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Higher IL-33/ST2 ratio dan ST2 levels in Uncontrolled Atopic Asthma

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Abstract

Introduction

Atopic asthma is a chronic airway inflammation begins with exposure to allergens causing activation of Th2 cells airway hyperresponsiveness. Interleukin-33 and ST2 have role in activation of Th2 cells and then cause chronic airway inflammation. IL33/ST2 ratio considered as a potential biomarker for predicting risk and asthma severity.

Aims & Methods

This case-control study aimed to evaluate serum levels of IL-33, ST2 dan IL-33/ST2 ratio in risk and level of asthma control. This study was performed in Dr. Wahidin Sudirohusodo and Hasanuddin University Hospitals Makassar Indonesia from June until September 2023. Subjects were 40 atopic asthma patients and 40 non-asthma.

Result

Serum levels of IL-33 higher in atopic asthma patients compared to non-asthma (1.776 $\pm$ 0.534 vs 1.505 $\pm$ 0.301, p=0.007), but ST2 did not significantly different. Serum levels of ST2 higher in uncontrolled atopic asthma patients compared to well controlled (9.541 $\pm$ 11.634 vs 16.675 $\pm$ 6.327, p=0.021), but IL-33 were not different (p>0.05). IL-33/ST2 ratio higher in uncontrolled atopic asthma patients compared to well controlled (0.266 $\pm$ 0.105 vs 0.127 $\pm$ 0.086, p=0.001).

Conclution

IL-33/ST2 ratio and levels of ST2 were significantly higher in uncontrolled atopic asthma patients compared to well controlled. IL-33 significantly higher in atopic asthma compared to non-asthma.

Keywords: IL-33, ST2, IL-33/ST2s ratio, atopic asthma

I. Introduction

Asthma is a serious global health problems affecting approximately 300 million people around the world. Asthma is a heterogeneous disease usually associated with airway hyperresponsiveness and airway inflammation.[1]

Interleukin-33 (IL-33) usually secreted upon damage induced cell or immune cells that can alert the immune system. In atopic asthma, IL-33 produced in immune cells during allergic inflammation. Suppression of tumorigenicity 2 (ST2) has been proposed as the receptor for IL33 that is expressed on various immune cells, such as T cells and mast cells, and plays a crucial role in mediating the effects of IL-33.[2,3,4,5]

ST2 is a receptor of the IL-33 and consists of 2 common subtypes: sST2 and ST2L. ST2L (also known IL-1RL1-b) is the specific IL-33 receptor and is mainly expressed on the Th2 and mast cells, whereas the sST2 is the decoy receptor that negatively regulates the IL-33/ST2 pathway.[6,7] IL-33/ST2 axis plays a main role in allergic inflammation and asthma. The sST2 inhibits binding of IL-33 to ST2L and negatively regulates IL-33, which is associated with several immune disorders. Asthma is basically characterized by allergic inflammation, elevated IgE, and increased Th2 cytokines levels. In atopic asthma, IL-33 is produced by mast cells after IgE-mediated activation and able to trigger proinflammatory cytokines releasing. IL-33 is a strong inducer of Th2. The IL-33/ST2 signalling pathway activates eosinophils in airway, which exacerbates airway inflammation. This pathway is important for the progression of allergy and IgE-dependent inflammation.[7]

This research focus on investigating the IL33/ST2 ratio as a potential biomarker for predicting risk and asthma severity. By analyzing the levels of these proteins in the blood or airway samples of asthma patients, researchers could potentially identify individuals who are at higher risk for uncontrolled asthma. Additionally, studying how the IL33/ST2 ratio changes over time in response to different treatments could provide valuable insights into the underlying mechanisms of asthma and help guide personalized treatment decisions. Further exploration of this biomarker could ultimately lead to more effective and tailored approaches to managing atopic asthma.

Methods

This was a case control study with 80 subjects aged 18-50 yo, 40 with atopic asthma and 40 non-asthma subjects as control recruited in Wahidin Sudirohusodo and Hasanuddin University Hospital Makassar Indonesia. The Inclution criteria were atopic asthma subjects without: acute exacerbation, diabetes, smoker and lung infection. Diagnosis of asthma based on bronchodilator reversibility with at least > 12% from baseline or 200 mL in FEV1. Atopic asthma diagnosed based on history of atopic with positif in skin prict test. Control status of asthma divided in to uncontrolled asthma and well controlled defined with GINA criteria. The criteria asthma symptoms control (In the past 4 weeks):

- Daytime asthma symptoms moe than > 2x/week
- Any night waking due to asthma
- SABA reliever for symptoms > 2x/week
- Any activity limitations due to asthma

Atopic asthma subjects with none of above criteria categoriesed as well controlled asthma. Subjects with 1-2 categoriesed as partly controlled and 3-4 of criteria as uncontrolled atopic asthma. This study combined partly control and uncontrolled as uncontrolled atopic asthma subjects. The research flow shown in (figure 1).

Statistical analysis

For descriptive study we calculated means and standard deviation. Mean comparison levels of IL-33, ST2 and IL-33/ST2 ratio using independent sample t test. The diffrences was significant if $p < 0.05$.

Ethical consideration

Informed consent was obtained from each participant prior to sample collection. Samples of blood were collected using standardized procedures to analyze levels of IL-33 and ST2. Examination of IL-33, ST2 levels from blood serum samples using an ELISA organon reader and Quantikine IL-33 D3300 Kit (R&D Systems) and Human ST2 Elisa Kit.

This study had received a recommendation for ethical approval from the Health Research Ethics Commission Faculty of Medicine, Hasanuddin University with number: 01186/H.4.8.4.5.31/PP.36-KOMETIK

Result

A total of eighty subjects aged 18-50 yo were enrolled in the study, 40 subjects with atopic asthma and 40 non-asthma as control subjects. (Table 1)

Table 1. Characteristics of research subjects.

Variabel	Atopic Asthma n = 40	Non-asthma n = 40	p*
Age (Years)	32.1 (7.7)	29.1 (7.4)	p=0.081
Man	20	20	
Woman	20	20	
Atopic Asthma			
Uncontrolled	20		
Well controlled	20		

Table 1 shows that the mean age was not significantly different between atopic asthmatic and non-asthma subjects.

Distribution of sample 40 subject with atopic asthma dan non-asthma as control 40, with gender distribution ratio woman and man 1:1. (Table 2)

Table 2. Differences in serum levels of IL-33 and ST2 and IL33/ST2 ratio in subjects with atopic asthma and non-asthma

Levels	Atopic Asthma n = 40	Non-asthma n = 40	p*
IL-33	1.776 $\pm$ 0.534	1.505 $\pm$ 0.301	0.007
ST2	13.108 $\pm$ 9.924	12.5 $\pm$ 8.032	0.753
IL-33/ST2 ratio	0.196 $\pm$ 0.118	0.164 $\pm$ 0.915	0.176

*Independent t test

Table 2 shows that the mean IL-33 levels were higher in atopic asthma compared to non-asthma (p=0.007).

The mean levels of ST2 and IL-33/ST2 did not differ between atopic asthma cases compared to non-asthma controls (p > 0.05). (Table 3)

Table 3. Mean levels of IL-33 and ST2 Serum based on degree of asthma control

Levels	Uncontrolled Atopic Asthma n = 20	Well controlled Asthma n = 20	p*
IL-33	1.806 ± 0.324	1.745 ± 0.691	0.725
ST2	9.541 ± 11.634	16.675 ± 6.327	0.021
IL-33/ST2 Ratio	0.266 ± 0.105	0.127 ± 0.086	0.001

*Independent t test

Table 3 shows ST2 levels were higher in atopic asthma cases compared to non-atopic asthma controls (p > 0.05). The IL-33/ST2 ratio was higher in atopic asthma cases compared to non-atopic asthma controls (p < 0.05). Meanwhile, the mean IL-33 levels were not different in Uncontrolled atopic asthma cases compared to well controlled (p > 0.05).

Discussion

IL-33 and risk of atopic asthma

This study found the mean IL-33 levels were higher in atopic asthma cases compared to non-asthma (p=0.007). However, in this study based on the degree of asthma control, there was no difference between uncontrolled and well-controlled asthma. Li R et al found that the serum IL33 serum higher in asthma patients compared to healthy people.[8] Another study by Ranran et al found that elevated levels of IL-33 were higher in asthma adults compared to healthy subject, whereas no significant difference in IL-33 level in serum was showed between asthma children and non-asthma.[9] In people with atopy repeated exposure to allergens and respiratory viral infections will cause epithelial damage and Endothelial cells exposed to stimuli followed by the release of IL-33. This finding in atopic asthma different with another fenotipe asthma in pregnancy levels of IL-33 serum were not higher asthma in pregnancy and also not different in level of asthma controlled.[10]

The IL-33 will induce pro-inflammatory cytokines that aggravate atopic diseases and developing asthma. IL-33 expression in endotracheal and bronchial biopsies of was found in higher in asthmatic subjects compared to non-asthma.[11] The similarity of the results of this research with the results of other studies may suggests IL-33 levels can be used as a biomarker for atopic asthma risk.

ST2 and risk for uncontrolled atopic asthma

This study found ST2 levels were not different in atopic asthma compared to non-asthma ($p > 0.05$). According to the level of asthma control serum levels of ST2 higher in uncontrolled atopic asthma patients compared to well controlled (9.541 ± 11.634 vs 16.675 ± 6.327, $p=0.021$). Li R et al found also serum ST2 level higher in asthma severe compared to moderate.[11] Soluble suppression of tumorigenicity 2 (ST2) is a receptor of the IL-33 and consists of two common subtypes: sST2 and ST2L. ST2L is the specific IL-33 receptor and is mainly expressed on the Th2 and mast cells, whereas the sST2 is the decoy receptor that negatively regulates the IL-33/ST2 pathway. In contrast, sST2 is released from bronchial epithelial cells and lung blood vessels by stimulation with proinflammatory cytokines, toll-like receptor (TLR) ligands, and Th2 cytokines. Serum sST2 levels are markedly increased when neutrophilic inflammation present. Patients with atopic asthma, serum sST2 levels are elevated during exacerbation and are associated with the severity of the attack. These indicate that the IL-33/ST2 balance affects granulocyte counts in the airway, and that high serum ST2 levels in asthmatics are associated with uncontrolled asthma and risk of exacerbation.[13]

Elevated levels of ST2 have been associated with increased airway inflammation and reduced lung function in patients with asthma proven from Endobronchial biopsies.[13] This study found higher ST2 levels could be used as a marker for uncontrolled asthma and may guide treatment decisions in the future. Another study found high serum sST2 levels predicted exacerbation within asthmatic population.[12]

Higher IL33/ST2s ratio and risk for uncontrolled atopic asthma

This study found according to the level of asthma control IL-33/ST2 ratio higher in uncontrolled atopic asthma patients compared to well controlled (0.266 ± 0.105 vs 0.127 ± 0.086, $p=0.001$). IL-33/ST2 ratio levels were not different in atopic asthma compared to non-asthma

($p > 0.05$). IL-33 usually released by bronchial epithelial cells and lung blood vessels when exposed to allergens and damaged due to inflammatory reactions. IL-33 is produced by mast cells after IgE-mediated activation and is able to trigger proinflammatory cytokines releasing.[7] ST2 in this case Soluble ST2 which is a decoy receptor by sequestering IL-33, thereby inhibiting IL-33 binding to the ST2 receptor ligand (ST2L) signaling.[6] Soluble ST is also released from bronchial epithelial cells and lung blood vessels which is stimulated by pro-inflammatory cytokines and Th2 cytokines. Serum ST2 tends to increase if atopic asthma is accompanied by increased neutrophilic inflammation. This happens when atopic asthma is not controlled or asthma exacerbations often occur.[12] This shows that the soluble IL33/ST2 ratio can increase in conditions of uncontrolled asthma or frequent exacerbations. This study found the potential of IL33/ST2 as a biomarker for status for asthma control, where IL33/ST2 higher in asthma uncontrolled and lower ratio in well controlled asthma and may become a biomarker for treatment response. Also have been reported the potensial of IL33/ST2 ratio as target in uncontrolled asthma for improving asthma management and reducing exacerbations.[13,14,15] Further investigation is needed to fully understand the implications of this ratio and its role in the management of atopic asthma.

Conclution

In conclusion, ratio IL-33/ST2 and also levels of ST2 higher in uncontrolled atopic asthma compared to well controlled asthma. IL-33 higher in patients with atopic asthma compared to subject non-asthma.

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All authors contributed equally to the manuscript and read and approved the final version of the manuscript.

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