Human & Veterinary Medicine
International Journal of the Bioflux Society HVM

OPEN ACCESS
Research Article

Clinical effectiveness of 6 months cetirizine administration to prevent atopic dermatitis recurrence in children: a randomized trial

[1]Zakiudin Munasir, [1]Nadia D. Esmeralda, [1]Lily Rundjan, [2]Mulya Safri, [2]Aulia R. Putra
[1] Department of Child Health, Cipto Mangunkusumo Hospital, University of Indonesia, Jakarta, Indonesia; [2] Department of Child Health, Dr. Zainoel Abidin Hospital, Syiah Kuala University, Banda Aceh, Indonesia.

Abstract. Background: Oral H1-antihistamines have been used extensively to reduce itching in atopic dermatitis (AD) but its effectiveness remains controversial. Cetirizine is a second-generation H1-antihistamine used in allergic diseases, including itching associated with AD. The Aim of this study : To assess the effectiveness of cetirizine compared with placebo in the treatment of AD. Material and Methods: A trial on 38 children aged 6 months to 15 years with moderate AD. Subject was recruited by consecutive sampling to achieve the required number of subjects, then randomization blocks to specify the group. The treatment group received cetirizine (0.25 milligrams /kg twice daily for patients < 2 years of age for 6 months and once a day for patients > 2 years old), while the control group received a placebo. The severity of the AD in both groups was measured by SCORAD index and AD recurrence evaluated every month for 6 months using per protocol analysis. Results: During the 6-month treatment, AD severity decreased to zero in both groups (p = 0.200). AD recurrence in the treatment group was not significantly lower than the control group (2 of 17 subjects vs 2 of 14 subjects, p = 1.000). Conclusions: Treatment of cetirizine for 6 months does not improve the recurrence and severity of AD in children.

Key Words: atopic dermatitis, recurrence, SCORAD index, cetirizine.

Corresponding Author: Z. Munasir, email: zakiudin.munasir@gmail.com

Introduction

Atopic dermatitis (AD) is an inflammatory disease of the skin that becomes chronic, recurrent, very itchy, and often precedes the onset of allergic rhinitis and asthma (Leung 2000). A prospective study in England with subjects aged 0–42 months showed a 21% incidence of AD at the age of 0–6 months, 11.2% at the age of 7–18 months and 3.8% at the age of 19–30 months (Munasir et al 2011).

Prolonged itching and skin irritation are major manifestations of AD. Atopic dermatitis in various degrees may impair the quality of life of patients and disturb school activities. It is a skin disorder that causes low self-esteem in older children, sleep disturbance due to the prolonged itching, as well as avoidance of diverse types of food allergens that may influence the nutrition state (Leung 2000; Munasir et al 2011; Adinoff et al 1996). The pathogenesis of AD is still unclear and the management of AD is also difficult. Many factors affect the occurrence of AD, among other genetic factors, environmental, host immune response and the barrier function of the skin. Dysfunction of the immune system in response to the host interaction with the environment cause hypersensitivity reactions, prolonged itching also triggered an inflammatory reaction that would be a vicious cycle which exacerbates the disease activity (Leung 2000; Amylynne et al 2011).

The management of AD includes avoidance of irritants and trigger factors, tackle itching and skin dryness, as well as cope with the inflammatory reaction and secondary infections. Current mode of treatment is to provide anti-inflammatory therapy with or without antibiotics, in oral or topical administration.. Topical preparations to improve the barrier function of the skin in some chronic cases that have lasted not quite effective in reducing of itching in patients, oral antihistamines later become the treatment of choice for reducing of itching in AD (Adinoff et al 1996).

Cetirizine is a potent second generation and selective antihistamine. ETAC (early treatment of the atopic child) study in 2002 showed its long-term use for 18 months in infants who suffer AD, which can reduce the probability of asthma by 50% in the group of children that were sensitized by pollen and house dust mites (Diepgen 2002). The drug acts by inhibiting the expression of intracellular adhesion molecule-1 (ICAM-1) in the nasal epithelium and conjunctiva, as well as the recruitment of eosinophils in the skin, nose, and lung (Fitzsimons et al 2014). It also serves as immunomodulators to suppress the production of IL-12 and IFN-γ (Ashenager et al 2007), and is expected to prevent the recurrence of the AD in the long-term administration. There is no prior study using cetirizine to prevent recurrence of

AD. This study used oral cetirizine to prevent AD relapse. The study was carried out in 6 months of intervention shorter than 18 months ETAC study.

The aim of this study is to determine the effectiveness of the use of cetirizine for 6 months to prevent recurrence of AD.

Material and methods

A randomized controlled clinical trial was conducted in private practice of pediatric allergy immunologist, Jakarta, from August 2014 to May 2015. The study required a minimum of 32 subjects, each 16 samples for the control and treatment groups. Subject was recruited by consecutive sampling to achieve the required number of subjects, then randomization blocks to specify the group. This study was approved by the Research Ethics Committee of Dr. Cipto Mangunkusumo Hospital , Medical Faculty , Universitas Indonesia

The inclusion criteria of the study were children aged over 6 months to 18 years with a diagnosis of mild to moderate atopic dermatitis according to Hanifin-Rajka criteria (Hanifin and Rajka 1980), maintained by pediatric allergy immunologist. Children's parents agreed to include them in the study and signed the informed consent sheet. The exclusion criteria of this study were patients with comorbid previous or severe atopic dermatitis who require systemic immunosuppressive therapy, and patients with a history of hypersensitivity to cetirizine.. AD severity was evaluated at the time of initial visit using the SCORAD index (European Taks Force on Atopic Dermatitis 1993). One week washout period for oral antihistamines and topical steroids was recommended.

The drug remained in use was moisturizer. The treatment group were treated with cetirizine (0.25 milligrams /kg twice daily for patients < 2 years of age and once a day for patients > 2 years old), while the control group received a placebo. The placebo is made by the cetirizine factory syrup form and the bottle similar with cetirizine syrup. The subject was allowed to use topical corticosteroids for reactivation of AD during 6 months of surveillance. AD severity in both groups was measured by SCORAD index and AD recurrence was evaluated every month for 6 months. The AD Analysis was carried out after 6 months. Study data were presented in narrative form and the table. Data were processed by Statistical Package for Social Science (SPSS) Program version 21. Recurrence of atopic dermatitis between the two groups was tested using Fisher's exact test. Improvement of atopic dermatitis symptoms by SCORAD index was tested using the Mann-Whitney test. All the test results revealed statistically significant if $p < 0.05$.

Results

There were 38 subjects enrolled of the study. After randomization, the subjects were divided into 2 groups: the control one which included 18 children and the experimental one with 20 children that received cetirizine . In the 6 months follow up, there were 7 dropped out patients (20% of the total research subjects) consisted of one patient in the control group and 6 patients in the treatment group.

Both groups had a homogeneous distribution in gender ($p = 0.267$) and age ($p = 0.536$). All subjects had a history of atopy in the family in parents or sibling by ananmnesis who had been diagnosed by the doctor with skin prick test or IgE specific measure. The SCORAD index of AD severity when patients were recruited was moderate. The median SCORAD index was 31.5 in the control group (27 to 48.3) and 34.75 (26.5 to 49) in the treatment group ($p = 0.138$).

Table 1. Hanifin-Rajka (1980) criteria for diagnosing atopic dermatitis

Major criteria	**1**	**Pruritus**
(at least 3 must be present)	2	Typical morphology and distribution (flexural
		lichenification or linearity in adults and facial or
		extensor involvement in infants and children)
	3	Chronic or chronically relapsing dermatitis
	4	Personal or family history of atopy (asthma, allergic
		rhinitis, atopic dermatitis)
Minor criteria	1	Anterior neck folds
(at least 3 must be present)	2	Anterior subcapsular cataracts
	3	Cheilitis
	4	Course influenced by environmental or emotional
		Factors
	5	Dennie-Morgan infraorbital fold
	6	Early age of onset
	7	Facial pallor or facial erythema
	8	Food intolerance
	9	Keratoconus
	10	Ichthyosis, palmar hyperlinearity, or keratosis pilaris
	11	Immediate skin reactivity
	12	Intolerance to wool and lipid solvents
	13	Itch when sweating
	14	Nipple eczema
	15	Orbital darkening
	16	Perifollicular accentuation
	17	Pityriasis alba
	18	Raised serum IgE
	19	Recurrent conjunctivitis
	20	Tendency toward cutaneous infections (especially S.
		aureus and herpes simplex) or impaired cell immunity
	21	Tendency toward nonspecific hand or foot dermatitis
	23	White dermatographism or delayed blanch
	23	Xerosis

Table 2. SCORAD index to assess extent and severity of atopic dermatitis

A: Extent	1	Head and neck: 9%	Rule of nine is used to determine
(Maximum	2	Upper limbs: 9% each	extent
score:100)	3	Lower limbs: 18% each	
	4	Anterior trunk: 18%	
	5	Posterior trunk: 18%	
	6	Back: 18%	
	7	Genital 1%	
B: Intensity	1	Erythema/redness	A representative area is chosen for
(maximum	2	Edema/papulation	each criterion. In each criterion,
score: 18)	3	Oozing/crust	give score 0 for none, 1 for mild,
	4	Excoriations/scratch	2 for moderate, or 3 for severe.
		marks	
	5	Lichenification	
	6	Dryness (assessed in area	
		without inflammation)	
C: Subjective	1	Pruritus	Each criterion is assessed using
Symptom	2	Sleep loss	visual analog scale. The score is
(maximum			0–10 for each one. Give score 0 for
score: 20)			no pruritus or sleep loss and 10
			for worst pruritus or sleep loss.
SCORAD: A/5 + 7B/2 + C (mild: < 25, moderate: 25–50, severe: > 50)			

Table 3. Study subjects' characteristics

Characteristics	Control (n=18)	Treatment (n=20)	P
Age (months)	58 ± 46.3	75.4 ± 48.73	0.267*
Sex			
Male	9	12	0.536**
Female	9	8	
SCORAD 0	31.5 (27 – 48.3)	34.75 (26.5 – 49)	0.138***

Table 4. Recurrence atopic dermatitis

Characteristics	Control (n=17)	Treatment (n=14)	p*
SCORAD 0	31.5 (27 – 48.3)	34.75 (26.5 – 49)	
SCORAD 1	14.9 (\0 – 42.5)	21.4 (9.6 – 37.4)	
SCORAD 2	9.4 (0 – 33)	11.25 (0 – 33.8)	
SCORAD 3	0 (0 – 29.5)	0 (0 – 19.3)	
SCORAD 4	0 (0 – 24)	0 (0 – 15.8)	
SCORAD 5	0 (0 – 23)	2.1 (0 – 15.8)	
SCORAD 6	0 (0 – 23)	0 (0 – 12.3)	0.2

The recurrence of AD between groups using Fisher's exact test can be seen in Table 4.

The total number of study subjects were 38 patients, 7 people did not finish the study.

The AD analysis, there were 31 research subjects with 79% power research. Recurrence in the control group was 2 out of 17 subjects. In the treatment group was 2 out of 14 subjects.

Table 5. SCORAD index

		Recurrence		
		No	**Yes**	**Total**
Subjects	Control	15	2	17
	Treatment	12	2	14
Total		27	4	31

Number needed to treat (NNT) of this study was 33. There was no statistically significant difference between the control group and the treatment group in AD recurrence (p = 1.000) for a total of 6 months.

AD symptoms were assessed in the two groups using the SCORAD index on a monthly basis (Table 5). The total number of samples that had completed follow up were 31.

Using Mann-Whitney test, there were no significant differences between the two groups regarding SCORAD index (p = 0.200) during the 6 months of surveillance.

Discussion

The genders were distributed homogeneously in the study: 17 female subjects (44.7%) and 21 male subjects (55.3%). According to the research in China in 2010, there were no significant difference between male and female for children aged 3-6 years (Xu et al 2012). This was consistently shown in the present study.

All subjects in the study had a family history of atopy, especially in parents. In an AD study of patients aged 0-4 months, AD incidence in patients with a history of atopy in one of the

parent was 37.9% and on both parents by 50%, whereas the incidence of AD in patients without a history of atopy was 27.1%. Family history of atopy is a risk factor AD, mainly mediated by IgE (OR 2.0; 95% CI 1.5-2.8) (Bohme et al 2003). The IgE level of the patient was not recorded but all the patients have atopy history in family.

According to Emerson et al (1998), AD occurrence distribution was mild in 84%, moderate (14%), and severe (3%). The majority of mild atopic dermatitis is managed by general practitioner. Second and third-line referral were associated with disease severity. The percentage of second-line referral were 3% for mild, 15% of moderate and 43% of all severe AD (Emerson et al 1998). All subjects were consulted to pediatric allergy immunologists. All subjects have moderated AD. Severe AD cases were excluded from the study because such patients may require systemic immunosuppressant.

The avoidance of precipitating factor is crucial factors in AD management (Munasir et al 2011). According to ETAC study in Europe and Canada in 2001, the use of cetirizine for 18 months in infants decreased 50% asthma incidence in patients sensitized to pollen and dust mites (Diepgen 2002). To determine the avoidance in the study was based on clinical observation, parent observation and patient's prior IgE laboratory results.

Genetic disorders in AD occurred due to FLG gene mutation on lq21 chromosome which encodes filaggrin, a protein barrier in epidermis. This caused damage to the skin barrier. The other genes which play role in AD were found on 5q31-33 chromosomes. This caused excess production of Th2 during exposure, resulting in increased IgE and eosinophils (Bieber 2010). Atopic history in the family is a genetic factor determines the risk of AD occurrence.

All the research subjects have history of atopy, therefore at higher risk of recurrence. There was no difference in recurrence between control and treatment group within 6 months' intervention. In the study showed that the recurrence was not lower in the treatment group compared to control. The pollen and house dust mites were not the allergen experienced by research subjects. The AD mechanism may not be mediated by IgE. According to ETAC study, cetirizine has not been proven effective in AD management for other causes except by pollen and house dust mites.

In multicenter ETAC study, patients were observed for additional 18 months following the initial 18 months on cetirizine. For house dust mites allergen, the control group has higher relative risk of asthma in comparison to the treatment group (RR 1.4; 95% CI: 1.3 to 1.9). While for pollen, the relative risk (RR) was 1.7 (95% CI 1.4-2.1) (Warner 2001). The immunomodulatory effect of cetirizine is expected to happen after 6 months of intervention, this however, could not be shown in our study due to limited observation time. This could be the reason why recurrence prevention was not seen in our treatment group.

The principles of AD management are the avoidance of AD trigger factors and allergens, eliminations, to improve skin barrier by adequate hydration, and the use of medications to reduce itch, overcome inflammation and secondary infection (Adinoff and Clark 1996; Ellis 2003). Skin hydration is essential in AD management. Dry skin may facilitate microbes' penetration as well as allergens and irritants. Skin moisturizer does not work as antipruritic; however, it can overcome skin dryness, reduce TEWL, and withhold skin's water content (Cork and Danby 2009). All the subjects in this study used skin moisturizer regularly.

ETAC multicenter study enrolled 817 infants aged 12-24 months from 12 countries in Europe and Canada, with similar baseline characteristics in AD severity according to SCORAD index (25.1 and 24.9 respectively) which was mild AD, an increase in IgE (total or specific), and the percentage of eosinophils > 0.7 x 109/l. In 18 months of study, AD severity in both placebo and intervention group reduced permanently without any statistical significance difference between the two groups (placebo 25.1 to 15.7 while in cetirizine group 24.9 to 15.2). Patients with increased IgE aeroallergen also experienced decrease in both groups (placebo decreased from 30.3 to 22.3 and cetirizine group decreased from 32.6 to 18.8) (Diepgen 2002).

In our study, SOCRAD value was almost similar at baseline between groups (31.5 versus 34.75). The difference of current study to ETAC study was in the degree of severity. ETAC study enrolled only mild AD while moderate severity subjects were enrolled in our study. We also did not measure IgE and eosinophil, therefore the types of AD was not revealed as such in ETAC study. Cetirizine is only effective in the AD which is mediated by IgE for pollen and house dust mites. The SCORAD 5 was slightly increase in the treatment grup may due to the exposure to the allergen.

This study was carried out in 6 months of intervention shorter than 18 months ETAC study. The study required a minimum of 32 subjects, each 16 samples for the control and treatment groups. The overall clinical improvement of our study subjects was better compared to those of ETAC. In ETAC study with 18 months of cetirizine administration, there was no statistically significant difference in AD improvement between the two groups (control group from 25.1 to 15.7 and cetirizine group from 24.9 to 15.2) (Diepgen 2002), which was similar to our study. Our study differed from the ETAC in terms of skin hydration as measures. Our subjects used emollient while only 76% of ETAC study used it (Diepgen 2002). Although not acting as antipruritic, emollient has decreased skin dryness, reduce TEWL, and retain skin water content. These have reduced AD symptoms (Cork and Danby 2009; Peter et al 2013). The emollient using seems more important in the prevention of AD recurrence than 6 months' cetirizine administration.

A limitation of our study was the high number of loss-to-follow-up subjects (7 subjects or 20% of total subjects). As another limitation, the severity of atopic dermatitis was measured only by clinical scoring using the SCORAD index. This is slightly different with the 2002 ETAC study, which included evaluation of the level of total specific IgE for pollen, cow's milk, and house dust mites.

Conclusion

In conclusion, 6 months use of cetirizine is not enough to improve AD recurrence in children. It is essential to know the AD trigger factors so that the patients can optimally avoid these factors. Further observation beyond 6 months is needed to evaluate the effectiveness of cetirizine in preventing AD relapse.

References

Adinoff AD, Clark RA. Atopic Dermatitis. In: [Allergy, Asthma and Immunology from Infancy to Adulthood]. Bierman CW, Pearlman DS, Shapiro GG, Busse WW. (ed). Philadelphia: WB Saunders Company; 1996. pp. 613-32.

Amylynne F, Andrew S, Rita V, Mark L. Bilateral comparison study of pimecrolimus cream 1% and a ceramide hyaluronic acid emollient foam in the Treatment of Patients with atopic dermatitis. J Drugs Dermatol 2011;10:666-72.

Ashenager M, Grgela T, Aragane Y, Kawada A. Inhibition of cytokine-induced expression of T-cell cytokines by antihistamines. J Investig Allergol Immunol 2007;17:20-6.

Bieber T. Atopic dermatitis. Ann Dermatol. 2010;22:125-33.

Bohme M, Wickman M, Lennart N, Svatengren MWC. Family history and risk of atopic dermatitis in children up to 4 years. Clin Exp Allergy 2003;9:1226-31.

Cork M, Danby S. Skin Barrier breakdown:a renaissance in emollient therapy. Br J Nursing 2009;14872-7.

Diepgen L. Long-term treatment with cetirizine in infants with atopic dermatitis:a multy-country, double-blind, randomized, placebo-controlled trial (the ETAC trial) over 18 months. Pediatr Allergy Immunol 2002;13:278-86.

Ellis C, T. Luger International Consensus Conference on Atopic Dermatitis II (ICCAD II*):clinical update and current treatment strategies. Br J Dermatol 2003;148:3-10.

Emerson R, William H, Allen B. Severity distribution of atopic dermatitis in the community and its relationship to secondary referral. Br J Dermatol 1998;139:73-6.

European Task Force on Atopic Dermatitis. Severity scoring of atopic dermatitis:the SCORAD index. Dermatology 1993;186(1):23-31.

Fitzsimons R, L Poel, Thornhill W, Toit G, Shah N, Brough H. antihistamine use in children. Arch Dis Child Educ Pract 2014;100:122-31.

Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. Acta Derm Venereol Suppl 1980;92:44-7.

Leung D. Atopic dermatitis:new insights and opportunities for therapeutic intervention. J Allergy Clin Immunol 2000;105:680-76.

Munasir Z, Sastroasmoro S, Djauzi S, Waspadji S, Ramelan W, Aminullah A, et al. The role of allergic and other risk factors that affect the occurrence of atopic dermatitis in the first months of life. Asia Pac Allergy 2011;1:73-9.

Peter D, Arkwright M, Motala C, H Subramanian, Spergel J, Schneider L, et al. Management of difficult, to treat atopic dermatitis. J Allergy Clin Immunol 2013;1:142-51.

Warner, JO. A double-blind, randomized, placebo-controlled trial of cetirizine in preventing the onset of asthma in children with atopic dermatitis:18 months of treatment and 18 months posttreatment follow-up. J Allergy Clin Immunol 2001;108:929-37.

Xu F, Yan S, Li F, Cai M, Chai W, Wu M, et al. Prevalence of childhood atopic dermatitis:an urban and rural community-based study in Shanghai, China. PLoS One 2012;7:1-4.

Authors

•Zakiudin Munasir, Department of Child Health, University of Indonesia, Salemba Raya Street, Depok, 16424, Jakarta, Indonesia. email: zakiudin.munasir@gmail.com

•Nadia Devina Esmeralda, Department of Child Health, University of Indonesia, Salemba Raya Street, Depok, 16424, Jakarta, Indonesia. email: devinaismail4@gmail.com

•Lily Rundjan, Department of Child Health, University of Indonesia, Salemba Raya Street, Depok, 16424, Jakarta, Indonesia. email: lily_kartono69@yahoo.co.uk

•Mulya Safri, Department of Child Health, Dr. Zainoel Abidin Hospital, Syiah Kuala University, Teuku Nyak Arief Street, Darussalam, 23111, Banda Aceh, Indonesia. email: mulya_anak@yahoo.com

•Aulia Rahman Putra, Dr. Zainoel Abidin Hospital, Syiah Kuala University, Teuku Nyak Arief Street, Darussalam, 23111, Banda Aceh, Indonesia. email: dr.auliarahmanputra@gmail.com

Citation	Munasir Z, Esmeralda ND, Rundjan L, Safri M, Putra AR. Clinical effectiveness of 6 months cetirizine administration to prevent atopic dermatitis recurrence in children: a randomized trial. HVM Bioflux 2017;9(2):53-57.
Editor	Ştefan C. Vesa
Received	5 May 2017
Accepted	9 June 2017
Published Online	19 June 2017
Funding	None reported
Conflicts/ Competing Interests	None reported