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Original Article

LIVER FUNCTIONS PROFILE OF TUBERCULOSIS PATIENTS IN INDONESIA DURING ANTITUBERCULOSIS TREATMENT

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ABSTRACT

Objective: The objective of this study is to define the profile of liver function of tuberculosis patients during the treatment.

Methods: We conducted the longitudinal study with adult tuberculosis patients treated with the first line of antituberculosis as the inclusion criteria. The pregnant and patients with comorbidities which related to liver function were excluded. We measured the total bilirubin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) over the 2nd, 4th, and 6th mo of the treatment.

Results: We recruited 202 patients, with 58.91% male patients, and the mean age was 39.91 (SD: 17.18) years old. As 9% of tuberculosis patients experienced increased levels of bilirubin, AST, and ALT, and 50% among them experienced increased levels of bilirubin, AST, and ALT starting from 2nd mo of the treatment. The total bilirubin level in the 2nd,4th, and 6th mo were 0.57, 0.59 and 0.67 mg/dl, respectively. The AST levels were 27, 22, and 26 U/l in 2nd,4th and 6th mo, respectively, and the ALT levels were 21,19 and 25 U/l in 2nd,4th and 6th mo, respectively. At the end of the treatment, around 4.5% tuberculosis patients experienced high levels of bilirubin, AST and ALT.

Conclusion: The monitoring treatment for tuberculosis patients should be conducted until the end of the treatment because the level of bilirubin, AST, and ALT increased after 6th mo of treatment.

Keywords: Liver Functions, Tuberculosis, Indonesia

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INTRODUCTION

Indonesia is now still in the third top position of the number of tuberculosis cases over the world [1]. Around 10-20% of tuberculosis patients experience adverse drug reactions, mainly due to the long duration of treatment. The adverse drug reaction is one of the factors influencing non-adherence in tuberculosis patients [2]. Additionally, the catastrophic cost due to tuberculosis treatment is also become a serious consideration in low-middle-income countries [3].

Drug-induced liver injury (DILI) is one of the most common adverse events due to antituberculosis treatment [4]. The medication combination, such as rifampicin, isoniazid, ethambutol and pyrazinamide, has a huge potential adverse effect of DILI. The previous study in United States mentioned that the cases of DILI reached 6.9% among TB patients. Moreover, around 50% of the cases occurred in the first 2 w of antituberculosis treatment and the rests occurred in later than 2 w after initial treatment [5]. Early monitoring of liver function may detect around 8% of DILI in the first 2 w of treatment [6]. Another study stated that early detection of antituberculosis-induced liver injury also may prevent mortality. Factors that considerably become the predictive factors of the DILI are female and extrapulmonary tuberculosis [7]. The vulnerable of DILI might increase due to some other factors, such as chronic liver disease, undernutrition, HIV infection, the treatment combination, and extensive tuberculosis disease [8, 9]. Our study is aimed to define the liver function profile during tuberculosis treatment.

MATERIALS AND METHODS

A longitudinal study was performed to adult tuberculosis patients treated with the first line of antituberculosis in 35 primary health cares including hospitals. The pregnant and patients with comorbidities which related to liver function were excluded.

We measured the total bilirubin, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) over the 2nd, 4th and 6th mo of the treatment. We did not define the DILI, but we only define the increased level of bilirubin, AST and ALT were over the upper limited number of those parameters. Our study has been approved by Ethical Committee of Universitas Ahmad Dahlan, number 012002010. We analyzed the data descriptively to describe the average of bilirubin, AST, ALT levels and the tuberculosis patients with increased level of bilirubin, AST and ALT.

RESULTS

We recruited 202 tuberculosis patients as the subjects in this study. Table 1 presents the charactersitics of tuberculosis patients. Most of the subject was male (58.91%) and the mean age was 39.91 y old (SD: 17.18). As 86.14% of subjects had elementary up to senior high school for the last education. Most of the subjects were working (88.11%) and had no comorbidities (59,90%).

There are slight decrease in the 2nd mo but at the end of the treatment, both AST and ALT level are increasing. The increase of AST level at the 6th mo of the treatment is lower than the initial level (2nd mo) but the increase of ALT level at the 6th mo of the treatment is higher than the initial condition. Moreover, there are also a slight increase on the level of total bilirubin at the 4th and 6th mo of the treatment (fig. 1). However, all of the average of liver function (Bilirubin, AST and ALT) level were in the normal range.

After 2 w from the initial treatment, there were 3% and 1.5% of tuberculosis patients who experience the high level of AST and ALT, respectively. Although, there were decreases at 2% and 1% of them who experienced the high level of AST and ALT, in the 4th weeks of the treatment, respectively. The final incidence of high level of bilirubin, AST and ALT, were around 5%, 4% and 2%, respectively. During the duration of tuberculosis treatment, there were 9 (4.5%) tuberculosis patients who experienced an increased of liver function, which half among them experiencing increased level start from 2nd mo of treatment. In conclusion, Proportion of tuberculosis patients with increased of bilirubin, AST and ALT levels is above the upper limited number (%).

Table 1: Tuberculosis patients' characteristics (n= 202)

Characteristics	Mean	SD
Age	39.91	17.18
	N	**%**
Sex		
Male	118	58.91
Female	84	41.09
Last education		
No schooling	8	3.96
Elementary up to senior high school	174	86.14
Academic	20	9,90
Working		
Yes	178	88.11
No	24	11.88
Comorbidities		
Yes	121	59.90
No	81	40.10

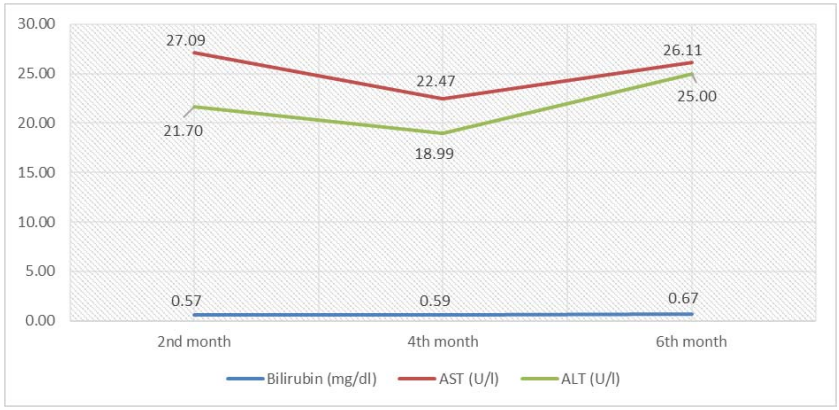

Fig. 1: Profile of liver function of tuberculosis patients during antituberculosis treatment

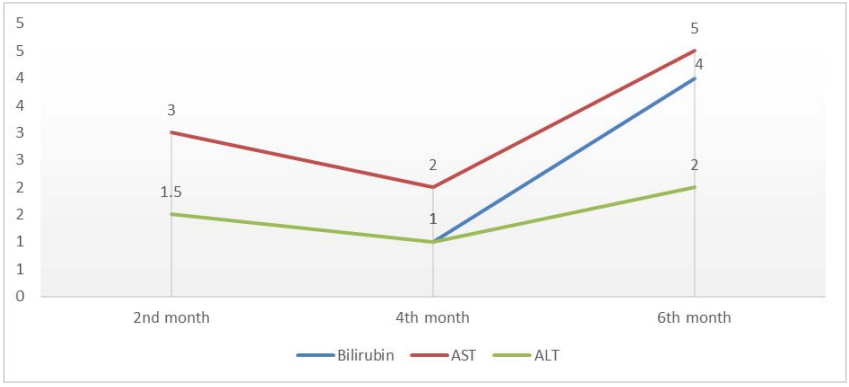

Fig. 2: Proportion of TB patients experiencing increased of bilirubin, AST and ALT

DISCUSSION

Our study found that during the course of tuberculosis treatment, the average of bilirubin, ALT and AST level were in the normal range. However, there are some increases at the 6th mo of the treatment. The proportion of tuberculosis patients with the increased level of bilirubin, AST and ALT, increased at the end of the treatment of tuberculosis. A previous study mentioned that the regular monitoring of liver function in tuberculosis patients could detect the liver injury earlier and lead less liver injury [10].

Our study presents the small proportion of tuberculosis patients with increased of bilirubin, AST and ALT level compared to the previous studies [6-8, 11]. Many factors may influence liver function during tuberculosis treatment such as, female gender, nutritional status, HIV infection, extrapulmonary tuberculosis and chronic liver disease [6]. However, the patients' characteristics in our study is different, such as, male tuberculosis patients dominantly exclusion of HIV and chronic liver disease. The increase of ALT ad AST in DILI patients can be used for predict the severity of DILI. Furthermore, age, sex and race were also associated with the severity of DILI [12]. The severity of the antituberculosis-induced liver injury may be predicted by the antituberculosis combination and the rechallenge procedure [9].

Based on types of the DILI, there are direct and indirect of DILI. The direct DILI could be caused by idiosyncratic factors and the indirect DILI could be caused by other drugs that are associated with HLA genotype [13]. Other factors which could possibly explain the DILI may be the polymorphisms of some genes like *NAT2, CYP2C9, HLA* and *GST1*, because these genes had significant roles in the metabolism of isoniazid [14, 15]. As we know, that each of tuberculosis treatment in the fixed-dose combination formulation

has a good effect in the potentiation of antituberculosis, However, all medication had potential adverse effect in liver as well. Thus, precision medicine in tuberculosis treatment must involve polymorphism factors and patients' characteristics factors. A previous study stated that, Indonesian people was slow acetylators of *NAT2*, thus the DILI risk could be higher than other ethnicities [15, 16]. Other study endoplasmic reticulum stress had a potentially pathogenic role in the hepatotoxicity caused by rifampicin [17].

The treatment for AT DILI patient is not specific. It is depend on the symptoms, such as itching, jaundice, nausea vomiting and coagulopathy [18]. N-acetylcysteine can be considered for the treatment for antituberculosis-induced liver injury due to the shortened length of the hospital stay [19]. In our country, we treat the antituberculosis liver injury patients with hepatoprotector agent, however previous study stated that the hepatoprotector agent has no preventive effect in tuberculosis patients receiving antituberculosis treatment [20].

Our study presented the real data of adverse events in 202 patients, and we did the monitor as part of the pharmacovigilance activities. We did not make any correlation among patients' characteristics and the liver function profile because we do not have enough characteristics data. We also did not collect the baseline data of liver function due to the limited facilities and pandemic situation. Future studies are suggested to consider the characteristics data in the analysis of factors predicting the DILI.

CONCLUSION

In general, 9% of tuberculosis patients experienced an increased level of bilirubin, AST and ALT. As 50% among them experienced the increased level of bilirubin, AST and ALT start from 2nd mo of treatment. The increased level of total bilirubin, AST and ALT at the end of antituberculosis treatment, may become the concern of the health providers to do the monitoring after the end of tuberculosis treatment.

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AUTHORS CONTRIBUTIONS

Conceptualization: DAP (for Dyah Aryani Perwitasari), Methodology: DAP, DS (for Didik Setiawan), Formal analysis: TS, HD (Triantoro Safaria and Haafizah Dania), Data curation: INF, HD (for Imaniar Noor Faridah), Software: LMI, INF, HD (for Lalu Muhammad Irham), Validation: DAP, DS, TS, Investigation: DS,TS, HD, Writing-original draft preparation: DAP, DS, INF, Writing-review and editing: DAP, DS, TS, HD, INF, LMI, Approval of final manuscript: all authors. All authors has approved the final manuscript.

CONFLICT OF INTERESTS

All authors have no conflict of interest

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