Adverse Cutaneous Drug Reactions Due to Antituberculosis Therapy in Dr. Sardjito General Hospital Yogyakarta

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Abstract: Tuberculosis (TB) is a major health problem worldwide. From 2014-2017, 577 cases of TB were recorded in Dr. Sardjito Hospital Yogyakarta. Use of specific agents against *Mycobacterium tuberculosis* is mainstay of TB treatment. First line anti-TB therapy used are rifampicin, isoniazid, pyrazinamide, and ethambutol. This regimen can cause various adverse drug reaction affecting several organs, including skin. Presence of adverse cutaneous drug reactions (ACDRs) to anti-TB therapy can reduce the effectiveness of therapy and increase the morbidity and mortality of TB patients. This study aimed to understand the type of ACDRs that frequently occur due to anti-TB therapy, the most common causative drugs, and to describe the clinical characteristics including the patch test results. This is a retrospective cross-sectional study on TB patients receiving anti-TB therapy in Dr. Sardjito General Hospital Yogyakarta from 2014-2017. Medical record investigation was conducted to find cutaneous reactions appeared during the course of anti-TB therapy. There were 33 out of 577 patients recorded with ACDRs, maculopapular rash was the most common type (66.7%), followed with Stevens Johnson-Syndrome (12%); Drug Reaction Eosinophilia & Systemic Symptoms (DRESS) (6%) and acneiform eruption (6%); erythroderma(3%), exfoliative dermatitis(3%), and bullous drug eruption (3%). Fifteen out of 33 patients had underwent patch tests examination. Rifampicin was found to be the most causative agent, followed by pyrazinamide, ethambutol and isoniazide. As conclusion, maculopapular rash is the most frequent anti-TB therapy-related ACDRs with rifampicin as the most frequent causative drug based on patch test results in Dr. Sardjito General Hospital Yogyakarta.

1 INTRODUCTION

Tuberculosis (TB) is still a major health problem in all over the world, including Indonesia. TB occurs almost in all countries but more than 80% of TB cases reported to occur in 22 countries worldwide. In 2013, 56 % of new cases of TB occurred in Southeast Asia and Western Pacific (WHO, 2004). Ranked at number 3 as the biggest contributor of TB after India and China, the prevalence of TB in Indonesia was 272/100,000 population in 2013, while the incidence rate was 183/100,000 population (Departemen Kesehatan RI, 2016). From 2014-2017, 577 cases of TB were recorded in Dr. Sardjito General Hospital Yogyakarta.

According to the National Guidelines of Tuberculosis Diagnosis and Management, use of specific agents against *Mycobacterium tuberculosis* is the mainstay of TB treatment. For the first line, anti-TB therapy used are rifampicin (RIF), isoniazid (INH), pyrazinamide (PZA), and ethambutol (EMB). To improve the compliance of TB patient, fixed dose combination (FDC) were produced and available in 2 forms, which consist of 4 drugs (RIF 150 mg, INH 75 mg, PZA 400 mg, EMB 275 mg) and 3 drugs (RIF 150 mg, INH 75 mg, PZA 400 mg) in each tablet (Departemen Kesehatan RI, 2016). This multidrug therapy of TB could cause various adverse drug effects, ranging from the mild to severe condition. Adverse drug reactions related to anti-TB therapy could happen in several organs, most common of them are hepatotoxicity, gastrointestinal intolerance peripheral neuropathy, optic neuritis and cutaneous lesions (Ton, 2008).

World Health Organization (WHO) classifies toxicity adverse drug reactions into 2 subtypes, type A and type B reactions. Type A reaction is the most common and related to pharmacological properties of a drug. It can occur in everyone, usually predictable and often dose-dependent. Symptoms may improve

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with drug dose reduction. Type A reactions may include drug interactiotoxicity, and side effects. Type B reaction occurs in 10-15% of patients. It has unpredictable characteristics, tends to occur in people who have predisposing factors. Type B reactions, both non-immunologic and hypersensitivity-based, are usually not dose-dependent and require drug discontinuation for resolution. Type B reactions include drug intolerance, hypersensitivity, or idiosyncratic reactions to drugs (Kardaun et al., 2013).

Adverse cutaneous drug reactions (ACDRs) of anti-TB therapy can present as a mild reactions such as flushing and/or itching of the skin with or without rashes, also can appear in conjunction with hot flashes, palpitations, headache and/or increased blood pressure. This can be considered as type A reactions. Moderate/severe reactions to anti-TB therapy are more related to type B reactions. Clinical presentations vary from hives and rashes until the severe conditions like exfoliative dermatitis and those involving mucous membranes, such as Stevens-Johnson Syndrome (SJS) (Lawrence Flick Memorial Tuberculosis Clinic, 1993).

The presence of ACDRs to anti-TB therapy could reduce the effectiveness of therapy; with regard of patients' reduced compliance or drugs cessation that leads to treatment failure or relapses.

Moreover, ACDRs as well could increase the morbidity and mortality of TB patients. This study aimed to understand the type of ACDRs that frequently occur due to anti-TB therapy, the causative drugs, and to describe the clinical characteristics including the patch test results to anti-TB therapy. We hope that it can increase the awareness and assist medical provider to perform the proper management.

2 METHODS

This is a retrospective cross-sectional study on TB patients receiving anti-TB therapy in Dr. Sardjito General Hospital Yogyakarta from 2014-2017. A study on patient's medical record was done to find ACDRs appeared during the course of anti-TB therapy. ACDRs due to anti-TB therapy was diagnosed based on anamnesis, physical and dermatological examination and laboratory examinations. DRESS was diagnosed based on RegiSCAR criteria.

3 RESULT

This study included 577 patients receiving anti-TB therapy in Dr. Sardjito General Hospital, Yogyakarta. Thirty-three patient were experiencing ACDRs due to anti-TB therapy**.**Characteristics of patients with cutaneous manifestations as an adverse effects of anti-TB therapy are described in Table 1.

Table 1: Baseline characteristics of patient with ACDRs due to anti-TB therapy.

Variable	**Number of patients**
	n (%)
Sex	
Female	11 (33.3%)
Male	22 (66.7%)
Age	
≤ 18 years	6 (18.2%)
19-35 years	14 (42.4%)
35-49 years	7 (21.2%)
≥50 years	6 (18.2%)
Types of ACDRs	
Maculopapular rash	22 (66.7%)
Erythroderma	1 (3%)
Drug Reaction Eosinophilia & Systemic Symptoms (DRESS)	2 (6%)
Stevens-Johnson Syndrome (SJS)	4(12%)
Exfoliative dermatitis	1 (3%)
Bullous drug eruption	1 (3%)
Acneiform eruption	2 (6%)

Table 2: Patch test results and culprit anti-TB drug.

Patch Test Results and Culprit Drug	n (%)
Positive	
Rifampicin	3 (20%)
Isoniazid	1 (6%)
Pyrazinamide	1 (6%)
Ethambutol	1 (6%)
4 FDC (RHZE)*	3 (20%)
Doubtful	
Rifampicin	2 (13%)
Isoniazid	-
Pyrazinamide	1 (6%)
Ethambutol	-
4 FDC (RHZE)*	1 (6%)
Negative	5 (27.7%)

Note: each patient can have more than one positive results to anti-TB therapy
*RHZE : rifampicin, isoniazid, pyrazinamide, ethambutol

The age of patients ranged from 3 to 58 years (mean = 31.09 years; median = 29 years). Most of the patients were male (66.7%) and came from 19-35 years age group (42.4%). Maculopapular rash (66.7%) was the most common type of ACDRs in patients receiving anti-TB therapy, followed by SJS, DRESS, and acneiform eruption. Erythroderma, exfoliative dermatitis, and bullous drug eruption was found in one patient each. Fifteen out of 33 patients were underwent patch test examination with anti-TB therapy to found the causative drugs. Patch test results are described Table 2.

Based on the patch testing results, rifampicin was found to be the most anti-TB therapy causing ACDRs, followed by pyrazinamide. Positive patch test results to isoniazid and ethambutol only found in each one patient.

4 DISCUSSION

Side effects and hypersensitivity to anti-TB therapy that manifests in many organs still remains a difficulty in treating TB patients, so as those affecting the skin. In severe ACDRs, it is recommended to withdraw the suspected drug in order to improve symptoms and outcomes (Dheda, 2012). Interruption of TB therapy could carry consequences in worsening the prognosis of patients, development of drug resistance, and risk of transmission to others. Tan *et al.* found that there is a significant association between TB treatment interruption and risk of death during the intensive phase of treatment ($p = 0.001$) (Tan et al., 2007). Clinicians should be very careful in determining the severity of ACDRs and to decide whether to stop one or all type of anti-TB therapy also when to re-introduce the therapy with thorough consideration.

From the result of the study, ACDRs found in 33 patient out of 577 patients receiving anti-TB therapy (5.7%). There were some other studies that also reported the rates of ACDRs related to anti-TB therapy were approximately 4.8%-6% (Farazi et al., 2014). Male gender counts higher than female.

Some studies showed no differences between the two genders in developing ADR to anti-TB therapy (Sharma et al., 2002).We also found that ACDRs appeared mostly in productive age (19-35 years).

Among all types of ACDRs, maculopapular rash was the most common presentation, about almost 95% of all cases (Bigby, 2001). In this study, maculopapular rash also found to be the most common ACDRs (66.7%). All types of anti-TB therapy can induce maculopapular rash, even though some studies reported it is most likely related to pyrazinamide as the most offending drug, followed by ethambutol, then isoniazid and rifampicin of all the 4 first-line anti-TB therapy (Tan et al., 2007). However, in our study, patch testing that conducted in 15 patients showed that rifampicin was the most causative agents. Any possible explanation of this is ACDRs may be associated with both type A and B reaction, wherein the patch test indicates a hypersensitivity reaction to a drug which is included in type B reaction. Maculopapular rash is one of the most common forms of allergic manifestations of rifampicin, as well as urticaria and anaphylactic reactions.

Stevens-Johnsons Syndrome (SJS) also found to be a common manifestation of ACDRs in anti-TB therapy recipients. Some studies reported cases of SJS during the course of TB therapy, mostly caused by rifampicin (Nyirenda & Gill, 1977). DRESS also found in patients receiving anti-TB therapy according to some reports. Anti-TB therapy that are known to cause DRESS include isoniazid, rifampicin, streptomycin, and pyrazinamide (Wang & Li, 2017). Isoniazid was associated to occurrence of acneiform eruption, as well as bullous drug reaction (Pantello & Kondo, 2013). Exfoliative dermatitis and erythroderma were least common manifestations to anti-TB therapy, it was related to administration of pyrazinamide and ethambutol (Jaisuresh, 2013).

Because of the limited type of effective anti-TB therapy that can reach the favorable outcomes and prevent TB relapse, correct assessment and management of ACDRs to anti-TB therapy are required. Rifampicin-based regimens are still superior to non-rifampicin based until nowadays. Rechallenge of anti-TB therapy by some steps of desensitization should be considered in any condition in which the advantages of TB therapy outweigh the risk of possible reaction. Severe or life-threatening history of ACDRs such as the bullous reactions, erythroderma, DRESS, anaphylaxis, systemic vasculitis and drug-induced autoimmune disease are contraindicated to anti-TB therapy rechallenge and therefore should be switched to alternative anti-TB drug combination (Ton, 2008; Dheda, 2012).

5 CONCLUSION

Maculopapular rash is the most frequent type of ACDRs induced by anti-TB therapy, while rifampicin found to be the most frequent anti-TB therapy inducing ACDRs according to patch test results in Dr. Sardjito General Hospital Yogyakarta in 2014-2017.

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