



The Overview Side Effects of MDR TB Short Term Regimen for Heart and Kidney Function in MDR TB Patients at H. Adam Malik General Hospital Medan, North Sumatra

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Abstract

Background: World Health Organization issued a recommendation for the use of standard 9–11 month Shorter Multidrug-Drug Resistant Tuberculosis (MDR TB) regimen. It will impact the number of patients treated and improve obedience because of the shorter, low cost, and well-tolerated. However, MDR TB drugs allow side effects both mild, moderate and severe. If severe side effects occur, the patient will stop treatment and close monitoring required. An optimal and adequate care of side effects is the key of the successful of MDR TB treatment. The aim of this study was to determine the side effects that occurred in the treatment of MDR TB patients with short term regimen (STR) on heart and kidney function at H. Adam Malik General Hospital Medan, North Sumatra.

Methods: A case series design with a total of 76 MDR TB patients who underwent a shorter regimen. Samples were obtained from the medical record in the pulmonary isolation ward and MDR TB polyclinic at Adam Malik Hospital, Indonesia. Data were analyzed descriptively to identify changes in heart (Prolong QTc) and kidney function of the nine months treatment.

Results: 76 data were collected, the number of male samples was 68.4% and 31.6% were women with the age group of the study subjects being mostly followed by 41–50 years of age. There was a significant increase in value occurred in 4–6 months of treatment related to the side effects of treatment on heart (Prolong QTc) and kidney function.

Conclusion: There was a trend to increase the value of heart (Prolong QTc) and kidney function significantly occurred 4–6 months after the patient underwent MDR TB treatment with STR.

Keywords: kidney function, MDR pulmonary tuberculosis, prolong QTc, short term regimen

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INTRODUCTION

The World Health Organization (WHO) in May 2016 issued recommendations for the use of a short-term standardized treatment regimen of 9–11 months. The treatment regimen recommended by WHO through the STREAM trial showed that the use of a gatifloxacin-based treatment mix with an intensive phase treatment duration of 4 months and a continuation phase treatment duration of 5 months provides satisfactory results in terms of therapeutic success, is easier to control, can treat samples with previous ofloxacin resistance, and is cheap in terms of financing.^{1,2}

This recommendation is based on the results of various observational studies in several Asian and African countries that showed the success rate of

standardized short-term regimen treatment reached 84% (95% CI=79–87%) compared to the success rate of standardized long-term treatment which only reached 62% (95 CI=53–70%).³

All anti-tuberculosis drugs used to treat Multidrug-Drug Resistant Tuberculosis (MDR TB) patients have the possibility of mild, moderate, or severe side effects. If side effects occur, the patient is likely to stop treatment without the knowledge of health facility staff, so monitoring of treatment side effects must be done before and when the patient starts short-term guideline treatment. In addition, good and adequate handling of side effects is the key to successful treatment of drug resistance tuberculosis (DR-TB) with short-term guidelines.³

Chronic Kidney Disease (CKD) is another comorbid disease that can reduce the success rate of treatment (RR=0.62; $P=0.024$). Patients with CKD have a weakened immune system due to chronic inflammatory conditions.⁴ A study conducted in Taiwan found that CKD could increase severe drug reactions and death in MDR-TB patients by 3.65 times (95% CI=1.71–7.76). Patients with chronic renal failure tend to be more difficult to treat because they experience a higher incidence of drug side effects and a progressive decline in kidney function.⁵ In Soeroto et al's study, the prevalence of CKD was very low and only accounted for 1–2% of cases in both groups. Thus, the exact relationship cannot be concluded.⁶ Diabetes mellitus increases tuberculosis (TB) treatment failure due to immune system disorders, impaired kidney function, risk of drug toxicity, including risk of liver toxicity.⁷

The purpose of this study is to determine the side effects that occur in the treatment of MDR TB patients with short-term guidelines (Short Term Regimen (STR)) on cardiac and renal function in MDR TB patients undergoing treatment at H. Adam Malik Hospital Medan, North Sumatra.

METHODS

This study was conducted at H. Adam Malik Hospital Medan during the period from October 2017 to January 2019. Data will be analyzed descriptively to see the frequency distribution based on demographic characteristics and the results of the analysis will be displayed in tabulation form. The sampling technique uses total sampling where all research subjects totaling 76 people are MDR TB patients undergoing treatment with standard short-term treatment guidelines (STR).

The shorter regimens as standardised regimens with an intended duration of 9–12 months including 4–6 months of kanamycin, moxifloxacin, prothionamide, clofazimine, pyrazinamide, ethambutol and high-dose isoniazid, followed by 5–8 months of moxifloxacin, clofazimine, pyrazinamide, ethambutol and, optionally, prothionamide.⁸

Each group of research subjects must meet the inclusion and exclusion criteria and be willing to participate in the study which is stated in writing after getting an explanation about this study (informed consent). Inclusion criteria are aged 18-65 years and MDR TB patients undergoing treatment with Short Term regimens. Exclusion criteria are suffering from complications or complications such as kidney disease, heart disease, liver disease, and malignancy, suffering from extra-pulmonary TB with clinical signs of extra-pulmonary TB abnormalities and the presence of anatomical histopathology results, having received second-line anti-tuberculosis drug (ATD) for >1 month, patients who are proven resistant to fluoroquinolones/second-line injection drugs, pregnant and lactating women, patients who have contact with pre-XDR/XDR patients, patients unable to follow the treatment period for 9 months.

ECG examination and renal function examination in this case the creatinine value at the beginning of treatment, two, four, six, and nine months of treatment. The research procedure was approved by the Health Research Ethics Committee.

RESULTS

The study subjects were 76 people, most of whom were male as many as 52 people (68.4%). The largest age group was 41-50 years as many as 30 people (39.5%). The final results of the treatment of patients who recovered were 34 people (44.8%). Patients dropped out 22 people (28.9%), failed treatment 13 people (15.8%), exitus patients 7 people (9.2%), and transfer patients 1 person (1.3%).

Frequency distribution of MDR TB patients based on ECG results found the average QTc wavelength is 429 ms. In each month of treatment evaluation, the QTc wave lengthening was 7.6% with the highest QTc value of 551 ms and the lowest of 298 ms.

The frequency distribution of renal function showed an increase in creatinine values every month of treatment evaluation by 42% where the average value was 1.04 mg/dl with the highest value being 5.62 mg/dl and the lowest value being 0.44 mg/dl.

Table 1. Characteristics of Research Subjects

Demographic Characteristics	n	%
Gender		
Man	52	68.4
Woman	24	31.6
Age		
18–30 years	12	15.8
31–40 years	18	23.7
41–50 years	30	39.5
>50 years	16	21.0
Final Results of Treatment		
Drop Out	22	28.9
Exitus	7	9.2
Regiment Change	12	15.8
Move	1	1.3
Healed	34	44.8

Table 2 shows an increase in the QTc wavelength seen in the 6th month of MDR TB treatment with short-term drug guidance (STR). There was no significant difference with gender, but patients aged >41 years had a greater risk of increasing the QTc wavelength. An increase in kidney function values was found, especially in the 4th month of treatment for drug-resistant TB with short-term drug guidelines (STR). This situation is possible due to the use of drugs belonging to the aminoglycoside class for a long time.

Table 2. Average Value (Mean), Middle Value (Median), Standard Deviation Value (SD), Minimum Value and Maximum Value Based on the QTc Wave Value

Value	QTc (ms)				
	0 th month	2 nd month	4 th month	6 th month	9 th month
Mean	404.63	413.10	440.42	450.00	439.24
Median	409.50	415.50	436.00	446.50	440.00
SD	37.560	41.156	45.573	37.803	34.121
Minimum	298	308	350	383	358
Maximum	495	510	540	551	502

Table 3. Average Value (Mean), Middle Value (Median), Standard Deviation Value (SD), Minimum Value and Maximum Value Based on Creatinine Value

Value	Creatinine (mg/dl)				
	0 th month	2 nd month	4 th month	6 th month	9 th month
Mean	0.7383	1.0380	1.2291	1.1563	1.0908
Median	0.7000	0.8550	0.9600	0.9700	0.9900
SD	0.19598	0.61412	0.87091	0.70340	0.56581
Minimum	0.44	0.56	0.45	0.48	0.60
Maximum	1.41	4.88	5.62	4.51	3.61

DISCUSSION

Globally, TB germ resistance has continued to increase since resistance to streptomycin was first

discovered in the mid-1940s. TB germ immunity to ATD has emerged since the 1970s with resistance to rifampicin. The WHO Stop TB Department in 2008 estimated that 490,000 cases of MDR-TB occur each year, with a death rate of more than 110,000 worldwide. The prevalence in the world is estimated to be 2-3 times higher than the incidence. The International Standard Tuberculosis Care (ISTC) in 2014 defined Multi Drug Resistant-TB (MDR-TB) as TB caused by TB germs resistant to 2 types of first-line ATD, INH and Rifampicin. Management of MDR TB is more difficult and requires a longer treatment period with a low cure rate.^{9–11}

The management of MDR TB cases is often associated with side effects ranging from mild to severe. In this study, the frequency distribution of drug-resistant TB patients based on side effects of impaired cardiac function (prolonged QTc) found that the average QTc wavelength of drug-resistant TB patients was 429 ms for males and 425 ms for females. Where in the month of treatment evaluation, it was seen that men found QTc wave lengthening of 7.6% with the highest QTc wavelength of 551 ms and the lowest value of 298 ms, while women found QTc wave lengthening of 6.6% with the highest value of 551 ms, QTc 540 ms and the lowest value 320 ms. This study shows a trend of increasing QTc wavelengths seen in the 6th month of treatment for drug-resistant TB with short-term drug guidelines (STR). There was no significant difference with gender, but patients aged >41 years had a greater risk of increasing the QTc wavelength.

The results of an epidemiological study of MDR-TB in Indonesia showed that 61.6% of MDR-TB patients were of reproductive age (18–50 years).¹² Physiological and biological changes in elderly can also interfere with microbial clearance mechanisms and reduce cellular immune responses.¹³ MDR-TB patients over 45 years are twice as likely to experience treatment failure, and three times as high in patients over 65 years due to comorbidities and atypical symptoms that make it difficult to diagnose and manage patients.¹⁴ Older age is associated with lower drug absorption due to decreased intestinal function and motility. Side effects and drug

interactions are also higher due to reduced liver and kidney function for drug elimination.¹⁵

The research by Khan et al in 2018 explained that moxifloxacin-induced QTc interval prolongation ranged from 11.5 to 19.5 ms. The reported incidence of QTc prolongation is as high as 30% in patients with pneumonia, approximately half of those patients with QTc prolongation in the 30–60 ms range of normal. Meanwhile, considerable prolongation of QTc waves (>60 ms) has also been reported in some patients. QTc prolongation is higher with intravenous moxifloxacin than with oral preparations. In obese patients (>30 kg/m²), the rate of QTc prolongation was substantially low (~6 ms), while no important differences were reported between different gender and ethnic groups. Maximum QTc prolongation values can be observed 2–4 hours after oral administration of moxifloxacin; for every 1 µg/ml increase in moxifloxacin concentration, a corresponding increase of 2.1–3.9 ms in the QTc interval has been estimated.¹⁶

In a study by Xu et al, volunteers who were given moxifloxacin at a dose of 400 mg orally showed a prolongation of the QTc interval ranging from 9.77 to 12.91 ms at an average maximum concentration of MX (4.36 µg/mL) and ethnic differences factors were not related.¹⁷

Although the results of this study showed a trend of increasing QTc waves with the use of moxifloxacin, the increase in QTc waves was still below 500 ms, which is the threshold for a very long QTc which is an indication for a regimen change. It means that moxifloxacin is still effective by evaluating the ECG every month in the intensive and advanced stages of treatment with short-term guidance (STR).

In this study, the frequency distribution of drug-resistant TB patients based on side effects of impaired kidney function found an average creatinine value increased by 42%, where the average value was 1.04 mg/dl with the highest value being 5.62 mg/dl and the lowest value 0.44mg/dl. There is an increase in kidney function values, especially in the 4th month of treatment for drug-resistant TB with short-term drug guidelines (STR). This situation is probably due to using aminoglycoside drugs for a

long time. Aminoglycosides are nephrotoxic because they induce proximal tubular necrosis ranging from focal to diffuse lesions. Most of the aminoglycosides are excreted through glomerular filtration. The necrosis and regeneration rates of the proximal tubular cells determine the clinical threshold for nephrotoxicity of aminoglycosides. The degree of severe side effects is more at age >41 compared to ages 18–40. Men and women experience about the same degree of side effects.

Research conducted by de Jager and van Althema showed a significant relationship between the occurrence of nephrotoxicity with the duration of treatment and the total dose of the aminoglycoside. This study also found that male renal impairment was more common than female ($P=0.033$).¹⁸ Nathanson et al also found that 1.1% of patients with renal failure/nephrotoxicity were given MDR TB therapy. This study said that patients with a history of TB treatment using category 2 had a significant relationship with renal impairment ($P=0.026$).¹⁹

The different findings in the study by Sturdy et al stated that there was no difference in nephrotoxicity between males and females ($P=0.944$). This difference still needs to be investigated further, and the possibility that genetic factors play a role.²⁰ The study by Bloss et al presented different things, namely that generally, women and older people tend to suffer more side effects in cases of MDR TB.²¹

WHO guidelines recommend second line injections (amikacin, kanamycin, and capreomycin) for MDR TB. A significant problem closely related to the administration of long-term injectable drugs is their toxic effects, where ototoxicity and nephrotoxicity have been reported as side effects of aminoglycosides related to the dose size and the duration of administration. Side effects such as arthralgia and hyperuricemia occur in the treatment of Drug Resistant TB, which may be caused by pyrazinamide or levofloxacin administration. This side effect can be managed with allopurinol, piroxicam, meloxicam, or tramadol can be given. In some patients, the pyrazinamide dose was reduced and evaluated at three days. If the uric acid

examination results return to normal, a pyrazinamide dose is given according to the predetermined dose.⁸

The strength of this study is that this study is the first drug-resistant TB study conducted in Indonesia with short-term guidelines (STR) that follow research subjects in the course of their disease from the initial diagnosis, side effects of treatment that occur, especially on heart function and kidney, routine treatment evaluation and patient treatment outcomes. The results of this study can later be used as input and advice to stakeholders in determining policies related to the treatment of drug-resistant TB in Indonesia.

CONCLUSION

In this study related to the side effects of treatment on heart function (prolonged QTc), it was found that there was a tendency for a significant increase in QTc wave values to occur in 4–6 months. And in kidney function, it was found that there was a tendency for a significant increase in value to occur 4 months after the patient underwent treatment with short-term guidance (STR).

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CONFLICT OF INTEREST

None.

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