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Early detection of elevated liver function test in drug-resistant tuberculosis with short term therapy and individual therapy

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ABSTRACT

Introduction: Tuberculosis (TB) treatment consists of more than one drug to achieve goal treatment. Hepatotoxicity is a form of side effect that causes the termination of TB treatment or regimen changes due to treatment failure, relapse, and drug resistance. Hepatotoxicity may increase the problem, covering more than 7% of all side effects. DILI is also one of the concerns in the treatment of TB. The objective of this study to assess the role of risk factor in the hepatotoxicity during drug-resistant TB treatment and investigate the time of onset hepatotoxicity during drug-resistant TB treatment.

Methods: The research method was retrospective study. Comprehensive demographic and clinical data, management, and outcome were recorded. Patients who were treated with drug-resistant treatment in Dr. Soetomo General Hospital between January 2018 and January 2020 were enrolled. The statistical method used SPSS ver 16.0. A total sample of 129 patients met the inclusion and exclusion criteria.

Results: Prevalence of hepatotoxic side effects was 54 cases. A total of 2 patients occurred hepatotoxicity in the first 2 weeks, and 52 patients developed hepatotoxicity in the late 2 weeks. There was one risk factor influencing the hepatotoxic side effects of drug-resistant Tuberculosis treatment. The history of alcohol consumption the only one risk factor (OR=3,182; 95% CI=0,120-9,927.

Conclusion: Hepatotoxicity is a common problem among patients during Antituberculosis Treatment, especially on drug-resistant Tuberculosis in our population. Early detection not only reduces the risk of developing hepatic injury but also prevents mortality.

Keywords: Hepatotoxic, DIH, adverse effect, TB MDR, drug-resistant, onset.
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INTRODUCTION

Tuberculosis (TB) is a disease that is still a big problem for several countries in the world. This disease is caused by Mycobacterium tuberculosis and most often attacks the lungs. The World Health Organization (WHO) in 2020 stated that there were 10 million new cases of TB in the world. Most cases occurred in men amounting to 5.6 million, women 3.3 million, and children as many as 1.1 million. Not only that, the number of deaths caused by TB in 2020 was recorded at 1.5 million and became the second infectious disease that caused the highest death after COVID-19. Some of the countries that have the highest TB prevalence are India, China, Indonesia, Nigeria, the Philippines, Bangladesh, Pakistan, and South Africa.[1]

Treatment that is currently the gold standard for TB is isoniazid and rifampin. Multidrug-resistant tuberculosis (MDR-TB) can be defined as bacteria that do not respond to anti-TB drugs, leaving patients with no further treatment options.[2] This is currently still a public health problem and threat. As many as 85% of TB cases had successful treatment, but the most common side effects were hepatotoxicity, skin reactions, gastrointestinal disturbances, and also neurological disorders which could significantly reduce the effectiveness of the therapy given.[3]

Hepatotoxicity is the most common cause of all side effects that can lead to discontinuation of therapy using the combination of isoniazid, rifampin, and pyrazinamide in 11% of patients.[3] The incidence of hepatotoxicity induced by the administration of anti-TB regimens is highly dependent on several things such as the drug regimen given, the threshold used to define hepatotoxicity, monitoring, and also reporting practices in treating TB cases. As much as 5%-28% incidence of hepatotoxicity is caused by therapy using anti-TB drugs.[4] TB treatment can also be a risk factor for Drug-Induced Liver Injury (DILI).[5]

Other factors such as age, sex and lifestyle have been associated with the incidence of hepatotoxicity, but these risk factors are often not associated with the incidence of hepatotoxicity in the treatment of TB patients.[6] Based on this, it is necessary to assess the role of risk factors for hepatotoxicity during treatment of drug-resistant TB and investigate the timing of the onset of hepatotoxicity during treatment of drug-resistant TB.

METHODS

General Background of Research

The dependent variables in this study was risk of ADR, while the independent

variables were the subject factors such as age, gender, body weight, social historical such as smoking and alcohol consumption, and comorbidities such as diabetes mellitus and hypertension.

Sample of Research

Sample of this study used 129 patients TB that have been selected based on inclusion and exclusion criteria. The inclusion criteria of this study namely got an individual regimen and short regimen, and complete the clinical laboratory examination data with minimum 2 times of examinations. The exclusion criteria of this study namely drug-resistant TB patients who do not have complete medical record data have a history of liver problems before starting TB therapy. liver disorders such as hepatitis, ascites, hepatic encephalopathy, have a history of using drugs before starting TB therapy RO ursodeoxycholic acid (EDCA), n-acetyl cysteine (NAC), curcuma because they are hepato-protective, have an account ofHIV, patient has taken the hepatitis vaccine, patient taking drugs that have drug interactions outside of anti-tuberculosis. Samples were divided into two groups, namely ADR group and non ADR group.

Instrument and Procedures

This study was conducted using secondary data that collected from patient's medical record. Data were taken from each medical record based on variables in this study and collected into database in order to run into data cleaning and analysis procedures.

Data Analysis

Data analysis was carried out using univariate analysis to obtain the percentages and mean value of each variable. Bivariate analysis was done to obtain the mean value data of each group and the percentages of each variable in each groups. The p value was obtained on bivariate analysis to determine the significance of each variable's relationship statistically. Bivariate analysis was done using independent sample t test and chi square test. Multivariate analysis was carried out using binary logistic regression to determine the independent relationship between independent variable and dependent variable.

RESULTS

Based on the WHO 2019 Drug-Resistant TB Services Ministry Guide, the MDR TB therapy regimen is divided into two regimens: Short-Term Regimen (STR) and Individual (Indiv) regimens. The short-term regimen has about 10-12 months and an individual regimen with about 20-24 months. The therapy regimen consists of a combination of antibiotics of about 4-6 drugs depending on the antimicrobial susceptibility test results and consideration of the patient's clinical condition before and during MDR TB therapy. The side effects of the drug administration of the drug with category <14 days were two patients. In the category y> 14 days, there were 52 patients. Some of the medications in Drug-Resistant TB therapy are hepatotoxic.

The significant results indicated by P-value <0.05 were the social history of alcohol, initial hepatology status, namely the ALT and AST values. The results showed that alcohol users' social history between the ESO and non-ESO groups (18.52% vs. 5.33%), where alcohol users had a greater hepatotoxic ESO significance. In addition, the initial hepatology profile, namely the levels of AKT and AST in the ADR group, was significantly higher than the ALT profile (14.96% vs 9.58%) and AST (21.64% vs 15.95%) in the non-ADR group.

The results showed from binary logistics analysis that one risk factor influenced the emergence of hepatotoxic side effects from RO TB therapy, namely a history of alcohol consumption with a p-value of 0.046 with a Crude Odds Ratio 3.182. Patients with a history of alcohol use have a higher risk of Hepatotoxic ESO therapy than patients without a history of alcohol use.

Table 1. Table Onset of Hepatotoxicity.

Onset (Days)	Total Amount Patients (n)	Treatment (n)		Mean AST/ALT (IU/ml)	
		Short Term	Individual	Pre	Post
< 14	2	1	1	30,5/51	53,5/54,5
> 14	52	40	12	25,7/31	81,4/86,7

Table 2. Result of Statistical Analysis.

Risk Factor	ADR Group (n=54)	Non – ADR Group (n=75)	P Value
Subject Factor			
Age, Mean, (SD)	44,28 (13,04)	47,05 (13,77)	0,232[a]
Sex Male, n (%)	30 (50,55)	36 (48)	0,397[b]
Weight (kg), Mean (SD)	51,63 (11,81)	51,45 (12,27)	0,905[a]
Social Historical			
Smoking, n (%)	20 (37,04)	25 (33,33)	0.663[b]
Alcohol Consuming, n (%)	**10 (18,52)**	**4 (5,33)**	**0.038***[b]
Comorbid			
Diabetes Melitus, n (%)	24 (44,44)	34 (45,33)	0,920[b]
Hypertension, n (%)	7 (12,96)	12 (16,00)	0,631[b]

[a]Analysis was carried out using independent sample t-test; [b] Analysis was carried out using chi square test; *Significant value if p<0,05.

Table 3. Result of Statistical Analysis Binary Logistic Univariat.

Risk Factor	Crude OR (95% CI)	P Value
Subject Factor		
Ages	1,665 (0,692 – 4,004)	0,255
Sex	1,354 (0,671 – 2,733)	0,398
Social Historical		
Smoking	1,176 (0,566 – 2,446)	0,663
Alcohol	**3,182 (0,120 – 9,927)**	**0,046***
Comorbid		
Diabetes Melitus	1,037 (0,513 – 2,095)	0,920
Hypertension	1,279 (0,468 – 3,497)	0,632
First Hepatological Status		
AST	3,724 (0,695 – 19,970)	0,125
ALT	2,275 (0,923 – 5,607)	0,074

OR : Odd Ratio, P value : From Wald; CIS: Confidence Interval; Analysis was carried out using Binary Logistic Univariat; *Significant value if p<0,05.

DISCUSSION

Hepatotoxicity remains a critical impediment in Tuberculosis treatment because it diminishes viability since it altogether contributes to noncompliance, eventually contributing to treatment disappointment, backslide, or the development of drug-resistance.

The time of ESO is partitioned into 2, specifically early (<14 days) and late (> 14 days) [8]. Time of event (onset) of medicate side impacts with category <14 days were two patients. Within the category> 14 days, there were 52 patients. The time of event of side impacts was 112 days with a run of as early as 9 days and no afterward than 305 days. Inside one month, the time for side impacts to happen is the quickest, 9 days, and 30 days at the most recent.. The timing of the side impacts shifts. Within the consider of Abera et al., 2016, the time interim from beginning treatment to the onset of hepatotoxicity was 13-58 days (middle 26 days). The middle interim between anti-TB treatment start and the onset of hepatotoxicity was 41 days (extend, 13 to 263 days).[7] Based on the study, the time of occurrence of TB drug-related hepatotoxicity in 1031 patients receiving first-line TB drugs the results that 108 patients (10.5%) developed ADIH with a mean of 39.6 ± 43, 7 days after starting treatment. Twenty-eight patients (25.9%) developed ADIH in 7 days, 73 (67.6%) in 30 days, and the rest after 30 days.[8]

Patient with alcohol cunsumption hystory had a more noteworthy hepatotoxic ADR centrality. The beginning hepatology profile, specifically ALT and AST within the ADR bunch, was essentially higher than the SGOT profile (14.96% vs. 9.58%) and SGPT (21.64% vs. 15.95%) within the non-ADR gather. Liquor abuse (characterized as expending> 35 units and> 28 units of liquor per week for at slightest 10 a long time for men and ladies, separately) was found to be essentially related with anti-DIH-TB frequency (rough chances proportion = 9.343, certainty interim 95 % 1.8–47.3).[7] Researcher moreover found no distinction in components other than liquor utilize history and standard SGOT / SGPT scores. Essentially, this ponder expressed that BMI (kg / m2), TB illness region, sex, and age were not altogether related with the frequency of anti-TB-DIH. A few ponders have proposed that more seasoned age inclines to TB therapy-induced hepatotoxicity. This could be due to aging-related changes such as decreased clearance of drugs metabolized by the CYP450 chemical and liver blood stream changes, liver degree, medicate official, or transport. In separate, a number of thinks almost have showed up that more young age slants to ATT-induced hepatotoxicity. Within the think about of Latief et al., 2017, the cruel age within the gather that did not create DILI was 45.99 (16.83) a long time, and the normal age of the DILI bunch was 47.31 (15.74) a long time. The age distinction between the two bunches was not measurably noteworthy (p value 0.764). Age does not play an fundamental part in impacting patients with ATT to create DILI in out study.[9]

A binary logistic regression test was performed to see whether the suspected variable was a chance figure for hepatotoxic side impacts. The examination comes about are seen from the noteworthiness of the p-value of the Wald test, where on the off chance that the p-value is <0.05, the variable in address is in fact a chance calculate for side impacts, at that point the chances proportion can be seen to decide the sum of introduction esteem. Points of interest of the examination comes about can be seen in figure 2. The comes about appeared one chance calculate that impacted the development of hepatotoxic side impacts from RO TB treatment, namely a history of alcohol consumption with a p-value of 0.046 with a Crude Odds Ratio of 3.182. Similar to research from Abera et al., 2016, a history of high alcohol consumption is a potential risk factor for anti-TB-DIH (p <0.007, likelihood ratio = 9.3). However, according to several studies, higher alcohol consumption as a risk factor is ascribed to malnutrition and depletion of glutathione stores.[8,10]

CONCLUSION

Hepatotoxicity could be a common issue among patients amid Antituberculosis Treatment, particularly on drug-resistant Tuberculosis in our populace. Early location not as it were decreases the chance of creating hepatic damage but too anticipates mortality. Our consider in this way implies the significance of early and more visit checking of liver capacities in all Tuberculosis patients put on ATT. Such an approach makes a difference in early location of liver damage, and convenient mediation in these cases would certainly diminish the mortality and dismalness related with ATT-induced liver harm. The authors suggest checking of liver capacities week after week within the seriously stage and each two months from that point, hence assist thinks about are required to approve this finding with bigger test estimate and more comprehensive design.

AUTHOR CONTRIBUTION

All creators similarly contribute to the consider from the inquire about concepts,

information acquisitions, information investigation, factual investigations, changing the paper, until announcing the ponder comes about through publication.

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CONFLICT OF INTEREST

There is no conflict of interest for this manuscript.

ETHICAL CONSIDERATION

This research was approved by the Health Research Ethics Committee of Dr. Soetomo General Hospital, with reference number 0047/LOE/301.4.2/VI/2020.

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