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Clinical and laboratory profiles of pediatric asthma patients with house dust mite (HDM)–specific subcutaneous immunotherapy: A single center, cross sectional study

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ABSTRACT

Introduction: House dust mite (HDM) allergy has been reported as an actual cause of asthma in children. Subcutaneous immunotherapy (SCIT) is a recommended treatment for HDM allergy patients. However, there were limited data about the characteristic of pediatric patients with HDM-SCIT, particularly in Indonesia. This study was aimed to evaluate the characteristic of pediatric patients with allergic asthma.

Methods: Study participants were pediatric patients confirmed with HDM allergy from Skin Prick Test (SPT) in the pediatric allergy-immunology outpatient clinic in Saiful Anwar Hospital Malang, Indonesia. Patients who were treated with HDM-SCIT in the early build-up phase of treatment were included in this study. Demographic and clinical characteristics of the patients were recorded. Peripheral blood samples were drawn to evaluate the total eosinophil count (TEC), total basophil count (TBC), neutrophil-lymphocyte ratio (NLR), specific IgE (sIgE) and total IgE (t-IgE) level. Clinical diagnosis of asthma was classified according to the Global Initiative for Asthma (GINA) criteria. The evaluation of asthma control was assessed by the Asthma Control Test (ACT) score.

Results: Thirty-two patients were enrolled in this study, including 14 male and 18 female. The mean age of children was 6.92 ± 2.60 years old. There were 21 subjects with uncontrolled asthma and 11 subjects with partially controlled asthma. Demographic characteristics including age, sex, nutritional status and family history were not significantly different between uncontrolled and partially controlled asthma groups ($p > 0.05$). TEC, TBC, NLR, and tIgE were not different significantly among groups ($p > 0.05$). This study showed that the mean of sIgE serum level was higher in uncontrolled asthma compared to partially controlled asthma group ($p = 0.022$). Moreover, it was a negative significant correlation between sIgE serum level and ACT score ($p = 0.002$, $r = -0.532$).

Conclusion: Higher sIgE levels were correlated with poor asthma control in HDM-SCIT patients.

Keywords: HDM Allergy; SCIT; sIgE; Asthma; ACT Score

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INTRODUCTION

House dust mite (HDM) allergen exposure is increasingly recognized as an essential cause of allergic asthma in children.[1,2] The prevalence of asthma in Indonesia ranges from 3–16%, and HDM allergens induce sensitization in 77% of asthmatic patients.[3] Allergen-specific immunotherapy (AIT) is an established recommended treatment for allergic rhinitis and asthma with a broad and potential evidence-based treatment. Allergen immunotherapy (AIT) is the only etiology-based treatment for allergic diseases capable of disease modification, as demonstrated by the prevention of both the onset of new allergic sensitizations and disease progression. Four two routes of AIT administration are widely used, including Subcutaneous Immunotherapy (SCIT) and Sublingual Immunotherapy (SLIT). Both SCIT and SLIT have been suggested, resulting in decreased immunoglobulin E (IgE) concentrations, a significant driver of allergen-specific TH2 responses. SCIT and SLIT also reported inducing the tolerance of dendritic cells, T cell and also B cell.[5] Systematic review conducted by The European Academy of Allergy and Clinical Immunology (EAACI) suggested that AIT can achieve substantial reductions and clinical symptoms in allergic asthma.[6]

Although there was a growing need for HDM-AIT as a therapeutic modality for allergic diseases, relatively little is known about patient characteristics, particularly in Indonesia. This study investigates the demographic, clinical and laboratory profile in patients with HDM allergy receiving SCIT in the pediatric allergy-immunology outpatient clinic in Saiful Anwar General Hospital Malang, Indonesia. Understanding the patient's characteristics was important information for consideration of treatment indication.

METHODS

Study Participant

This study was a cross sectional study conducted in the pediatric allergy-immunology outpatient clinic in Saiful Anwar General Hospital Malang, Indonesia. The method of sample recruitment was through consecutive sampling. Patients who met the following inclusion criteria: >5 years of age, a suspected diagnosis of asthma due to HDMs based on clinical presentation and prior history, allergic sensitization confirmed by positive skin-prick test *Dermatophagoides sp,* and receiving HDM-SCIT in the build-up phase were included in this study. All patients (or the parents/legal guardian in the case of pediatric patients) signed a written informed consent to allow their data to be used in the analysis. Confidentiality of the patients' data was maintained at all times. This study was evaluated and approved by the reference Ethics Committee Faculty of Medicine, Brawijaya University, Indonesia, with reference number: 111/EC/KEPK/06/2020.

Study Variable

Data were collected during a single study visit, including sociodemographics, history of atopic disease, general clinical characteristics of the patients, diagnosis, prior therapies for rhinitis and asthma, and the schedule of build-up phase HDM-SCIT. Diagnosis of asthma was performed using the Global Initiative for Asthma (GINA) definitions. Furthermore, the evaluation of asthma control was assessed by the Asthma Control Test (ACT) score. A peripheral blood sample was drawn to evaluate complete blood count, total Immunoglobulin (tIgE) and HDM-specific Immunoglobulin E (IgE) serum level. Complete blood count was performed by hematology analyzer (Cobas m511, Roche, Germany) to evaluate the number of Total Eosinophil Count (TEC), Total Basophil Count (TBC) and neutrophil-lymphocyte ratio (NLR). Total IgE (tIgE) serum level was measured by the immunoassay (Cobas e400, Roche, Germany). tIgE concentrations > 15 IU/mL were considered to be increased. Simultaneously, all subjects were examined the HDM specific IgE serum using a commercial kit (Euroline Test®, Euroimmune, Germany). It was affirmed of specific IgE serum if IgE specific concentration was > 0.35 kU/L. All the study variables were collected simultaneously in the early build-up phase of SCIT (≤ 4 weeks of treatment).

Statistical Analysis

All of the study data were presented using descriptive statistics. Quantitative variables are expressed as means ± standard deviations or median values with interquartile range. Qualitative variables were described as frequency. Also, patients were divided into two groups based on ACT scores, those with uncontrolled asthma (ACT score <20) and partially controlled asthma (ACT score 20-24). The differences of mean value between groups were analyzed using Chi-Square, T-test or Mann-Whitney-test. The correlation analyses were performed using Pearson or Spearman correlation test. All statistical analyses were performed using IBM SPSS Statistics ver. 25.0 (IBM Corporation, New York City, USA), with *a P-value* of <0.05 was considered statistically significant

RESULTS

Characteristics of Subjects

Demographic, clinical and laboratory characteristics of the study subjects were shown in Table 1**.** Thirty-two children with HDM allergy receiving HDM-SCIT were enrolled in this study. The mean age was 6.92 ± 2.60 years, including 14 males and 18 females. Almost all of the study subjects (93.7%) had good nutritional status. This study reported a family history of atopic diseases such as asthma, allergic rhinitis, rhino-conjunctivitis allergy and food allergy in twenty subjects (62.5%). Nineteen (59.3%) subjects were diagnosed with asthma, and there were 13 (40.7%) subjects with combined asthma and allergic rhinitis. According to the frequency of symptoms, six subjects with mild persistent asthma and 26 subjects had moderate persistent asthma. From ACT classification, there were 21 subjects with uncontrolled asthma (ACT score < 20) and 11 subjects with partially controlled asthma (ACT score 20 – 24).

All of the subjects showed sensitization to HDM allergen from the Skin Prick Test. It was also confirmed by HDM sIgE serum measurement. From laboratory examination, the mean of TEC was 0.47 ± 0.27, the mean of TBC was 0.03 ± 0.02, and the mean of NLR was 1.76 ± 1.66. This study found that the mean of HDM sIgE serum measurement was 16.36 ± 14.35 kuA/L. Thirty subjects were categorized as positive sensitization to HDM (sIgE > 0.35 kuA/L) and there were only two subjects had sIgE < 0.35 kuA/L. It has also reported a higher mean tIgE serum level (463.28 ± 391.09 IU/mL). It was categorized as an increased level if the tIgE serum concentration was >15 IU/mL).

Comparison of subject's characteristic based on ACT score

In this study, we found that there were no significant differences in demographic characteristics of subjects between the uncontrolled asthma group and partially controlled asthma group, including age

Table 1. The demographic and clinical characteristics of subjects

Characteristis	Value
Age (years) (mean ± sd)	6.92 ± 2.60
Sex (n)	
Male	14/32
Female	18/32
Nutritional status (n)	
Underweight	2/32
Normoweight	30/32
Family history of atopic disease (n)	
Yes	20/32
No	12/32
Diagnosis (n)	
Asthma	19/32
Asthma and Allergic Rhinitis	13/32
According to frequency of symptom (n)	
Mild Persistent	6/32
Moderate Persistent	26/32
ACT Score (mean ± sd)	17.38 ± 3.48
ACT Classification (n)	
Uncontrolled	21/32
Partially controlled	11/32
Skin Prick Test (n)	
HDM allergy (+)	32
HDM allergy (-)	0
TEC (10^3/μL) (mean ± sd)	0.47 ± 0.27
TBC (10^3/μL) (mean ± sd)	0.03 ± 0.02
NLR (mean ± sd)	1.76 ± 1.66
tIgE serum level (IU/mL) (mean ± sd)	463.28 ± 391.09
HDM sIgE serum level (kuA/L) (mean ± sd)	16.36 ± 14.35

(p= 0.496), sex (p= 0.101) and nutritional status (p= 0.891). No difference was found in the family history of atopic disease (p= 0.501). Clinical characteristics of asthma were also not different among groups, especially in the frequency of symptoms (p= 0.153). There was no significant TEC difference, TBC and NLR between uncontrolled asthma and partially controlled asthma groups (p> 0.05). Total serum IgE level was higher in uncontrolled asthma groups than partially controlled asthma groups, but there was no statistical difference (p= 0.254). Only the HDM sIgE serum level was significantly higher in the uncontrolled asthma group than the partially controlled asthma group (p= 0.022). The comparison of demographic, clinical, and laboratory parameters between groups based on the ACT score was described in Table 2.

Correlation between sIgE and ACT score

Our study analyzed the correlation between HDM sIgE serum level and ACT score. From Spearman correlation analysis, there was a negative significant correlation between HDM sIgE serum level and ACT score (p= 0.002, r= -0.532). Figure 1 showed the correlation graph between HDM sIgE serum level and ACT score.

DISCUSSION

A limited study conducted in Indonesia evaluated the clinical and laboratory profiles of allergic asthma patients receiving HDM-SCIT. In this cross sectional study, there was 32 subject confirmed with HDM allergy receiving subcutaneous immunotherapy during eight months of recruitment. A previous study reported a high prevalence of sensitization to HDM among Indonesian children aged 5–15 years old associated with asthma and allergic disease.[7] This study reported that the mean age was 6.92 ± 2.60 years, including 56.25% female and 43.75% male. A similar subject's characteristic was found in a study conducted by Endaryanto et al. (2019), a retrospective cohort study comprised 65 children with allergic asthma due to HDM allergens. They reported that the mean age was 9.3 ± 1.99 years with no difference among gender (49.23% female and 50.77% male).[8]

Over half of the subjects in this study (62.5%) had a family history of atopic diseases such as asthma, allergic rhinitis, rhinoconjunctivitis allergy and food allergy. Family history of the atopic disease was suggested a decisive risk factor for the development of allergy in children. A study reported that children with a history of any allergic disease in family members showed an increased risk of allergy.[9] Most of the subjects diagnosed with asthma (71.8%) and combined asthma and allergic rhinitis (28.2%), which was similar to the study in Korea; the prevalence of allergic rhinitis in children with asthma was 64.3%, and that of asthma in children with allergic rhinitis was 21.6%. A multicenter cross-sectional study in Spain reported 10 Other similar results; among 519 subjects with allergic rhinitis caused by HDM allergy, approximately 38% had concurrent asthma.[11] Recent data showed a high comorbid asthma rate and rhinitis as 60% to 80% of patients with asthma had rhinitis symptoms. It was considered that AR and asthma shared common pathophysiological mechanisms.[12]

According to the frequency and severity of asthma symptoms, most of the subjects presented moderate persistent asthma with moderate or severe exacerbation symptoms. Allergen immunotherapy (AIT) is a proven therapeutic option for the treatment of allergic rhinitis and/or asthma with

Table 2. Comparison of demographic, clinical and and laboratory parameters between groups based on ACT Score Classification

Parameters	Uncontrolled Asthma (n=21)	Partially controlled Asthma (n=11)	P value
Age (years)	6.69 ±2.88	7.36 ± 2.03	0.496[a]
Sex (%)			0.101[b]
Male	10	4	
Female	11	7	
Nutritional status			0.891[b]
Underweight	2	0	
Normoweight	19	11	
Family history of atopic disease			0.501[b]
Yes	13	6	
No	7	5	
Frequency of asthma symptom			0.153[b]
Mild Persistent	1	5	
Moderate Persistent	20	6	
Time of SCIT	3.76 ± 2.12	3.82 ± 2.75	0.295[c]
TEC (10^3/µL)	0.51 ± 0.30	0.41 ± 0.21	0.558[c]
TBC (10^3/µL)	0.04 ± 0.02	0.03 ± 0.02	0.785[c]
NLR	1.66 ± 1.52	1.96 ± 1.96	0.558[c]
tIgE serum level (IU/mL)	497.89 ± 380.97	397.21 ± 420.20	0.254[c]
HDM sIgE serum level (kuA/L)	20.32 ± 15.52	8.81 ± 7.82	0.022[c]*

*p< 0.05 was statistically significant, [a]Independent T-Test, [b]Chi Square Test, [c]Mann-Whitney Test

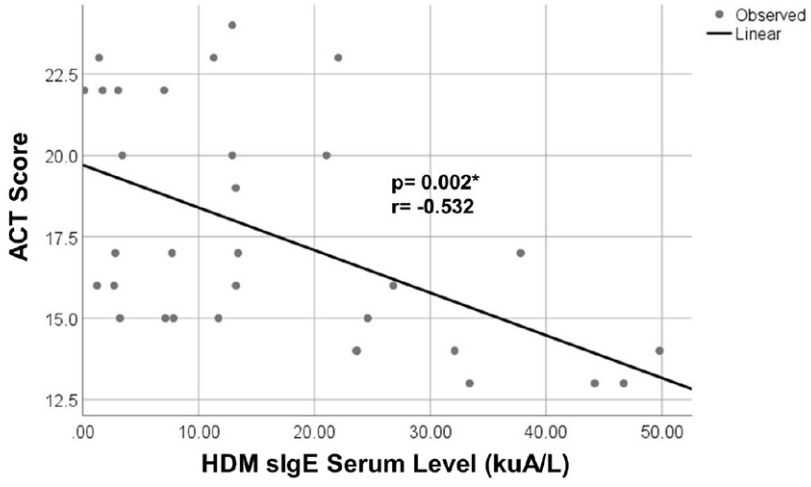

Figure 1. Correlation between HDM sIgE serum level and ACT score

several indications such as uncontrolled asthma and/or allergic rhinitis patients after optimal medication and avoidance; patients who need a higher dose and more medication for their asthma and/or allergic rhinitis.[13] Assessment of asthma control level were conducted by ACT score (25: controlled; 20–24: partly controlled; <20: uncontrolled).14 In this study, there were 21 subjects with uncontrolled asthma and 11 subjects with partially controlled asthma. This study reported no significant difference between subjects' demographic and clinical characteristics between uncontrolled asthma and partially controlled asthma groups. There was also no difference in immune parameters such as TEC, TBC, and NLR from complete blood count analysis. These results differed from those reported in other studies; there was a significantly higher eosinophil count in uncontrolled asthma patients than partially controlled and controlled asthma groups receiving HDM-SCIT.[8] A study analyzed the correlation between basophil in HDM allergy patients and reported that basophil response assessed by Basophil Activation Test (BAT) did not correlate with clinical response to immunotherapy in allergic rhinitis were received subcutaneous immunotherapy for the inhalant allergens HDM.[15] Other study also reported different results; NLR was found significantly higher in asthma patients with ACT score < 20 compared to those with ACT score ≥ 20, and a significant correlation was determined between NLR and ACT.[16]

The formation of IgE-specific antibodies against allergen is the essential part of diagnosing allergen sensitization. Measurement of IgE-specific antibodies can be conducted in vivo with a skin prick test or in vitro with IgE-specific serum measurement.[17] In this study, a skin prick test shows that *Dermatophagoides pteronyssinus (Der p)* and *Dermatophagoides farinae (Der f)* were the most commonly found house dust mite allergen. A previous study in Jakarta showed similar results; Der p had the highest prevalence (77.5%), followed by Der f (69.6%) and Blo t (72%).[18] In tropical countries, house dust mites exposure is an important factor causing respiratory allergy development.[19] Serum-specific IgE testing was used to detect Der p and Der f allergen's sensitization in this study. It was reported that thirty subjects were categorized as positive sensitization to HDM (sIgE > 0.35 kuA/L), and there were only two subjects who had sIgE < 0.35 kuA/L. It means that serum specific IgE testing might be used to detect asthma and/or allergic rhinitis patients who are genuinely sensitized by Der p allergen and Der f allergen, as useful as skin prick test. World Allergy Organization (WAO) mentions that the skin prick test is the gold

standard in detecting IgE.[20] A study compared serum specific IgE testing to gold standard skin prick test to determine Der p and Der f allergen's sensitivity in patients with asthma and/or allergic rhinitis in Ukraine. They reported high sensitivity and specificity of serum specific IgE testing for Der p and Der f allergens [(85%, 93.3%) and (87.5%, 89.6%)].[21]

Moreover, this study showed that sIgE serum levels were higher in uncontrolled asthma than partially controlled asthma. There was no difference in tIgE serum level among the group, although there was an increase in both groups. Similarly reported by a previous study, there was no difference in tIgE serum level among controlled, partially controlled and uncontrolled asthma patients receiving HDM-SCIT.8 Interestingly, this study found that sIgE inversely correlates with ACT score, which means that the higher the level of sIgE, the more severe the asthma control. A study conducted in Italy showed that serum specific-IgE before AIT could be a useful biomarker for predicting response to AIT with the value of 96.4%, the specificity of 100%, and an area under the receiver operator characteristic curve of 0.987.[22] This study was conducted at early weeks in the built-up phase of SCIT, with the mean of treatment weeks was 4.44 ± 2.35 weeks. It was suggested that it was still represented by the baseline or the early response of SCIT. Because during the initial sensitization phase in patients with AIT, there were transient increases in serum allergen-specific IgE antibody levels that are followed by blunting of the usual seasonal increases in IgE levels during natural allergen exposure, resulting in a decrease of allergen-specific IgE (sIgE) concentrations and might contribute to long-term tolerance.[23]

In conclusion, this study showed a high level of sIgE and tIgE in asthma patients receiving HDM-SCIT. Interestingly, higher sIgE levels were correlated with poor asthma control in HDM-SCIT patients. This study results might be continued to study further whether specific IgE levels can predict clinical improvement in HDM allergy patients treated with immunotherapy. The present study had several limitations. In addition to the cross-sectional design, the minimal sample size and conducted in a single-institution made it challenging to describe generally the demographic, clinical and laboratory parameters of pediatric patients with HDM allergy receiving SCIT. Further studies with a large scale that evaluated the profiles and effectiveness of SCIT in HDM allergy were needed.

CONFLICT OF INTEREST

None

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