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Levels of Serum Interleukin-6, Tumor Necrosis Factor-α, and Interferon-γin Patients with Tuberculous Spondylitis After Anti-Tuberculosis Drugs Therapy and Its Relationship to Clinical Changes

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Abstract
Background*: This study aims to monitor changes in IFN-γ, TNF-α and IL-6 serum levels in patients with tuberculous spondylitis during oral antituberculosis administration.*
Methods: *With a observational prospective cohort study involving 27 patients with tuberculosis spondylitis treated at Saiful Anwar Hospital, Malang in January-December 2017, serum IFN-γ, TNF-α and IL-6 levels were measured by enzyme-linked immunosorbant assay (ELISA) at the time prior to oral antituberculous therapy, and after 2 months of therapy. Assessed correlation relationship of cytokine levels change compared with clinical change after 2 months of anti tuberculosis drug therapy. The degree of pain was measured by VAS scores and neurologic deficits measured by Frankel score.*
Result: *The mean TNF-α levels increased after 2 months of OAT therapy. Pearson correlation test showed insignificant results with negative correlation relationship between improvement of degree of pain with elevated levels of TNF-α (r=-0.106; p=0.598). Pearson correlation test showed insignificant results with a positive correlation relationship between neurological deficit improvement with elevated levels of TNF-α TNF-α (r=-0.291; p=0.140). The mean IFN-γ and IL-6 levels decreased after 2 months of OAT therapy. Pearson correlation test showed significant result with positive correlation correlation between improvement of degree of pain with decrease level of IFN-γ (r=0.561; p = 0.002) and IL-6 (r=0.591; p=0.001). The Pearson correlation test showed significant results with a positive correlation relationship between neurologic deficit improvement IFN-γ (r=0.570; p=0.002) dan IL-6 (r=0.080; p=0.690).*
Conclusion*: TNF-α levels tend to increase during therapy, but are not significant. IFN-γ and IL-6 levels decreased significantly during oral antituberculous therapy and may be considered for monitoring the success of therapy.*
Keywords*: IFN-γ, TNF-α, IL-6, tuberculous spondylitis,*

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I. Introduction

Tuberculous (TB) spondylitis is an infection of Mycobacterium tuberculosis in the spine (Tuli, 2002). Indonesia ranks third after India and China as the country with the highest TB population (WHO, 2017). At least up to 20 percent of pulmonary TB sufferers experience the spread of extrapulmonary TB. 10% of extrapulmonary TB is osteoarticular TB, and approximately half of patients with osteoarticular TB experience spinal TB infection (Tuli, 2002; Leibert, 2004; Sharma, 2004).

TB spondylitis has a relatively indolent disease course, making it difficult for early diagnosis (Camillo, 2008). This disease has the potential to cause serious morbidity, including neurological deficits and permanent spinal deformity. Often,patients get treatment in advanced conditions where the kyphosis deformity and neurological disability have been relatively irreversible (Sinan, 2004; Cormican, 2006).

The general management of TB spondylitis is chemotherapy with anti-tuberculosis drugs (ATD), immobilization, and orthopedic/nerve surgical interventions (Sinan, 2004; Camillo, 2008). The administration of anti-tuberculosis drugs is the best initial treatment option in the initial phase, but there is no ideal duration of treatment for ATD administration and no standard method for monitoring TB spondylitis therapy, so that many patients require longer ATD therapy (Sharma, 2004). Various studies have been conducted to evaluate the effectiveness of the approach to handling TB spondylitis with diverse results and recommendations.

The role of cytokines as biomarkers of TB disease activity has been widely investigated. Both proinflammatory and anti-inflammatory cytokines play an important role in the development and control of

infection by MTB (Patil, 2014). This is indicated by different cytokine profiles in various stages of the disease (Fiske, 2012). Wong et al (2003) show that the examination of IL-6, TNF-α, and IFN-γ cytokines in pleural fluid can be used to diagnose pleural TB; IL-6 levels have a correlation with clinical improvement after therapy (Wong, 2003). Mattos et al. (2009) found that IgG1, IL-6, and IFN-γ levels in patients with active pulmonary TB decreased significantly after chemotherapy (Mattos, 2010) . Patil et al (2014) concluded in their study that TNF-α, IFN-c, CSF MMP-9 and IL-10 levels have a correlation with clinical improvement in the degree of disability of TB spondylitis patients after chemotherapy (Patil, 2014). The study conducted by Jiang et al found that IL-8, IL-15 and IP-10 can be used as biomarkers for the diagnosis of osteoarticular TB (Jiang, 2017). The understanding of protective immunity against M. tuberculosis infection is still incomplete. At present, there are no biomarkers that can quickly monitor the response to therapy.

Based on the above background, the researcher proposed a study to measure the levels of IL-6, TNF-α and IFN-γ cytokines in TB spondylitis and determine the effect of ATD treatment on cytokine levels associated with clinical improvement in patients.

II. Material And Method

Material

The design of this study was observational cohort. This study was carried out in vivo in patients with tuberculous spondylitis. Patients who have been diagnosed with TB spondylitis underwent clinical evaluation, CRP and LED laboratory tests and measurements of the levels of serum interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α) and interferon-γ (IFN- γ). Examination was carried out at the initial evaluation or before treatment, followed by re-examination in the 2nd and 6th month during the treatment of Anti Tuberculosis Drugs. Patients were recommended for bed rest and spinal stabilization was performed as indicated.

Research Design

Reachable population was patients with diagnosis who carried out examination and treatment at the general surgery poly of Saiful Anwar Hospital. The sample was taken by consectives sampling (non random sampling) where all subjects who met the inclusion and exclusion criteria were included in the study until the required number of sample was met.

Research Procedure

The collected data were primary data from patients treated with a diagnosis of tuberculous spondylitis at the General Surgery Poly of Saiful Anwar Hospital Malang during the study period. Laboratory tests for the levels of IL-6, TNF-α, and IFN-γ were carried out at the Clinical Pathology laboratory, Faculty of Medicine, Brawijaya University Malang. Each prospective sample wasrequired to fill out a questionnaire. The prospective samples for the TB spondylitis group who met the inclusion and exclusion criteria were required to fill out informed consent. Patients with TB spondylitis group was clinically examined for the degree of pain scored using VAS (Visual Analog Scale) and neurological deficits, as well as examination of serum IL-6, TNF-α, and IFN-γ cytokines. After that, the patient followed 2 months of ATD treatment, and clinical and serum cytokines re-examinations were performed.

Re-examination was carried out at months 0 and 2 during treatment. Data were in the form of clinical data and the levels of serum cytokines were tested using statistical analysis test. The data collection procedure follows the flow chart shown in the figure below:

III. Result

Since January - December 2017, observational cohort study has been carried out on 27 cases of tuberculous spondylitis that met the inclusion criteria. The characteristics of the study population can be seen in the following table:

Table8 Characteristics of Patient

Characteristics of Patient		**TB Spondylitis (n=27)**
Gender	Male	8 (29.6%)
	Female	19 (70.4%)
Age	< 20 years	4 (14.8%)
	20 – 39 years	15 (55.6%)
	40 – 59 years	7 (26%)
	> 60 years	1 (3.7%)
Clinical Symptom	Fever	18 (66.7%)
	Weight Loss	82%
	Pain	27 (100%)
Radiological Picture	Involvement of ≤ 2 vertebral sites	18 (66.7%)
	Involvement of > 2 vertebral sites	9 (33.3%)

Source: Result of Research Data

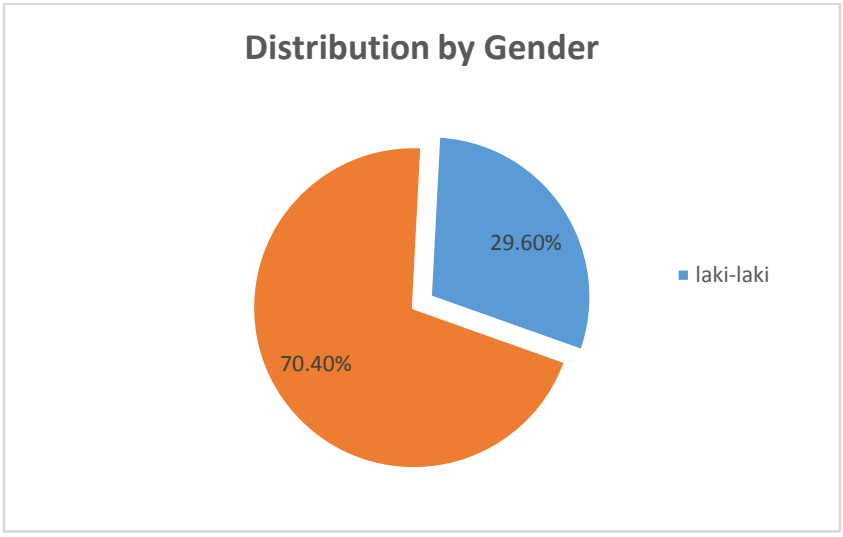

Figure 6. Distribution by gender of the research subject (Source: Research Data)

Levels of interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6)

The levels of serum IFN-γ before treatment (0th month) had the lowest value of 145 pg/ml and the highest value was 241 pg/ml with an average of 196.36 pg/ml. In 2nd month of ATD administration, the level of serum IFN-γ was the lowest by 46 pg/ml and the highest level was 102 with an average of 72.926 pg/ml. The average level of IFN-γ decreased in 2nd month of ATD administration.

The level of serum TNF-α before treatment (0th month) had the lowest value of 46.74 pg/ml and the highest value was 81.64 pg/ml with an average of 63.54 pg/ml. In 2nd month of ATD administration, the level of serum TNF-α was the lowest by 103.55 pg/ml and the highest level was 129.72 pg/ml with an average of 119.01 pg/ml. The average level of IFN-γ increased in 2nd monthof Atd administration.

The level of serum IL-6 l before treatment (0th month) had the lowest value of 8.06 pg/ml and the highest value of 12.67 pg/ml with an average of 10.00 pg/ml. In 2nd month of ATD administration, the level of serum IL-6 was the lowest by 3.16 pg/ml and the highest level was 10.56 with an average of 5.55 pg/ml. The average level of IL-6 decreased in 2nd monthof ATD administration.

Table 9 Average levels of IFN-γ, TNF-α, IL-6 in Tuberculous Spondylitis of patients before ATD and 2 months after ATD

Variable	0th month (pg/ml)	2nd month (pg/ml)	Change (Δ)
Level of IFN-γ	194.70	72.92	48.86
Level of TNF-α	63.54	119.00	55.46
Level of IL-6	10.00	5.55	4.45

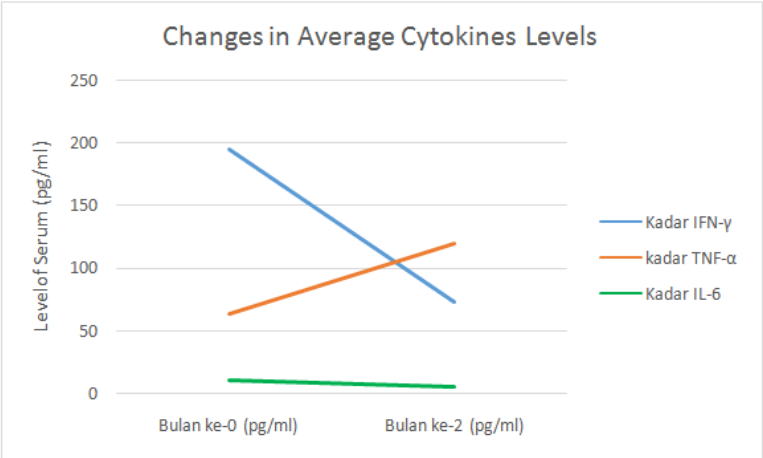

Figure10. Changes in the average levels of serum IFN-γ, TNF-α, and IL-6 cytokines in patients with TB Spondylitis before the ATD administration and2 months after the ATD administration (source: Research Data)

Analysis of the relationship between the levels of IFN-γ, TNF-α, and IL-6 with Clinical Improvement of Patients with TB Spondylitis

5.3.1 Relationship between the levels of IFN-γ, TNF-α, and IL-6 with fever

Clinical Parameter	IFN- γ (pg/ml)	TNF-α (pg/ml)	IL-6 (pg/ml)
Fever (n=18)	194.33	65.01	10.67
No Fever (n=9)	195.44	60.58	8.68

Relationship between the levels of IFN-γ, TNF-α, and IL-6 with the number of destructed vertebrae bones

Table 11. Comparison of average levels of serum IFN-γ, TNF-α, and IL-6 with the number of vertebral bones undergoing destruction in TB spondylitis before ATD therapy

Clinical Parameter	IFN- γ (pg/ml)	TNF-α (pg/ml)	IL-6 (pg/ml)
Lesions of ≤ 2 vertebrae (n=18)	179.94	62.33	10.09
Lesions of>2 vertebrae (n=9)	224.22	65.94	9.84

Relationship between changes in the levels of IFN-γ, TNF-α, and IL-6 with degrees of pain

Table12. Result of Pearson correlation test on changes in the levels of IFN- γ, TNF-α, and IL-6 with degrees of pain (VAS)

Variable	Pearson correlation (r)	Significance (p)
IFN- γ	0.561	0.002
TNF-α	0.106	0.598
IL-6	0.591	0.001

Relationship between the changes in the levels of IFN-γ, TNF-α, and IL-6 with neurological deficits

Table13. Result of the Spearman correlation test on changes in the levels ofIFN- γ, TNF-α, and IL-6 with neurological deficits

Variable	Spearman correlation (r)	Significance (p)
IFN- γ	0.570	0.002
TNF-α	0.291	0.140
IL-6	0.080	0.690

IV. Discussion

This study used 23 TB spondylitis patients as research subjects. 19 patients (70.4%) as subjects aged < 40 years. This was similar to the prevalence of TB spondylitis in developing countries, where it was mostly found at a young age (Lauerman, 1996). 18 patients (66.7%) developed bone tuberculosis in the thoraco-lumbar area. In the existing study, it was stated that the thoraco-lumbar area, especially the lower thoracic region (generally T 10) and upper lumbar region were the most frequently involved because in these regions, the mobility and pressure of the weight bearing reached a maximum, followed by the cervical and sacral areas (Miller, 1997; Savant, 1999).

At the initial diagnosis of TB spondylitis, 18 patients (66.7%) complained of a mild fever and the rest did not. The average levels of IFN-γ and TNF-α cytokines between patients who had fever and no fever were not much different. It was found that the average level of IL-6 was higher in patients with fever (10.67 pg/ml) compared to patients without fever (8.68 pg/ml). Fever complaints are obtained from previous clinical history or anamnesa. IFN-γ, TNF-α and IL-6 create proinflammatory reactions, mainly IFN-γ and IL-6 which play a role in the acute phase response where symptoms can occur, one of which is fever (Cao, 2017; Mootoo, 2007).

18 (66.7%) patients experienced bone destruction lesions in more than 2 vertebrae. There was no difference between the average levels of TNF-α and IL-6 between groups of patients with lesions in > 2 vertebrae and lesions in ≤2 vertebrae, but there were differences in average level of IFN-γ. The average level of IFN-γ was higher in patients with bone destruction lesions in> 2 vertebrae. This was in accordance with the study conducted by Patil et al., stating that TB spondylitis patients with worse clinical manifestation have higher IFN-γ and higher IFN-γ levels were associated with the degree of tissue damage (Patil et al, 2014).

The clinical manifestations assessed in this study were pain and the level of disability. All patients complained of back pain with a degree of pain on the VAS scale of 4-6 before treatment. After ATD administration, the degree of pain decreased. The degree of neurological deficit was measured using Frankel's score. Before ATD administration, 70.4% of patients had complaints of motor and sensory disorders with various Frankel scores (A = 11.1%; B = 3%; C = 29.6%; D = 25.9%, E = 29.6%). After 2 months of ATD administration, there was an improvement in the nerulogic level where 59.2% of patients had E score or normal.

Based on these data, it can be concluded that the administration of ATD for 2 months had a positive effect on clinical improvement, namely degrees of pain and neurological deficit in patients with TB spondylitis.

TB spondylitis patients usually complain of non-specific local pain in the infected vertebral region and experience destruction. Pain can be caused by a local inflammatory reaction in the infected bone, radicular pain due to neurological deficits arise or are caused by compression lesions due to bone destruction (Vitriana , 2002; Jain, 2010; Zuwanda, 2013).

The body's immune system against anti-tuberculosis works by phagocytosing microbacteria on the intertitial. These cells also stimulate the immune system's auto-protective mechanism which then strengthens phagocytosis and digestion of tubercle bacilli by macrophages, thereby suppressing reproduction and the spread of tubercle bacilli (Flynn, 2001). ATD works by inhibiting the development of bacteria, both by eliminating the acid-fast bacteria, bactericidal in acidic to bacteriostatic conditions under normal condition (He, 2016).

In this study, there was a significant relationship between changes in the decreasing levels of IFN-γ and IL-6 ($\alpha = 0.007$ and $\alpha = 0.006$) with improvement in pain after 2 months of ATD therapy. The levels of these two cytokines had a correlation with changes in pain complained by the patients. This result was in accordance with the study conducted by Patil et al. examining cytokine profiles in TB spondylitis, including IFN-γ and IL-6 whose levels decreased in the administration of ATD, and the high IFN-γ level was associated with clinical deterioration in patients. In addition, the high level of interleukin at the initial treatment indicated the level of immunological response in patients, where-Interleukin-6 can play a role in the protective immune response.

In this study, there was a significant relationship between changes in the decreasing levels of IFN-γ and IL-6 ($\alpha = 0.018$ and $\alpha = 0.002$) with improvement in disability after 2 months of ATD therapy. The level of patient disability was measured using the Frankel score. In the second month after ATD administration, 93% of the research subjects experienced improvement in disability, where the Frankel score was normal. This result was in accordance with the study conducted by Patil et al. examining cytokine profiles including IFN-γ and IL-6 which decreased with improvement in neurological deficits as measured by the Modified Barthel Index (MBI) (9). In addition to showing the level of immune response at the initial bacterial infection, the high level of Interleukin6 at the onset can appear due to the high level of tissue damage caused by mycobacterium. Proinflammatory cytokines such as IL-1, IL-6 and TNF-α have long been known to involve in early periods of fracture healing and bone remodeling. Interleukin6 is not only related to natural tissue responses to injury or bacterial challenges, but also increases extracellular matrix synthesis, stimulates angiogenesis, attracts mesenchymal cells to the site of injury and plays a crucial role in callus formation through osteoclastogenesis (He, 2016). In another study, it was stated that lipopolysaccharides inducing synthesis of Interleukin 6 plays a role in the process of bone resorption. Decreased levels of interleukin 6 accompanied by clinical improvement can show that bacterial infections and the process of damage are reduced and undergo improvement.

IFN-γ contributes to the protection of intracellular pathogens by activating macrophages. IFN-γ activates several antimicrobial functions that suppress MTB replication after undergoing infection with high multiplication rates (Ferrara, 2009). IFN-γ is the main activator of macrophages, and together with TNF-alpha, it stimulates the production of nitric oxide synthase (N)S-2) which has bactericidal ability to MTB. IFN-γ together with LRG-47 (new p47 GTPase) is able to increase autophagy processes in macrophages by obstructing MTB survivability in cells (Gutierrez, 2004; Cooper, 2009).

IL-6 is mainly secreted by monocytes. Other studies have shown that IL-6 levels in patients with TB spondylitis are higher than in healthy people. Clinically, TB spondylitis provides manifestations as erosive bone disease, which indicates a close relationship between osteoporosis and intervertebral disc lesions in TB spondylitis. IL-6 is a proinflammatory cytokine resulting in pathological changes in the intervertebral disc and induces an autoimmune mechanism by regulating changes in inflammatory cytokines (Cao, 2017). IL-6 plays a role in the acute phase response to MTB infection and plays a role in the process of antibody formation by B cells, and stimulates the proliferation of cytotoxic T cells (CTL).

In this study, there was no significant relationship between changes in TNF-α levels and improvement in pain and neurological deficits after 2 months of ATD therapy ($\alpha = 0.719$ and $\alpha = 0.140$). Previous studies examining cytokine profiles of TNF-α in TB spondylitis showed various results. Jiang et al. examining cytokines as a diagnostic tool for osteoarticular TB showed that an increase in TNF-α levels was not significant in this case. The result was not in accordance with the study conducted by Cao et al. that changes in TNF-α levels in TB spondylitis had a significant clinical significance.

TNF-α is a cytokine with diverse biological activities and acts as a regulator in the immune system. Some of the roles of TNF-α include stimulating cells to produce preotease and prostaglandin, pro-inflammation by stimulating vascular permeability, and absorption functions by inducing bone resorption. TNF-α is an inflammatory mediator that plays a role in cancellous bone damage and causes intervertebral disc destruction. The study of Cao et al. stated that TNF-α can form a pathway that allows the absorption and differentiation of osteoclasts. Through this pathway, TNF-α induces osteoblasts to express macrophage colony-stimulating factor and NF-kB receptor activator, which ultimately results in bone lesions, resulting in intervertebral disc necrosis and loss of intervertebral space. TNF-α directly affects peripheral tissues and blood, lymph vessels and nerves,

thus inhibiting nutrient diffusion in the intervertebral disc between the vertebral bodies. As a result, inflammatory cells are formed and regeneration of TNF-α increases (Cao, 2017).

In this study, the average levels of TNF-α decreased after administration of ATD in the second month, but the results of statistical analysis showed that this decrease did not have a significant relationship with clinical improvement, namely the degree of pain and disability (Frankel score). The profile of each cytokine is different at various stages of tuberculosis infection. The limitation of this study was that the measurement time was relatively short, which was done only 2 times, the 0th month and the 2nd month. For this reason, the researcher suggest that further research is needed to assess cytokine profiles, especially TNF-α during ATD treatment, given that the administration of ATD in TB spondylitis requires a duration of 6-9 months.

V. Conclusion

Changes in the levels of interleukin-6 (IL-6) and interferon-γ (IFN-γ) cytokines had a positive correlation with clinical improvement of the degree of pain and neurological deficits in patients with tuberculous spondylitis receiving anti-tuberculosis drug therapy for 2 months.There was no significant relationship between changes in the level of tumor necrosis factor-α (TNF-α) cytokine and clinical improvement of the degree of pain and neurological deficit in patients with tuberculous spondylitis receiving anti-tuberculosis drug therapy for 2 months.

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