The Impact Of Adverse Drug Reaction Occurrence To Drug Adherence Level: A Cross-Sectional Study In Patients With Tuberculosis

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ABSTRACT

Tuberculosis is well-known as an ancient disease that remains a global challenge until this era. The main goals of the treatment are to eradicate the colonisation of acid-resistant basil and prevent the occurrence of drug resistance. However, the accomplishment of this multi-drugs therapy is not always achieved due to several obstacles, one of which is patient adherence to the treatment. Patient adherence is a considerable determinator that is influenced by a number of factors including the adverse drug reaction (ADR) which appeared to the patients. This study aimed to examine the correlation between adverse drug reaction and patients' adherence to the anti-tuberculosis category 1 regimen during the intensive phase. This observational analytic study used cross-sectional method and involved 35 subjects. Drug adherence level was measured using Medication Adherence Scale-8 (MMAS-8) questionnaire, the characteristics of ADR were collected using checklist sheet of ADR, and the probability of ADR was analyzed using Naranjo Algorithm. The results showed that the majority of patients in this study were adherence to anti-tuberculosis drugs (62,8%) and experienced ADR (74,3%). Bivariate analysis using chi-square statistical test showed there was a significant correlation between adverse drug reaction and adherence to anti-tuberculosis drugs during the intensive phase treatment (P-value = 0,02288).

Keywords: tuberculosis; adverse drug reactions; adherence

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INTRODUCTION

The World Health Organization report in 2018 states that of the 30 countries with the highest TB burden, Indonesia is in third place after India and China which are recorded as contributing 87% of TB cases worldwide. The total number of TB cases in Indonesia in 2018 were 566,623 cases, where this number has increased from 2017 which was 446,732 cases (Kemenkes RI, 2020). Aceh Province, according to data from the Aceh Health Office the number of TB cases found in 2016 was 3,410 cases and increased in 2017 to 6,638 cases. The success rate of therapy for the provincial average in 2018 only reached 84.6%, this number has decreased from 2017 which was 85.7% (Kemenkes RI, 2019). This indicates that Indonesia can carry out treatment but still lacks in controlling it. One of the challenges in treating this disease is the low compliance of patients in taking medication. Many factors influence drug non-adherence including age, lack of access to treatment facilities, the complexity of therapeutic regimens, drug side effects, high treatment costs, and lack of social support (Bagchi et al., 2010). The incidence of side effects of antituberculosis drugs most commonly appear in the intensive phase. As the consequence the probability of patients' non-adherence at this phase is bigger than in the continuation phase (Kemenkes RI, 2019).

METHODS

The study was conducted at the Directly Observed Treatment Shortcourse (DOTS) Polyclinic of the Integrated Tuberculosis Service (PTT) in Regional General Hospital dr. Zainoel Abidin (RSUDZA), Banda Aceh, during April 2019. This research was an analytic observational study using a cross-sectional method. Data collection was carried out prospectively using the Naranjo Algorithm to assess the occurrence of ADR and the MMAS-8 questionnaire to assess patient medication adherence which was completed through guided interviews. The Naranjo algorithm (also known as the Naranjo scale) is a questionnaire designed to determine

whether an adverse effect is caused by the drug or other factors. This scale can be used to identify side effects caused by drugs more quantitatively (BPOM, 2012).

The population in this study were TB patients who were taking intensive phase of category 1 treatment at RSUDZA. We involved 35 subjects that were selected based on inclusion and exclusion criteria with a quota sampling method. The inclusion criteria were TB patients with: (1) age more than 19 years; (2) using OAT category 1; (3) ambulatory care; and (4) treatment of intensive phase. The exclusion criteria were TB patients with: (1) any co-morbidity; (2) taking drugs other than OAT; and (3) incomplete medical records.

The demographic data of the subjects and each research variable were analyzed univariately, while data on patient adherence and ADR occurrence were analyzed bivariately. The correlation of the determined variables was examined using the Chi-square test.

RESULTS AND DISCUSSION

Characteristics of Respondents

The sociodemographic characteristics of the respondents are presented in the following table.

Table 1. General characteristics of research respondents

Characteristics	Frequency	Percentage
Gender		
Male	23	65,7
Female	12	34,3
Age		
15-64 y.o	31	88,6
≥65 y.o	4	11,4
Last education		
Basic (SD-SMP)	9	25,7
Intermediate (SMA)	20	57,1
College	6	17,2
Occupation		
Government	2	5,7
Private sector	16	45,7
Housewife	7	20,0
Student	5	14,3
Private employee	5	14,3
TB categories		
Pulmonal	29	82,9
Extra-pulmonal	6	17,1
Duration of treatment		
<1 month	2	5,7
1 month	13	37,2
2 months	20	57,1
Medication supervisor		
Present	27	77,1
None	8	22,9
Type of antituberculosis drugs taken		
FDC	35	100
Combipack	0	0

Adherence Level

The assessment of adherence level using the MMAS-8 questionnaire is generally divided into 3 levels: (1) score of ≤ 6 implies low compliance; (2) score of >6 and <8 implies

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moderate compliance; and (3) score of 8 implies high compliance (Morisky et al., 2008). In addition, we classified compliance levels into further categories: obedient and disobedient. The obedient category is applied for high and moderate compliance, while the non-compliant category is applied for the low compliance category. The description of patient adherence level in this study is presented in table 2.

Table 2. Level of medication adherence based on the MMAS-8 questionnaire

Adherence level	Number n (%)	Compliance level	Number n (%)
High	7 (20,0)	Obedient	22 (62,9)
Moderate	15 (42,9)		
Low	13 (37,1)	Non-obedient	13 (37,1)

Table 2 revealed that most subjects in this study (62.9%) adhered to anti-tuberculosis treatment. This condition is congruent to Pameswari's study at a hospital in West Sumatra that showed 88.9% of TB patients taking antituberculosis drugs were obedient in their treatment (Pameswari et al., 2016). Adherence is an important predictor to achieve success in tuberculosis treatment. The Level of compliance is an essential factor because if the treatment is not administered appropriately based on its frequency, the probability of antituberculosis resistance occurrence will increase. These resistant patients potentially become sources of acid-fast bacterial transmission in the community (Zhang & Yew, 2015). TB patients in the intensive phase of treatment are more likely to be non-adherent because patients have to take medication every day for 2 months. This triggers boredom and becomes a burden for the patient. However, adherence to taking medication at this stage is essential because if treatment at this stage could be administered appropriately, then within 2 weeks the *M. tuberculosis* bacteria will become non-infectious because of seroconversion.

ADR experienced by patients is known through guided interviews conducted by researchers. The researcher mentions any Adverse Drug Reaction (ADR) that may be experienced by the patient and then goes through a checklist on the ADR

list sheet. The number of patients experiencing ADR in this study can be seen in table 3.

Table 3. Number of patients experiencing ADR and Non-ADR

Category	Number of patients	Percentage
ADR	26	74,3
Non-ADR	9	25,7
Total	35	100

Based on table 3 the results obtained are that there are 26 patients who experienced ADR (74.3%) and 9 patients who did not experience ADR (25.7%). Not all patients experience ADR because there are other factors that influence the incidence of ADR, one of which is the age factor. The incidence of ADR is considered to be more common in the elderly or adults. This is due to changes in pharmacokinetic and pharmacodynamic parameters. Pharmacokinetic changes occur with age as a result of anatomical and physiological changes that occur over time, such as loss of functional units of organs (e.g. nephrons and neurons) and disruption of several regulatory processes between cells and organs resulting in a decrease in the function of body systems (Syamsudin, 2011). From the results of the study, it is known that each patient generally experiences more than one type of ADR. The distribution of ADR experienced by patients is presented in table 4.

From the results of the study, it is known that each patient generally experiences more than one type of ADR. Based on table 4, it can be seen that of the 35 patients who were the sample of the study, the majority of ADRs complained of redness in the urine (68.6%), followed by nausea and abdominal pain (51.4%), flu syndrome (34.3%). , joint pain (28.6%), no appetite (22.9%), red rash (rash) on the skin (14.3%), tingling (14.3%), and visual disturbances (2.90%).

Table 4. Distribution of ADR experienced by TB patients in intensive treatment

No	Symptoms of ADR	Number of patients (n)	Percentage (%)
1.	Anorexia/ decrease of appetite	8	22,9
2.	Nausea and abdominal uncomfortness	18	51,4
3.	Arhtralgia	10	28,6
4.	Numbness, burning sensation in extremities	5	14,3
5.	Reddish urine	24	68,6
6.	Flu-like syndrome (fever, shivering, weakness, headache)	12	34,3
7.	Skin rash (itchy, non-itchy)	5	14,3
8.	Unknown jaundice	0	0
9.	Hepatitis*	0	0
10.	Vision disturbance	1	2,90
11.	Severe symptoms: Purpura, anaphylactic shock, acute kidney injury*	0	0

Note: * = data obtained from medical records or results of patient laboratory examinations

Table 5. Relationship between ADR and patient medication adherence

	Patuh	Tidak Patuh	Total n (%)	*P-value*
ROTD (26)	13	13	26 (74,3)	0,02288
Non-ROTD (9)	9	0	9 (25,7)	
Total	22	13	100	

Reddish urine colour was the first ADR experienced by the patients in this study (68.6%). The results obtained were in line with the previous study conducted by Priyandani et al (2017) that found the type of side effect of OAT which appears the most was a reddish colour in the urine (71.5%). Reddish urine color is a mild ADR caused by rifampin. The red colour occurs due to the metabolic process of rifampin and can be used as a reference for monitoring effective drug absorption (Syamsudin, 2011).

Nausea and abdominal pain were the second most common ADR experienced by patients (51.4%). This result was also proven by Abbas (2017) who was conducted in Makassar City, where nausea and abdominal pain were the most common ADRs experienced by patients in the first and second weeks of treatment during the intensive phase. Nausea and abdominal pain are mild ADRs most often caused by Rifampicin. In addition to rifampin, isoniazid and pyrazinamide also have the potential to cause nausea and abdominal pain (Sumantri & Nugroho, 2018).

Based on the results of the analysis in table 5, it shows that a total of 26 patients (74.2%) who experienced ADRs were compliant and experienced ADRs were 13 (37.1%), while patients who were not compliant and had ADRs also amounted to 13. people (37.1%). The total number of compliant patients was 22 people. There were 9 patients who did not experience ADR (Non-ADR) in this study (25.7%). All patients who did not experience ADR were included in the adherent category because none of the patients who did not have ADR did not adhere to medication. The results obtained are in line with research conducted by Raflythenu which states that patients without side effects are more obedient (32.5%), compared to patients with side effects who are adherent (20.8%) (Raflythenu, 2019).

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The relationship between ADR and adherence to medication for TB patients in the intensive phase of treatment was analyzed using the R i386 software version 3.4.4 with the statistical test method of chi-square. The results of the chi-square test indicate that the *P-value* (0.02288) is smaller than the significance level of 0.05 (*P-value* <0.05), so based on the *P-value* it can be concluded that there is a significant relationship between ADR and medication adherence. TB patients in intensive care. However, the results obtained cannot explain the conclusion definitively because the number of patients who are compliant and non-adherent after undergoing ADR is the same. Thus, it is suspected that there are other factors besides ADR that cause non-adherence to take medication in patients. One of the causes of non-adherence to medication in TB patients is therapeutic factors, which include the complexity of therapy (number of drugs and daily doses required), frequency of taking medication, duration of treatment, ADR, feelings of improvement in a short time, and cost of treatment (Mekonnen & Azagew, 2018).

Therapeutic factors other than ADR which are suspected to be the cause of patient non-adherence to taking medication are the complexity of therapy related to the number of drugs and daily doses that must be taken by the patient. Based on the research that has been done, the results show that the number of drugs and the daily dose of OAT taken varies depending on the patient's weight. After statistical analysis using the chi-square test related to whether there was a relationship between the complexity of therapy and patient medication adherence, the results were that the *P-value* (0.381) exceeded the significance level of 0.05 (*P-value* < 0.05), so it can be concluded that there is no significant relationship between the complexity of therapy with medication adherence of TB patients in the intensive phase of treatment. Therefore, it is suspected that there are other factors that can affect drug adherence of TB patients in addition to suspected therapeutic factors, such as health facilities factors (lack of

communication between patients and health workers, lack of access to health facilities, and lack of continuity of care), patient condition factors (depression, physical disorders such as vision and dexterity problems as well as cognitive impairment), socio-economic factors (low level of education and lack of support from family).

ADRs that appear during the treatment period cause the patient to feel uncomfortable so that it has an impact on medication adherence and can even lead to drug withdrawal (loss to follow-up) (Sugiarto, 2020). On the other hand, patients who do not experience ADR will be more obedient in following the treatment regimen because there are no factors that cause the patient to feel uncomfortable or feel that his condition is getting worse after taking the drug. Therefore, there is a need for collaboration between health workers and TB patients in terms of ADR management and increasing drug adherence. Health workers are required to provide information regarding any ADRs that may arise after the use of OAT at the beginning of treatment and ask the patient to continue using the drug even though the patient has several complaints. There are several non-pharmacological therapies that can be delivered to patients in dealing with complaints due to OAT, such as drinking lots of water to neutralize the reddish colour in the urine, and taking medication before going to bed or with a little bit food to treat nausea and abdominal pain. Meanwhile, from the patient's side, if the complaints or ADR experienced are getting worse, they must immediately consult with health workers (Priyandani et al., 2017).

CONCLUSION

There is a significant relationship between adverse drug reactions occurrence in tuberculosis patients and adherence to anti-tuberculosis drugs in the intensive phase of treatment at the General Hospital dr. Zainoel Abidin Banda Aceh.

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