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Prevalence and Onset of Hepatotoxicity Caused by Anti-Tuberculosis Drugs on Pulmonary TB Patients in Wangaya General Hospital Denpasar – Bali in 2016

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Abstract

Introduction: As tuberculosis (TB) endemic country, TB becomes a community health problem in Indonesia. Data from the Global TB Report in 2016 showed that Indonesia is the second most country with TB burden after India. WHO and the Ministry of Health issue a TB prevention program based on the End TB Strategy aimed to reduce morbidity, mortality, and disability due to TB. One of the challenges faced in the management of TB is the side effects of the anti-tuberculosis drug. Hepatotoxicity is the most common side effect. **Aims:** This study aims to determine the prevalence and onset of anti-TB drug-induced hepatotoxicity in TB patients after receiving the anti-TB drug in Wangaya Hospital Denpasar Bali. **Method:** This study used a cross-sectional method by obtaining secondary data of pulmonary TB patients visiting the pulmonary clinic in Wangaya General Hospital from January to December 2016. **Result:** Of 77 subjects, fifty-six percent of them were men. The highest prevalence was found in the 41-50 years age group (26.9%), while the lowest was found in the 81-90 years age group (1.2%). Anti-TB drug-induced hepatotoxicity occurred in 6.5% of subjects. The most frequent onset of hepatotoxicity occurred within the second week of medication. Anti-TB drug-induced hepatotoxicity occurred in 6.5% of subjects. The most frequent onset of hepatotoxicity occurred within the second week of medication. **Conclusion:** Based on this study, we suggest a liver function test before and after two weeks of an anti-TB drug.

Keyword — Prevalence, Tuberculosis, Pulmonary TB, Hepatotoxicity, ANTI-TB DRUG

Abstrak

Pendahuluan: *Sebagai negara endemis tuberkulosis (TB), TB menjadi masalah kesehatan masyarakat di Indonesia. Data Global TB Report tahun 2016 menunjukkan bahwa Indonesia merupakan negara dengan beban TB terbanyak kedua setelah India. WHO dan Kementerian Kesehatan mengeluarkan program pencegahan TB berdasarkan Strategi End TB yang bertujuan untuk menurunkan angka kesakitan, kematian, dan kecacatan akibat TB. Salah satu tantangan yang dihadapi dalam pengelolaan TB adalah efek samping obat anti tuberkulosis. Hepatotoksisitas adalah efek samping yang paling umum.* ***Tujuan:*** *Penelitian ini bertujuan untuk mengetahui prevalensi dan onset hepatotoksisitas akibat obat anti TB pada pasien TB setelah menerima obat anti TB di Rumah Sakit Wangaya Denpasar Bali.* ***Metode:*** *Penelitian ini menggunakan metode potong lintang dengan memperoleh data sekunder pasien TB paru yang berkunjung ke poli paru di RSUD Wangaya dari bulan Januari sampai Desember 2016.* ***Hasil:*** *Dari 77 subjek, lima puluh enam persen di antaranya adalah laki-laki.*

Prevalensi tertinggi ditemukan pada kelompok usia 41-50 tahun (26,9%), sedangkan terendah ditemukan pada kelompok usia 81-90 tahun (1,2%). Hepatotoksisitas akibat obat anti-TB terjadi pada 6,5% subjek. Onset hepatotoksisitas yang paling sering terjadi dalam minggu kedua pengobatan. Hepatotoksisitas akibat obat anti-TB terjadi pada 6,5% subjek. Onset hepatotoksisitas yang paling sering terjadi dalam minggu kedua pengobatan. ***Kesimpulan:*** *Berdasarkan penelitian ini, kami menyarankan tes fungsi hati sebelum dan setelah dua minggu menggunakan obat anti-TB.*

Kata kunci— Prevalensi, Tuberkulosis, TB Paru, Hepatotoksisitas, OBAT ANTI TB

I. INTRODUCTION

Indonesia placed third in the highest TB burden after India based on a report from the Global TB Report in 2016.[1] In respect to the high incidence, Indonesia works together with the World Health Organization (WHO) in implementing a strategy in the management of TB in Indonesia, known as the Directly Observed Treatment Short Course (DOTS). One of the programs is implementing tuberculosis management using anti-tuberculosis drug.[2–4]

The management of tuberculosis is divided into two phases, i.e. the intensive phase (2 months) and the advanced phase (4 months). The first-line drugs include isoniazid (INH), rifampicin, pyrazinamide (PZA), streptomycin, and ethambutol.[5–7] These first-line medications are commonly used and resulted in various side effects. Long-term use can cause side effects such as skin reaction, gastrointestinal dysfunction, and neurological dysfunction.[8,9]

Hepatotoxicity is a side effect that most type of first-line ANTI-TB DRUG has. This effect also has the most serious impact. Anti-TB drug-induced hepatotoxicity is an inflammation of the liver organ caused by a reaction to the antituberculosis drug. The medicines that can cause hepatotoxicity are PZA, INH, and rifampicin. Rifampicin as the main drugs for TB has the lowest hepatotoxic effect compared to PZA and INH.[5]

Hepatotoxic symptoms usually resemble other hepatitis symptoms. An early marker of hepatotoxic is an increase of transaminase enzymes in serum which consists of aspartate amino transaminase/glutamate oxaloacetate transaminase (AST/GOT) excreted in parallel with alanine aminotransferase/glutamate pyruvate transaminase (ALT/GPT), which is a more specific marker to detect liver damage.[5,10]

The WHO classifies hepatotoxic into four grades. Grade I is marked by an increase of ALT > 1.25 – ≤ 3x normal, grade II increase > 3 – ≤ 5x normal, grade III ALT increase > 5 – ≤ 10x normal, and grade IV if ALT increase > 10x normal.[5,8]

Studies conducted in several countries found that the incidence of anti-TB drug-induced hepatotoxicity varies. For example, a study in Nepal showed a prevalence of anti-TB drug-induced hepatotoxicity of 38%, while in Iran, the prevalence of anti-TB drug-induced hepatotoxicity reaches 27%.[8,11]

Every individual has a different vulnerability. Therefore, side effects such as liver dysfunction have a different onset. Usually, the side effect of anti-TB drug-induced hepatotoxicity occurred 1-2 months after anti-TB drug consumption. Other things that can affect onset are risk factors of the patients. Based on several studies, the risk factors of anti-TB drug-induced hepatotoxicity include age, gender, nutritional status, history of previous liver disease, other infectious diseases such as HIV, alcoholism, hepatitis B or hepatitis C carrier, abusive use of drugs, and its acetylation status.[12]

There are limited studies on the incidence of anti-TB drug-induced hepatotoxicity and other related factors in Indonesia and they are outdated. Thus, there is a lack of data. Therefore, a study on the number of pulmonary tuberculosis patients with anti-TB drug-induced hepatotoxicity and the onset of hepatotoxicity should be conducted.

This study was conducted in the Wangaya General Hospital. By knowing the incidence and onset of anti-TB drug-induced hepatotoxicity, medical personnel, especially general physician and pulmonary medicine specialist who manage cases of TB patients is expected to be more aware in educating patients, especially pulmonary TB patients with risk factors of liver dysfunction. It can

also become a consideration and anticipation in the administration of an anti-TB drug. If the risk factors are previously known, the cost of medication is expected to be minimized. Pulmonary TB patients, especially those with certain risk factors of anti-TB drug-induced hepatotoxicity, are expected to become more aware and avoid triggering factors.

II. Material And Methods

This study used an observational or non-experimental cross-sectional design by following a descriptive design. We used secondary data from pulmonary TB patients who visited the pulmonary clinic in Wangaya General Hospital from January – December 2016 from the patients' register.

The population and sample of this study were all outpatients and inpatients diagnosed with pulmonary TB aged ≥ 17 years old who visited the pulmonary clinic of Wangaya General Hospital from January – December 2016 and fulfilled the inclusion and exclusion criteria. Inclusion criteria: Pulmonary TB patient aged ≥ 17 years who received ANTI-TB DRUG in the pulmonary clinic and the treatment ward of Wangaya Hospital. Exclusion criteria: pulmonary TB patients referred to other health facilities.

III. Results

A. Incidence of pulmonary TB patients

The incidence of pulmonary TB patients visited the pulmonary clinic of Wangaya General Hospital Denpasar from January – December 2016 was 77 patients and 5 of them had anti-TB drug-induced hepatotoxicity.

Table 1. Distribution of pulmonary TB patient proportion based on gender (N = 77)

Gender	n	%
Male	43	56
Female	34	44

B. Samples characteristic

Pulmonary TB was more common in male patients, with 43 people (56%) compared to female patients with 34 people (44%), as seen in Table 1. Pulmonary TB was mostly found in patients aged 41-50 years old, with 20 people (26.9%), followed by 21-30 years old with 15 people (19.3%), 51-60 years old with 14 people (18%), 31-40 years old with 10 people (12.9%), 61-70 years old with 9 people (11.6%), 17-20 years old with 5 people (6.3%), 71-80 years old with 3 people (3.8%), and the lowest in 81-90 years old group with 1 person (1.2%) (Table 2).

Table 2. Distribution of pulmonary TB patient proportion based on age

Age (year)	n	%
17 – 20	5	6.3
21 – 30	15	19.3
31 – 40	10	12.9
41 – 50	20	26.9
51 – 60	14	18
61 – 70	9	11.6
71 – 80	3	3.8
81 – 90	1	1.2

The incidence of anti-TB drug-induced hepatotoxicity in pulmonary TB patients was 5 people (6.5%) and incidence in patients without anti-TB drug-induced hepatotoxicity was 72 people (93.5%) (Table 3).

Table 3. Distribution of patient proportion with anti-TB drug-induced hepatotoxicity and without anti-TB drug-induced hepatotoxicity

Anti-TB drug-induced hepatotoxicity	n	%
Yes	5	6.5
No	72	93.5

C. The onset of anti-TB drug-induced hepatotoxicity

The onset of anti-TB drug-induced hepatotoxicity in week 2 was found in 3 people (60%), week 2 was found in 1 person (20%), and week 4 in 1 person (20%) (Table 4).

TABLE 4. ONSET DISTRIBUTION OF ANTI-TB DRUG-INDUCED HEPATOTOXICITY IN PULMONARY TB PATIENTS WHO RECEIVED ANTI-TB DRUGS

The onset of anti-TB drug-induced hepatotoxicity	n	%
Week 2	3	60
Week 3	1	20
Week 4	1	20

IV. DISCUSSION

With the increase of TB incidence around the world, many patients have a potential risk of hepatotoxicity due to anti-tuberculosis drugs. Anti-TB drug-induced hepatotoxicity is a type of liver disease caused by various kinds of drugs. The use of combination drugs in the management of TB such as isoniazid, rifampicin, and pyrazinamide is associated with the increase of hepatotoxicity incidence compared to isoniazid alone for TB prophylaxis.[12] This study was conducted to determine the prevalence and onset of hepatotoxicity due to Category I anti-TB drugs in Wangaya Hospital, Denpasar in 2016.

This study was conducted in Wangaya Hospital using the register of pulmonary TB patients visiting the pulmonary clinic from January – December 2016. There were 77 samples diagnosed with pulmonary TB. Based on the results of this study, the highest percentage was male patients with 56%, while female patients consisted only of 44%. The previous study found similar result that male patients consisted of 81.2%, while female patients were 18.8%.[13]

Several journals also stated that the incidence was higher in male patients because of higher mobility. Patients aged 41-50 years old showed the most percentage, with 20 people (26.9%) and the lowest was 81-90 years old with 1 person (1.2%). This was in accordance with the previous study, where 75% of pulmonary TB patients were found in the most economically productive age (15-49 years old).[14]

Drug-induced hepatitis (DIH) is a form of inflammation to the liver organ caused by anti-tuberculosis drugs. In Indonesia, it is known as anti-TB drug-induced hepatotoxicity. The anti-tuberculosis drug is a regimen used to treat tuberculosis. Anti-TB drug-induced hepatotoxicity has various definitions based on several studies.[15,16] In general, however, the definition of anti-TB drug-induced hepatitis is the increase of ALT level of 1.5 times more than normal, which occurred after a minimum of 4 weeks of therapy. The prevalence of anti-TB drug-induced hepatotoxicity is almost different in each country.[17,18]

However, developing countries tend to show a higher prevalence. In Wangaya Hospital from January to December 2016, there were 5 people (6.5%) who experienced anti-TB drug-induced hepatotoxicity and 72 people (93.5%) did not experience anti-TB drug-induced hepatotoxicity. From these 5 people, the onset of anti-TB drug-induced hepatotoxicity in week 2 was found in 3 people (60%), in week 3 in 1 person (20%), and week 4 in 1 person (20%).

This was in line with Zhao et al (2019)[19] who stated that around 10% of tuberculosis patients receiving isoniazid experienced an increase in the concentration of aminotransferase serum within the first weeks of therapy and seem to show an adaptive response to drugs' toxic metabolites. The concentrate of aminotransferase will continue to decrease to normal limits within several weeks whether the isoniazid is continued or not. Only 1% developed into viral hepatitis, 50% of cases occurred within the first two months, and the rest occurred several months later.

The onset is generally fast. The symptoms include malaise, icterus, acute liver failure, especially if the drug is continued after the onset of hepatotoxicity. If the hepatocyte lesion is more dominant, then the concentration of aminotransferase can

increase to at least five times the normal limit, while the increase of alkaline phosphatase and bilirubin stands out in cholestasis. Most idiosyncratic drug reaction includes hepatocyte damage of all hepatic lobules with varies necrotic and apoptotic degree. In this case, the hepatitis symptoms usually occur within several days or weeks after consuming drugs and may keep developing even after discontinuation of drugs.[10,11,18,20]

The reaction of liver cells dysfunction and damage more often occur within the first 2 months of anti-tuberculosis treatment. However, it may also occur anytime within the medication period. The symptoms and clinical signs of liver dysfunction are nausea, vomiting, followed by reduced appetite. After the liver and gallbladder have been damaged, the sclera of the eye and the skin on the body will turn yellow and may be accompanied by pain in the upper abdominal area. However, these symptoms and clinical signs must be supported with blood laboratory tests to assess liver function and damage to liver cells and gallbladder.[5,8]

The main pathway of rifampicin is deacetylation into deacetyl rifampicin and separated hydrolysis produced 3-formyl rifampicin. Rifampicin can cause hepatocellular dysfunction during early therapy which may be cured without discontinuation of the drug. The mechanism of rifampicin-induced hepatotoxicity is not clear and unpredictable. No proof shows a toxic metabolite from this drug.[5,20]

The side effect reaction of tuberculosis therapy is affected by the genotype of patients in certain races. The Asian race, which genotype is considered a rapid acetylator tends to be more vulnerable to isoniazid-induced hepatotoxicity. For example, in India, the risk of hepatotoxicity is higher compared to the western countries (11.5% vs 4.3%). Indonesians are mostly included in the Asian race and may be classified into the rapid acetylator genotype.[5] The British Thoracic Society suggested that if the increase of ALT and or AST enzyme is more than 3 times the normal value, or there is an increase of bilirubin, or if the patient shows clinical symptoms of hepatitis, then the drugs should be discontinued and reviewed until the hepatotoxicity parameter declines into a normal level. Within several days after discontinuation of the anti-TB drug, liver enzymes will return to normal.[9,11] This showed that the signs and symptoms in patients are related to the regulation of anti-TB drug use. The American Thoracic Society recommends adequate supervision on clinical symptoms and liver function value to avoid morbidity and mortality, thus reducing the cost of the disease.[12,20]

V. CONCLUSION

The prevalence of anti-TB drug-induced hepatotoxicity is almost different in every country. However, developing countries tend to show a higher prevalence.17 In Wangaya General Hospital, from January to December 2016, there were 5 people (6.5%) with anti-TB drug-induced hepatotoxicity and 72 people (93.5%) without anti-TB drug-induced hepatotoxicity. From these 5 people, the onset of anti-TB drug-induced hepatotoxicity in the second week was found in 3 people (60%), the third week in 1 person (20%), and the fourth week in 1 person (20%).

Liver function assessment should be conducted in pulmonary TB patients who will receive anti-TB drug therapy to minimize the incidence of anti-TB drug-induced hepatotoxicity.

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REFERENCES

[1] Kementerian Kesehatan Republik Indonesia. Petunjuk teknis pemeriksaan TB menggunakan tes cepat molekuler. Jakarta: Kementerian Kesehatan RI; 2017.
[2] Kementerian Kesehatan Republik Indonesia. Tuberkulosis: Temukan Obati Sampai Sembuh. Jakarta; 2016.
[3] World Health Organization (WHO). WHO treatment guidelines for drugresistant tuberculosis. Geneva: World Health Organization's; 2016.
[4] World Health Organization (WHO). Global Tuberculosis Report 2019. 2019.
[5] Soedarsono, Riadi ARW. Tuberculosis drug-induced liver injury. J Respirasi. 2020;6(2):49–54.
[6] Kementerian Kesehatan Republik Indonesia. Petunjuk Teknis Manajemen dan Tatalaksana Tuberkulosis (TB). Jakarta: Kementerian Kesehatan RI; 2016.
[7] Kemenkes RI. Pedoman Nasional Penangulangan Tuberkulosis. Jakarta: Kementerian Kesehatan RI; 2014.
[8] Song JH, Yoon S, Park TY, et al. The clinical impact of durg-induced hepatotoxicity on anti-tuberculosis therapy: A case control study. Respir Res. 2019;20:1–8.
[9] Fishman JA, Grippi MA, Kotloff RM, et al. Fishman's Pulmonary Disease and Disorders Fifth Edition. New York: Elsevier Saunder; 2016.
[10] Yu CY; Mao YM; Chen JJ; et al. CSH guidelines for the diagnosis and treatment of drug-induced liver injury. Hepatol Int. 2017;11(3):221–41.
[11] Abera W, Cheneke W, Abebe G. Incidence of antituberculosis-drug-induced hepatotoxicity and associated risk factors among tuberculosis patients in Dawro Zone, South Ethiopia: A cohort study. Int J Mycobacteriology. 2016;5:14–20.
[12] Saskar S, Ganguly A, Sunwoo HH. Current overview of anti-tuberculosis drugs: Metabolism and toxicities. Mycobact Dis. 2016;6(2):1–6.
[13] Mirlohi M, Ekrami A, Shirali S, et al. Pourmotahari F. 2016. Hematological and liver toxicity of anti-tuberculosis drugs. Electron Physician. 2016;8(9):3005–10.
[14] Jeong I, Park J, Cho Y, et al. Drug-induced hepatotoxicity of anti-tuberculosis drugs and their serum levels. J Korean Med Sci. 2015;30:167–72.
[15] Kasper; Denis L; et al. Harrison's Principles of Internal Medicine 19th Edition. New York: McGraw-Hill Education; 2018.
[16] Aru W; Idrus A; Marcelus S; et al. Buku Ajar Ilmu Penyakit Dalam. 5th ed. Jakarta: Interna; 2013.
[17] European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Drug-induced liver injury. J Hepatol. 2019;30(20):1–40.
[18] Bjornsson E. Review article: drug-induced liver injury in clinical practice. Aliment Pharmacol Ther. 2010;32:3–13.
[19] Zhao H, Wang Y, Zhang T, et al. Drug-induced liver injury from anti-tuberculosis treatment: A retrospective cohort study. Med Sci Monit. 2019;26:1–8.
[20] Ambreen K, Sharma R, Singh KP, et al. Anti-tuberculosis drug-induced hepatotoxicity: A review. Int J Adv Biotechnol Res. 2014;5(3):423–37.
[21] Anggraini D, Laboratory Examination in Hepatocellular carcinoma. Health & Medical Journal. 2019 1(2): 50-3. https://doi.org/10.33854/heme.v1i2.241.g191
[22] Anggraini, D., & Oktora, M. Z. (2021). Hematology Profile of Tuberculosis Lymphadenitis Patients at Siti Rahmah Hospital, Padang, Indonesia. INDONESIAN JOURNAL OF CLINICAL PATHOLOGY AND MEDICAL LABORATORY, 27(3), 271-275.