THE EFFECTS OF THE PHASES OF ANTI-TUBERCULOSIS DRUG (OAT) CONSUMPTION ON AST AND ALT ENZYME LEVEL OF PATIENTS WITH PULMONARY TUBERCULOSIS

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ABSTRACT

Pulmonary tuberculosis became one of the ten biggest diseases that caused mortality. In Indonesia, it was ranked second to cause mortality. WHO recommended treatment with anti-tuberculosis drugs (OAT) for at least six months. The treatment consisted of intensive phase (two months) and advanced phase (four months). Long-term treatment might have side effects on liver because OAT was hepatotoxic. The purpose of this research was to find out the effect of anti-tuberculosis drug consumption phase on AST and ALT enzyme levels to monitor hepatotoxic risk. This research was based on secondary examination results on AST and ALT enzyme on 60 patients with pulmonary tuberculosis at Persahabatan Hospital. It was conducted using cross sectional method with statistic Friedman and Wilcoxon Sign Test. AST enzyme levels before treatment, during intensive phase, and during advanced phase were 18.20 U/L, 38.80 U/L, and 24.33 U/L respectively. Meanwhile ALT enzyme levels before treatment, during intensive phase, and during advanced phase were 13.60 U/L, 28.07 U/L, and 14.98 U/L respectively. There was a difference among AST and ALT enzyme levels between before treatment, that during intensive phase, and that during advanced phase (P = 0.000 < 0.05), except ALT level before treatment and during advanced phase (P = 0.317 > 0.05). The findings indicated the effects of anti-tuberculosis drug on AST and ALT levels of patients with tuberculosis. The treatment given during the intensive phase gave the highest hepatotoxic effect. It was because in the phase, combination and frequency of OAT were more than that in the advanced phase.

Keywords: Pulmonary Tuberculosis, AST, ALT, Hepatotoxicity

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INTRODUCTION

Tuberculosis (TB) is one of the communicable diseases caused by Mycobacterium tuberculosis. WHO reported in 2015 tuberculosis became one of ten leading causes in the world. In 2016 10.4 million new tuberculosis cases were globally reported[1]. With 2.8 million cases occurring, India remains to be a country with the most tuberculosis cases. Moreover, Indonesia is ranked second with 1.02 million cases happening[2]. According to Global Tuberculosis Report in 2016 there were 351,893 pulmonary tuberculosis cases occurring in Indonesia. The number was higher than that in 2015 that was 330,729[3].

Pulmonary tuberculosis treatment consists of two stages i.e. intensive and advanced stage[1]. In the intensive stage, antibiotics isoniazid, rifampicin, pyrazinamide, and ethambutol were daily administered for two months. Moreover in the advanced stage antibiotics isoniazid, rifampicin, and/or ethambutol were administered for four months[4]. Although ±85% of TB cases could be successfully

treated, the side effects the treatment caused had degraded its effectiveness[5] .

Hepatotoxicity is the most common side effects that halt treatments given to 11% of patients treated using antibiotics rifampicin, isoniazid, and pyrazinamide combined[5]. 5-28% of patients consuming OAT were reportedly hepatotoxic6. The condition occurs due to damaged hepatocyte cells caused by OAT toxic metabolism[7]. Meanwhile abnormal inflammatory or damaged liver cells can be identified by the liver test function[8]. The most common parameter to identify the liver function is aspartate transaminase (AST) and alanine transferase (ALT) enzyme test[9]. Moreover at RSUP Persahabatan Jakarta AST and ALT levels of patients given OAT treatment were continuously monitored during the intensive and advanced phase. The monitoring was to detect OAT hepatotoxic risks[10]. In respect of the issue, we investigated the effects of the phase of anti-tuberculosis drugs (OAT) consumption on AST and ALT levels of patients with pulmonary tuberculosis at RSUP Persahabatan.

RESEARCH METHODS

It was secondary data analytical research with cross-sectional design. We collected the data at RSUP Persahabatan Jakarta Timur in March-June 2018. Our independent variable was OAT consumption phases i.e. intensive phase, the first 2-month treatment phase using isoniazid, rifampicin, pyrazinamide, and ethambutol combined and advance phase, the 4-month treatment given during intensive phase using isoniazid, rifampicin, and/or ethambutol combined. Moreover the dependent variables were AST and ALT levels. The levels were identified using Architect Plush C4000 with photometer principle (normal AST and AST levels were 5-34 U/L and 0-55 U/L respectively).

Our research sample consisted of patients with pulmonary tuberculosis treated at RSUP Persahabatan in 2017. We checked their AST and ALT levels before and after 2-month and 6-month OAT treatment. Sample consisted of 60 patients we selected randomly (probability sampling) using simple random sampling technique. We determined several specific inclusion criteria i.e. a) Patients with pulmonary tuberculosis administered with OAT for six months and b) Patients with pulmonary tuberculosis but with normal AST and ALT levels before OAT administration. Meanwhile our exclusion criteria were a) Patients with pulmonary tuberculosis quitting the treatment, b) Patients with pulmonary tuberculosis and a history of liver diseases (identified by observing their medical records), and c) Patients with pulmonary tuberculosis with incomplete medical records.

Research Procedures

Secondary data were collected through these following steps:

We proposed a formal permission letter to the Division of Education and Training RSUP Persahabatan. The permission letter explained our intention to collect data at RSUP Persahabatan. After that we checked AST and ALT levels of patients with pulmonary tuberculosis treated there in a laboratory and medical record division. Our final data were AST and ALT levels before and after treatment, age, and sex of the patients.

Data Analysis

We conducted statistic test using mean difference test more than two paired sample group with a 95% confidence level ($\alpha = 0.05$). The statistic test was initiated by Kolmogorov-Smirnov data abnormality test. As the data were proven abnormal, we made a non-parametric test (Friendman test) also.

Research Findings

We successfully gathered 60 patients with pulmonary tuberculosis (35 males and 25 females). Normal AST and ALT levels were 5-34 U/L and 0-55 U/L respectively.

Table 1 The Lowest, Highest, and Average AST and ALT Levels of Patients with Pulmonary Tuberculosis Consuming OAT
(n = 60 patients)

	Variable	n	AST Level			ALT Level		
			Lowest (U/L)	Highest (U/L)	Average (U/L)	Lowest (U/L)	Highest (U/L)	Average (U/L)
1.	Before treatment	60	7	33	18.20	6	33	13.60
2.	Intensive phase	60	9	204	38.80	6	88	28.07
3.	Advanced phase	60	6	151	24.33	6	55	14.98

Table 1 indicates that the average AST level before OAT consumption was normal (18.20 U/L). However, after the intensive phase, the level increased above the normal value (38.80 U/L). Fortunately, it returned to normal after the advanced phase (24.33 U/L). In term of ALT level, the level remained normal either before OAT consumption (13.60 U/L), after the intensive phase (28.07 U/L), or after the advanced phase (14.98 U/L).

Table 2 The Number of Patients with Pulmonary Tuberculosis and Abnormal AST and ALT Levels Consuming OAT in Intensive and Advanced Phases

No.	Treatment Phase Variable	N	AST		N	ALT	
			N	aN		N	aN
1.	Before treatment	60 (100%)	60 (100%)	0 (0%)	60 (100%)	60 (100%)	0 (0%)
2.	Intensive phase	60 (100%)	34 (56,7%)	26 (43,3%)	60 (100%)	51 (85%)	9 (15%)
3.	Advanced phase	60 (100%)	56 (93,4%)	4 (6,6%)	60 (100%)	60 (100%)	0 (0%)

Description: N = Normal, aN = Abnormal

26 (43.3%) and 4 (6.6%) patients had abnormal AST level during intensive phase and during advanced phase respectively. Meanwhile, nine patients (15%) were identified to have abnormal ALT level during intensive phase.

According to the result of Friedman test ($\alpha = 0.05$), p-value < α ($0.000 < 0.05$). It implied that AST levels before treatment, during intensive phase, and during advanced phase were significantly different, so were ALT levels.

Table 3 Post Hoc Test (Wilcoxon Sign Test): Different Effects of Treatment Phase on AST and ALT Levels

No.	Treatment Phase Variable	P	
		AST	ALT
1.	Before treatment – intensive phase	0.000*	0.000*
2.	Intensive phase – advanced phase	0.000*	0.000*
3.	Before treatment – advanced phase	0.000*	0.317

*) Significantly different

By the means of Post Hoc test (Wilcoxon Sign Test), AST level before treatment was significantly different from that during either intensive or advanced phase ($p = 0.000 < 0.05$). Additionally the level during intensive phase and that during advanced phase were also significantly different. Moreover ALT level before treatment was significantly different from that during either intensive phase. The level during intensive phase and that during advanced phase were significantly different as well. Contrastively, ALT level before treatment and that during advanced phase were the same ($p = 0.317 > 0.05$).

Discussion

Tuberculosis (TB) was caused by Mycobacterium tuberculosis. It was one of the communicable diseases that caused the highest mortality rate in the world, especially in developing countries. India had the highest number of tuberculosis diseases (2.8 million cases); while Indonesia was ranked second (1.02 million cases)[2].

TB was treated by administering antibiotics in two phases (intensive and

advanced) more or less for six months in two phases. The antibiotic dose should be in accordance with OAT guidelines[11]. During intensive phase, patients were given antibiotics isoniazid, rifampicin, pyrazinamide, and ethambutol on a daily basis for two months. The administration was aimed to reduce the number of bacteria, also reducing TB communicability. Meanwhile during advanced phase, they were given antibiotics isoniazid, rifampicin, and/or ethambutol for four months. It was to kill the bacteria staying in patients' body, preventing any relapse[1].

However, the effects of treatment would be found in patients consuming OAT in a long term. One of the effects was on the liver, causing hepatotoxicity due to the drugs or DILI[6]. Hepatotoxicity was one of the side effects of the treatment. In the hepatocytes, drugs became hydrophilic and soluble. Then it was excreted through urine or the bile[8]. During the metabolism process, complex was formed between cytochrome P-450 as a catalyst and the drugs. The complex would trigger cell dysfunction, membrane dysfunction, and cytotoxic response of T cell, causing apoptosis[12]. Enzymes often related to damaged liver cells belonged to aminotransferase group. The enzymes were Amino Transaminase (AST) and Alanine transaminase (ALT). When liver cells were damaged, the level of those two enzymes would increase[13].

Table 1 indicates that before OAT consumption, the average AST and ALT levels were 18.20 U/L and 13.60 U/L respectively; while transaminase enzyme level was normal. During intensive phase, the average levels of both enzymes increased to be 38.80 U/L and 28.07 U/L respectively. It showed an increased transaminase enzyme level during intensive phase. It was in accordance with several research conducted to patients treated with OAT therapy. Their transaminase enzyme level increased without any clinical symptoms (asymptomatic)[15]. Moreover hepatotoxic effects would be identified in the first and second months of treatment (intensive phase). The high AST/ALT levels during the period were the initial effects of OAT consumption[16].

Moreover during advanced phase AST and ALT levels declined by 24.33 U/L and 14.98 U/L respectively. It was in line with several researchers finding declined transaminase level during advanced phase[15]. Hepatotoxicity level of patients with pulmonary tuberculosis was 13.2% in early treatment but declined by 2.6% during advanced phase[17]. Two types of antibiotics i.e. isoniazid and rifampicin were given in the advanced phase. During the phase, patients had been adapted to antibiotics they were consuming. It reduced and even eliminated the side effects of the treatment.

Table 2 indicates that 26 (43.4%) and 9 (15%) patients had abnormal AST

level and abnormal ALT level during intensive level respectively.

According to the result of Friedman test, AST/ALT levels before treatment, during intensive phase, and during advanced phase were significantly different. We could conclude that the treatment affected both AST and ALT levels. The differences were tested using Post Hoc (Wilcoxon Sign Test). The test result (Table 3) indicated a significant difference between AST level before treatment and that during intensive and advanced phases. Another significant difference was also found in AST level during intensive phase and during advanced phase. Meanwhile, ALT level before treatment and that during intensive phase were also significantly different, so were ALT level during intensive phase and that during advanced phase. It signified OAT consumption affecting AST and ALT levels of patients with pulmonary tuberculosis. In contrast, ALT level before treatment and that during advanced phase were the same ($p = 0.317 > 0.05$).

Side effects due to OAT consumption could be identified by significantly different AST and ALT levels before treatment and that during intensive phase. During intensive phase the levels were normal. As a result, treatment phase highly potential to cause hepatotoxicity was intensive phase. During the phase, patients were given four antibiotics combined. The four antibiotics, isoniazid, rifampicin, pyrazinamide, and ethambutol were given on a daily basis. Of the four antibiotics, pyrazinamide gave hepatotoxic effects[4]. Meanwhile if consumed for a long-term, pyrazinamide and isoniazid might cause multilobular necrosis, hence an increased transaminase enzyme level[18]. Nevertheless, without pyrazinamide INH and rifampicin were safe to consume[19].

Moreover ALT level before treatment and that during advanced phase were similar. The similarity was due to normal ALT level before the advanced phase. Meanwhile although significantly different, AST level before treatment and that during advance phase were still considered normal. It was because during advanced phase, patients were only given two types of antibiotics i.e. isoniazid and rifampicin three times a week. It was in accordance with the research claiming that hepatotoxicity might emerge during the first month of treatment. However, liver enzyme profiles were recovered in the following five months[20]. Furthermore during advanced phase, the side effects disappeared. Meanwhile less frequent drug and combined drug consumption affected hepatotoxic risks in advanced phase. We should notify that AST was found in various tissues including the liver, brains, pancreas, the heart, kidneys, lungs, and muscles. When the tissues were damaged, AST released in blood circulation. It implied that increased ALT level indicated mild injury instead of liver

issues. On the other hand, ALT was majorly found in the liver. Increased ALT level indicated either minor or major. Continuously increased ALT level caused issues leading to liver failure[21].

CONCLUSION

Anti-tuberculosis drug (OAT) consumption affected AST and ALT levels. AST levels before treatment, during intensive phase, and during advanced phase were different, so were ALT levels ($p = 0.000 < 0.05$). However, ALT level before treatment and that during advanced phase were the same ($p = 0.317 > 0.05$). OAT administered during intensive phase gave the highest hepatotoxic effect due to pyrazinamide.

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