

## Effect of House Dust Mite Immunotherapy in Indonesian Children with Chronic Sinusitis

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### Abstract

The aimed was associated to effect of HDM immunotherapy in children with chronic sinusitis due to HDM allergies.

Participants were divided into 2 groups, consisting of treatment group (immunotherapy) with 23 patients, and control group with 22 patients. Treatment groups received HDM immunotherapy for 14 weeks. The statistical analysis used McNemar and Chi-Square test with 95% confidence interval (CI) and  $p < 0.05$ .

There was a significant difference in the improvement of Waters' view in the treatment and control groups ( $p < 0.001$ ). There were significant differences in the absence of itchy nose symptom ( $p = 0.003$ ), colored secretion ( $p = 0.024$ ), itchy eyes ( $p = 0.019$ ), wheezing ( $p = 0.024$ ), shortness of breath ( $p = 0.039$ ), sneezing ( $p < 0.001$ ), postnasal drip ( $p < 0.001$ ), stuffy nose ( $p < 0.001$ ), snoring ( $p < 0.001$ ), cough ( $p < 0.001$ ), phlegm ( $p < 0.001$ ), and rhinorrhea ( $p < 0.001$ ).

There is an improvement in pediatric chronic sinusitis before and after HDM immunotherapy.

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### Introduction

Sinusitis is a common health problem in children with a high prevalence and increasing cases every year<sup>1,2</sup>. Allergic airway diseases are the main risk factors for pediatric sinusitis that can lead to a chronic condition<sup>3</sup>. Inhaled allergic patients have a tendency to suffer from sinusitis. There is research which states that the two disorders namely rhinitis and sinusitis occur in the same patients 25-70% of the time<sup>4,5</sup>, and another study states that 72 of 121 patients who have chronic nasal symptoms with positive skin tests for allergic inhalation have a positive sinus tomography scan result which shows sinusitis<sup>5,6</sup>. Chronic sinusitis is reported to interfere with physical activity, cause a decrease in quality of life<sup>2,7</sup>.

Inhaled allergic sensitivity as a primary pathological mechanism influences the development of chronic sinusitis in adults and children<sup>2</sup>.

Nose disorders, either anatomically, physiologically, or immunologically, both systemically and locally will have an effect on the structure of other organs nearby, one of which is the paranasal sinuses. The composition of inflammatory substrates in chronic sinusitis resembles inflammatory substrates in allergic rhinitis<sup>3,8</sup>. Children with allergic rhinitis, both seasonally and persistently, radiologically have significantly more sinusitis. Allergic rhinitis is a risk factor for sinusitis<sup>9,10</sup>.

Exposure to allergies constantly plays an important role in the incidence of recurrent and chronic sinusitis. The high prevalence of those diseases particularly occurs in children with allergies to HDM or fungi<sup>11</sup>. A prospective study in Thailand found positive inhaled allergens in most children aged 1-15 years with acute and chronic sinusitis (96.6%), who carried out skin prick test. The three most inhaled allergens were HDM (83%), cockroaches (58%) and grass (34.1%)<sup>12</sup>. A study in Israel found that 100% adult patients suffering from allergic rhinitis and asthma had sensitization to HDM<sup>13</sup>.

Evaluation of primary causes underlying recurrent and chronic sinusitis in pediatric patients is needed to provide appropriate therapy<sup>14</sup>. HDM immunotherapy is a proven treatment in reducing long-term HDM allergic

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symptoms<sup>15</sup>. The administration of allergen HDM extracts subcutaneously with slow dose increase is a specific treatment for HDM IgE specific-related allergies<sup>16</sup>. Thus, the therapy should consider patients without respond to conventional therapy, and can be used in children who are allergic to HDM<sup>17</sup>.

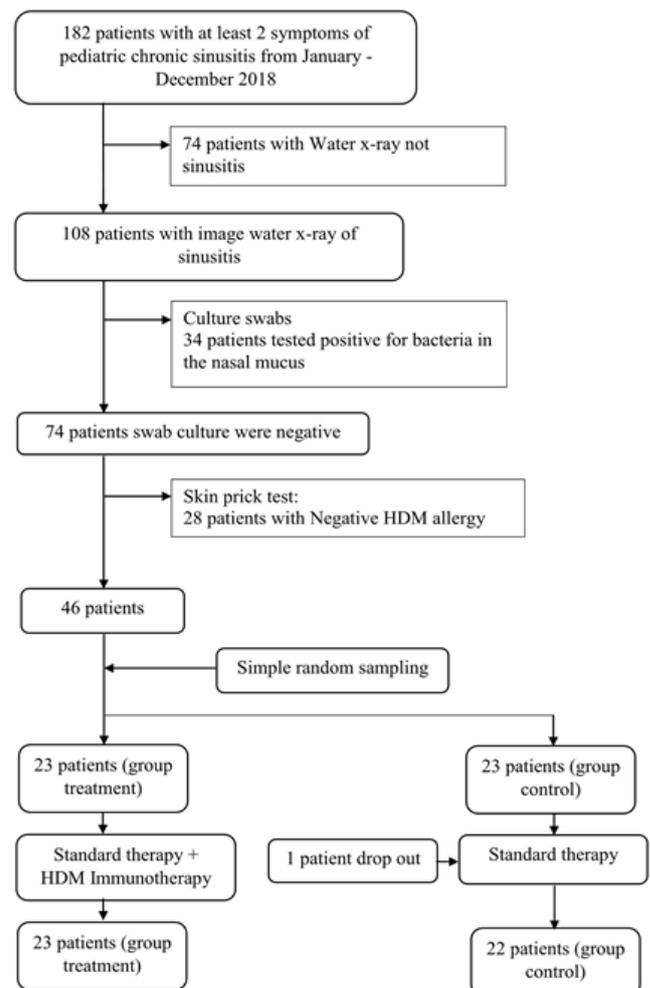
Since there is only limited evidence available on the success rate and administration of HDM immunotherapy to sinusitis patients with allergies to HDM, this study examined further about the benefits of HDM immunotherapy in chronic sinusitis patients aged 3-14 years with allergies to HDM in Indonesia.

### Materials and methods

Participants in this study were children with chronic sinusitis treated at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia. The inclusion criteria were patients aged 3-14 years, diagnosed with chronic sinusitis symptoms<sup>7</sup>, positive skin prick test<sup>18</sup> using HDM serum for 20 minutes, negative nasofaringeal culture, and waters x-ray showing sinusitis<sup>19</sup>. We used Waters' X-ray instead of CT-Scan as most society in Indonesia had limited capability to access proper health facilities. Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, is one of the highest referral hospitals in East Java, Indonesia. Moreover, the health insurance system in Indonesia still does not cover CT scans for sinusitis. Meanwhile, patients with anatomic abnormalities of nose and paranasal sinuses, respiratory infections, autoimmune diseases, and malignancy/cancer were excluded. The participants received an explanation regarding the aims and benefits of the research. Participants filled out consent forms before the study.

A quasi-experimental design with consecutive sampling method was employed as the design of this study. This research was conducted at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia from January to December 2018. There were 45 patients who were randomly divided into 2 groups (23 patients in treatment group and 22 patients in control group; Figure 1). At the beginning of the study, the number of patients in the control group was 23 participants. However, 1 participant was dropped out because the participant did not follow the therapy on schedule. The researchers

first conducted an ethical approval at The Ethics Committee of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia (54/Panke.KKE/I/2016). The participants were assessed based on healing time of sneezing, rhinorrhea and stuffy nose, as proposed by Asakura et al<sup>20</sup>. We also added some criteria often found in pediatric patients with sinusitis, including dizziness, fatigue, swallowing pain, itchy nose, colored secretions, ear pain, itchy eyes, red eyes, watery eyes, burning eyes, wheezing, shortness of breath, fussiness, postnasal drip, snoring, cough, and phlegm, as recommended by several staff at the Department of Child Health, Faculty of Medicine, Airlangga University-Dr. Soetomo General Academic Hospital, Surabaya, Indonesia.



**Figure 1.** Sampling process on the participant of children with chronic sinusitis.

The research procedures included clinical examination and Waters x-ray before and after

therapy. Participants in the treatment group received standard treatment for sinusitis patients<sup>16,21</sup> plus immunotherapy for 14 weeks. Meanwhile, participants in the control group were given standard sinusitis therapy for 14 weeks. Immunotherapy was given once a week, with different dose in each week. The immunotherapy dose in week I = 0.1 cc, week II = 0.15 cc, week III = 0.22 cc, week IV = 0.32 cc, week V = 0.48 cc, week VI = 0.72 cc, week VII = 1 cc, week VIII = 0.1 cc, week IX = 0.15 cc, week X = 0.22 cc, week XI = 0.32 cc, week XII = 0.48 cc, week XIII = 0.72 cc, and week XIV = 1 cc. Participants in the control group only received standard therapy for 14 weeks. The immunotherapy used in the therapy was HDM immunotherapy produced at Universitas Airlangga-Dr. Soetomo General Academic Hospital, Surabaya, Indonesia<sup>22</sup>.

The standard therapy given to pediatric chronic sinusitis is short wave diathermia<sup>23</sup>. The HDM immunotherapy was given subcutaneously in the deltoid region, using a 2 mg syringe injection. HDM immunotherapy is a therapeutic regimen given to patients whose dosage and duration of administration<sup>24</sup> followed a previous study conducted by the Department of Child Health, Faculty of Medicine, Airlangga University-Dr. Soetomo General Academic Hospital, Surabaya, Indonesia<sup>22</sup>.

Waters' x-ray was taken using a Promax tool (Planmeca Inc., Helsinki, Finland) with the position of the frontal head facing the film with an X-ray tube angle of 30°. We compared the results of Waters' x-ray before and after administration of HDM immunotherapy for 14 weeks in both groups.

The numerical and categorical results of this study were presented in the form of tables and figures. Clinical trials used number-needed to treat. The analysis used in this study included McNemar test and chi-square with 95% confidence interval (CI) and  $p < 0.05$ . Statistical analysis used IBM SPSS Statistics software version 23.0 (IBM Corp., Armonk, NY, USA).

## Results

### Characteristics of Participant

Most participants aged 5-9 years, with percentage as much as 65.22% in the treatment group and 72.73% in the control group ( $p = 0.290$ ). Most of the participants in the treatment group were female (56.52%), while most

participants in the control group were male (54.54%). There were no statistically significant differences in terms of sex, however participants in the treatment group were dominated by female, while in the control group were male ( $p = 0.657$ ). Most participants had a history of atopic sinusitis obtained from parents, with percentage as much as 73.91% in the treatment group and 63.64% in the control group. There were no participants in the treatment group with a history of chronic sinusitis atopy from siblings. There were participants in the treatment group with a history of atopy from parents and siblings (Table 1).

Variables	Group		p
	Treatment (n=23)	Control (n=22)	
Age			
< 5 years old	5 (21.74)	2 (9.09)	0.290
5-9 years old	15 (65.22)	16 (72.73)	
10-14 years old	3 (13.04)	4 (18.18)	
Sex			
Male	10 (43.48)	12 (54.54)	0.657
Female	13 (56.52)	10 (45.46)	
Family Medical History			
None	4 (17.39)	1 (4.54)	-
Parents	17 (73.91)	14 (63.64)	
Siblings	0 (0.00)	3 (13.64)	
Grandparents	1 (4.35)	4 (18.18)	
Parents and Siblings	1 (4.35)	0 (0.00)	
Waters x-ray			
Disappeared sinusitis	13 (56.52)	1 (4.54)	0.000*
Improved sinusitis	4 (17.39)	4 (18.18)	
Persistent sinusitis	5 (21.74)	12 (54.54)	
Worsened sinusitis	1 (4.35)	5 (22.73)	

\*significant  $p < 0.05$ ; \*\*significant  $p < 0.001$

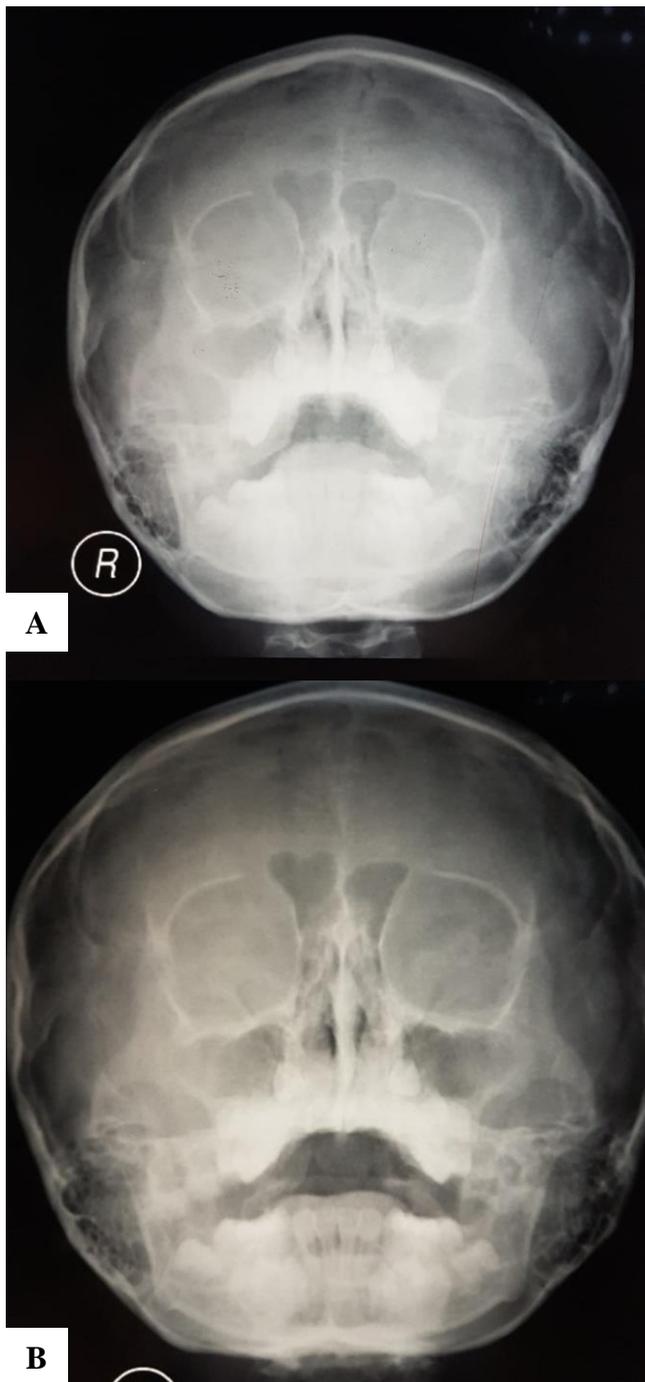
**Table 1.** Characteristics of participant.

### Waters' X-ray

The results of Waters' x-ray both in the treatment group and the control group before and after therapy showed a significant difference ( $p < 0.001$ ). Most Waters' x-ray of participants in the treatment group before and after the administration of immunotherapy showed sinusitis disappeared by 56.52%. In the control group, most participants showed persistent sinusitis before and after therapy (Table 1; figure 2).

### Time Course of Sinus Symptom Disappearance

In week 7, dizziness symptom felt by participants in the treatment group disappeared by 83%, and by 100% in week 14, with an average time of disappearance =  $2.4 \pm 0.9$  weeks. Meanwhile, dizziness experienced by participants in the control group disappeared by 78% and 90% in week 7 and 14, respectively, with an average time of disappearing =  $7.8 \pm 1.3$  weeks ( $p = 0.631$ ).



**Figure 2.** Water x-ray before being given house dust mites immunotherapy (A), after being given house dust mites immunotherapy (B) on Indonesian children with chronic sinusitis.

Fatigue symptom experienced by participants in the treatment group disappeared by 90% and 100% in week 7 and 14, respectively, with an average time of disappearance =  $1.8 \pm 0.5$  weeks. On the other hand, fatigue felt by participants in the control group disappeared by 81% in week 7, and 100% in week 14, with an

average time of disappearance =  $3.2 \pm 1.0$  weeks ( $p = 0.200$ ). Swallowing pain experienced by participants in the treatment group disappeared by 80% in week 7, and 100% in week 14, with an average time of disappearance =  $0.7 \pm 0.6$  weeks. Meanwhile, swallowing pain felt by participants in the control group disappeared by 55% and 70% in week 7 and 14, respectively, with an average time of disappearance =  $1.7 \pm 0.9$  weeks ( $p = 0.573$ ; Table 2).

Symptoms	Group		p
	Treatment (n=23)	Control (n=22)	
Dizziness	$2.4 \pm 0.9$	$3.0 \pm 1.1$	0.631
Fatigue	$1.8 \pm 0.5$	$3.2 \pm 1.0$	0.200
Swallowing pain	$0.7 \pm 0.6$	$1.7 \pm 0.9$	0.573
Itchy nose	$3.5 \pm 0.8$	$7.8 \pm 1.3$	0.003*
Colored secretion	$0.8 \pm 0.8$	$1.7 \pm 0.7$	0.024*
Ear pain	$0.1 \pm 0.1$	$0.5 \pm 0.4$	0.215
Itchy eyes	$1.3 \pm 0.5$	$4.0 \pm 1.1$	0.019*
Red eyes	$0.5 \pm 0.3$	$0.8 \pm 0.5$	0.709
Watery eyes	$0.3 \pm 0.3$	$2.5 \pm 1.0$	0.053
Burning eyes	$0.5 \pm 0.3$	$1.0 \pm 0.7$	0.144
Wheezing	$0.3 \pm 0.3$	$4.6 \pm 1.3$	0.024*
Shortness of breath	$0.0 \pm 0.0$	$3.3 \pm 1.1$	0.039*
Fussiness	$1.5 \pm 0.5$	$2.7 \pm 1.0$	0.152
Sneezing	$7.2 \pm 0.7$	$14.5 \pm 0.3$	0.000**
Postnasal drip	$4.1 \pm 0.7$	$14.7 \pm 0.1$	0.000**
Stuffy nose	$4.3 \pm 0.5$	$12.9 \pm 0.5$	0.000**
Snoring	$2.0 \pm 0.5$	$10.6 \pm 1.0$	0.000**
Cough	$10.2 \pm 0.5$	$14.7 \pm 0.2$	0.000**
Phlegm	$4.3 \pm 0.67$	$13.6 \pm 0.5$	0.000**
Rhinorrhea	$10.4 \pm 0.4$	$14.9 \pm 0.0$	0.000**

\*significant  $p < 0.05$ ; \*\*significant  $p < 0.001$ .

**Table 2.** Time course of symptom disappearance in the treatment and control groups pre and post usage house dust mites immunotherapy.

Itchy nose experienced by participants in the treatment group disappeared by 80% and 100% in week 7 and 14, respectively, with an average time of disappearance =  $3.5 \pm 0.8$  weeks. Meanwhile, the symptom in the control group disappeared by 55% and 70% in week 7 and 14, respectively, with an average time of disappearance =  $7.8 \pm 1.3$  weeks ( $p = 0.003$ ). Symptom of colored secretion experienced by participants in the treatment group disappeared by 100% in week 7 and 14, with an average time of disappearance  $0.8 \pm 0.8$  weeks. On the other hand, the symptoms in the control group disappeared by 80% and 100% in week 7 and 14, respectively, with an average time of disappearance =  $1.7 \pm 0.7$  weeks ( $p = 0.024$ ). Ear pain symptom experienced by participants in the treatment group disappeared by 100% in week 7

and 14, with an average time of disappearance =  $0.1 \pm 0.1$  weeks. Meanwhile, the symptom in the control group disappeared by 95% and 100% in week 7 and 14, with an average time of disappearance =  $0.5 \pm 0.4$  weeks ( $p = 0.215$ ; Table 2).

Symptom of itchy eyes experienced by participants in the treatment group disappeared by 90% and 100% in week 7 and 14, respectively, with an average time of disappearance =  $1.3 \pm 0.5$  weeks. Meanwhile, the symptom in the control group disappeared by 75% and 95% in week 7 and 14, respectively, with an average time of disappearance =  $4.0 \pm 1.1$  weeks ( $p = 0.019$ ). Red eye symptom experienced by participants in the treatment group disappeared by 95% and 100% in week 7 and 14, respectively, with an average time of disappearance =  $0.5 \pm 0.3$  weeks. On the other hand, the symptom in the control group disappeared by 95% and 100% in week 7 and 14, respectively, with an average time of disappearance =  $0.8 \pm 0.5$  weeks ( $p = 0.709$ ). Symptom of watering eyes in the treatment group disappeared by 95% and 100% in week 7 and 14, with an average time of disappearance =  $0.3 \pm 0.3$  weeks. Meanwhile, the symptom in the control group disappeared by 81% and 90% in week 7 and 14, respectively, with an average time of disappearance =  $2.5 \pm 1.0$  weeks ( $p = 0.053$ ; Table 2).

Symptom of burning eyes were only experienced by participants in the treatment group. The symptom disappeared by 90% and 95% in week 7 and 14, respectively, with an average time of disappearance =  $1.0 \pm 0.7$  weeks ( $p = 0.144$ ). Wheezing experienced by participants in the treatment group disappeared by 100% in week 7 and 14, with an average time of disappearance =  $1.5 \pm 0.5$  weeks. On the other hand, the symptom in the control group disappeared by 75% and 80% in week 7 and 14, respectively, with an average time of disappearance =  $4.6 \pm 1.3$  weeks ( $p = 0.024$ ). Shortness symptom in the treatment group disappeared by 100% in week 7 and 14, with an average time of disappearance =  $0.9 \pm 0.4$  weeks. Meanwhile, the symptom in the control group disappeared by 80% and 90% in week 7 and 14, respectively, with an average time of disappearance =  $3.3 \pm 1.1$  weeks ( $p = 0.039$ ; Table 2).

Symptom of fussiness found in the participants of treatment group disappeared by

100% in week 7 and 14, with an average time of disappearance =  $0.7 \pm 0.2$  weeks ( $p = 0.144$ ). Meanwhile, the symptom in the control group disappeared by 81% and 95% in week 7 and 14, respectively, with an average time of disappearance =  $2.7 \pm 1.0$  weeks ( $p = 0.152$ ). Sneezing experienced by participants in the treatment group disappeared by 50% and 100% in week 7 and 14, respectively, with an average time of disappearance =  $7.2 \pm 0.7$  weeks. On the other hand, the symptom in the control group disappeared by 0% and 10% in week 7 and 14, respectively, with an average time of disappearance =  $14.5 \pm 0.3$  weeks ( $p < 0.001$ ). Postnasal drip symptom found in the participants of treatment group disappeared by 80% and 100% in week 7 and 14, respectively, with an average time of disappearance =  $4.1 \pm 0.7$  weeks. Meanwhile, the symptom in the control group disappeared by 0% and 15% in week 7 and 14, respectively, with an average time of disappearance =  $14.7 \pm 0.1$  weeks ( $p < 0.001$ ; Table 2).

Symptom of stuffy nose experienced by the participants of treatment group disappeared by 80% and 100% in week 7 and 14, respectively, with an average time of disappearance =  $4.3 \pm 0.5$  weeks. Meanwhile, the symptom in the control group disappeared by 5% and 50% in week 7 and 14, respectively, with an average time of disappearance =  $12.9 \pm 0.5$  weeks ( $p < 0.001$ ). Snoring symptom found in the participants of treatment group disappeared by 85% and 100% in week 7 and 14, respectively, with an average time of disappearance =  $2.0 \pm 0.5$  weeks. On the other hand, the symptom in the control group disappeared by 20% and 55% in week 7 and 14, respectively, with an average time of disappearance =  $10.6 \pm 1.0$  weeks ( $p < 0.001$ ). Cough symptom in the treatment group disappeared by 5% and 100% in week 7 and 14, respectively, with an average time of disappearance =  $10.2 \pm 0.5$  weeks. Meanwhile, the symptom in the control group disappeared by 0% and 2.5% in week 7 and 14, respectively, with an average time of disappearance =  $14.7 \pm 0.2$  weeks ( $p < 0.001$ ; Table 2).

Phlegm symptom found in the participants of treatment group disappeared by 85% and 100% in week 7 and 14, respectively, with an average time of disappearance =  $4.3 \pm 0.67$  weeks. Meanwhile, the symptom in the control group disappeared by 0% and 30% in week 7 and 14,

respectively, with an average time of disappearance =  $13.6 \pm 0.5$  weeks ( $p < 0.001$ ). Rhinorrhea symptom experienced by the participants of treatment group disappeared by 15% and 100% in week 7 and 14, respectively, with an average time of disappearance =  $10.4 \pm 0.4$  weeks. On the other hand, the symptom in the control group disappeared by 0% and 25% in week 7 and 14, respectively, with an average time of disappearance =  $14.9 \pm 0.0$  weeks ( $p < 0.001$ ; Table 2).

## Discussion

This study found significant results based on Waters' x-ray examination in children with chronic sinusitis before and after therapy, however participants receiving immunotherapy showed a better improvement<sup>20</sup>. Immunotherapy is a proven treatment for reducing long-term allergic symptoms<sup>15</sup>, because it can reduce inflammation, especially in patients with stubborn allergies<sup>16</sup>. The mechanism of immunotherapy works in the body through increased levels of IgG specific to allergens in the first few months of therapy, which functions as blocking antibodies against IgE specific at the FcERI receptor on mast cells or basophils. There is a shift in the balance of Th cells towards Th1, so that interleukin associated with Th2 is suppressed. This also increases T regulators and even leads to T cell anergy. This condition decreases IgE production, mast cells and basophils as well as eosinophils that can cause allergic. As a result of the reduction in cytokines and various immunocompetent cells, there is a decrease in inflammation so that vascular permeability, serous glands and mucus secretions return normal. Therefore, drainage obstruction from the paranasal sinuses will disappear after prolonged inflammation of the nasal mucosa in the ostial meatal complex area is resolved. This is reflected through sinus photographs that show reduced sinus area after mucosal thickening therapy<sup>2, 25</sup>.

This study obtained similar results with a study conducted by Asakura et al., although their study only evaluate three symptoms (sneezing, rhinorrhea and stuffy nose). These studies had similar duration of immunotherapy, which was 2-3 months. Asakura et al found a significant improvement ( $p < 0.01$ ) in all three symptoms (sneezing, rhinorrhea and stuffy nose) after giving HDM immunotherapy in chronic HDM

allergic sinusitis group<sup>20</sup>. Meanwhile, Nathan et al used questionnaire in their study, and found a significant improvement for all symptoms ( $p < 0.01$ ). They gave HDM immunotherapy for at least 1 year, with an average of 3.3 years of immunotherapy<sup>26</sup>. Both of these studies used a symptom severity scoring system and did not calculate the time of symptom disappearance. They only compared the progress of symptoms before and after administering immunotherapy.

Children with chronic atopic sinusitis, who receive medical treatment with immunotherapy, show reduced symptoms in immunotherapy group at the 4-month follow-up. A few years later, the symptoms are much lower in the immunotherapy group compared to non-immunotherapy. Specific allergen immunotherapy induces immune competence through allergen recognition by slowly increasing the concentration from the lowest dose<sup>27</sup>. The therapeutic effect increases with the duration of treatment. New improvements appear after several months of therapy. It may be necessary to increase the dose of allergen to reach levels that have clinical and immunological effects<sup>16</sup>.

Immunotherapy can provide a repair effect about 2 months after a routine administration<sup>28</sup>. The build-up phase begins with the administration of allergens with a low concentration dose once a week, and reaches a maintenance dose after some period of around 12-15 weeks. This administration method has an objective basis in progressively inducing tolerance in individuals<sup>29</sup>. During build-up phase, Th2 changes to Th1, where Th1 and its cytokines cause B cells to produce allergen-specific IgG that leads to reduced IgE production, also an increase in IgG4 which is a competitive IgE in attachment to the receptor. IgG4 increases significantly in the first 3 months after SCIT administration, as seen from the allergen-specific ratio of IgG4/IgE. Furthermore, the maintenance phase shows decreased Th2/Th1 cell ratio that indicates a change from Th2 immunity to Th1, then followed by increasing IgG4 levels during SCIT administration. During this phase, there is also a T cell regulator (Treg) induction phase which is mediated among others by IL-10, TGF- $\beta$  which produces T regulatory type 1 (Tr1) cells. Treg can directly suppress innate mediators from allergic responses through inhibition of mast cell granulation. Treg also has the potential to induce IgA and IgG4 production. Through IL-10, Treg

has a suppression effect on T cells, inhibits the CD28 costimulatory pathway and increases the threshold value of T cell activation that results in anergy<sup>2,25,30</sup>.

## Conclusions

Sinusitis is a common health problem in children, one of the causes of sinusitis due to dust allergies. Faculty of Medicine, Airlangga University-Dr. Soetomo General Academic Hospital, and Ministry of Health, Indonesia collaborated and discovered HDM immunotherapy. HDM immunotherapy was carried out by randomized control trial on children who were identified as sensitive to HDM for one years. There is an improvement in clinical symptoms and recovery with immunotherapy treatment of HDM extracts in Indonesian children suffering from sinusitis and allergies to HDM.

## Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical approval at The Ethics Committee in Dr. Soetomo General Academic Hospital, Surabaya, Indonesia (54/Panke.KKE/II/2016).

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## Declaration of Interest

The authors report no conflict of interest.

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