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Relationship of Interleukin (IL-10) Level to Sputum Conversion and Influence Factors in Drug-Resistant Tuberculosis

Irawaty Djaharuddin[1], Harun Iskandar[1], Nur Ahmad Tabri[1], Erwin Arief[1], Jamaluddin Madolangan[1], Etien Andriani[1]

[1]Department of Pulmonology and Respiratory Medicine, Medical Faculty Hasanuddin University-Dr. Wahidin Sudirohusodo General Hospital Makassar, Indonesia

Corresponding Author: Irawaty Djaharuddin

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ABSTRACT

Introduction: Pulmonary tuberculosis (TB) is an infection causative agent of Mycobacterium tuberculosis. Indonesia is in fifth place with drug-resistant tuberculosis. The achievement of TB management is surprisingly dependent on the analysis, suitable remedy, and comparing its remedy. Many TB patients who are present process similarly anti-tuberculosis remedies have issued sputum elimination for acid-resistant bacillus smear examination so that the healing display is not optimal.
Objective: The study analyzes the relationship between interleukin 10 (IL-10) level and sputum conversion and influence factors in drug-resistant tuberculosis.
Methods: A total of 45 resistance tuberculosis mycobacterium with inclusion criteria are 18-65 years old, shorter regimen, acid-fast bacilli sputum conversion, and serum IL-10 levels were recorded in the medical record—the research analytic observational with a retrospective cohort design.
Results: Interleukin 10 levels show that the higher the anti-inflammatory response, the faster the sputum conversion occurs. It can be a marker of the weakened immune response of Th1 to MTB infection. Based on the AFB sputum conversion, other studies supported that the increase of IL-10 levels in serum could be used as a prognostic marker of the therapeutic success of TB. Cut off point IL-10 level in this study was 5,83 pg/ml with 94,29% sensitivity and 100% specificity in predicting conversion time.
Conclusion: The higher IL-10 production in TBRO indicates suppression of immune response. Comorbid factors of diabetes mellitus and initial bacterial load affect the sputum conversion influence of TBRO patients.

Keywords: Interleukin 10, influence factor, TBRO, conversion

INTRODUCTION

Tuberculosis (TB) is caused by Mycobacterium tuberculosis (M.tb) infection. Pulmonary tuberculosis is still an important health problem in the world because this disease affects millions of people and is the second leading cause of death among infectious diseases, after Human Immunodeficiency Virus (HIV). There were nine million new instances in 2011 and 1.4 million deaths because of TB. WHO states that out of twenty-two international locations with an excessive burden of TB (excessive burden country), Indonesia is in fourth place (after India, China, and South Africa) with a TB occurrence of 289 in line with the 100,000 population, a TB prevalence of 189 in line

with 100,000 population, and a 27 in line with 100,000 population.[1] Multi-drug resistant tuberculosis (MDR-TB) is an in vitro resistance to isoniazid (H) and rifampicin (R).[2] In Indonesia, it was described as resistance to, as a minimum, H and R simultaneously, without or with resistance to different first-line anti-tuberculosis (OAT) drugs. Three data from WHO indicate the superiority is improved annually. Worldwide, there are 3.7% new MDR-TB instances and 20% MDR-TB with records of preceding OAT treatment. [3]

The immune response required to control M. tuberculosis infection was regulated by various cytokines, chemokines, and immune regulatory elements that participate in the immune system and the inflammatory response that influences the disease. There is some evidence that overexpression of Th2 cytokines increases the severity of TB. Observing Mtb strains that induce Th2 cytokine expression, less virulent strains induce Th1 cytokines, including IFN-γ and TNF-α. The expression of IL-10 cytokines during the immune response against M. tuberculosis appears during later stages compared to other cytokines that suppress various inflammatory and Th1 cytokines. Dendritic cells, macrophages, and lymphocytes are the primary sources of IL-10 present in several diseases.[4,5] In this resource hypothesis, high levels of Interleukin 10 (IL-10) accelerate the conversion of TBRO treatment sputum.

METHODS

This study was an analytical observational with a retrospective cohort design. The population was newly diagnosed patients with pulmonary tuberculosis drug resistance. Patients confirmed by molecular rapid test sputum, 18-65 years old, underwent treatment shorter regimen and visits at the respiratory polyclinic at Labuang Baji Hospital registered during 2019, conducted from September to October 2021. Serum IL-10 levels were recorded in the medical record. The sampling technique used was total sampling.

There were 45 blood samples of pulmonary tuberculosis drug resistance patients in this study. This research included pulmonary tuberculosis drug resistance patients willing to participate in the research, with exclusion criteria of HIV, drug resistance extrapulmonary, stop treatment, or died before four months of treatments. The research subjects received informed consent explaining the purpose of sampling and obtaining approval to be employed in this research. This study was conducted with the permission of the Research Ethics Commission of the Faculty of Medicine, Hasanuddin University, with approval recommendation Number: 686/UN4.6.4.5.31/PP36/2021. Protocol No: UH21090615.

Lung tuberculosis drug resistance is proof based on rapid molecular test resistance to rifampicin. Intensive phase treatment is an early phase of lung TB treatment (the first four months). It rapidly reduced the number of MTB infections and minimalized the risk of transmission. Serum IL-10 levels were done in HUMR-C laboratory, using ELISA biotech, with a detection range of 15,63-1000pg/mL. Body mass index (BMI) in kg/m2 was grouped by underweight (<18.5), normal (18.5 – 24.9), and overweight (>25). AFB sputum conversion converts from positive to negative. AFB sputum uses Ziehl-Neelsen and is classified as negative (no BTA on 100 fields of view), the number of bacteria (1-9 BTA on 100 fields of view), 1+ (10-99 BTA on 100 fields of view), 2+ (1 -10 BTA on one field of view), and 3+ (> 10 BTA on one field of view).

Bivariate analysis used an independent sample t-test, Mann-Whitney, Kruskal Wallis, X2 (Chi-square) test. The Mann-Whitney test was used for an unpaired group for abnormally distributed ordinal or numerical variables. The receiver operator curve (ROC) was used to determine a prognostic value (PLR/ NLR/ PNI score). X2 test or Fisher Exact test was used to compare categorical data.

RESULTS

The study subjects had been carried out, and 45 medical records were collected and met the inclusion and exclusion criteria of the study. The characteristics of the subjects in this study are presented in Table 1.

Table 1. Characteristics of the study sample.

Variables	**N (%)**
Gender	
Male	27 (60)
Female	18 (40)
Age	
18 - 25 years old	5 (11,1)
26 - 45 years old	18 (40)
> 45 years old	22 (48,9)
Education level	
Elementary / Equal	9 (20)
Junior high school / Equal	11 (24,4)
Senior high school / Equal	23 (51,1)
S1/ Equal	2 (4,4)
Treatment criteria	
Relapse	26 (57,8)
New	19 (42,2)
Body Mass Index	
Underweight	27 (60)
Normal	16 (35,6)
Overweight	2 (4,4)
Diabetes Mellitus comorbid	
Yes	11 (24,4)
No	34 (75,6)
AFB (0 month)	
Scanty	3 (6,7)
1+	13 (28,9)
2+	19 (42,2)
3+	10 (22,2)
Resistant pattern	
Monoresistence	5 (11,1)
Poliresistence	7 (15,6)
Multidrug.resistance	28 (62,2)
Rifampisin resistance	5 (11,1)
Conversion	
Yes	35 (77,8)
No	10 (22,2)

Table 2. The Factor that influences conversion sputum

Diabetes mellitus	**Conversion**					**P Value**
	Yes			**Not**		
	N	**%**		**N**	**%**	
Diabetes mellitus (N=11)	1	9,1		10	90,9	0.00*
Not Diabetes mellitus (N=34)	34	100		0	0	

*p-value obtained by X^2 (Chi-square) test

Table 2 illustrates that subjects with comorbid diabetes mellitus have as many as 11 samples. The group that experienced a conversion of only one person (9.1%) and who did not experience a conversion of 10 people (90.9%). This result illustrates that the condition of subjects with comorbid diabetes mellitus can prolong statistically significant sputum conversion ($p<0.05$).

Table 3. Acid fast bacilli with sputum conversion

AFB Sputum	IL-10 (pg/ml)		P Value
	Mean±SD (pg/ml)	Median (min-max) (pg/ml)	
Scanty	25,21±36,81	3,97 (3,94-67,72)	**0,025***
1+	39,65±28,17	33,58 (6,89-78,44)	
2+	19,82±19,28	12,12 (3,89-70,67)	
3+	12,01±9,23	10,10 (3,90-32,05)	

***p*-value obtained by Kruskal Wallis test**

In the initial examination of this study, microbiological examinations (acid-fast bacilli sputum and drug sensitivity tests were also carried out) were also performed (Table 3). The results of the examination of acid-fast bacilli (BTA) sputum at the beginning were degraded in the number of bacteria per field of view. In this study, 19 people (42.2%) found 1-10 AFB per field of view (2+), as many as 13 people (28.9%) found 10-99 AFB in 100 visual fields (+1), as many as ten people (22.2%) found more than 10 AFB per field of view (3 +) and as many as three people (6.7%) found 1-9 AFB in 100 visual fields.

Levels increased with the decrease in the density of TB bacilli in sputum smear examination, with a median value of IL-10 levels in the group sputum AFB 1+ is higher than the sputum AFB 2+ group and sputum smear group 3+. The BTA 1+ group had a median value of IL-10 of 33.48 pg/ml with a minimum value of 6.89 pg/ml and a value of a maximum of 78.44 pg/ml. Statistically, the relationship between levels of interleukin 10 (IL-10) means (< 0.05).

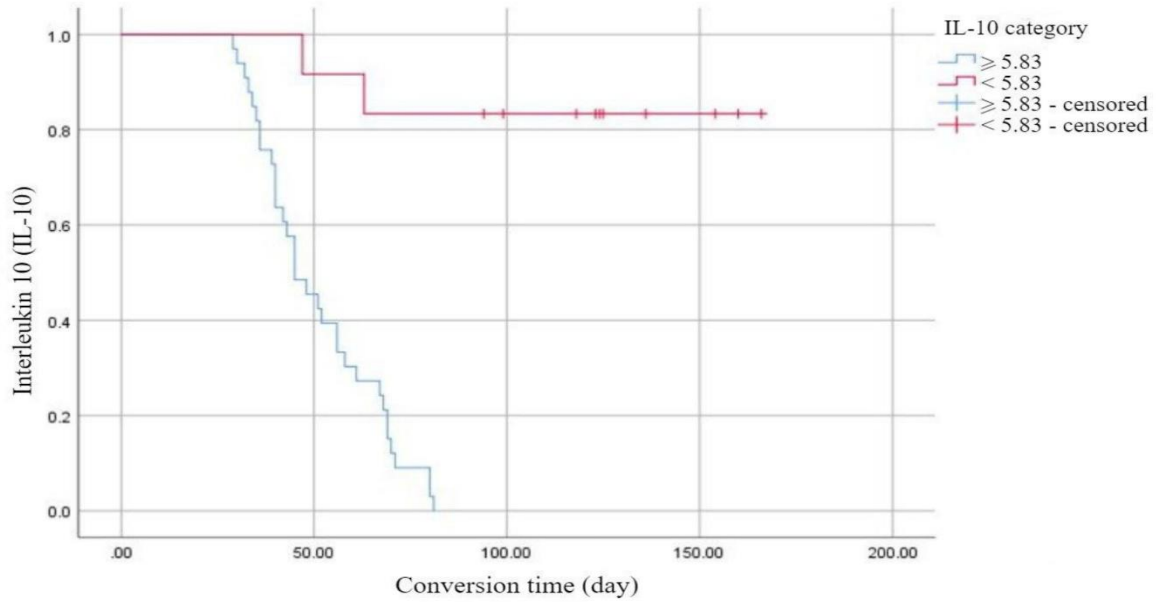

Figure 1. The relationship between IL-10 levels and initial sputum smear examination

From Kaplan Meier's analysis, there was a significant difference from time to time conversion based on IL-10 increase with median conversion time sputum. In patients who have IL-10 levels (≥5.83 pg/ml) require an estimated time of 51 days. 50% of the total conversion can occur overall. In comparison, the IL-10 level (<5.83 pg/ml) takes time estimated 96 days longer to experience conversions than 50% of the total in the treatment of TBRO (Figure 1).

DISCUSSION

In this study, the Receiver Operating Characteristics (ROC) curve IL-10 is associated with sputum conversion time

showing a sensitivity AUC value of 0.987 (p <0.05) by displaying a cut-off point of 5.83 pg/ml in predicting conversion time. The average concentration of IL-10 measured in the serum of research subjects was found at 21.23 pg/ml with a minimum concentration of 4.33 pg/ml and a maximum concentration of 78.44 pg/ml. Statistically significant (p<0.05). Obeagu et al. (2019) showed that IL-10 was significantly higher in TB. Patients compared to healthy subjects (p<0.05).[6]

In the initial treatment period, high density of sputum bacilli at diagnosis and comorbid diabetes mellitus are factors that we found to be associated with a slower sputum conversion rate. Pajankar (2008) found that sputum with smear 3+ is a significant factor in influencing conversion by evaluating 112 sputum-positive TB cases after DOT.[7] Lee (2014) found that patients with a high bacterial load have a long sputum conversion. So that takes time to clear basil if the basil load is high. This phenomenon is associated with a reduced bactericidal effect of bacteria and reduced sterilization activity of anti-tuberculosis drugs. It takes time for a sputum culture to occur.[8]

Penaloza et al. (2018) explained that IL-10 levels have a dual role in tuberculosis. In RS TB conditions, IL-10 production is required for the host's survival during bacterial infections extracellular. The TBRO IL-10 condition interferes with host survival and bacterial clearance as long as bacteria pro weak intracellular inflammation. During extracellular bacterial infection, some pathogens neutralize or eliminate the effectors of the immune response. IL-10 production modulates the intensity of the immune response and pathogen clearance. The resulting damage to the host tissue is more severe than host survival. IL-10 levels in antibiotic resistance conditions involve hydrolytic enzymes and changes in protein structure or gene expression involved in virulence, such as porins, two-component systems, and others. On polymyxin B drug resistance in infectious pathogens, capsule bacteria recognition by receptors identifiers (PRRs) trigger the production of IL-10 in myeloid cells. Enhancement This resistance is associated with increased virulence and decreased production of TNF-alpha. [9,10]

This study aligns with the theory that the increase in IL-10 levels shows that the higher the anti-inflammatory response, the faster the sputum conversion occurs. It can be a marker of the weakened immune response of Th1 to MTB infection. Based on the AFB sputum conversion, this study and other studies supported that the increase in IL-10 levels in serum could be used as a prognostic marker of the therapeutic success of TB.

This study had a limitation. It only measured the IL-10 levels at the beginning of treatment, and at the end of treatment was not measured, so it cannot assess the dynamics of Il-10 levels in pulmonary TB treatment.

CONCLUSION

The cut-off point of IL-10 levels was 5,83 pg/ml with a 94,29 % sensitivity and 100% specificity. There was a relationship between the higher IL-10 levels with positivity rate and the AFB sputum conversion. A further study is needed to measure the dynamic of IL-10 levels (before and after treatment) associated with the treatment response of lung TB. Comorbid factors of diabetes mellitus and initial bacterial load affect the sputum conversion of TBRO patients.

Declaration by Authors

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