Comparison of Drug Induced Hepatotoxicity Incident of Fixed-Dose Combination and Separate Formulations Regimen for Pulmonary Tuberculosis Treatment in Hospital Sukabumi

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Abstract. Pulmonary Tuberculosis is still a health problem in the world, including in Indonesia. The World Health Organization reports that Indonesia ranks third the highest pulmonary tuberculosis case in the world. The regimen for treatment of pulmonary tuberculosis is isoniazid, rifampicin, pyrazinamide, and ethambutol, which has been used either as Fix-Dose Combination (FDC) or as SF (SF). These drugs induced hepatotoxicity side effect. The aims of this study was the comparison of drug induced hepatotoxicity incident of FDC and SF regimen for pulmonary tuberculosis treatment. This study was an observational with retrospective method in 130 pulmonary tuberculosis patients with category I (65 patients have used FDC and 65 patients have used SF). The result showed that based on the severity level of DIH were the following stage I as many as 36 patients for FDC and 34 patients for SF, stage II as many as 14 patients for FDC and 13 patients for SF, stage III as many as 8 patients for FDC and 8 patients for SF, stage IV as many as 7 patients for FDC and 10 patients for SF. The Mann-Whitney test show no significant differences in the severity level of DIH (P=0,253) in two group.

1. Introduction
Tuberculosis is a health problem in developing countries, one of which is in Indonesia. TB case in Indonesia reached 842 thousand. As many as 442 thousand people with TB reported and around 400 thousand other did not report or were not diagnosed. The number of TB cases in Indonesia is the third largest in the world after India which reached 2.4 million cases and China 889 thousand cases [1].

Tuberculosis is an infectious disease caused by the bacteria Mycobacterium tuberculosis[2]. The pulmonary TB prevention strategy through a program introduced by WHO with Directly Observed Treatment Shortcourse (DOTS) has been implemented comprehensively in Indonesia since March 24, 1999. Initially the implementation of the DOTS strategy program in Indonesia was only implemented in Puskesmas and the developed in other health services such as in Community Lung Health Center and Government and Private Hospitals. TB treatment aims to cure patients and improve productivity and quality of life, prevent deaths, prevent recurrence, reduce transmission and prevent drug resistance[3].

Treatment of TB disease caused by M. tuberculosis still Sensitive Drug-Sensitive Tuberculosis (DS-TB) requires drug combination consisting of 4-5 types of drug for 6 months or more. Standard therapy for DS-TB patients includes a combination of isoniazid, rifampicin, pyrazinamide and
ethambutol for the first 2 months and a combination of isoniazid and rifampicin alone for the next 4 months[4].

The problems in the treatment of TB are low compliance, inaccuracy in drug use, treatment failure, side effects experienced and the occurrence of drug therapy dropouts, so it is necessary to evaluate the use of OAT, one of which is the evaluation of side effects of OAT. Based on the TB treatment conditions have a long duration of drug administration and many types of drugs, will appear high effects of side effects or toxicity. Side effects experienced are mild and severe side effects. Minor side effects include no appetite, nausea, abdominal pain, redness of the urine, tingling or burning sensation in the legs, joint pain and flu syndrome. As for severe side effects including hearing loss, visual disturbances, shock, jaundice without other causes, confusion and vomiting, rash and drug induced hepatotoxic (DIH) which is characterized by increasing levels of ALT and AST[5].

Hepatotoxicity is defined with the condition of increasing alanine (ALT) or aspartate transaminase (AST) by three times the upper limit of normal (ULN) accompanied by symptoms (abdominal pain, nausea, vomiting, unexplained fatigue, or jaundice) or increase five times that of ULN without symptoms[6]

Based on the result of the study of Jiun-Ting Wu et al., in 2015 in the “comparison of the safety and efficacy of fixed-dose combination regimens and separate formulation for pulmonary tuberculosis treatment” conducted on 161 patents the results showed that there were no significant differences between both types of OAT are associated with side effects. The most commonly reported side effects for both types of OAT were 56.3% skin disorders for FDC and 41.0% for separate formulation. Blurred vision 46.9% for FDC and 47.43% for separate formulation. Other side effects most frequently reported were impaired liver function for FDC 42.2% and 39.7% for SF but this difference was not significant. In addition one patient using FDC and one patient using SF had severe hepatotoxicity (DIH) due to TB treatment[6]

Based on information obtained from hospital in Sukabumi, it was recorded that Tuberculosis was ranked first in the list. Tuberculosis treatment at the Sukabumi hospital recorded in the DOTS program for category I uses types of preparations, namely a fixed dose combination and Separate Formulations. Based on this description, researchers are interested for researching “Comparison of Drug Induced Hepatotoxicity Incident of Fixed-Dose Combination and Separate Formulations Regimen for Pulmonary Tuberculosis Treatment in Hospital Sukabumi” which aims to determine the side effects and drug induced hepatotoxicity incident during the use of OAT so that appropriate selection of OAT preparations and management of side effects appropriately.

2. Material and methods
A retrospective observational study, involving 130 pulmonary TB patients using FDC and SF at Sukabumi hospital. The data used are secondary data obtained from medical records of pulmonary TB patients in 2017 selected by purposeful sampling. The study include man and women, aged between 16 to 55 years, without comorbidities, patients received FDC and SF in the intensive phase category I, patients who have complete medical record data that include dosage, combination of therapies, adverse events, type of patient, patient identity, treatment given, treatment result and laboratory data.

In total, 130 patients were allocated into two groups. In group I, a lot of 65 patients received FDC and in group II a lot of 65 patients received SF. The data collected was in the form of patient sociodemographic data, types of side effects and DIH levels. Category of the Side effects experienced are mild and severe side effects. Minor side effects include no appetite, nausea, abdominal pain, redness of the urine, tingling or burning sensation in the legs, joint pain and flu syndrome. As for severe side effects including hearing loss, visual disturbances, shock, jaundice without other causes, confusion and vomiting, rash and drug induced hepatotoxic (DIH) which is characterized by increasing levels of ALT and AST[5]. Categories of DIH levels due to OAT in pulmonary TB patients according to DIH with anti tubercular chemotherapy (2010), namely stage 1 (ALT 51-125 U/L), stage 2 (ALT 126-250 U/L), stage 3 (ALT 251 – 500 U/L), stage 4 (ALT>500).
Statistical analysis was performed and initially we evaluated the data normality using the Kolmogorov-smirnov test. Then we chose to use non-parametric test because the data did not reach normal distribution. To compare means of two groups, we used the Mann-whitney test. All analyzes were performed using SPSS version 23 software, and p-value <0.05 was considered statistically significant.

3. Result and Discussion

| TABLE 1. Patient’s characteristics and side effects description |
|---------------------------------------------------------------|
| VARIABLE | GROUP | FDC | SF | P |
| - Gender | | | | |
| - Male | FDC | 41 | 59 | 29 | 48 | 0.726 |
| - Female | SF | 29 | 41 | 31 | 52 | |
| - Age | | | | |
| - 17-25 Years Old | FDC | 14 | 22 | 14 | 21 | 0.032 |
| - 26-35 Years Old | SF | 21 | 32 | 27 | 42 | |
| - 36-45 Years Old | FDC | 19 | 29 | 20 | 31 | |
| - 46-55 Years Old | SF | 11 | 17 | 4 | 6 | |
| - Side Effects | | | | |
| - Mild | FDC | 36 | 55 | 35 | 53 | 0.220 |
| - severe | SF | 29 | 45 | 31 | 47 | |
| - DIH Levels | | | | |
| - stage 1 | FDC | 36 | 55 | 34 | 52 | 0.253 |
| - stage 2 | SF | 14 | 22 | 13 | 20 | |
| - stage 3 | FDC | 8 | 12 | 8 | 12 | |
| - stage 4 | SF | 7 | 11 | 10 | 16 | |

aPatients received FDC  
bPatients received SF  
cP-value was obtained from Mann Whitney test

3.1 Gender
Based on table 1, pulmonary TB attacks more men than women because men have a greater risk factor more susceptible to pulmonary TB. This is because men do more activities so they are more often exposed to disease. The lifestyle of men who are also smoke and consume alcohol thereby reducing the body’s immune system[7]

This is consistent with research conducted by Telarolli et al (2015) which also shows that patients with the most pulmonary TB are men with a percentage of 82.35% compared to women as much as 17.65%[8] The results of the Mann-Whitney statistical test performed showed that there were no significant differences in the gender variables of FDC and SF groups P>0.05 (P=0.726).

3.2 Age
Based on the age variable in the FDC and SF groups, the most age category is at the age of 26-35 years. This is because at the productive age do more activities outside the home, with the frequency of leaving the house which often can allow the transmission of pulmonary TB disease.
This is consistent with the result of research conducted by Nurjana and Agus (2015) which shows that patients with the most pulmonary TB are of productive age of 17 – 35 years[9]. Mann-Whitney test results conducted showed a significant difference in the age variable in FDC and SF groups P<0.05 (P=0.032)

3.3 Side Effect
Based on the variable side effects in the FDC and SF groups, the two types of OAT have different percentages to cause side effects. In mild side effects FDC has a greater percentage of 55% compared to SF at 53%. In severe side effects, SFs has a greater percentage of 47% compared to FDC of 45%.

Minor side effects include redness in the urine, no appetite, nausea, fever, weakness and joint pain. For severe side effects that occur are itching accompanied by redness of the skin, vomiting (suspected liver function disorders occur) and skin color to yellow without any other cause. But after analyzing the data using Mann-Whitney showed no significant differences in the side effects of FDC and SF groups P>0.05 (P=0.0220). this is consistent with the research conducted by Jiun-ting Wu et al (2015). The result show that there are no significant differences between the two types of OAT related to side effects.

3.4 DIH Levels
In this study, we found the highest DIH level (stage 4) in patients who received the SF regimen was higher than in patients who received the FDC regimen during treatment. However, hepatotoxicity (all stage) did not differences significantly between the two regimens. It can be seen form the Mann-whitney test P-value > 0.05 (P-value = 0.253). Cholestasis is considered to be a side effect of Rifampicin treatment which may be dangerous and can be treated without drugs. The combination of using Rifampicin and INH has succeed in increasing the risk hepatotoxicity[6].

The FDC regimen, which simplifies drug aid and prevents the development of drug resistance, has been approved as a standarad anti-TB treatment regimen. However, the composition and contribution of doses for FDC difference from thos for SF. Which isi a major concern for doctors. We found compilation of treatment with anti-TB drug supervised using DOTS, the incident rate of side effects did not difference significantly between FDC and SF regimens[6]

4. Conclusion
There were no significant differences in side effect and DIH levels variable in the administration of FDC and SF regimens in pulmonary TB patients.

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