Original Research

IL-17 AND DISEASE ACTIVITY IN SPONDYLOARTHRITIS

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ABSTRACT

IL-17 is a new cytokine involved in the pathogenesis of Spondyloarthritis (SpA). Recent studies show that IL-17 level correlates to disease activity, and it is used as a basis in treating SpA patients who do not respond to anti-TNF-α. This study identified the correlation of IL-17 to disease activity measured by The Ankylosing Spondylitis Disease Activity Score C-Reactive Protein (ASDAS-CRP). This study was a cross-sectional study involving SpA patients according to the 2009 ASAS criteria in Dr. Soetomo General Academic Hospital, Surabaya. Disease activity and IL-17 level were analyzed using Spearman correlation test to see the strength of correlation. Forty SpA patients showed mean age of 53.58 ± 9.28 years with a body mass index of 24.36 ± 3.23 kg/m2, ESR of 39.50 ± 18.76 mm/hour, clinically obtained Schober Test of 13.11 ± 1.22 cm, chest extension test of 1.45 ± 0.77 cm, and tragus-to-wall test 13.53 ± 1.99 cm. The median CRP and IL-17 were 0.3 (0.10-5.70) mg/dL and 9.30 (7.70-13.60) pg/dL, respectively. Based on the ASDAS-CRP system, the patients showed disease activities that fall into the category was high (62.5%), moderate (35%), and inactivity (2.5%). IL-17 level is strongly correlated to disease activity in SpA patients (p=0.000, r=0.711).

Keywords: *IL-17; spondyloarthritis; health risks; disease*

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Highlights:

1. The correlation of IL-17 to disease activity by The Ankylosing Spondylitis Disease Activity Score C-Reactive Protein (ASDAS-CRP) was identified.
2. IL-17 level is strongly correlated to disease activity in SpA patients.

INTRODUCTION

Spondyloarthritis (SpA) is a chronic inflammatory arthritis group that primarily affects the axial and peripheral bones. The characteristics of the SpA are sacroiliitis, inflammatory back pain, oligoarthritis, enthesitis, and negative rheumatoid factors (Ehrenfeld 2012, McGuckin et al. 2010) In general, the symptoms are rarely well described by the patient and frequently overlooked and undiagnosed by physicians, which then lead to increased morbidity and high economic burden due to disability (Dincer et al. 2008). Until recently, the pathogenesis of SpA had not been fully discovered. The pathogenesis of SpA is allegedly related to Human Leukocyte Antigen-B27 (HLA-B27) gene. The HLA-B27 misfolding hypothesis is currently the most widely accepted pathogenesis of SpA which also explains the presence of Interleukin (IL)-17 in SpA.

The HLA-B27 misfolding hypothesis explains the emergence of endoplasmic reticulum (ER) stress and Unfolded Protein Response (UPR). UPR activation triggers the Toll-Like Receptor (TLR) influenced by Interferon (IFN)-β to induce IL-23 secretion through UPR Target Gene that has a correlation with HLA-B27 and Th17 Cell-Driven Disease. (Colbert et al. 2009, Dincer et al. 2008). Triggered by unfolded proteins, the malfunctioning ER or ER-stress causes interference in signal transduction. The function of UPR is to strictly regulate protein translation, degradation of misfolded proteins, and activation of signalling to increase the synthesis of chaperone molecules involved in protein folding. If UPR function is disrupted, apoptosis will occur.

ER stress further leads to the production of pro-inflammatory cytokines, such as IL-23, IL-6, and Transforming Growth Factor (TGF)-β. IL-23 is the largest cytokine in UPR, and it will stimulate the conversion of naive CD4 T cells to T-helper-17 (Th17) that secretes IL-17 (Chabaud et al. 2000). There is currently no full explanation about the mechanism of IL-17 in its correlation to disease activity in SpA. However, several studies have found that IL-17 increases the expression of Receptor Activator of Nuclear factor-κB Ligand (RANKL), expression of molecular adhesion, chemokine secretion, and MMP enzyme secretion. The increased pro-inflammatory cytokines can cause synovitis, cartilage degradation, and enthesitis which lead to arthritis and joint stiffness (Braun & Zwerina 2011, Machado et al. 2011).

Assessing the actual disease activity in SpA is not easy. Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Bath Ankylosing Spondylitis Functional Index (BASFI) are among other scoring systems to determine disease activity in SpA. Assessment of the Spondyloarthritis International Society (ASAS) in 2009 proposed a new system in the form of ASDAS (Ankylosing Spondylitis Disease Activity Score) which adopted several points in BASDAI and added several points, such as CRP and the Blood Depth (ESR). Demir (2013) compared some parameters about disease activity in SpA and found that ASDAS was significantly more appropriate in describing actual activity of SpA compared to BASDAI and BASFI. Until recently, research on the correlation of IL-17 with ASDAS scores was still lacking. This study investigates the correlation of IL-17 serum with parameters of disease activity in SpA using ASDAS-CRP.

MATERIALS AND METHODS

This study involved 40 patients from Javanese ethnicity in Dr. Soetomo General Academic Hospital, Surabaya who were diagnosed with SpA based on 2009 ASAS criteria. The patients were sampled using consecutive sampling methods. Patients with BMI >30kg/m2, diabetes mellitus, liver cirrhosis, asthma, tuberculosis, and smoking history were all excluded. Every patient enrolled in this study had voluntarily signed an informed consent form before participating as a study subject. All study subjects were aware that they were involved in this study, and their rights and confidentiality were ultimately respected. This study was approved by the Ethical Committee of Dr. Soetomo General Academic Hospital, Surabaya and conducted according to Good Clinical Practice (GCP).

This was a cross-sectional study, where clinical and laboratory assessments of the patients were performed on the same day. We evaluated the disease activity using the ASDAS- CRP whilst physical examinations were performed to determine physical mobility, including tragus-to-wall (TWD) distance and lumbar flexion (Schober index).

Serum IL-17 level is measured by Enzyme-Linked Immunosorbent Assay (ELISA), using Human IL-17 (Quantikine® ELISA Human IL-17 Immunoassay, R&D System, IncCatalog D1700) as a reagent. The minimum detectable level was 7.8 pg/ml. A blood sample was drawn in a serum separator tube for 30 minutes, then centrifuged for 15 minutes and stored in <-20 C fridge. 100 µL of each standard, control, and sample were added into tubes containing 100 µL of Assay Diluent RD1-19. Tubes were sealed with adhesives and incubated at room temperature for 2 hours before aspirated and washed four times. Aspiration and washing were repeated after adding 200 µL of IL-17 Conjugate and a one-hour incubation period. Furthermore, 200 µL of substrate solution was added, and tubes were stored in light-proof storage for a 30-minute incubation period. Then, 50 µL of stop solution was added, ELISA reader: 450 nm (620nm, reference wave).

Disease activity is a condition that describes the severity of SpA assessed by the ASDAS (Ankylosing Spondylitis Disease Activity Score) system (Table 1). The components of the ASDAS scoring system consisted of back pain, morning stiff duration, peripheral pain or swelling, and global assessment of disease activity, in the scale of zero to ten, and CRP level or Erythrocyte Sedimentation Rate (ESR). Each item was inserted in the ASDAS formula to generate an assessment score and its category.

Table 1. Ankylosing spondylitis disease activity score with C-reactive protein (ASDAS-CRP)

ASDAS CRP = (0.12 × back pain score) + (0.06 × morning stiffness score) + (0.11 × global assessment score) + (0.07 × peripheral pain /swelling score) + [0.58 × ln (CRP + 1)]	
Total score is classified as:	
1.	Inactive (score < 1.3)
2.	Moderate disease activity (score: 1.3-2.1)
3.	High disease activity (score: 2.1-3.5)
4.	Very high disease activity (score > 3.5)

All data was entered into a computer through a statistical progra (SPSS edition 17) and delivered in descriptive statistics. Kolmogorov-Smirnov tested the data distribution which appeared to be abnormally distributed. Hence, Spearman's rank correlation test (for non-parametric) analyzed the correlation of IL-17 level and ASDAS-CRP score. The strength of correlation (r) with a value of 0.00-0.199 was interpreted as óvery

weak'. Values 0.20-0.399 were interpreted as weak, values 0.40-0.599 as moderate correlation, values 0.60-0.799 as strong correlation, and 0.80-1.00 as very strong correlation. The significance level was 5%.

RESULTS

In Table 2, forty patients with SpA aged 53.58±9.28-year-old showed mean body mass index of 24.36±3.23 kg/m2, ESR of 39.50±18.76 mm/hour, Schober test of 13.11±1.22 cm, chest expansion test of 1.45±0.77 cm, and tragus-to-wall test of 13.53 ± 1.99 cm. Medians of CRP and IL-17 were 0.3(0.10-5.70) mg/dL and 9.30 (7.70-13.60) pg/dL respectively. ASDAS-CRP scores showed 2.5% inactive, 35% moderate, and 62.5% high disease activities. None had very high disease activity.

Table 2. Characteristics of research subjects

General Characteristics		Result
Gender	Man	11 (27,5%)
	Women	29 (72,5%)
SpA subtypes	Axial SpA	24 (60%)
	Peripheral SpA	16 (40%)
Old (year)	Mean ± SD	53.58 ± 9.28
Body Mass Index (BMI)	Mean ± SD	24.36 ± 3.23
Schober Test (cm)	Mean ± SD	13.11 ± 1.22
Chest Expansion Test	Mean ± SD	1.45 ± 0.77
Targus-to-Wall (cm)	Mean ± SD	13.53 ± 1.99
ESR (mm/hour)	Mean ± SD	39.50 ± 18.76
CRP (mg/dl)	Median (min-max)	0.3 (0.10-5.70)
Albumin (g/dL)	Mean ± SD	3.86 ± 0.32
IL-17 level (pg/dL)	Median (Min-Max)	9.30 (7.70-13.60)
Axial SpA	Mean ± SD	10.01 ± 1.49
Peripheral SpA	Median (Min-Max)	9.10 (7.70-11.50)

Gender distribution varied in numerous studies. Some reports showed more significant male incidents than women, but other researchers claimed that there was no difference. In this study, the proportion of women and men was 3:1 classified as 29 patients (72.5%) were women, and 11 (27.5%) were men. SpA generally occurs at a young age ranging from 20 to 30. In this study, the average age of the sample was 53±9 years. Patients' average age might be different because, in developing countries, patients are usually constrained by economic problems that result in patients coming late to health services. Moreover, diagnosis takes about 8-10 years after the earliest manifestation of SpA symptoms, because they were often unnoticed (insidious).

Twenty-four patients (60%) were categorized as Axial SpA group and 16 patients (40%) as Peripheral SpA group. The average Body Mass Index (BMI) of patients was 24.36 kg/m^2 and categorized as normal. The average Schober test was 13.11±1.22 centimetres which indicated the measurement of the Schober test was also relatively homogeneous. The average value of the ESR was 39.50±18.76 mm/hour.

The CRP level did not follow a normal distribution and had a median of 0.3 (0.10-5.70). The inflammation in RA was different from that of SpA. The SpA was characterized by a low-grade inflammation with elevated cytokines concentration and acute-phase proteins of two to three times normal level (Anne et al. 2005). In this study, the mean ESR and median CRP level were 39.50±18.76 and 0.3 (0.10-5.70) mg/dl respectively. Woloshin and Schwartz (2005) reported that in the United States, the normal value of CRP was <0.3 mg/dl, but the range 0.1-1.0 mg/dl was a normal variant in individuals without pathological abnormalities, so that the inflammatory condition in the SpA patient in this study was categorized as a low-grade inflammation. Besides, the CRP level and ESR were lower than those in Yildirim et al. (2004) and Arthur et al. (2010) which reported Rheumatoid Arthritis (RA) patients. In contrast, Kay et al. (2014) reported that most of the patients with active RA were not followed by elevated CRP levels, but CRP was reported to be related to the prognosis.

Table 3. Clinical Characteristics According to ASAS criteria

ASAS Criteria	n	%
Inflammatory Back Pain	26	65
Arthritis	18	45
Enthesitis (heel)	16	40
Uveitis	1	2.5
Dactylitis	3	7.5
Psoriasis	12	30
Inflammatory Bowel Disease	Not examined	-
Good Response to NSAID	35	87.5
Family History for SpA	2	5
Elevated CRP	13	32.5
HLA-B27	Not examined	-
Sacroiliitis by Radiograph	28	70

In general (Table 3), complaints of patients with SpA were back pain (inflammatory in nature), oligoarthritis, especially in the lower legs, dactylitis (sausage-like digits), enthesitis in the heel or other places, and extra-articular manifestations, such as uveitis, inflammatory bowel disease and psoriasis (Rudwaleit 2010). In this study, Table 3 indicated the main complaints of patients were low back pain (inflammatory back pain) in as many as 26 patients (65%) patients followed by arthritis

(45%), symptoms of Frank's arthritis—stiff joints and heel pain (enthesitis)—in 16 people (40%), and acute uveitis in only 1 person (2.5%). Sacroiliitis by plain radiograph were apparent in 28 patients (70 %). Finally, as the subjects visited the clinic not in the early stage of disease, 87.5 % of patients responded to NSAIDs.

Table 4. Levels of IL-17 in patients with SpA

IL-17 Level		Result (pg/dl)
IL-17 level (pg/dL)	Median (Min-Max)	9.30 (7.70-13.60)
Axial SpA	Mean ± SD	10.01 ± 1.49
Peripheral SpA	Median (Min-Max)	9.10 (7.70-11.50)

In Table 4, the median result of IL-17 in this study was 9.30 (7.70-13.60) pg/dL. The lowest IL-17 level was 7.70 pg/dl whilst the highest was 13.60 pg/dl. The mean IL-17 level in the Axial SpA group was 10.01±0.30 pg/dL, while the peripheral SpA group showed a median value of 9.10(7.70-11.50) pg/dL.

Table 5. Disease activity according to ASDAS-CRP and corresponding IL-17 level

ASDAS-CRP Median 2.20(1.20-3.50)		IL-17 level (pg/dl)
Inactive Disease (skor < 1.3)	1 subject (2.5%)	7.7
Moderate Disease (1.3≤ skor <2.1)	14 subject (35.0%)	8.79±0.53
High Disease (2.1≤ skor <3.5)	25 subject (62.5%)	10.36±1.35
Very High Disease (skor >3.5)	0 subject (0.0%)	-

Furthermore, the median value of the disease activity score of 40 SpA patients measured by the ASDAS-CRP score was 2.20 (1.20-3.50) pg/dL (Table 5). The number of SpA patients who are classified according to ASDAS-CRP score is one person (2.5%) for inactive disease-based, 14 people (35.0%) for moderate disease activity, 25 people (62.5%) for high disease activity, and none for the very high disease.

Hypothesis testing of the association between serum IL-17 levels and disease activity in patients with SpA was carried out by association analysis. The Kolmogorov-Smirnov data normality test should conclude that the data distribution was normal when the p-value was above the significance level of 5%. The results for the IL-17 and ASDAS-CRP distribution test resulted in a p-value of 0.003 and 0.013 respectively, which concluded that the obtained data were not distributed normally. Thus, the Spearman's rank test for non-parametric association was used to analyze the association between IL-17 levels and ASDAS-CRP scores.

Table 6. Spearman's rank for the correlation of IL-17 level and ASDAS-CRP

Variable 1	Variable 2	r-value	p-value
IL-17	ASDAS-CRP	0.711	0.000

Analysis of the association between IL-17 levels and the ASDAS-CRP score with the Spearman's rank resulted in a Spearman r-value of 0.711 with a p-value of 0.000 (Table 6). These results concluded a significant correlation between IL-17 level and the ASDAS-CRP score in the study subjects. The correlation was positive or unidirectional, which indicated that the more elevated the IL-17 level in SpA patient was, the higher ASDAS-CRP score would be, the more severe disease activity could be. The association between IL-17 levels and ASDAS-CRP scores was shown in Figure 1.

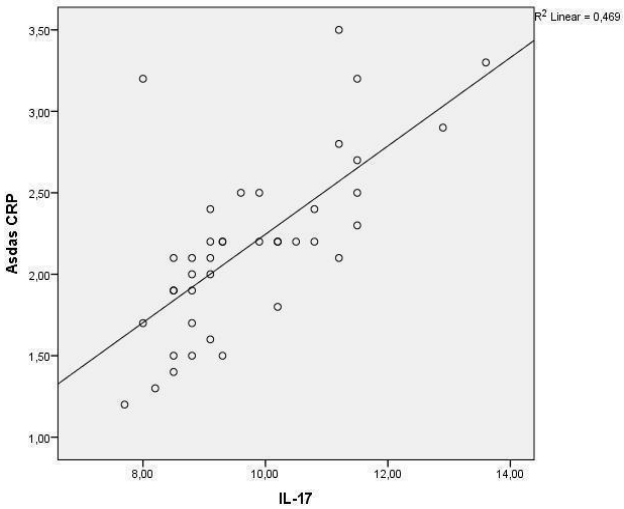

Figure 1. Correlation of IL-17 level and ASDAS-CRP (disease activity) in SpA patients

DISCUSSION

Spondyloarthritis. (SpA) is caused by genetic factors that are triggered by environmental factors originating from gastrointestinal and genitourinary infections. Various hypotheses of the pathogenesis of SpA arise, because the exact pathogenesis is not particularly clear at this time. The hypotheses that have been developed to date are the arthritogenic-peptide hypothesis, misfolding, and the HLAB27 homodimer or monomer hypothesis. The discovery of Th17 cells and the resulting cytokines raised questions on autoimmune disease induced by auto-reactive cells in an early study by Wendling et al. (2007) who evaluated IL-12/IL-23 levels in serum and synovial fluid of SpA patients

reported a significant association. However, many studies showed a significantly associated relationship between IL-17 in the pathogenesis of SPA. Wang et al. (2009) reported a correlation between the significantly elevated IL-17 and IL-23 levels in SpA patients with BASDAI scores higher than 4. Furthermore, they also found that IL-17 level correlated with ASDAS–CRP axis.

The normal range of IL-17 levels varies in healthy individuals. Ciprandi et al. (2008) reported IL-17 level of 0.28–5.47 pg/dL in healthy individuals and 31.37 ± 8.4 pg/dL in healthy controls, while Hussein et al. (2008) and Arican et al. (2005) mentioned 0.01±0.0 pg/dl. Arthur et al. (2010) reported that IL-17 level in RA patients elevated by an average of 17.28 pg/ml, while Hussein et al. (2008) reported a mean IL-17 level 0.2±0.1 pg/dl in RA patients. Arican et al. (2005) and Petersen and Pedersen (2005) in studies with psoriatic arthritis population reported serum IL-17 levels were 8.3±3.8 pg/dl, while Chen et al. (2012) reported in patients with Ankylosing spondylitis IL-17 levels of 66.03±17.8 pg/dl. Julija et al. (2013) reported average IL-17 level of 18.9±39.6 pg/dl in patients with ankylosing spondylitis with control of 5.4±26.0 pg/dl. These various results might be correlated with diseases activity or different ethnicity related to genetic factor. In this study, the median serum IL-17 level for SpA patients was 9.30 pg/ml, and the lowest serum IL-17 level was 7.70 pg/ml, while the highest serum IL-17 level was 13.60 pg/ml. These results were lower than average IL-17 levels in healthy individuals that have been reported but lower than some other studies.

Baraliakos et al. (2014) reported that ASDAS has a better ability to determine disease activity than BASDAI in axial SpA patients receiving treatment with Non-Steroidal Anti-Inflammatory Drugs (NSAIDs). They reported a mean ASDAS-CRP score in SpA patients of 2.5±0.6. Madej et al. (2015) reported on SpA patients in Poland the ASDAS-CRP value of 3.0±1.2. In this study, the median ASDAS-CRP score was 2.20 (1.2-3.5). The axial and peripheral SpA groups' scores showed no significant difference, considering the study subjects in each group were mostly in high disease activity condition. In this study, the majority of subjects showed high disease activity. The therapeutic modality which only consisted of a combination of NSAIDs, sulfasalazine (SSZ), and methotrexate (MTX) as well as patients' compliance in taking medication might contribute to disease activity. Dougados et al (1992) reported in a retrospective study that out of 372 SpA patients who received SSZ, there were only 59% who showed proper clinical development (Singh et al. 2007).

In this study, the correlation between serum IL-17 levels with ASDAS-CRP scores resulted in a p-value of 0.000 (α=5%). It is concluded that there was an association between IL-17 level and disease activity in SpA patients in Dr. Soetomo General Academic Hospital, Surabaya. The association between IL-17 levels and disease activity in patients with SpA in Dr. Soetomo General Academic Hospital, Surabaya, was strong (r=0.711). The results of this study were consistent with those reported by Chen et al (2012) in Taiwan on levels of IL-17 in patients with Ankylosing Spondylitis (AS), reported that IL-17 had an association with disease activity measured by BASDAI. However, Julija et al. (2013) study in Latvia, IL-17 had no association with disease activity in AS patients (Baraliakos et al. 2014).

According to the RESPONDIA study (Gallinaro et al. 2010), the most common clinical manifestations were inflammatory back pain (58.7%) and peripheral arthritis (37.7%). The RESPONDIA study involved 4,405 SpA patients from Ibero-American ethnicity in 10 countries. Among 1,168 patients with SpA in Spain, the most common clinical manifestations were inflammatory back pain (55.2%) and psoriatic arthritis (22.2%). Tayel et al. (2012) in Egypt reported that the dominant clinical manifestations in patients with SpA were inflammatory back pain (34%) and enthesitis (29.3%). Zhang et al. (2011) reported that the clinical picture of SpA in Asia was not much different from in various other parts of the world. In this study, the most common clinical manifestations were inflammatory back pain 65% and peripheral arthritis 45%. Thus, this study shows similar reports from various geographical areas worldwide (Europe, Latin America, the Middle East, and Asia).

Inflammatory arthritis is currently distinguished according to the degree of inflammation. In arthritis with obvious inflammatory symptoms in clinical examination (warm, painful, joint effusion) are classified as arthritis with high-grade inflammation (e.g., Rheumatoid Arthritis or RA). RA is characterized by severe inflammation characterized by high levels of inflammatory cytokines and acute-phase proteins (Siloşi et al. 2016). A study by Yildirim et al. (2004) in RA subjects described CRP levels of 2.4±1.9 (mg/dl) and LED values of 36.0±23.5 (mm/hour), while Arthur et al. (2010) mentioned that the average ESR in RA patients at Cipto Mangunkusumo Hospital in Jakarta was 58.50±32.10 (mm/hour).

The CRP and LED levels in this study were lower than those reports. Inflammation in RA was different from what happened in SpA. The SpA had the characteristics of low-grade inflammation. Low-grade inflammation is defined as inflammation with an increase in the concentration of cytokines and acute-phase proteins by 2-3 times the normal level. In this study, the mean value

of ESR and median CRP levels were 39.50±18.76 and 0.3(0.10-5.70) mg/dl. Woloshin and Schwartz (2005) also reported the normal CRP value was <0.3 mg/dl, but the range 0.1-1.0 mg/dl was a normal variant in individuals without pathological abnormalities. Therefore, the inflammatory conditions in SpA patients in this study were categorized as low-grade inflammation.

Albumin is known as a negative acute-phase reactant or an acute phase protein and its synthesis decreases when inflammation occurs (Ballantyne et al. 1971). In high-grade inflammation like RA, most patients experienced hypoalbuminemia (Ciprandi et al. 2008). In this study, the mean albumin level was within a normal range (3.86±0.32 g/dl). It was possibly due to the inflammation, where it was not severe enough to suppress albumin synthesis and cause hypoalbuminemia.

As measured by the ASDAS-CRP score, SpA disease activity has several measurement components, namely pain in the axial joints, joint stiffness in the morning, and pain or swelling in the peripheral joints. IL-17 increases the activity of SpA disease by causing axial and peripheral joint pain, causing joint stiffness and joint edema. Singh et al. (2007) reported that, in 51 patients with Reactive arthritis (ReA) and Undifferentiated SpA (uSpA), IL-17 levels in synovial were found to be higher than in RA patients, so that IL-17 was also thought to be a cytokine that had a dominant role in ReA and uSpA. Appel et al. (2011) reported that IL-17 levels in the vertebral joint facet area of patients with ankylosing spondylitis increased. Appel also mentioned that the number of cells producing IL-17 was more in the inflamed joints. The increased IL-17 in joints could cause joint pain and stiffness (Pinto et al. 2010).

Pain in patients with SpA is deemed to be related to IL-17. In animal (rate) study, Pinto et al. (2010) described that IL-17 could cause pain in arthritis (RA) due to increased nociceptive excitations resulting in hypernociception. Richter et al. (2012) reported a trial, where mice were given IL-17A injections in the knee joint area. In these mice, prolonged nociceptive sensitization did not disappear by giving anti-TNF-α and IL-6. IL-17A was found to cause rapid phosphorylation of protein kinase B and extracellular-signal-regulated kinase (ERK), and this increased excitability quickly. Richter et al. (2012) raised a suspicion that IL-17 acted as a pain mediator that caused hyperalgesia. The increased levels of IL-17 in the blood and joints of patients with SpA were thought to exacerbate disease activity, because they caused joint pain and joint stiffness.

IL-17 caused bone remodelling and new bone formation in SpA through its effects on osteoclasts and osteoblasts. IL-17 stimulated the production of PGE2, nitric oxide (NO), and receptor activator of NFκB ligand (RANKL) by osteoblasts. This could cause osteoclast activation and differentiation, which ended with increased bone destruction. IL-17 upregulated fibroblasts, epithelial cells, endothelial cells, monocytes, and osteoblasts to increase pro-inflammatory cytokines, such as IL-6 and granulocyte monocyte colony-stimulating factor (GM-CSF), IFN-γ, and TNF-α. These pro-inflammatory cytokines acted as mediators of bone destruction. Ruddy et al. (2004) found that IL-17 stimulate osteoblasts to increase the expression of chemotactic factors, such as CCL2 and CXCL5 that stimulated the recruitment of leukocytes, such as neutrophils and T cells. Mobilization of inflammatory cells caused an increase in inflammatory mediators, such as IL-6, IL-1, TNF-α, and RANKL, that could cause bone destruction and new bone formation (Onishi & Gaffen, 2010).

Synovial inflammation in SpA patients is not as significant as in RA. Synoviocytes play a role in causing bone and cartilage damage due to stimulation by IL-17. IL-17 stimulates synovial macrocytes and macrophages to produce chemokines (e.g., IL-8, CXCL2, CCL20, CCL2, CXC5, and CCL5), the mobilization of neutrophils, lymphocytes, and macrophages to synovium and further increases the inflammatory process. Park et al. (2011) reported their studies in experimental animals in mice, where IL-17 increased cadherin-11, an adhesion molecule that played a role in synovial inflammation and cartilage degradation. IL-17 stimulates synoviocytes to increase pro-inflammatory cytokines and chemokines, such as IL-6, IL-8, CCL20, TNF-α, and p19 subunit IL-23.

Chowdhury et al (2013) found that IL-17 inhibited mRNA degradation that encoded TNF-α cytokines. The final result of this process caused mRNA to be translated longer, so that the levels increased. Hot and Miossec (2011) stated that IL-17 was also responsible for increasing the production of matrix metalloproteinases (MMP), such as MMP3, MMP9, and MMP13. Moz et al (2017) reported that MMP in the synovium was associated with parameters of arthritis activity, such as cell infiltration. A cohort study by Yang et al. (2004) showed that MMP-3 levels correlated with disease activity in ankylosing spondylitis.

Cartilage is a target organ attacked in SpA. In SpA, cartilage will experience degradation. From various research reports, IL-17 was said to mediate the pathological process of cartilage degradation. Honorati et al. (2002) experimented on human chondrocyte cells which were given IL-17. They found that IL-17 stimulated chondrocytes to produce NO and increase gene expression associated with joint inflammation and cartilage degradation (NO synthase, cyclooxygenase 2, IL-1β, IL-6, IL-8, CCL2, and MMP). Dudler et al (2000) reported intra-articular injection of IL-17 in mice causing inhibition of proteoglycan synthesis by cartilage and causing destruction of cartilage. The effect of cartilage degradation was further investigated by Koenders et al. (2005) in in-vivo mouse experiments. Koenders et al. (2005) found that the IL-17 receptor blockade reduced the occurrence of cartilage degradation.

From the data of animal studies, in vitro studies, and clinical studies, it is reported that IL-17 was a cytokine that was highly potent as a pro-inflammatory cytokine (Miossec & Kolls 2012). Besides, it also played a role in osteoclastogenesis and had the ability to induce the formation of blood vessels as the characteristic of inflammation. It is suspected that IL-17 was a highly strong cytokine in inducing inflammation responsible for the immunopathogenesis of SpA (Yago et al. 2009). The formation of Th17 is induced by antigen stimulation on naïve CD4 + T cells which caused differentiation into Th1, Th2, and Th17. In mice, TGF-β and IL-6 had a role in the differentiation of CD4 T cells to Th17. Along with IL-1 and TNF-α, triggered this process. TGF-β and IL-6 regulated retinoic acid orphan receptors (RORγt and RORα) on naïve T cells resulting in upregulation of IR-23 receptors that caused cells to respond to IL-23. IL-23 is a family of IL-12 consisting of IL-12p40 and IL-23. IL-23 plays a role in triggering the secretion of IL-17. TGF-β and IL-6 regulate RORγt in humans (Miossec & Kolls 2012).

A recent study examining macrophages derived from PBMCs of AS patients also found defects in IFN-γ expression. From these data, it is concluded that IFN-γ expression was very low in SpA compared to other immune-mediated inflammatory diseases. The low level of IFN-γ in infection could increase the organism's survival which could lead to reactive arthritis. IFN-γ expression was low, but Th17 expression was increased, and it was suspected that cytokine had a role in the protection of SpA patients. The decrease in IFN-γ levels in SpA might have triggered the increase in Th17 (Taams et al. 2018). IFN-γ can play a dual role, increasing the expression of HLA-B27, and ultimately increasing the Unfolded Protein Response (UPR). UPR triggers the production of several cytokines against bacterial products captured by TLRs, and Pattern Recognition Receptors, such as IFN-β that induces IL-23 overexpression. This is very interesting, because the increase in IL-23 will stimulate Th17 to secrete IL-17. Th17 and its cytokines affect several immune-mediated inflammatory diseases whilst the IL-23/IL-17 axis is activated in the AS and the SpA (Colbert et al. 2009).

Various research reports on IL-17 further reinforced the alleged role of IL-17 in the pathogenesis of SpA. Chen et al. (2012) found a significant association between IL-17 and SpA disease activity in their study. IL-17 causes clinical manifestations and symptoms that are characteristic of SpA, such as pain, axial and peripheral joint inflammation, enthesitis, cartilage degradation, and new bone formation. Therefore, the hypothesis that IL-17 correlates to SpA disease activity was progressively being proven.

Strength and limitation

In this study, as the correlation between IL-17 level and SpA disease activity appeared to be strong, this study further supported the notion of IL-17 being a highly favourable biomarker for disease activity in SpA in the future. However, this study was conducted using cross-sectional design due to timeline and resource limitations. Therefore, the results could not describe the fluctuation in IL-17 level and its correlation with the course of the SpA as the subjects were not followed up prospectively. Finally, as the study was conducted at the Outpatient Clinics, Dr. Soetomo General Academic Hospital, Surabaya, that was relatively isolated considering the limited sample numbers, the report was unable to represent the general community's situation.

CONCLUSION

IL-17 level strongly correlated to the disease activity in SpA patients evaluated using the ASDAS-CRP system. As the correlation goes unidirectionally, the elevated IL-17 level in patients with SpA resulted in higher ASDAS-CRP score reflected through worsening disease activity in SpA patients. However, the result of this study was unable to fully represent the condition of the more general population conducted in an isolated setting with limited samples.

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Conflict of interest

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Author contribution

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REFERENCES

Appel H, Maier R, Wu P, et al (2011). Analysis of Il-17+cells in facet joints of patients with spondyloarthritis suggests that the innate immune pathway might be of greater relevance than the th17-mediated adaptive immune response. Arthritis Research & Therapy 13, 1-9.

Arican O, Aral M, Sasmaz S, et al (2005). Serum levels of Tnf-alpha, Ifn-gamma, Il-6, Il-8, Il-12, Il-17, and Il-18 in patients with active psoriasis and correlation with disease severity. Mediators Inflamm 2005**,** 273-279.

Ballantyne FC, Fleck A, Dick WC (1971). Albumin Metabolism in rheumatoid arthritis. Annals of The Rheumatic Diseases 30**,** 265-270.

Baraliakos X, Kiltz U, Heldmann F, et al (2014). Thu0108 different performance of the major disease activity measures asdas and basdai in patients with axial spondyloarthritis treated with non-steroidal anti-inflammatory agents (Nsaids) - Results from a prospective study. Annals of The Rheumatic Diseases 73**,** 214-215.

Braun T, Zwerina J (2011). Positive regulators of osteoclastogenesis and bone resorption in rheumatoid arthritis. Arthritis Research & Therapy 13**,** 1-11.

Chabaud M, Garnero P, Dayer J-M, et al (2000). Contribution of interleukin 17 to synovium matrix destruction in rheumatoid arthritis. Cytokine 12**,** 1092-1099.

Chen W-S, Chang Y-S, Lin K-C, et al (2012). Association of serum interleukin-17 and interleukin-23 levels with disease activity in chinese patients with ankylosing spondylitis. Journal of The Chinese Medical Association 75**,** 303-308.

Chowdhury S, Dijkhuis A, Steiert S, et al (2013). Il-17 attenuates degradation of are-mrnas by changing the cooperation between au-binding proteins and microrna16. Plos Genetics 9**,** 1-13.

Ciprandi G, Fenoglio D, De Amici M, et al (2008). Serum Il-17 levels in patients with allergic rhinitis. Journal of Allergy And Clinical Immunology 122**,** 650-651.

Colbert RA, Delay ML, Layh-Schmitt G, et al (2009). Hla-B27 misfolding and spondyloarthropathies. Prion 3**,** 15-26.

Dincer U, Cakar E, Kiralp MZ, et al (2008). Diagnosis delay in patients with ankylosing spondylitis: possible reasons and proposals for new diagnostic criteria. Clin Rheumatol 27**,** 457-462.

Dougados M, Maetzel A, Mijiyawa M, et al (1992). Evaluation Of sulphasalazine in the treatment of spondyloarthropathies. Annals of The Rheumatic Diseases 51**,** 955-958.

Dudler J, Renggli-Zulliger N, Busso N, et al (2000). Effect of interleukin 17 on proteoglycan degradation in murine knee joints. Annals of The Rheumatic Diseases 59**,** 529-532.

Ehrenfeld M (2012). Spondyloarthropathies. Best Practice & amp; Research. Clinical Rheumatology 26**,** 135-145.

Gallinaro A, Ventura C, Sampaio-Barros P, et al (2010). Spondyloarthritis: Analysis of a Brazilian series compared with a large ibero-american registry (respondia group). Revista Brasileira De Reumatologia 50**,** 581-589.

Honorati MC, Bovara M, Cattini L, et al (2002). Contribution Of interleukin 17 to human cartilage degradation and synovial inflammation in osteoarthritis. Osteoarthritis and Cartilage 10**,** 799-807.

Hot A, Miossec P (2011). Effects of interleukin (Il)-17a and Il-17f in human rheumatoid arthritis synoviocytes. Annals of The Rheumatic Diseases 70**,** 727-732.

Hussein MR, Fathi NA, El-Din AME, et al (2008). Alterations of the Cd4+, Cd8+ T cell subsets, interleukins-1β, Il-10, Il-17, tumor necrosis factor-A and soluble intercellular adhesion molecule-1 in rheumatoid arthritis and osteoarthritis: preliminary observations. Pathology & Oncology Research 14**,** 321-328.

Jeffrey AO, Bambang S, IdaArthur O, et al (2010). Correlation of interleukin-17 with disease activity and hand joint damage in patients with rheumatoid arthritis. Indonesian Journal of Rheumatology 2, 26-30.

Julija Z, Inita B, Liene N-Z, et al (2013). A10.18 lack of association of serum interleukin-17 and interleukin-23 levels with disease activity in patients with ankylosing spondylitis in Latvia. Annals of The Rheumatic Diseases 72**,** A78-A78.

Kay J, Morgacheva O, Messing SP, et al (2014). Clinical disease activity and acute phase reactant levels are discordant among patients with active rheumatoid arthritis: acute phase reactant levels contribute separately to predicting outcome at one year. Arthritis Research & Therapy 16**,** R40-R40.

Koenders MI, Kolls JK, Oppers-Walgreen B, et al (2005). Interleukin-17 receptor deficiency results in impaired synovial expression of interleukin-1 and matrix metalloproteinases 3, 9, and 13 and prevents cartilage destruction during chronic reactivated streptococcal cell wall-induced arthritis. Arthritis Rheum 52**,** 3239-3247.

Machado P, Landewé R, Lie E, et al (2011). Ankylosing spondylitis disease activity score (Asdas): Defining cut-off values for disease activity states and improvement scores. Ann Rheum Dis 70**,** 47-53.

Madej M, Nowak B, Świerkot J, et al (2015). Cytokine profiles in axial spondyloarthritis. Reumatologia 53**,** 9-13.

Mcguckin MA, Eri RD, Das I, et al (2010). Er stress and the unfolded protein response in intestinal inflammation. American Journal of Physiology-Gastrointestinal and Liver Physiology 298**,** G820-G832.

Miossec P, Kolls JK (2012). Targeting Il-17 and Th17 cells in chronic inflammation. Nature Reviews Drug Discovery 11**,** 763-776.

Moz S, Aita A, Basso D, et al (2017). Spondyloarthritis: Matrix metalloproteinases as biomarkers of pathogenesis and response to tumor necrosis factor (Tnf) inhibitors. International Journal of Molecular Sciences 18**,** 1-14.

Onishi RM, Gaffen SL (2010). Interleukin-17 and its target genes: Mechanisms of interleukin-17 Function in disease. Immunology 129**,** 311-321.

Park YE, Woo YJ, Park SH, et al (2011). Il-17 increases cadherin-11 expression in a model of autoimmune experimental arthritis and in rheumatoid arthritis. Immunol Lett 140**,** 97-103.

Petersen AMW, Pedersen BK (2005). The Anti-inflammatory effect of exercise. Journal of Applied Physiology 98**,** 1154-1162.

Pinto LG, Cunha TM, Vieira SM, et al (2010). Il-17 mediates articular hypernociception in antigen-induced arthritis in mice. Pain 148, 247-256.

Richter F, Natura G, Ebbinghaus M, et al (2012). Interleukin-17 sensitizes joint nociceptors to mechanical stimuli and contributes to arthritic pain through neuronal interleukin-17 receptors in rodents. Arthritis & Rheumatism 64**,** 4125-4134.

Ruddy MJ, Shen F, Smith JB, et al (2004). Interleukin-17 regulates expression of the Cxc chemokine Lix/Cxcl5 in osteoblasts: Implications for inflammation and neutrophil recruitment. Journal of Leukocyte Biology 76**,** 135-144.

Rudwaleit M (2010). New approaches to diagnosis and classification of axial and peripheral spondyloarthritis. Current Opinion in Rheumatology 22**,** 375-380.

Siloşi I, Boldeanu MV, Cojocaru M, et al (2016). The relationship of cytokines Il-13 and Il-17 with autoantibodies profile in early rheumatoid arthritis. Journal of Immunology Research 2016**,** 1-10.

Singh R, Aggarwal A, Misra R (2007). Th1/Th17 cytokine profiles in patients with reactive arthritis/undifferentiated spondyloarthropathy. The Journal of Rheumatology 34**,** 2285-2290.

Taams LS, Steel KJA, Srenathan U, et al (2018). Il-17 in the immunopathogenesis of spondyloarthritis. Nature Reviews Rheumatology,14**,** 453-466.

Tayel MY, Soliman E, El Baz WF, et al (2012). Registry of the clinical characteristics of spondyloarthritis in a cohort of the Egyptian population. Rheumatology International 32**,** 2837-2842.

Wang X, Lin Z, Wei Q, et al (2009). Expression Of Il-23 and Il-17 and effect of Il-23 on Il-17 production in ankylosing spondylitis. Rheumatology International 29**,** 1343-1347.

Wendling D, Cedoz J-P, Racadot E, et al (2007). Serum Il-17, Bmp-7, and bone turnover markers in patients with ankylosing spondylitis. Joint Bone Spine 74**,** 304-305.

Woloshin S, Schwartz LM (2005). Distribution of C-reactive protein values in the United States. New England Journal of Medicine 352**,** 1611-1613.

Yago T, Nanke Y, Ichikawa N, et al (2009). Il-17 induces osteoclastogenesis from human monocytes alone in the absence of osteoblasts, which is potently inhibited by anti-Tnf-A antibody: A novel mechanism of osteoclastogenesis by Il-17. Journal of Cellular Biochemistry 108**,** 947-955.

Yang C, Gu J, Rihl M, et al (2004). Serum levels of matrix metalloproteinase 3 and macrophage colony-stimulating factor 1 correlate with disease activity in ankylosing spondylitis. Arthritis and Rheumatism 51**,** 691-699.

Yildirim K, Melikoglu M, Gureser G, et al (2004). Association between acute phase reactant levels and disease activity score (Das28) In patients with rheumatoid arthritis. Annals of Clinical and Laboratory Science 4**,** 423-426.

Zhang S, Li Y, Deng X, et al (2011). Similarities and differences between spondyloarthritis in Asia and other parts of the world. Current Opinion in Rheumatology 23**,** 334-338.