ARTIKEL PENELITIAN

THE POTENTIAL OF INTERLEUKIN-17 AS A PROGNOSTIC BIOMARKER AND A TARGET OF THERAPEUTIC MODALITIES IN ATOPIC DERMATITIS

POTENSI INTERLEUKIN-17 SEBAGAI BIOMARKER PROGNOSTIK DAN TARGET MODALITAS TERAPI PADA DERMATITIS ATOPIK

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ABSTRAK
Pendahuluan: *Dermatitis Atopik (DA) merupakan salah satu penyakit kulit peradangan kronik berulang tersering. DA menyebabkan dampak negatif pada sosioekonomi, terutama pada kualitas hidup pasien dan keluarganya. Gangguan imun pada DA dapat menyebabkan kerusakan sawar keratinosit dan inflamasi pada DA diasosiasikan dengan respon Th17 yang menghasilkan Interleukin-17 (IL-17). Tujuan dari penelitian ini adalah untuk melihat korelasi antara IL-17 dan tingkat keparahan DA.*
Metode: *penelitian kohor retrospektif ini dilakukan di unit rawat jalan poliklinik kulit dan kelamin. Sampling konsekutif dilakukan selama periode penelitian pada pasien dengan usia lebih dari sama dengan 14 tahun dengan diagnosis DA. Data demografis, indeks Scoring for AD (SCORAD), skor stres, onset dan durasi penyakit, dan tiga mililiter darah dalam vakutainer diambil dari pasien. Analisis kadar serum IL-17 diukur pada darah dengan teknik ELISA berdasarkan protokol pabrik. Nilai p kurang dari 0,05 dinilai sebagai signifikan.*
Hasil: *Kadar serum IL-17 yang lebih tinggi ditemukan pada pasien DA dibandingkan dengan kontrol. Terdapat kadar serum IL-17 yang lebih tinggi pada pasien DA sedang-berat dibandingkan dengan DA ringan. Pasien DA sedang-berat memiliki durasi sakit yang lebih lama dan indeks SCORAD yang lebih tinggi dibandingkan dengan pasien DA ringan. Terdapat korelasi positif yang sangat kuat antara kadar serum IL-17 dan indeks SCORAD.*
Simpulan: *Hasil dari penelitian ini menekankan potensi IL-17 sebagai biomarker prognostik dan juga sebagai potensi target modalitas terapi.*
Kata Kunci: *dermatitis atopik, interleukin-17, indeks SCORAD, korelasi, mediator pro-inflamasi.*

ABSTRACT
Introduction: Atopic dermatitis (AD) is one of the most common chronic relapsing inflammatory skin diseases. AD causes negative social and economic impacts, especially on the patients' and their families quality of life. The immune dysregulation in AD disrupts the keratinocyte barrier and induces inflammation. AD recently was associated with the response of TH17, which produce IL-17. This study aims to investigate the correlation of IL-17 with the severity of AD.
Methods: This retrospective cohort study was conducted in the dermatovenerology outpatient department. Consecutive sampling was done during the study period on patients aged more than 14 years old diagnosed with AD. Demographic data, Scoring for AD (SCORAD) index, stress score, onset and duration of disease, and three milliliters of whole blood in vacutainer were obtained. IL-17 serum level analysis was measured on the blood by ELISA technique according to the manufacturer's protocol. A P-value smaller than 0.05 was appraised as statistically significant.
Results: There was a significantly higher IL-17 serum level in AD patients than in control patients. There was a higher IL-17 serum level in moderate-severe compared to mild AD patients. There were also significantly longer disease duration and higher SCORAD index in moderate-severe compared to mild AD patients. There was a robust positive correlation between IL-17 serum level and SCORAD index.
Conclusions: The findings of this study emphasize the potency of IL-17 as a prognostic biomarker and as the potential target of therapeutic modalities.
Key Words: atopic dermatitis, correlation, interleukin-17, pro-inflammatory mediator, SCORAD index.

INTRODUCTION

Atopic dermatitis (AD) is one of the most common chronic relapsing inflammatory skin diseases associated with significant cutaneous and systemic disease burden and poor quality of life.[1,2] AD has negative impacts on social and economic, especially on the patients' and their families' quality of life.[3] Pathogenesis of AD was fathomed due to the complex interaction between environment, host susceptibility genes, altered skin barrier functions, immune system, and pruritus.[4] AD was considered an allergic T helper-2 (Th2)-mediated disease, characterized by abnormal IgE production, peripheral eosinophilia, activation of mast cells, and induction of Th2 lymphocytes, and in addition to the Th2, roles of T helper-17 (Th17) must also be considered, as it was found in high percentage in AD patients.[4]

The immune dysregulation in AD disrupts the keratinocyte barrier and induces inflammation.[5] AD was recently associated with the response of Th17, which produces IL-17. It was shown that this type of cell infiltrates the skin lesion of AD, especially during the acute phase.[6] This finding leads to the suggestion that IL-17 produced by Th17 decreases the tight junction function by several mechanisms, such as inhibiting the synthesis of zonula occludens (ZO)-1, claudin-1, and also claudin-4.[7] IL-17 was found increased in severe AD, as it was demonstrated to promote eosinophil production of CXCL1, IL-8, CCL4, IL-1β, and also IL6.[8] It was also known that IL-17 downregulates the expression of filaggrin leading to the impairment of epidermal formation.[9] This study aims to investigate the correlation of IL-17 with the severity of AD.

METHODS

This retrospective cohort study was conducted in the dermatovenerology outpatient department in RSUP dr. Kariadi, Semarang, Indonesia, from January until March 2014. Written informed consent was taken from all subjects after sufficient information about the study before study enrollment. Ethical Committee of Faculty of Medicine, Diponegoro University and RSUP dr. Kariadi Semarang approved this study with register number 013/EC/FK-RSDK/2014.

Consecutive sampling was done based on inclusion and exclusion criteria during the study period. Patients aged more than 14 years old diagnosed with AD were included in this study. Patients diagnosed with infectious diseases, other inflammatory diseases, autoimmune diseases, and currently under steroid or other oral immunosuppressants were excluded two weeks before the study. Demographic data (sex and age), Scoring for AD (SCORAD) index, stress score (National Stress Awareness Day Questionnaire from International Stress Management Association), onset and duration of disease, and three milliliters of whole blood in vacutainer were obtained from patients upon a visit to the outpatient department. Patients' SCORAD index scoring was done by calculating the extent of the lesions, the intensity of the lesions, and the subjective symptoms. The SCORAD index scoring was evaluated by three dermatovenerologist independently

(Figure 1). Whole blood was centrifuged, and serum was collected and stored at -80°C before IL-17 serum level analysis. IL-17 serum level analysis was done using Human IL-17 Immunoassay R&D Quantikine® ELISA Kit (R&D Systems Inc., Minneapolis, USA) according to the manufacturer's protocol. The samples were read at 450 nm wavelength using a BioTek ELx800 microplate reader (BioTek Inc., Winooski, VT, USA).
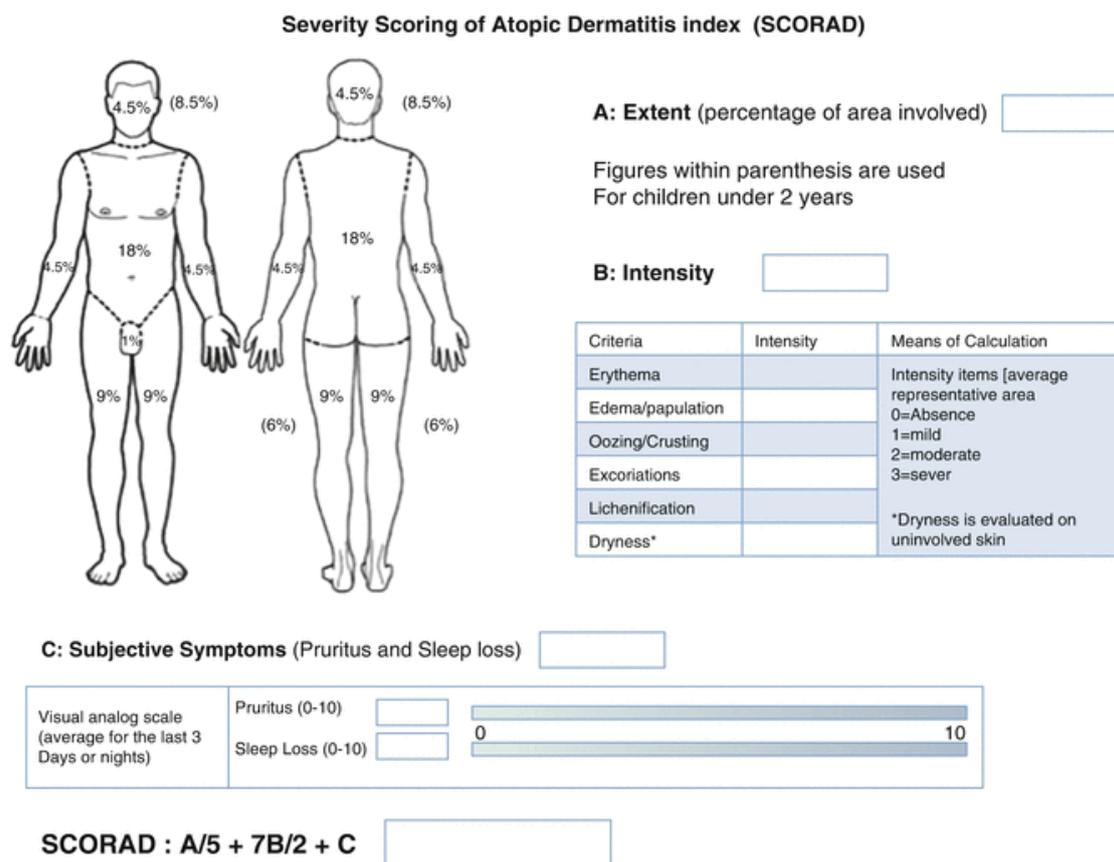
Figure 1. SCORAD index.[10]

Statistical analysis was performed using Statistical Programs for Social Science (SPSS) version 15.0. Cohen's Kappa coefficient was analyzed for the SCORAD index. The agreement was considered very strong if κ was more than 0.8. Demographic data, disease duration and onset, stress score, SCORAD index, and IL-17 serum level were compared between AD patients and control. Mild AD compared with moderate-severe AD patients using independent t-test and Chi-square test. If data were not normally distributed and independent t-test assumptions were not met, the Mann-Whitney U test would be used, and the chi-square test was used. Spearmen's Correlation analysis (data were not normally distributed) was done on IL-17 serum level and SCORAD index. A P-value smaller than 0.05 was appraised as statistically significant.

Table 1. Demographics of AD compared to control

Demographics	AD (n=36)	Control (n =16)	p-value
Age (years) Mean (SD)	38.19 (20.42)	33.75 ± 14.74	0.3809*
Gender Male Female	16 (44.44%) 20 (55.56%)	9 (56.25%) 7 (43.75%)	0.432#
IL-17 (pg/ml) Median (min-max)	34.04 (17.08 – 69.48)	10.92 (5.78 – 15.029)	**< 0.0001^**

*unpaired t-test, #Chi^2; ^Mann-Whitney U test

Table 2. Demographics of AD based on Severity of Disease

| Demographics | Severity | | p-value |
	Mild (n=19)	Moderate-Severe (n=17)	
Age (years) Median (min-max)	25 (16 - 72)	32 (17 - 86)	0.5241^
Gender Male Female	9 (47.37%) 10 (52.63%)	7 (41.18%) 10 (58.82%)	0.709#
IL-17 (pg/ml) Median (min-max)	21.19 (17.08 – 41.74)	50.99 (31.46 – 69.48)	**< 0.0001^**
Onset (years) Median (min-max)	19 (6 - 65)	17 (1 - 70)	0.2602^
Duration of disease (years) Median (min-max)	7 (0.5 - 25)	16 (5 - 50)	**0.0023^**
Stress score Mean (SD)	7.58 (0.84)	8.65 (1.09)	0.4394*
SCORAD index Median (min-max)	17.1 (10.5 – 22.6)	44.3 (26.1 – 51.5)	**< 0.0001^**

*unpaired t-test, #Chi^2; ^Mann-Whitney U test

RESULTS

This study was conducted on 52 patients with a mean age of 36.82 (SD=18.82) years, consisting of 36 AD patients and 16 controls (Table 1). There were no significant differenpces between AD patients and control patients in age and gender. Still, there was a significantly higher IL-17 serum level (p < 0.0001) in AD patients (Median=34.04 pg/ml) compared with control patients (Median= 10.92 pg/ml).

When AD patients were classified into mild and moderate-severe (Table 2), there were no significant differences between mild and moderate-severe AD patients in age, gender, the onset of the disease, and stress score. Cohen's κ coefficient for the SCORAD index was 0.989 and considered a firm agreement. There was a significantly higher IL-17 serum level (p<0.0001) in moderate-severe (Median=50.99) compared to mild (Median=21.19) AD patients. There was also a significantly longer the duration of the disease (p=0.0023) in moderate-severe (Median=16 years) compared to mild (Median=7 years) AD patients, and also a higher SCORAD index (p<0.0001) in moderate-severe disease (Median=44.3) compared to mild (Median=17.1) AD patients. There was a very strong positive correlation (r=0.8348, p < 0.0001) between IL-17 serum level and SCORAD index (Figure 2).
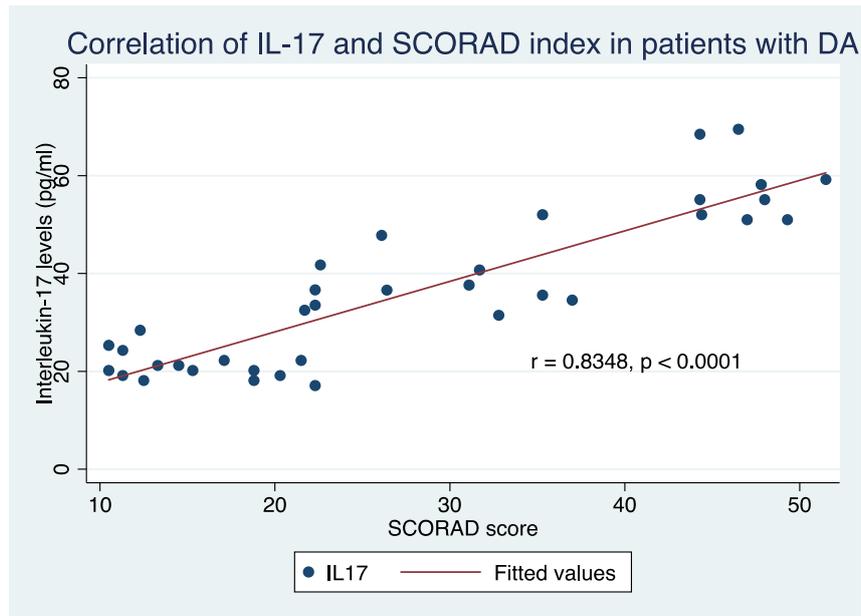
Figure 2. Correlation between IL-17 and SCORAD index

DISCUSSION

IL-17 family functions in host defense against pathogens and have various roles as inflammation mediators in autoimmune, allergic, and chronic inflammatory diseases.[11] IL-17 axis was correlated with allergic skin reactions, such as AD and contact dermatitis.[11] IL-17 was mainly produced by Th17, which promotes the inflammatory response, such as activating immune cells, improving T cells' immune response, and helping to express pro-inflammatory factors and chemokines.[12] The association between AD and the Th17/IL-17 immune system was reported in several studies.[7,13,14] Skin specimens treated with IL-17 decrease the synthesis of claudin-1 and claudin-4 in a dose-dependent manner causing the tight junction dysfunction in the skin-equivalent model.[7]

A study by Batista et al. found higher IL-17 serum levels in AD patients compared to controls. The team also saw an increase in Th17 cells in the peripheral blood of AD patients correlated with disease severity.[15] This finding is concordant with our result, which found that IL-17 serum levels were higher in AD patients than in control and also that the IL-17 serum levels in moderate-severe AD were higher than the mild AD patients. In addition, the longer duration of the disease, the AD tends to be more severe.

A previous study by Leonardi et al. found that IL-17 serum levels in children with AD were correlated positively with disease severity.[16] This finding is concordant with the result of our study. We found a robust positive correlation between IL-17 serum level and SCORAD index in adult patients. This finding suggests that IL-17 is a potential targeted therapy to cure AD and the prognostic biomarker to evaluate the severity.

CONCLUSION

The obscure immune dysregulation of AD has to be unraveled to discover more biomarkers and therapeutic modalities. The

findings of this study emphasize the IL-17 as a prognostic biomarker and as the potential target of therapeutic modalities.

Declarations

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Conflict of interest: None declared

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