Association between the Adverse Drug Reactions to Anti-tubercular Drugs and the Treatment Outcome: A Retrospective, Cohort Study

Kurniaty Linggom[1]*, Purwantyastuti[1], Nafrialdi[1], Rasmin Menaldi[2], Febriony Citra[1]

1. Department of Clinical and Therapeutic Pharmacology, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia.
2. Department of Pulmonology and Respiration, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia.

Abstract

Patients with tuberculosis (TB) and positive sputum smears are source of disease transmission, effective treatment will break chain. The problem of therapeutic success seen from the success rate of treatment in Indonesia, especially in government hospitals is still 50%. We determined the association between adverse drug reactions (ADRs) and successful TB treatment at the Persahabatan Hospital.

In this retrospective cohort study (174 subjects), the number of ARDs was compared with treatment outcomes among patients with positive sputum smears TB and receiving category I treatment between September 1, 2015, and September 30, 2016. Data were analyzed by chi-square and Fisher's exact tests.

The number of ADRs was 34.5% (60/174 subjects). Minor ADRs were more common than major ADRs (46/60, 76.6 % vs 14/60, 23.3 %). The Success of TB treatment was 70.9% (39/55) in group with ADRs and 62 % (49/79) in group without ADRs.

There was no association between incidence of ADRs and successful TB treatment (*P* = 0.29, chi-square test). However, the categorized of ADRS was related to the success rate of TB treatment, (*P* = 0.03; Relative Risk = 0.5; CI= 0.2-1). Incidence of ADRs was 34.5% with minor adverse events being more common. There was no association between occurrence of ADRs and successful TB treatment.

Clinical article (J Int Dent Med Res 2019; 12(3): 1170-1173)

Keywords: Tuberculosis, Adverse Drug Reaction, Successful.

Received date: 11 February 2019 **Accept date: 19 March 2019**

Introduction

Tuberculosis (TB) is an infectious disease caused by the Mycobacterium tuberculosis.[1,2] In 2011, Indonesia recorded the fourth largest number of TB cases in the world after India, China, and South Africa.[3] The World Health Organization (WHO) Global Report 2015 data shows that the incidence of TB in Indonesia remains high, ranking second in the world after India.[4] An effective treatment strategy is important for controlling the spread of TB and for breaking the chain of transmission.[3]

Xu et al, reported that the most common events leading to the failure of TB treatment, include side effects (37.8%); symptom improvement, but failure to complete the treatment regime (26.8%); long treatment duration and high drug dose (15,9%); concerns of side effects (15,9%); other health problems (15.9%); and medical costs (15.9%).[5]

According to the ministry of Health of Republic of Indonesia, 42% of patients with TB received treatment at government hospital in 2004.[6] The aim of this study was to determine the association between the occurrence of adverse drug reactions (ADRs) and successful treatment of TB at Persahabatan Hospital (Jakarta, Indonesia).

Materials and methods

The protocol of this retrospective cohort study was approved by the Ethics Committee of Persahabatan Hospital. Data were obtained from patient medical records and TB cards. The inclusion criteria were: 1) New patients with sputum smears- positive for TB; 2) Treatment

Corresponding author:
Kurniaty Linggom
Department of Clinical and Therapeutic Pharmacology, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia.
E-mail: linggom.kurniaty@gmail.com

with category I fixed- dose drug combinations (FDCs); 3) Age, 18-65 years. While the exclusions criteria were: 1) Extra lung TB; 2) Diagnosis of Human Immunodeficiency Virus (HIV); 3) Incomplete medical records.

All patient who fulfilled the inclusion and exclusion criteria for the period September 1, 2015 to September 30, 2016 were eligible for inclusion to obtain an overview the number of ADRs.

Adverse drug reactions (ADRs) were categorized as major or minor according to Ministry of Health.[3] Researcher gets medical records to saw the sympton and follow-up until end of TB therapy. The treatment outcomes were classified in accordance with the lung doctors association Indonesia.[2]

The estimated sample size was calculated using the following formulas for nominal data with a single sample for estimated proportion of a population. Therefore, the minimum subject recruited in this study were 89 subjects.

All research data were recorded on forms and software. Data analysis was conducted with the chi-squared and Fisher's exact tests with IBM SPSS Statistics for windows, version 20.0, software (IBM Corp, Armonk, NY, USA). Data are presented in narrative form and descriptive tables.

Results

Of 251 patients with TB pulmonary smear-positive treated category I FDCs, only 174 patients met the inclusion and exclusion criteria.

Subject characteristics

As shown in Table 1, ADRs were more common in male subjects 43/60 (71.7%) with the highest incidence among those aged 18-35 years (48.35%).

Variable		ADR			
		Yes		No	
		n=60	(%)	n=114	(%)
Sex	Male	43	(71.7)	80	(70.2)
	Female	17	(28.3)	34	(29.8)
Age, years	18–35	29	(48.3)	41	(36)
	36–45	7	(11.7)	30	(21.3)
	46–55	13	(21.7)	25	(21.9)
	56–65	11	(18.3)	18	(15.8)

Table 1. Distribution of Subjects Characteristics.

Adverse reactions to anti-TB drug

As shown in Table 2, ADRs occurred in 60/174 subjects with minor ARDs more common than major drug reactions (46/60, 76.7% vs 14/60, 23.3%). Management of ADRs is based on the symptoms observed. According to available data, major ADRs are managed by temporary stopping treatment. In addition, of 46 patients with minor ADRs, treatment was continued without additional therapy in 21 (45.7%), while additional treatment or change to the therapeutic dose was used in the remaining 25 (54.3%).

Side effects are typically treated with analgesic drugs (ibuprofen and meloxicam), anti-allergy (cetirizine), anti-nausea and vomiting (domperidone), antiulcer drugs (sucralfate and omeprazole), uric acid synthesis inhibitor (allopurinol), vitamins (vitamin B6, vitamin B complex), and complementary medicine (curcuma).

Variable		n	(%)
ADR			
A. Major		14	(23.3)
	Drug-induced hepatitis	5	(8.3)
	Erythema and itching	8	(13.3)
	Death	1	(1.6)
B. Minor		46	(76.7)
	Itching	7	(11.6)
	Itching, nausea, and vomiting	1	(1.6)
	Itching and visual impairment	1	(1.6)
	Nausea	10	(16.6)
	Nausea, vomiting	6	(10)
	Dyspepsia	1	(1.6)
	Nausea, itching, and join pain	2	(3.3)
	Join pain	5	(8.3)
	Myalgia	4	(6.6)
	Swollen joints	2	(3.3)
	Cramping	1	(1.6)
	Neuropathy	3	(5)
	Common cold	1	(1.6)
	Vertigo	1	(1.6)
	Yellowing of the skin	1	(1.6)
Time of ADR		60	
	Intensive phase	46	(76.7)
	Continuous phase	14	(23.3)
FDC Therapy		60	
	Continuous	46	(76.7)
	Cessation of FDC or alternative regimens	14	(23.3)

Table 2. Overview of Pharmacotherapy Effects of Anti-TB drugs, Time of ADRs, and FDC Therapy (n = 60).

The association between ADRs and successful TB treatment

As shown in Table 3, treatment was more successful for patients with ADRs than without ADRs (39/56, 72 % vs 49/79, 62 %).

Variable	ADRs			
	Yes		No	
	n =60	(%)	n = 114	(%)
Outcome				
Cured (BTA conversion)	29	(48.3)	28	(24.6)
Complete (clinical and X-rays)	10	(16.7)	21	(18.4)
Failure	0		1	(0.8)
Lost to follow-up	15	(25)	27	(23.7)
Not evaluated	4	(6.7)	35	(30.7)
Died	1	(1.7)	2	(1.8)
Still in Therapy	1	(1.7)	0	(0)

Table 3. TB Treatment Outcomes.

As shown in table 4, there was no association between the incidence of ADRs and successful TB treatment [*P* = 0.36, relative risk (RR) = 1.1; 95% confidence interval (CI) = 0.87 – 1.4]. But the categorized of side effects was association to successful TB treatment, (*P* = 0.03; RR =0.5: 95% CI =0.2 -1).

Variable	Outcome of TB Therapy			*p* value
	Successful n (%)	Not successful n (%)		
ADR				
Yes	39 (70)	17 (30)	56 (100)	0.36
No	49 (62)	30 (38)	79 (100)	
Total	88 (65)	47 (35)	135 (100)	
Category ADR				
Major	5 (42)	7 (58)	12 (100)	0.03*
Minor	34 (77)	10 (23)	44 (100)	
Total	39 (70)	17 (30)	56 (100)	

Chi-square and Fisher's exact tests, * significant difference

Table 4. The Association Between the Number and Categorized of ADRs with The Outcome TB Treatment.

Discussion

The study cohort included 174 patients with TB (80 men and 34 women). According to the 2015 Health Profile Data of the Ministry of Health of Indonesia, TB occurs in 1.5 fold more in men than women.[7]

According to a report by Athira et al.,[8] ADRs were more common in males than females (69% vs. 31%), which is in agreement with the findings of the present study number of ADRs male 43/60 (71.7%) and female 17/60 (28.3%). However, if we look at the data of number of males and females in the sample, the percentage is similar to subject with or without ADRs.

The Incidence of ADRs was 34% (60/174 subjects), which was higher than reported by the WHO in 2002 (3%-6%) [9], and prospective observational studies conducted in India in 2013 and 2014 (93/511, 18.2%).[8]

In this study, ADRs were categorized as major or minor (table 2). The incidence of major 14/60 (23.3%) and minor 46/60 (76.7%) ADRs encountered in this study were in accordance with previous studies of possible treatment options for TB.[2,9-11] A study conducted in Columbia by Marra et al.[12] to evaluate the treatment of patients with active pulmonary TB from 2000–2005 reported that the incidence of ADRs was 30% (318 of 954 subjects).

Most ADRs in this study happened during the intensive phase (46/60, 76.7%). Athira et al, [8] reported that the incidence of ADRs in the intensive phase was greater than in the continuous phase. This problem can cause a decision to stop treatment and cause the bacteria to become resistant to existing drugs.[8] Thus, it is very important for health workers to explain to patients the importance of continuing treatment.

The target national success rate of TB treatment in 2015 is the same as the figure set by the WHO of 85%.[7,11]In this study, the treatment success rates was 39/56 (70%) in the group with ADRs and 49/79 (62%) in the group without side effects, both of which were lower than the national success rate of TB treatment.

In this study, 3 (1.7%) of 174 patients were died during TB treatment. The cause of death recorded in the group with ADRs adverse included peritonitis due to perforation of the viscus, sepsis, pulmonary TB, anemia, and leukopenia. In the group without ADRs, the causes of death were type II respiratory failure, bronchiectasis, pulmonary TB, and immunocompromised but HIV-negative. The mortality rate due to TB was still high as compared to the 2015 WHO data which reported a death rate of 12.5% (1.2/9.6 million patients).[13]

Chi-square and Fisher's exact tests analysis showed that there was no association between the incidence of ADRs and successful TB treatment (*p* = 0.36; RR =1.1; 95% CI = 0.87–1.4), while the categorized of ADRs was association to successful TB treatment (*p* = 0.03; RR = 0.5; 95% CI = 0.2–1).

A study conducted in a tertiary hospital by Bai et al.[14] in India reported that 96 (22.1%) of 434 patients with pulmonary TB experienced

drug side effects. The incidence of side effects of the drug resulted in 3 (3%) of 96 patients discontinuing treatment.

The limitation of the study were other external factors could not be known and outcome evaluation of further data of patients who were not evaluated.

Conclusion

The incidence of ADRs in this study was 34.5%. Most ADRs in this study were minor. There was no association between occurrence of ADRs and successful TB treatment based on the chi-square test. But a higher treatment success rate was seen in those with minor adverse drug reactions compared with that in those with major reactions.

Declaration of Interest

There are no conflicts of interest to declare. All authors have made substantive contribution to this study and manuscript, and all have reviewed the final paper prior to this submission. The authors would like to thank staff members of department of clinical and therapeutic Pharmacology University of Indonesia, management and education center of Persahabatan Hospital.

References

1. Kemeterian Kesehatan RI 2015. Laporan Akuntabilitas Kinerja Kementerian Kesehatan Tahun 2014. Jakarta: Kementerian Kesehatan RI 2015; hal. 46-57. [ISBN 978-602-235-824-4].
2. Isbaniyah F, Thabrani Z, Soepandi ZS, et al. Tuberkulosis Pedoman Diagnostik dan Penatalaksanaan di Indonesia. Jakarta: Perhimpunan Dokter Paru Indonesia 2011; p.1-66.
3. Kementrian Kesehatan RI. Pedoman Nasional Pelayanan Kedokteran Tata Laksana Tuberkulosis. Jakarta: Kementrian Kesehatan RI 2013; p.1-103.
4. World Health Organization. Disease Burden and 2015 Target Assessment. Dalam: Global tuberculosis report, 2015. 20th ed. 2015; p.8-35.
5. Xu W, Lu Wei, Zhou Y, Zhu L, Shen H, Wang Z. Adherence to antituberkulosis among pulmonary tuberkulosis patient: a qualitative and quantitative study. BMC Health Service Res 2009;9(169):1-8.
6. Kementrian Kesehatan RI. Terobosan menuju akses universal: Strategi Nasional Pengendalian TB di Indonesia 2010-2014. Jakarta: Kementrian Kesehatan RI 2011.
7. Kementrian Kesehatan Republik Indonesia. 2015 Profil Kesehatan Indonesia. Kemenkes RI 2016; p.160-7.
8. Athira B, Manju CS, Jyothi E. A study on adverse drug reaction to first line antitubercular drugs in dots therapy. International Journal of Pharmacology and Clinical Sciences 2015(4); p.7-11.
9. Phanouvong S, Vrakking H, Blanc L, et al. Operational guide for national tuberculosis control programmes on the introduction and use of fixed dose combination drugs. WHO 2002; p.18.
10. Departemen Kesehatan RI dan IDI. Panduan Tatalaksana Tuberkulosis sesuai dengan strategi DOTS untuk dokter praktek swasta. Jakarta: Menteri Kesehatan RI 2009; p.1-28.
11. Kementrian Kesehatan RI Direktorat Jendral Pengendalian Penyakit dan Penyehatan Lingkungan. Pedoman Nasional Pengendalian Tuberkulosis. Jakarta: Kementerian Kesehatan RI 2014; hal.1-150.
12. Marra F, Marrs CA, Bruchet N, et al. Adverse drug reaction associated with first-line anti-tuberculosis drug regimens. Int J Tuberc Lung Dis 2007; 11(8):868-75.
13. Deck DH, Winston LG. Antimycobacterial Drugs. In: Katzung BG, Masters SB, Trevor AJ, eds. Basic and clinical Pharmacology. 12th ed. United States: The McGraw-Hill companies; 2012:p.839-47.
14. Bai GP, Ravikumar P, Salma U. A study of adverse drug reaction among pulmonary tuberculosis patients treated under DOTS in a tertiary care hospital. Int J Basic ClinPharmacol 2017; 6(4):779-83.