

# Urinary leukotriene e4 level profile in various degrees of severity in atopic dermatitis patients in dermatovenereology outpatient clinic

## Dr. Soetomo General Hospital, Surabaya: A descriptive study

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### Abstract

Atopic dermatitis (AD) is a chronic, relapsing skin inflammatory disease. Corticosteroid as the cornerstone treatment for AD has some flaw, especially for the chronic recalcitrant AD, since it has side effects and high possibility of rebound. Leukotriene receptor antagonist (LTRA) which has been used for asthma and allergic rhinitis now has been developed for treating AD, based on the similar mechanism of inflammation. Leukotriene (LT) is an inflammatory mediator that is thought to play role in the asthma, allergic rhinitis, and AD. Urinary leukotriene E4 (U-LTE4), the stable metabolite of LT, can be found in urine. This research aims to evaluate the role of LT in various degrees of severity in AD patients by measuring U-LTE4 levels using Enzyme Linked Immunosorbent Assay (ELISA). Twenty two AD patients who were in a flare state and came to the outpatient clinic on April – July 2017 were measured their U-LTE4 levels. The results demonstrated that mean of U-LTE4 levels increases consistently with intensity of the degree of severity, and this finding supports previous study that LT plays role in AD.

### Introduction

Atopic dermatitis (AD) is a chronic, relapsing skin inflammatory disease. The prevalence of AD in children is approximately 15-20%, meanwhile prevalence of AD in adults is about 1-3% and both always increase over time.<sup>1</sup> The incidence of AD in Dr. Soetomo General Hospital, Surabaya in 2013-2015 is 0.6% (327 patients) in adults, and 0.62% (366 patients) in children, and also increase in each year. AD still becomes a substantial

health problem recently, since the itchy sensation can cause lack of sleep and affect the patient's quality of life, and disease treatment costs much money.<sup>2</sup> Leukotriene (LT), a potent inflammatory mediator which is derived from arachidonic acid in a pathway that involves 5-lipoxygenase (5-LO), is believed to play a role in AD's pathogenesis as in asthma's and allergic rhinitis'. Those 3 diseases are known as the atopic triad.<sup>3</sup> One of LT's classes, cysteinyl leukotriene (Cys-LT), which consists of LTC4, LTD4, and LTE4 is a potent mediator of inflammation.<sup>4,5</sup> Cys-LT production increases substantially in association with allergic inflammation, likely reflecting the activation of mast cells and eosinophils in the lesional tissues. Urinary leukotriene E4 (U-LTE4) levels increase during asthma, allergic rhinitis, and AD.<sup>6</sup> This finding is supported by previous studies that measured U-LTE4 levels in AD patients, and there was significant correlation between U-LTE4 levels and clinical symptoms (such as degree of severity) and also laboratory marker in AD such as Ig-E serum levels and absolute eosinophilic count.<sup>3,4,7</sup>

Corticosteroid is the cornerstone of AD's treatment line, but its use in chronic and recalcitrant AD becomes a challenge due to the side effects and high possibility of rebound. Leukotriene receptor antagonist (LTRA) has been used in asthma and allergic rhinitis treatments, and it has been introduced in AD.<sup>8</sup> Some studies revealed that LTRA exhibited positive progression in subjective complaints, skin lesions, and eosinophilic cationic protein.<sup>9</sup> U-LTE4 is the stable end product of LT metabolite, and excreted in the human urine. U-LTE4 is supposed to be reflecting the total body production of LT, because LTC4 and LTD4 are rapidly metabolized into LTE4.<sup>10</sup> Urine examination is a non-invasive method than blood examination so we try to measure the levels in AD patients at our setting and see how the profile is, so that we can consider the use of LTRA in AD treatment.

### Materials and Methods

This research was a descriptive study, using cross-sectional method to evaluate U-LTE4 levels in various degrees of severity based on SCORAD index in AD patient. Samples of the study were all AD patients that came to Dermatovenereology Outpatient Clinic Dr. Soetomo General Hospital Surabaya, and were taken consecutively in 4 months (April 2017-July 2017). Inclusion criteria was in a flare or acute condition of AD skin lesion,

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diagnosed by Williams criteria. Patients who were in corticosteroid treatment in the last 2 weeks, antihistamin treatment in the last 1 week, and other antiinflammation or immunosuppressant treatment include LTRA in the last 4 weeks were excluded from the study. Other exclusion criterias were patients with asthma or allergic rhinitis history, patients who were in the acute phase of allergic or inflammation disease, have kidney dysfunction, smokers or in pregnant condition since it can affect the U-LTE4 levels.

Informed consent was obtained from the patients or the parents if the patient was a child. Then the patients diagnosed according to Williams criteria, subjected to history taking, clinical examination, and determined their degrees of severity according to SCORAD index. After that urine sample was taken, then centrifuged and stored in -80°C freezer until the study period had finished. Then all urine samples were measured its U-LTE4 levels by double-antibody sandwich enzyme-linked immunosorbent assay (ELISA) technique, with Human Leukotriene E4 ELISA Kit reagent from Shanghai Crystal Biotech Co., LTD using Humareader® Single. Data are expressed as mean ± SD. No analysis test are performed since this was a descriptive study. Ethical clearance had been approved for this study by the Ethical Committee in the hospital.

## Results

This research involved total 22 AD patients in Dermatovenereology Outpatient Clinic General Hospital Surabaya. They were 7 males and 15 females, and their age ranged between 2-51 years old with a mean age of  $17.16 \pm 13.61$  years old. There were 8 patients (36.36%) with mild degree of AD based on SCORAD index, 11 patients (50.00%) with moderate degree, and 3 patients (13.64%) with severe degree. The mean of U-LTE4 levels in total subjects was  $24.02 \pm 11.02$  pg/ml, meanwhile the mean of U-LTE4 levels in mild, moderate, and severe AD based on SCORAD index were  $16.43 \pm 8.01$  pg/ml,  $27.45 \pm 9.35$  pg/ml, and  $31.70 \pm 15.17$  pg/ml, respectively (Figure 1). The least U-LTE4 level in the samples was 1.2 pg/ml and was found in mild AD group, otherwise the greatest was 41.1 pg/ml and belonged to severe AD group. Table 1 shows that the mean of U-LTE4 levels in each degree of severity are higher in accordance with degree of severity.

## Discussion

The purpose of U-LTE4 level measurement is to know the representative of Cys-LT production as inflammatory marker *in vivo*.<sup>3,4</sup> Results of this study showed that more severe the degree of severity, the mean of U-LTE4 level were increased. This increasing production of Cys-LT might be caused by increasing immune cells that produce Cys-LT, which are mast cells, basophils, eosinophils, and macrophages.<sup>11</sup> Same observations were reported by Miyoshi *et al* (1999), Emam *et al* (2003), Hon *et al* (2004), and Fathi *et al* (2007), who concluded that U-LTE4 in moderate and severe degree of AD were significantly higher than the mild degree. They also stated that U-LTE4 levels in AD patients were higher significantly rather than the control subjects.<sup>3,12,13</sup> Hishinuma *et al* also reported that U-LTE4 levels in AD patients were significantly higher than non-AD patient.<sup>4</sup> This study didn't use controls since we only want to know about the

profile of U-LTE4 levels in each degree of severity of AD, whether increase or not.

U-LTE4 is a marker of Cys-LT production *in vivo*, since LTC<sub>4</sub> and LTD<sub>4</sub> are rapidly metabolised into LTE<sub>4</sub> and also rapidly excreted in the urine.<sup>11</sup> Growing evidence suggests that leukotrienes play an important role in the pathogenesis of bronchial asthma and allergic rhinitis. They cause smooth muscle contraction, impair mucocilliary clearance, enhance mucus secretion, attract eosinophils to the airways, and increase vascular permeability producing edema. Spector *et al* reported that LTRA treatment could decrease day and night asthma symptoms, less frequent use of short-acting  $\beta_2$ -agonist on demand, and higher values of evening lung function parameters (FEV<sub>1</sub> and PEF rate).<sup>14</sup> AD, along with bronchial asthma and allergic rhinitis, are known as the atopic triad. Some studies has reported rational evidence of LTRA use in AD, however, its exact mechanism of action in AD hasn't been established yet.<sup>15</sup>

AD is a disease that is influenced by multifactorial entity, so we shouldn't only depend on the leukotriene as the exact cause of AD exacerbation. This U-LTE4 level measurement might be considered in AD chronic patient who is recalcitrant to other

treatments, and could be used before someone decides to take LTRA treatment since this is such a pricey drug. This study has some limitations, so that continued studies on this subject should be conducted, such as study to determine the U-LTE4 cut-off value in Indonesia since it has never been done. Other studies in primary health settings to get more subjects also should be done, and so should the studies that compare other clinical parameters in AD with U-LTE4 levels such as total IgE serum levels. Other limitation of this study is that we didn't measure the urine creatinine because we only want to see the profile in each degree of severity.

## Conclusions

Our findings support other studies that LT plays role in AD, so the use of LTRA might be considered especially in chronic AD patient who is recalcitrant to any other modalities. Other study that use analytic design still needs to be perform later, so it could demonstrate the relation between U-LTE4 levels and AD degree of severity statistically. Study that compares other laboratoric parameters such as total IgE serum is also needed.

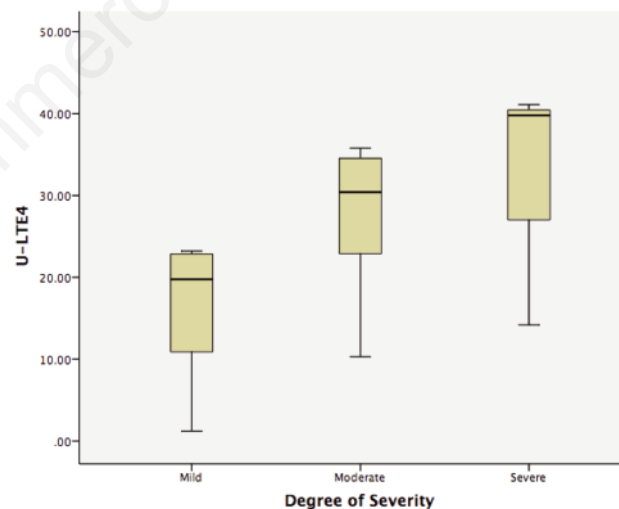


Figure 1. U-LTE4 levels distribution based on degrees of severity (SCORAD index) in box-plot.

Table 1. U-LTE4 levels profile based on degrees of severity in the study subjects (n = 22).

| Degrees of severity | Number (Percentage) | Mean of SCORAD index | Minimum value (pg/ml) | Maksimum value (pg/ml) | Mean $\pm$ SD (pg/ml) |
|---------------------|---------------------|----------------------|-----------------------|------------------------|-----------------------|
| Mild                | 8 (36.36%)          | $20.58 \pm 4.02$     | 1,2                   | 23,2                   | $16,43 \pm 8,01$      |
| Moderate            | 11 (50.00%)         | $34.82 \pm 4.29$     | 10,3                  | 35,8                   | $27,45 \pm 9,35$      |
| Severe              | 3 (13.64%)          | $58.13 \pm 3.35$     | 14,2                  | 41,1                   | $31,70 \pm 15,17$     |
| Total               | 22                  |                      |                       |                        |                       |

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