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SUBMISSION ID	1403295388	CHARACTER COUNT	11270

FACTORS THAT INFLUENCE THE INCIDENCE OF DRUG INDUCED LIVER INJURY IN PULMONARY TUBERCULOSIS PATIENT

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ABSTRACT **Background:** The use of anti-tuberculosis drugs (ATD) is not uncommon to find side effects that complicate treatment. One of the side effects caused by ATD treatment is Drug-Induced Liver Injury (DILI). Risk factors that trigger the incidence of DILI during tuberculosis (TB) treatment involving a variety of factors. This study was conducted to determine the risk factors of DILI in pulmonary tuberculosis patient. **Method:** A Conducted retrospective case-control study. Study subjects were all patients who underwent first category ATD treatment at Dr Wahidin Sudirohusodo hospital of Makassar, Indonesia. Risk factors examined were age, gender, nutritional status, alcohol consumption, smoking, history of liver disease, consumption of another drug, ATD preparation of Fixed Dose Combination (FDC) and abnormality of SGPT/ total bilirubin control value at a minimum of 2 weeks after starting treatment. **Result:** From total of 47 samples which took part in the study, ten samples (21.3%) suffered DILI. Samples characteristics who suffered from DILI were an average age of 52.7 years old ($P < 0.05$), and consumption of another drug 29.4% ($P < 0.05$). There was no significant relationship between gender, nutritional status, alcohol consumption, smoking, and history of liver disease in the incidence of DILI. **Conclusion:** Old age and history of consumption of other drug have a significant relationship as a risk factor for the incidence of DILI in TB patients who consume ATD, while no significant relationship found between gender, malnutrition, alcohol consumption, smoking, and history of liver disease.

KEYWORDS DILI, Pulmonary Tuberculosis, ATD

Introduction

The use of ATD is not uncommon to find a side effect that complicates the treatment. One of the side effects caused by ATD treatment is DILI.[1] Clinically; the manifestations of DILI is similar to acute viral hepatitis. Drug-induced liver injury can cause a variety of hepatotoxicity, range from asymptomatic elevation of liver serum to severe manifestations.[2]

Drug-induced liver injury can resemble almost all types of liver disease. Currently, the diagnosis of DILI is carried out per exclusionem because there are no biological markers or specific examinations that can diagnose DILI. Therefore, all causes of liver injury that has similar manifestations must be excluded.[3] This study aims to determine the risk factors that influence the incidence of DILI in patients undergoing ATD treatment.

Materials and Methods

Conducted a descriptive study with retrospective design at Wahidin Sudirohusodo hospital of Makassar, Indonesia, from October to December 2018. This study has been approved by the Ethics Committee of Faculty of Medicine with reference number:

DOI:10.5455/IJMRCR.drug-induced-liver-injury-pulmonary-tuberculosis
First Received: March 01, 2019
Accepted: March 27, 2019
Associate Editor: Ivan Inkov (BG)

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19 / UN4.6.4.5.31 / PP 36-KOMETIK / 2019.

Table 1 Distribution of study variable categories (n=47).

Variable		n	%
Gender	Men	36	76.6
	Women	11	23.4
Nutrional status	Normal	27	57.4
	Low	20	42.6
HbsAg	Reactive	7	14.9
	Negative	40	85.1
HCV	Positive	0	0.0
	Negative	47	100.0
Hepatitis	Yes	2	4.3
	No	45	95.7
History of alcohol consumption	Yes	15	31.9
	No	32	68.1
History of liver disease	Yes	2	4.3
	No	45	95.7
Smoking	Yes	28	59.6
	No	19	40.4
Consumption of other drug	Yes	34	72.3
	No	13	27.7
DILI	Yes	10	21.3
	No	37	78.7

Population

Subjects diagnosed with pulmonary TB who will undergo the first category of ATD treatment at Wahidin Sudirohusodo hospital and UNHAS hospital since October 2018 until samples are fulfilled. Subjects were drawn from populations that met the research criteria.

Method and data collection

Sampling is done by looking at medical records of pulmonary TB patients who consume the first category of ATD treatment throughout 2018. Laboratory control carried out at minimum two weeks or if there were symptoms with an examination of SGOT, SGPT, and total bilirubin. Data collection aims to determine the factors that influence the incidence of DILI caused by the use of ATD.

Table 2 Mean of age according to DILI.

DILI	n	Mean	SD	p
Yes	10	52.7	20.4	0.033
No	37	40.1	14.8	

Table 3 The relationship between the consumption of other drugs with DILI.

DILI					
Drug history		Yes	No	Total	p
Yes	N	10	24	24	
	%	29.4%	70.6%	100.0%	
No	N	0	13	13	0.043
	%	0.0%	100.0%	100.0%	
Total	N	10	37	47	
	%	21.3%	78.7%	100.0%	
*OR Cannot be measured due to the value of 0 in the table					

Statistical analysis

Using version 22nd of SPSS for windows. Statistical analysis was the calculation of descriptive statistics, frequency distribution and independent-t and Chi-square statistics. Results are significant if $P < 0.05$.

Results

From 47 subjects aged between 19-81 years with an average of 42.79 ± 16.74 years. Subjects consisted of men (76.6%) and women (23.4%). There were ten samples (21.3%) who suffered DILI, and the rest did not. Based on the results of identification, old age (52.7 ± 20.4 years) affected the incidence of DILI $p < 0.05$ and consumption of another drug 29.4% ($P < 0.05$). Meanwhile, gender did not affect the incidence of DILI with p-value > 0.05, although there were nine men (25.0%) compared to 1 woman (9.1%) in the subject. Only three subjects (15.0%) from 10 had malnutrition; therefor nutritional status statistically did not affect the incidence of DILI with p-value > 0.05. Alcohol consumption did not affect the incidence of DILI with p-value > 0.05 where three subjects (20.0%) consumed alcohol compared to 7 subjects (21.9%) did not. There was no positive relationship between the history of liver disease with a risk of DILI ($p > 0.05$), where only 2 of 10 subjects who suffered DILI with a history of liver disease. Smoking did not have a statistically significant effect on the incidence of DILI with $p > 0.05$, although there were 8 of 10 subjects (28.6%) who smoked than those who did not (10.5%).

Discussion

Clinically, the manifestation of DILI is similar to acute viral hepatitis. Drug-induced liver injury can cause a variety of hep-

atotoxicity, range from asymptomatic elevation of liver serum to severe manifestations.[2] Clinical observations over several decades have identified some drug-related factors associated with an increased risk of ATD induced hepatotoxicity, although most studies are retrospective with a variety of case definitions and samples.[4] Based on literature study it is known that several factors associated with the increased risk of DILI incidence during tuberculosis treatment, such as age, gender, history of liver disease, malnutrition/ nutritional status, alcohol, consumption of other drugs and smoking.[5]

In this study, there were significant differences in the mean age between DILI and without DILI, which was around 52.7 years compared to 40.1 years ($P < 0.05$). Oliviera, I et al., aged 40-59 years caused ATD side effects in 16 patients (53,3%) of 30 subjects.[11] Older subjects are associated with decreased blood flow to the liver, changes in drug distribution and metabolism, thus potentially reducing effective drug clearance.[4] The proportion of DILI incidence was found to be significantly higher in a subject with a history of drug consumption compared to subjects without history, i.e. 29.4% compared to 0.0% ($P < 0.05$). Abbara et al., there is a positive relationship between consumption of other drugs together with ATD, with the incidence of DILI.[10] Subjects with consumption of other drugs together with ATD will increase the workload of liver because they metabolise various types of drugs, which make liver susceptible to inflammation.[6] The proportion of DILI incidence did not differ significantly between subjects with normal nutritional status and malnutrition, 25.9% and 15.0% respectively ($P > 0.05$). Shayka et al. reported that malnutrition is more vulnerable to DILI.[7] Adequate nutritional intake are essential for the integrity of liver metabolism and detoxification of ATD. Cytochrome P450 which responsible for such functions is influenced by nutritional intake, fasting and malnutrition.[4]

There was no significant relationship between subjects who had a history of liver disease with subjects without a history of liver disease, 0.0% and 22.2% respectively ($P > 0.05$). Luthariana et al., one of the reasons unable to obtain the factors associated with the incidence of DILI such as hepatitis B and hepatitis C is because samples are fairly homogenous.[5] Patients with a history of liver disease tend to have fibrous connective tissue, which is part of the healing process when a liver disease such as hepatitis occurred.[8] The proportion of DILI incidence did not differ significantly between subjects who had a history of smoking and subjects without smoking, 28.6% and 10.5% respectively ($P > 0.05$). Pramod Avti et al., smoking can affect liver function because it can reduce the activity of glutathione peroxidase which acts as antioxidant and antitoxin.[9]

The proportion of DILI incidence did not differ significantly between subject who has a history of alcohol consumption and a subject who has no history of alcohol consumption, 20.0% and 21.9% respectively ($P > 0.05$). Butura et al. reported that alcohol is also able to trigger the incidence of DILI due to its ethanol content. The process of ethanol breakdown can produce toxic chemicals such as acetaldehyde which can trigger inflammation and destroy liver cells. This will interfere with the physiological function of the liver, plus liver must metabolize ATD in large quantities and over a long period.[6] The proportion of DILI incidence did not significantly different between gender, although DILI incidence found higher in males than females, 25% and 9.1% respectively ($P > 0.05$). Abbara et al. found no positive relationship between gender and DILI indicende.10 Women has a four-fold risk of DILI during ATD treatment. Higher activity of CYP3A in women makes it more susceptible to hepatotoxicity [4].

The conclusion of this study is that old age and consumption of other drugs have a significant relationship as a risk factor for the incidence of DILI in TB patients who are undergoing ATD treatment, while gender, malnutrition, history of alcohol, smoking, and history of liver disease no significant relationship was found.

Competing Interests

There were no financial supports or relationships between authors and any organization or professional bodes that could pose any conflict of interest.

Funding

None.

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