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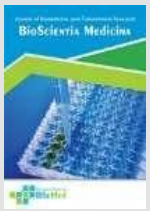

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The Differences in Indoleamine 2,3-dioxygenase 1 Plasma Activity of HIV-Positive Pulmonary Tuberculosis and HIV-Negative Pulmonary Tuberculosis

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A B S T R A C T

Background: Tuberculosis is the most common cause of death in HIV patients. Indoleamine 2,3-dioxygenase 1 (IDO1) is an enzyme that plays a crucial role in the immune response to TB and HIV infection. Increased plasma IDO1 activity in TB patients can be a promising marker for the diagnosis of TB, especially in HIV patients. This study aimed to evaluate the differences in the activity of indoleamine 2,3-dioxygenase 1 plasma of HIV-positive pulmonary TB with HIV-negative pulmonary TB patients. **Methods**: This study is an analytic observational study. Plasma IDO1 activity was assessed by calculating the kynurenine/tryptophan ratio (K/T ratio). This indicator was assessed on 28 lung TB patients divided into two groups, HIV-positive pulmonary TB and HIV-negative pulmonary TB group. **Results:** Twenty-eight subjects were included in this study with a mean age of 42,96 (16,17) years, with more males than females. This study's mean K/T ratio was 0.18 (0.16), with HIV-positive pulmonary TB is higher than HIV-negative pulmonary TB (0.24 vs 0.12, p = 0.027). **Conclusion:** There is a significant difference in the Indoleamine 2,3-dioxygenase 1 (IDO1) plasma in HIV-positive pulmonary TB and HIV-negative pulmonary TB groups. Thus the IDO1 plasma can be used as a new biomarker in diagnosed TB in HIV patients.

1. Introduction

Tuberculosis is the most common cause of death in HIV patients. Based on the Global TB Report 2020, the number of TB patients worldwide in 2019 is estimated at around 10 million people. Meanwhile, TB patients with HIV were positive, about 8.2% of the total cases.[1] High mortality, especially in smear-negative pulmonary TB and extrapulmonary TB, is caused by delays in diagnosis and treatment of TB.[2] Tuberculosis is the most common opportunistic infection in HIV patients. About 50-60% of people living with HIV/AIDS (PLWHA) who are infected with mycobacterium tuberculosis will become ill during their lifetime, while for people with HIV-negative, the risk is much lower at around 10%.[3] Although antiretroviral therapy (ARV) has been shown to protect against TB and reduce the risk, full recovery of the immune response does not occur. In areas with a high TB burden, the incidence rate of TB in HIV patients is still 4.4 times higher despite using ARV therapy and a CD4 cell count of more than 700 cells/µL.[2]

Despite the recent advances in TB diagnosis, missed (undiagnosed or unreported) TB cases in HIV patients are still high. Gupta et al. found that TB accounts for about 40% of HIV-AIDS-related adult

deaths in Sub-Saharan Africa. Nearly half of these cases are found at post-mortem and are undiagnosed at death. These missed cases of TB cause increased morbidity and mortality, and transmission will continue in the community. One of the causes of many missed cases in HIV patients is the low sensitivity of sputum-based diagnostic tests. The sputum-based diagnostic test is one of the weaknesses of current TB/HIV services.[4,5]

To support efforts for early detection of TB cases involving cases with negative smears that are often associated with HIV infection, the World Health Organization (WHO) issued a TB prevention, care, and control strategy for 2015-2035, known as the end TB strategy. This strategy supports the discovery, development, and rapid use of new diagnostic tools for the early diagnosis of TB.[6] The difficulty of diagnosing TB in HIV patients and the low sensitivity of sputum-based tests have led to the need for new testing modalities that are more efficient, inexpensive, fast, and easy to perform. Several immunological biomarkers from non-sputum samples have been developed in recent decades. Measurement of plasma indoleamine 2,3-dioxygenase 1 (IDO1) activity has been proposed as an additional diagnostic tool in TB, especially in the diagnosis of active TB in HIV-positive patients.[7]

IDO1 activity plays a role in the immune response to TB and HIV infection. When infecting the host, Mycobacterium tuberculosis and HIV will affect each other. Although the pathogenesis of TB and HIV infection is different, their coexistence will lead to an increase in disease progression. Tuberculosis infection can increase the replication and persistence of HIV. On the other hand, HIV infection will cause CD4 T cell depletion, which will decrease the immune response to TB infection. In addition, both infections can lead to chronic immune activation that will induce IDO1 activity. A high cumulative increase in IDO1 in TB-HIV co-infection was found in the progression of TB to active TB in HIV patients, so the examination of IDO1 activity could be a promising biomarker to be used to diagnose TB in HIV patients.[8] This study aimed to evaluate the differences in the activity of indoleamine 2,3-dioxygenase 1 plasma of HIV-positive pulmonary TB with HIV-negative pulmonary TB patients.

2. Methods

This study is an analytic observational study. The study was conducted for 6 months at Dr. M. Djamil General Hospital Padang. A total 28 research subjects participated in this study and were divided into 2 groups, HIV-positive pulmonary TB and HIV-negative pulmonary TB. The research sample is the population that meets the inclusion and exclusion criteria. Inclusion criteria were new HIV-positive pulmonary TB patients, new HIV-negative pulmonary TB patients aged > 18 years and willing to participate in the study. Exclusion criteria included patients with autoimmune disease, malignancy, sepsis, pregnancy, organ transplantation, chronic kidney disease, and chronic liver disease. The diagnosis of pulmonary TB is confirmed by the Lowenstein Jensen culture and Gene X-pert test. The diagnosis of HIV is confirmed by serological tests. Plasma IDO1 activity was assessed by calculating the plasma kynurenine/tryptophan ratio. The concentrations of kynurenine and tryptophan were checked by the ELISA method and expressed in μmol/L, respectively. The basic data of the study included age and gender. Numerical data is written in the form of mean and standard deviation. Then the plasma K/T ratio analysis was performed on the patient samples. Numerical data with these two variables were tested by unpaired T-test if the data were normally distributed and the Mann-Whitney test if the data were not normally distributed. This study has been approved by the medical research ethics committee of Dr. M. Djamil General Hospital, Padang, Indonesia.

3. Results

The basic characteristics of the study include gender and age. The description of these characteristics can be seen in table 1. In this study, the research subjects consisted of 18 (64.28%) men and 10 (35.72%) women, with a mean age of 42.96

(16.17) years. In the HIV-positive pulmonary TB group, there were more males than females, namely 78.57% compared to 21.43%, with a mean age of 37.00 (10.64) years. Meanwhile, in the HIV-negative pulmonary TB group, the number of men and women was the same, with an average age of 48.93 (18.80) years.

Table 1. Basic characteristics of patients.

Variable	TB+/HIV+			TB+/HIV-			Total		
	n	%	Mean (SD)	n	%	Mean (SD)	n	%	Mean (SD)
Gender									
Male	11	78,57		7	50,00		18	64,28	
Female	3	21,43		7	50,00		10	35,72	
Age	14		37,00 (10,64)	14		48,93 (18,80)	28		42,96 (16,17)
K/T Ratio	14		0,24 (0,21)	14		0,12 (0,07)	28		0,18 (0,16)

Descriptive analysis was performed on the K/T ratio. This study's average K/T ratio was 0.18 (0.16). The mean K/T ratio in the HIV-positive pulmonary TB group was higher than in the HIV-negative pulmonary TB group (0.24 and 0.12). In this study, the normality test was carried out with the Shapiro-Wilk test, the results of which were not normally distributed. Then a comparison test was carried out with the Mann-Whitney test, with p=0,027. There is a significant difference in the mean K/T ratio in the HIV-positive pulmonary TB and the HIV-negative pulmonary TB group. The difference in the K/T ratio can be seen in Figure 1.

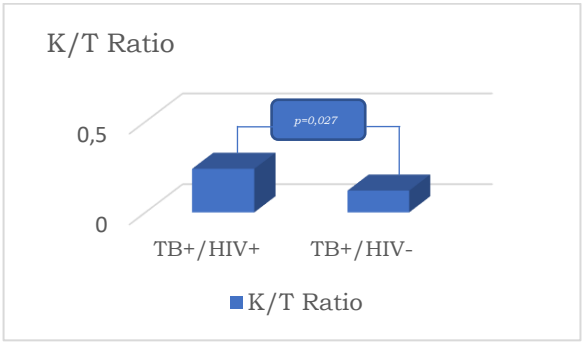

Figure 1. Diagram of the difference in plasma K/T ratio of HIV-positive pulmonary TB and HIV-negative pulmonary TB group.

4. Discussion

This study was conducted to determine differences in plasma IDO1 activity in HIV-negative and HIV-positive pulmonary TB patients. There were more males than females in this study. Globally in 2019, it is estimated that around 10 million people have TB. Approximately 1.2 million deaths from TB in HIV-negative patients and approximately 208,000 deaths in HIV-positive patients. Based on the Global TB Report 2020, there are more male TB sufferers than women, namely 56% compared to 32% women and 12% children.[1] Based on RISKESDAS data, there are more male TB patients than women in Indonesia. This study is also by research by Collins et al., who get fewer women with a percentage of 34.8%.[9,10]

The mean age of the patients in this study was 42.96 (16.17) years. The mean age in this study was higher than the mean age of active TB patients in the study by Adu-Gyamfi et al. and Adu-Gyamfi et al. in South Africa, where in each of these studies, the average age of active pulmonary TB patients was 36 and 38 years.[11,12] Meanwhile, the study by Collins et al. in Georgia found that the median age of active pulmonary TB patients was 31 years. The mean age of HIV-positive TB patients in this study was 37 years.[10] These results are in agreement with the study of

Olsson et al., who obtained the mean age of HIV patients with suspected TB with a median of 35 years.[13]

This study found that HIV-positive pulmonary TB groups had higher plasma IDO1 activity than HIV-negative pulmonary TB groups. This was indicated by the higher K/T ratio in the HIV-positive pulmonary TB group. There was a significant difference in the mean K/T ratio in the HIV-positive pulmonary TB group and the HIV-negative pulmonary TB group based on statistical analysis. These results follow the study by Collins et al., who studied tryptophan catabolism in active pulmonary TB in South Africa and found that the K/T ratio was higher in TB-HIV co-infection.[10] Study by Adu-Gyamfi et al. also obtained the same results as this study, where TB-HIV co-infected patients had a mean K/T ratio that was significantly different from the mean K/T ratio in TB monoinfected patients with a p-value < 0.0001. Previous research by Adu-Gyamfi et al. also found a higher K/T ratio in TB-HIV co-infected patients compared to controls, with a p-value < 0.001.[11,12]

The mean K/T ratio in TB-HIV co-infected patients was higher than in HIV-only or TB-only patients. This is due to the interaction between HIV infection and TB, both causing chronic immune activation, which will increase inflammatory mediators, especially IFN-γ, which will induce an increase in IDO1 activity. Increased IDO1 activity will cause an increase in kynurenine levels and a decrease in tryptophan levels which will then affect T cells so that a condition of immune tolerance occurs. This condition will lead to an increase in HIV and TB infections in patients. HIV infection will cause the activation of TB to become active TB, while an increase in the burden of Mycobacterium tuberculosis will cause an increase in the replication and spread of HIV, which will further worsen the patient's immunity.[8]

5. Conclusion

There was a significant difference in plasma Indoleamine 2,3-dioxygenase 1 (IDO1) activity in the HIV-positive and HIV-negative pulmonary TB groups. The IDO1 plasma can be used as a new biomarker in diagnosed TB in HIV patients.

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