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Immunotherapy in reducing clinical symptoms of children with house dust mite-induced allergic rhinitis

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Abstract---Allergic rhinitis in children is mostly caused by house dust mites (HDM). It requires long-term therapy and decreases the quality of life of patients and their caregivers. Immunotherapy provides long-term improvement of clinical symptoms in children with allergic rhinitis. However, there are not many studies on the benefit of immunotherapy in children with allergic rhinitis in Indonesia. This study aimed to analyze the benefits of immunotherapy in reducing clinical symptoms in children with HDM-induced allergic rhinitis. A secondary data-based retrospective cohort study was conducted on HDM-induced allergic rhinitis children between 2015-2019 in Surabaya. The diagnosis of HDM-induced allergic rhinitis was established from typical allergic symptoms and a positive skin prick test result for HDM allergens. The improvement of clinical symptoms was assessed based on total symptom score (TSS), total medication score (TMS), and combination of symptom and medication score (CSMS) of the EAACI/WAO scoring. Observation on each score was carried out at the time of initial diagnosis and after 18 months of therapy. Mann-Whitney comparative analysis statistical test was for comparing immunotherapy group and non-immunotherapy group. TSS, TMS, and CSMS of the immunotherapy group were significantly lower ($p < 0.05$) than in the non-immunotherapy group.

Keywords---Allergic rhinitis, house dust mite, immunotherapy, children, symptom score, medication score

Introduction

Allergic rhinitis is an inflammatory disease of the nasal cavity caused by an allergic reaction to allergens in atopic patients. It is a common allergy manifestation in school-aged children. House dust mite is the most aeroallergen that cause allergic rhinitis in children (Yang et al., 2018). Allergic rhinitis is rarely be life threatening, but it can affect the quality of life of patients and their caregivers (WAO, 2013). The current management of allergic rhinitis aims at controlling the symptoms and improved the quality of life. One of the currently developed treatment strategies for allergic rhinitis is allergen-specific immunotherapy (Calderon et al., 2015).

Immunotherapy provides an improvement of clinical symptoms in children with allergic rhinitis (Meadows et al., 2013). The ARIA (Allergic Rhinitis and its Impact on Asthma) guidelines stated that immunotherapy is effective for treatment of children with moderate to severe, persistent, or intermittent allergic rhinitis (Brozek et al., 2010). Immunotherapy has shown more consistent results in reducing allergic symptoms and pharmacological drug consumption in children with allergic rhinitis (Eifan et al., 2010). However, there have not been many studies about the benefits of immunotherapy use in allergic rhinitis children in Indonesia. Therefore, the objective of this study is to explain the benefits of immunotherapy in reducing clinical symptoms of children with house dust mite-induced allergic rhinitis.

Method

This retrospective cohort study was conducted based on secondary data of house dust mite-induced allergic rhinitis children in Surabaya from 2015-2019. The subjects of this study were children who newly diagnosed as house dust mite-induced allergic rhinitis in pediatric allergy-immunology outpatient clinic at Dr. Soetomo Hospital and pediatric allergist practice from 1 January 2015 to 31 December 2019. This study was approved by the Ethical Committee of Dr. Soetomo Academic General Hospital (Number 0297/LOE/301.4.2/I/2021).

Data analysis

Inclusion criteria were ≤ 18 years old children, newly diagnosed with allergic rhinitis, with or without comorbidities, by pediatric allergist and children who had positive skin prick test to house dust mite allergen. Children with incomplete medical record data, follow-up time < 18 months, previous immunotherapy, and patients with malignancy, Down's syndrome, and cerebral palsy were excluded. Before analyzing the data, a matching process on age, gender, family history of allergies, parents' education, baseline TSS, TMS, and CSMS were carried out. The immunotherapy group data were obtained from the medical records of pediatric allergy-immunology outpatient clinic of Dr. Soetomo General Hospital from January 2015 to December 2015. Due to limited availability of complete data from participants who did not get immunotherapy at the hospital, the data for this group were derived from a cohort of patients who visited the pediatric allergist practice in Surabaya between January 2015 and December 2019. Prior to data analysis, a matching process was conducted using age, gender, location, family

history of allergies, parents' current degree, and TSS, TMS, also CSMS before therapy as baseline. Thus, 130 children in each immunotherapy and non-immunotherapy group were included in this study's subjects. This study assessed the improvement of clinical symptoms based on EAACI/WAO scores, which consisted of TSS, TMS, and CSMS. Each score was assessed before therapy and after 18 months of therapy. The data were processed using SPSS version 26.0 and analyse with Mann-Whitney comparative test.

Results

General characteristics

A total of 260 children with newly diagnosed house dust mite-induced allergic rhinitis became subjects in this study. They consist of matched 130 children who underwent immunotherapy and 130 children who did not undergo immunotherapy. General characteristics were presented descriptively in table 1. There were no differences in characteristics between the immunotherapy and non-immunotherapy groups. Most of the subjects had allergic comorbidities, with asthma being the most common comorbidities in this study.

Table 1
Basic characteristics of children with house dust mite allergic rhinitis

Characteristics	Total (n = 260)	Non- immunotherapy (n = 130)	Immunotherapy (n = 130)	p*
Sex (%)				>0.05
Male	167 (64.2)	80 (61.5)	87 (66.9)	
Female	93 (35.8)	50 (38.5)	43 (33.1)	
Mean (\pm DS) age (years)	5.48 (\pm 3.5)	5.62 (\pm 3.61)	5.33 (\pm 3.38)	>0.05
Mean (\pm DS) age of allergies (years)	3.29 (\pm 3.04)	3.59 (\pm 3.3)	2.99 (\pm 2.75)	>0.05
Mean (\pm DS) SPT diameter (mm)	10.01(\pm 3.86)	9.55 (\pm 2.92)	10.46 (\pm 4.58)	>0.05
Allergic comorbidities (%)				>0,05
0	8 (3,1)	3 (2,3)	5 (3,8)	
1	195 (75)	92 (70,8)	103 (79,2)	
2	54 (20,8)	33 (25,4)	21 (16,2)	
3	3 (1,1)	2 (1,5)	1 (0,8)	

* Differences between the immunotherapy and non-immunotherapy group

Clinical symptoms of the immunotherapy and non-immunotherapy groups

A comparative numerical test of two unpaired groups with Mann-Whitney test was performed on TSS, TMS, and CSMS, respectively. Based on this analytical statistic, there were significant differences in TSS, TMS, and CSMS scores after

18 months immunotherapy. Lower mean TSS, TMS, and CSMS were showed in the immunotherapy group than the non-immunotherapy group.

Table 2
Comparison of the difference between TSS, TMS, and CSMS on research subjects

	Non-immunotherapy	Immunotherapy	<i>p</i>
TSS, mean (\pm DS)			
Baseline (before therapy)	2.38 \pm 0.60	2.4 \pm 0.67	0.58
18 th month of therapy	2.05 \pm 0.46	1.08 \pm 0.27	<0.001*
TMS, mean (\pm DS)			
Baseline (before therapy)	2.56 \pm 0.50	2.58 \pm 0.49	0.8
18 th month of therapy	2.17 \pm 0.66	0.36 \pm 0.63	<0.001*
CSMS, mean (\pm DS)			
Baseline (before therapy)	4.94 \pm 0.78	4.98 \pm 0.88	0.63
18 th month of therapy	4.21 \pm 0.70	1.44 \pm 0.70	<0.001*

Discussion

In this study, house dust mite-induced allergic rhinitis was found in 64.2% of boys and 35.8% of girls. The average age of the child at diagnosis was 5.48 years old, however allergy symptoms began at younger age of 3.29 years old. According to research of children aged five years with rhino-conjunctivitis, up to 60.6% of children with rhino-conjunctivitis were boys (Marinho et al., 2007). Another study found that the prevalence of allergic illnesses such as asthma, rhinitis, and eczema was much greater in males than in girls, according to the results of the study (Yao et al., 2011). Rhinitis prevalence continued to rise throughout childhood, eventually affecting more than a third of the population by the age of 18 years (Kurukulaaratchy et al., 2011).

The skin prick test was ruled positive when the diameter of the induration was 3 mm or greater. The average diameter of the skin prick test to house dust mite allergen was 10.01 mm in this study. Tschopp et al. (1998) investigated the diagnostic accuracy of total serum IgE, SPT, and Phadiatop® assays in allergic rhinitis. According to the findings of that study, when compared to other tests, the skin prick test had the highest positive predictive value. According to a meta-analysis research, the skin prick test has a sensitivity of up to 100% and a specificity of up to 91% for detecting patients with suspected allergic rhinitis symptoms (Nevis et al., 2016). There was no widely acknowledged clinical symptom evaluation system for immunotherapy at the time of writing. A widely utilized, simple-to-apply technique based on a 4-point (0-3) symptom rating scale (TSS) from EAACI was widely adopted. According to additional EAACI recommendations, clinical symptom assessment using TSS should be paired with drug use (TMS). CSMS is a term that refers to the combination of TSS and TMS (Pfaar et al., 2014).

Almost all subjects in this study had comorbidities, with 22% having more than one allergy comorbidity. Asthma was the most often encountered concomitant conditions in this study's subjects, followed by recurrent chronic cough, sinusitis,

atopic dermatitis, conjunctivitis, and urticaria. This is consistent with another study's findings that the majority of children and adolescents with allergic rhinitis also have extra nasal comorbidities such as rhinosinusitis, asthma, atopic dermatitis, and conjunctivitis ([Marino-Sanchez et al., 2019](#)).

The results of the comparative analysis of clinical symptoms in this study revealed that there were statistically significant differences in the variables of TSS, TMS, and CSMS after 18 months of treatment between the immunotherapy and non-immunotherapy groups. When receiving immunotherapy, the improvement in clinical symptoms typically occurs after six months or longer ([Endaryanto, 2015](#)). In a trial of 48 children with house dust mite-induced rhinitis/asthma, the individuals were separated into three groups: sublingual immunotherapy (n=16), subcutaneous immunotherapy (n=16), and pharmacotherapy (n=16). Clinical symptoms were assessed by TSS, TMS, and Visual Analogue Scale (VAS) at the start of the observation and 12 months following the therapy. After 12 months of therapy, TSS, TMS, and VAS scores were considerably lower in the immunotherapy group (both sublingual and subcutaneous) than in the pharmacotherapy group. The median TSS improvement in the sublingual and subcutaneous immunotherapy groups was 77% and 81%, respectively, compared to the pharmacotherapy group. The absence of statistically significant differences between sublingual and subcutaneous immunotherapy groups indicated that both immunotherapy methods were equally effective. The sublingual immunotherapy group experienced a significant drop in drug use/TMS, but not the subcutaneous immunotherapy group. This could be explained by the fact that two participants in the subcutaneous immunotherapy group encountered serious adverse events ([Eifan et al., 2010](#)). Meanwhile, no adverse events were reported in the immunotherapy group during the course of this current study.

For a three-year observation period, a randomized clinical trial was conducted in 48 children with persistent asthma and/or sensitive rhinitis to house dust mites. The TSS and TMS were evaluated at baseline and three years later. At three years of observation, the study demonstrated a significant improvement in TSS and TMS in the immunotherapy group, both subcutaneously and sublingually ([Karakoc-Aydiner et al., 2015](#)). Former study on immunotherapy for children with allergic rhinitis in Indonesia have been conducted. In comparison to this study, which involved pediatric patients in Surabaya who received immunotherapy at a tertiary referral hospital with national health insurance funding, that study involved children with house dust mite-induced allergic rhinitis from 92 cities in Indonesia who received treatment at pediatric allergists' private practice with private financing. The study reported that after 6 months, 12 months, and 18 months of immunotherapy, significant differences in TSS, TMS, and CSMS were observed between children who received immunotherapy and children who did not receive immunotherapy ([Endaryanto & Nugraha, 2021](#)).

A retrospective cohort research is observational in nature and therefore does not give the same degree of evidence as randomized controlled trials and meta-analyses. Due to the enormous number of confounding variables, the effect of external variables is technically challenging to regulate and measure.

Conclusion

There was a significant difference in the improvement of clinical symptoms between children with house dust mite-induced allergic rhinitis who received immunotherapy and those who did not get immunotherapy. After 18 months, children with house dust mite-induced allergic rhinitis who received immunotherapy had significantly lower TSS, TMS, and CSMS than those who did not get immunotherapy.

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