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Case Reports on Severe Antituberculosis-Drug Induced Hepatotoxicity in Tuberculosis Patients: The Post-Incidence Therapy

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ABSTRACT

Introduction: *The first-line regimen for tuberculosis (TB) treatment comprises Isoniazid, Rifampicin, Pyrazinamide, and Ethambutol. However, these drugs are known to potentially cause hepatotoxicity. This study aimed to evaluate hepatotoxicity incidence in patients during intensive phase of anti-tuberculosis treatment focusing on post-incidence therapy.* ***Methods:*** *The study involved pulmonary TB patients who were admitted to the National Lung Health Center due to hepatotoxicity after receiving fixed-dose combination of antituberculosis drugs (FDC-AT) in September-October 2019. Drug-related hepatotoxicity is defined as an increase in serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels greater than 2.5 times of the normal upper limit (ULN) with an increase in bilirubin level.* ***Results:*** *There were 8 patients admitted to the center due to hepatotoxicity, 4 of them experienced grade 3 (severe) hepatotoxicity, during which the ALT, AST, bilirubin levels increased 5-10 times of the ULN. The post-hepatotoxicity treatment includes the cessation of FDC-AT treatment followed by hepatoprotective supplements. Following two weeks of treatments, the biomarker levels of two out of four patients went back to normal and the AT therapy was resumed. Meanwhile, the other two patients continued to receive the hepatoprotective therapy for up to 8 weeks. However, when the treatment failed to bring the*

transaminase level back to normal, a different AT regimen was prescribed. ***Conclusions:*** *The cessation of FDC-AT and the use of hepatoprotective supplements for two to eight weeks were able to alleviate the AT-induced severe hepatotoxicity. A close monitoring of liver biomarkers is warranted to prevent the incidence of hepatotoxicity in patients receiving antituberculosis*

1. INTRODUCTION

Tuberculosis is an infectious disease caused by *Mycobacterium tuberculosis* that mainly attacks the lungs (pulmonary TB), but can also affect other organs (extrapulmonary TB) [1]. The first-line antituberculosis (AT) treatment comprises Isoniazid (INH), Rifampicin (RMP), Pyrazinamide (PZA), and Ethambutol (EMB) in a fixed-dose combination [2]. Unfortunately, three out of the four antituberculosis drugs, such as isoniazid, rifampicin, and pyrazinamide, may produce reactive metabolites or modulate liver enzyme activities, and therefore, potentially induce hepatotoxicity [3]. The combination of INH was initially considered safe without side effects, but in the early 1970s several studies with large sample sizes suggested that INH can actually induces hepatotoxicity. The frequency of these effects varies from population to population: about 1–30 in 100 individuals on INH and RMP treatment [4].

Drug induced hepatotoxicity (DIH) can be defined as liver damage in the form of serious adverse reactions with significant morbidity, and even cause death (rarely) [5]. It can be detected using liver function test by measuring the aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels [6]. If hepatotoxicity occurs, it can force treatment termination, which may lead to increased risk of AT drug resistance and worse outcome in TB patients [7]. The guidelines also recommend treating the AT-induced hepatotoxicity by changing the antituberculosis treatment to a lower-risk regimen [8]. In addition, hepatoprotective supplements, such as curcumin, can be used to improve hepatotoxicity [9]. The aim of this study is to report the cases of AT drug-induced hepatotoxicity at the National Lung Health Center in Makassar focusing on the effectiveness of the hepatoprotective treatment following the incidence.

2. METHODS

The study involved pulmonary tuberculosis patients in National Lung Health Center Makassar who was admitted due to hepatotoxicity clinical signs after receiving fixed dose combination of anti-tuberculosis drugs (FDC AT) during the period of September-October 2019. All patients have signed the informed consent prior to data acquisition. The presence of hepatotoxicity is confirmed if the increase in serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) or bilirubin is more than 2.5 times of the upper limit of normal (ULN) with or without symptoms of hepatitis [5]. The severity of hepatotoxicity is divided into mild (if the ALT or AST increases <2.5 times ULN), moderate (ALT or AST 2.5-5 times that of ULN), severe (ALT or AST 5-10 times that of ULN) and very severe (ALT or AST >10 times ULN) and for bilirubin values >1.2

mg/dL [6,7]. All protocols have been approved by the Institutional Research Ethic Committee with ethical clearance number of 185/UN4.6.4.5.31/PP36/2020.

2.1 Inclusion criteria

Adult (>17 years old) TB patients treated with intensive phase FDC-AT (category 1) and were diagnosed with hepatotoxicity at the National Lung Health Center Makassar during September-October 2019.

2.2 Exclusion Criteria

Patients who have suffered from liver disease before starting TB treatment or received AT therapy other than FDC AT category 1, or patients with HIV complication, or patients who were prescribed with statin, anticonvulsant, and antiretroviral drugs since those drugs are known to potentially increase AST and ALT levels.

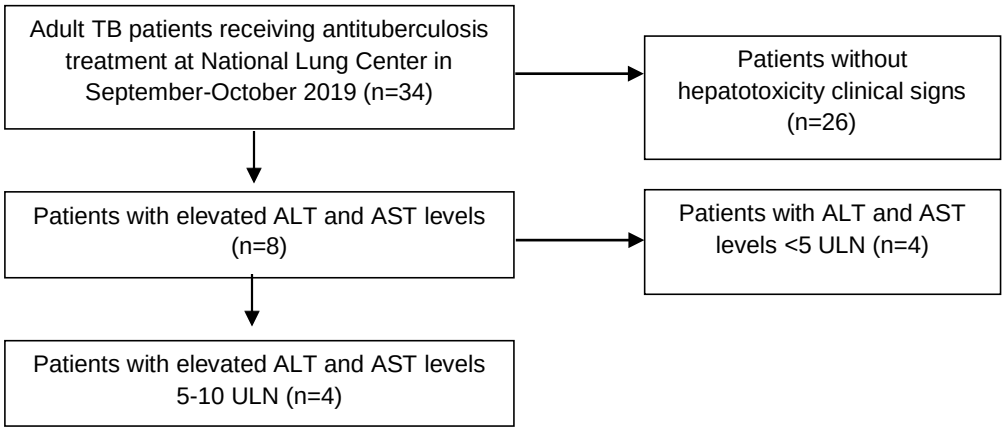

Figure 1. The flow diagram of the study

3. RESULTS

There were 8 patients who met the inclusion criteria and all of them experienced hepatotoxicity during the intensive phase of FDC-AT treatment. From 8 patients, there was 3 patients admitted with grade 1 hepatotoxicity (ALT and AST <2.5 times the ULN), 1 patient with grade 2 hepatotoxicity (ALT 2.5-5 times the ULN), and 4 had grade 3 hepatotoxicity (ALT, AST, bilirubin 5-10 times the ULN) (see table 1).

Table 1. The demography and liver biomarker levels of patients diagnosed with hepatotoxicity at the National Lung Health Center following FDC AT treatment

Patient Code	Sex	Age (years old)	Body weight (kg)	Biomarker levels			Duration of FDC-AT treatment	Hepatotoxicity Grade
				ALT (U/L)	AST (U/L)	Bilirubin (mg/dl)		
A	Male	45	70	75	118	1.75	3 days	1 (Mild)
B	Male	44	38	121	93	1.6	3 weeks	1 (Mild)
C	Female	33	35	101	73	0.86	8 weeks	1 (Mild)
D	Female	30	38	137	74	2.01	8 weeks	2 (Moderate)
E	Female	20	38	250	405	1.34	10 days	3 (Severe)
F	Male	61	55	279	285	13.00	8 weeks	3 (Severe)
G	Male	50	81	358	144	2.03	4 weeks	3 (Severe)
H	Male	27	45	343	330	1.82	5 days	3 (Severe)

In this report, we focus on the severe cases and how the post incidence treatment can alleviate the severity of FDC-AT induced hepatotoxicity.

3.1 Case 1

Patient E, female, aged 20 years old, admitted to the National Lung Center complaining vomiting excessively, at least four times a day. The patient also experienced heartburn, coughing, left abdominal pain and dyspepsia. The patient was prescribed with antiemetic medication, such as ondansetron injection and omeprazole injection, to treat the symptoms. The patient had a history of tuberculosis and had been taking FDC-AT for 10 days. Blood analysis showed the AST level of 405 U/L and ALT of 250 U/L. This suggests that patients experienced impaired hepatic function or grade 3 (severe), as there was an increase in ALT and AST of5-10 times ULN (AST and ALT: 251-500 U/L). The FDC-AT treatment was terminated and the patients was treated with hepatoprotective supplement in the form of Curcuma tablet (*Curcuma xanthorrhiza* 20 mg) every 8 hours and Hepatin (750 mg) every 12 hours. Four days after the hepatoprotective drug administration, the patient's AST and ALT levels were re-examined and showed an improvement (AST 29 U/L and ALT 235 U/L). Two weeks later, after AST and AST values returned to normal, the patient resumed the FDC-AT treatment with close monitoring.

3.3 Case 2

Patient F, male, aged 61 years, admitted to the national Lung Center due to shortness of breath, cough with phlegm, and lethargic. The patient had been suffered from tuberculosis and started FDC-AT treatment in the last 2 months. The patient was hospitalized at the National Lung Health Center for 16 days. Patient's AT treatment was discontinued as the sign of hepatotoxicity was confirmed by a mark elevation of AST (285 U/L), ALT (279 U/L), and total bilirubin (13.00 mg/dL) levels. As the increase in AST and ALT values were 5-10 times ULN, the patients were diagnosed with grade 3 (severe) hepatotoxicity). The patient was then prescribed with hepatoprotective drugs, including Curcuma for every 8 hours and Hepatin for every 12 hours. After administering the hepatoprotective drug for 2 weeks, the AST level decreased to 30 U/L, the ALT to 22 U/L. Although at the time, the bilirubin level was still above the ULN (2.65 mg/dl). As soon as the transaminase enzymes were back to normal, the administration antituberculosis was resumed, however, the form of FDC AT was replaced with single tablet combination of AT drugs to allow time intervals between AT drug administration.

3.2 Case 3

Patient G, aged 50 years old, male, with a history of tuberculosis and FDC-AT treatment for 2 months, complaint for shortness of breath, coughing, chest pain, headaches, and vomiting with a frequency of four times a day. The result of blood examination before consuming FDC-AT showed a normal AST (27 U/L) and ALT (17 U/L) levels. Following the FDC-AT treatment for 4 weeks, the AST level rose to 358 U/L and ALT to 144 U/L. This patient was diagnosed with grade 3 (severe) hepatotoxicity, with an increase in ALT, AST, and bilirubin 5-10 times of the ULN. The FDC-AT treatment was terminated and the hepatoprotective supplement was prescribed in the form of curcuma tablets. Two weeks after curcuma treatments, the AST and ALT levels were re-examined. At that time, the AST and ALT levels of the patients were lower but they were still above the normal levels (137 U/L and 155 U/L for AST and ALT, respectively). The hepatoprotective therapy was continued for 8 weeks. Once the AST and ALT levels

returned to normal, the FDC-AT regimen was changed to the combination of AT single tablets, starting from a lower dose with a close monitoring of hepatotoxicity signs.

3.4 Case 4

Patient H, 27 years old male, was treated due to hemoptysis or coughing up blood for 2 days, left chest pain, heartburn, nausea, vomiting and weakness. The patients had been consuming FDC-AT for 5 days when the clinical symptoms emerged. At the time of admission, the AST level was 330 U/L and ALT was 343 U/L, which indicates level 3 (severe) hepatotoxicity with elevated AST and ALT values of 5-10 times ULN. The FDC-AT treatment was immediately discontinued and hepatoprotective drug was prescribed in the form of Curcuma and Hepatin tablets. In addition to the administration of hepatoprotective drugs, the patient also received omeprazole injection therapy (40 mg i.v daily), codeine tablet (20 mg per 8 hours), and tranexamic acid injection to treat symptoms of heartburn, nausea, vomiting and bloody cough. Following the therapy, the AST level of the patients decreased near the ULN (78 U/L). However, the ALT level was still markedly elevated (389 U/L). For this patient, the AT regimen was changed to a lower risk regimen comprises streptomycin, ethambutol, and rifampicin.

4. DISCUSSIONS

FDC AT regimen has been recommended by WHO as an efficient regimen to treat TB. However, many hepatotoxicity cases in TB patients have been reported after consuming this regimen. An animal model study has shown the administration of FDC AT in rats started to induce liver dysfunction within 2 weeks of administration [10]. In humans, we found the incidence of hepatotoxicity can develop as soon as 3 days following initiation of FDC AT treatment.

To prevent hepatotoxicity, several clinics and hospitals in Indonesia has introduced the use of hepatoprotective supplements from natural sources, such as *Curcuma xanthorriza*, Silymarin, Echinacea extract, etc. Our study showed that in severe cases, the temporary cessation of AT drugs and initiation of herbal supplements to patients seemed to be effective to improve hepatotoxicity in two out of four patients. Consistent with this finding, a previous study has shown Curcuma supplement was able reduce the incidence and severity of hepatotoxicity, shown by a significant decrease in ALT and AST values in TB patients after 4 weeks of treatments [9]. However, in our study, the other two patients did not show a decrease in either ALT or bilirubin even after 2 weeks of receiving hepatoprotective therapy. For one of these patients, the AT treatment regimen was changed into streptomycin, ethambutol, and rifampicin. This is consistent with the guidelines for the management of Drug-Induced Hepatotoxicity (DIH) [7].

The use of herbal supplementation in Indonesia is not only popular in TB patients, but also for other liver injury condition as demonstrated by other clinical study. It has been demonstrated that herbal supplementation of 75 mg *Curcuma xanthoririza*, 50 mg *Arcangelisia flava*, 100 mg *Nigella sativa*, 100 mg *Kleinhovia hospita* and 100 mg *Ophiocephalus striatus* as hepatoprotectors could reduce the levels of ALT by 45.06% and AST by 48.63% after 7 days of treatments in patients with chronic hepatitis [10]. Curcumin has also been used for the treatment of inflammatory disorders of the liver as an antioxidant since it has the capability to increase glutathione S-transferase (GST).

This may improve the free radical scavenger activity of GST and protects cells from harmful reaction, such as lipid peroxidation [11].

5. CONCLUSION

The use of FDC-AT in tuberculosis patients can cause liver dysfunction or hepatotoxicity. The management of hepatotoxicity applied in the National Lung Health Center Makassar is the termination of FDC-AT and initiation of hepatoprotective therapy in the form of herbal supplementation. This therapy is usually well responded; however, in severe cases, it failed to normalized two out of four patients' ALT and bilirubin levels. For patients who regained normal ALT and AST levels, the continuation of the first-line AT drugs was recommended, with a close monitoring of hepatotoxicity symptoms. On the other hand, switching to streptomycin regimen was required for patients whose liver biomarkers did not return to normal after 8 weeks of hepatoprotective treatment. Further research is required to investigate if the improvement of hepatotoxicity occurred due to the herbal supplementation or simply because of the discontinuation of FDC AT therapy.

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