*. and D.*f*. Tolerance with high-dose SLIT was good with few minor adverse events reported. Our results indicated that a 24-week SLIT is of clinical benefit to mite-sensitive asthmatic children in Taiwan.

Introduction

The use of sublingual immunotherapy (SLIT) to treat allergic airway diseases has increased over the past few decades and its effectiveness has been demonstrated in several clinical trials, though some of the early studies tended to be small scale and had methodological flaws.[1] In 1998, the WHO has recommended SLIT as a suitable treatment for allergic rhinoconjunctivitis in adults based on six double-blind, placebo-controlled studies.[2–7] Two of the studies were carried out in children, with systemic side effects being reported in one.[4] It was concluded that more studies were needed before SLIT could be recommended for general use in children as an alternative to subcutaneous immunotherapy. In 2001, Rakoski et al.[8] reviewed 20 published studies on SLIT, eighteen of which were performed in patients with rhinitis,[2–19] and two in patients with asthma.[20,21] Controversy still remains over the use of SLIT in children with asthma. Although recently, there are several studies focused on the SLIT on grass pollen allergic children,[22–24] only four double-blind placebo-controlled trials have focused on asthmatic children sensitive to house dust mites (HDM).[5,20,21,25] Two of them showed improvement in symptoms and drug scores with few minor side effects.[20,21] The other two comparable studies did not substantiate the clinical efficacy of SLIT, though they reported the safety and tolerance of SLIT to be promising.[5,25]

Although SLIT appears to be effective to a degree and relatively safe, current evidence indicates the needs in defining the route of administration (sublingual-swallow vs. sublingual-spit), the duration of treatment, the optimal dose of standardized allergen extracts, and most importantly in the different ethnic population for the global application. Therefore, to know the efficacy and safety of this new therapy of SLIT in mite-sensitive asthmatic children is important before its wide application of treating allergic asthma in children. As far as we know, there have been no reports in Asian countries. In the present study, we have applied high doses of mite allergens as final accumulated doses over 500 times higher than those given in subcutaneous immunotherapy, in a relatively short time. Our primary aim is to evaluate the efficacy of SLIT with Staloral™, the standardized combined HDM extracts, *Dermatophagoides pteronyssinus* (D.*p*.) and *Dermatophagoides farinae* (D.*f*.), in asthmatic children sensitized to HDM. Secondary objective is to evaluate the safety and tolerability of this SLIT in our asthmatic children.

Materials and methods

Patients

Asthmatic children, aged 6–12 years with at least 1-year history of mildly persistent to moderately persistent (GINA—global initiative for asthma, step 2–3), were enrolled in this study. They were allergic to HDM only. The diagnosis of a single allergy HDM (D.*p*.) and (D.*f*.) was based on clinical history, positive skin tests using standardized extracts (Stallergenes SA, Antony, France), and the presence of specific IgE against mites as shown in MAST with or over class 3+as the cutoff value. Patients were excluded if they were sensitive to either cockroach, *Alternaria*, *Cladosporium*, dog, cat danders, or pollens, by skin prick tests (wheal $\geqslant$5 mm), or has allergen-specific IgE antibodies ($\geqslant$1+, tested by MAST CLA allergen test, Hitachi chemical Diagnostics, Inc. (CA, USA) against above allergens. Children were enrolled in this study only if their forced expiratory volume in 1 s (FEV_1) were greater than 70% of that predicted, and the reversible peak expiratory flow (PEF) rate exceeded 15% after inhalation of β_2-agonists. Patients who had previously been treated with immunotherapy, oral or parenteral corticosteroids for more than 15 consecutive days, depot steroids, inhaled corticosteroids in doses greater than 1000 μg/day (beclomethasone dipropionate), inhaled β_2-agonists more than four times/day, and those suffering from other respiratory diseases that were not suitable for immunotherapy, such as anatomical abnormality of upper respiratory tract, and congenital cardiovascular diseases, were excluded.