Factors Cause of Switching Shorter Regimen to Longer Regimen in Multidrug-Resistant/ Rifampicin-Resistant Tuberculosis Treated Patients in Dr. Soetomo Hospital Surabaya, Indonesia

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Abstract

Background: Indonesia started to implement the Shorter Regimen (STR) since 2017, but not all of MDR/ RR-TB patients were treated with STR until the end of treatment. The presence of side effects of one or several drugs in the STR and the resistance to fluoroquinolone and or 2nd line injection drug after starting treatment caused a switch in regimen from STR to a longer regimen. This study was conducted to evaluate the factors that caused switch STR to the longer regimen.

Methods: This was a descriptive study in MDR/RR-TB patients who received STR from October 2017 to December 2019. Patients who switch their regimen were analyzed and determine the factors cause of switching STR to a longer regimen.

Conclusion: The major cause of switching was due to the presence of resistance to fluoroquinolone and 2nd line injection drugs and incidence of prolonged QT. A diagnostic rapid test such as the line probe assay 2nd line TB drugs is absolutely a screening tool to determine MDR-TB patients, pre-XDR-TB or XDR TB as soon as the regimen is given. Monitoring and efforts to overcome prolonged QT side effects are also needed to prevent switch regimens that can affect the patient's psychological condition.

***Keyword**: Shorter MDR/RR-TB Regimen, MDR-TB Longer Regimen, Switch Regimen*

Introduction

Multidrug-resistant tuberculosis (MDR-TB) is a public health crisis. Indonesia is one of 30 countries with the highest MDR or Rifampicin Resistant (RR)-TB cases in the world with 24,000 cases.[1] MDR-TB defined as TB caused by strains *Mycobacterium tuberculosis* that are resistant to at least isoniazid and rifampicin.[2] The treatment of MDR-TB is challenging. Patients with MDR/RR-TB are treated with a different combination of 2nd line drugs, usually for 18 months or more. Its long duration is associated with high cost, greater incidence of adverse reactions, and a high rate of lost-to follow up.[3] Therefore, the finding of a shorter regimen (STR), more effective, lower-cost treatments for MDR-TB remains a priority. WHO updated its treatment guidelines for drug-resistant TB in May 2016 and included a recommendation on the use of the shorter MDR-TB regimen under specific conditions.[3]

Unfortunately, not all of STR patients were treated with STR until the end of MDR-TB treatment. The presence of drug side effects and the DST (*drug*

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susceptibility test) results that showed resistance to fluoroquinolone and 2nd line injection drug (SLID) after the starting treatment caused a switch in regimen from STR to the longer regimen.

If phenotypic DST result shows resistance to fluoroquinolone and SLID, it must be reviewed and switched to the longer treatment regimen and also in consideration of using new drugs (bedaquiline, delamanid). Patients with QTc prolongation from baseline also concerned to decrease Mfx dose to 400 mg or may switch to drugs with a least cardio-toxic side effect.[4] Programmes and their stakeholders using the standardized shorter MDR-TB regimen should intensify clinical, safety and microbiological monitoring in order to rapidly switch patients to new longer MDR-TB regimens upon first signs of non-response, ototoxicity or drug intolerance and also upon the first signs of non-response or drug intolerance.[5]

At present, no evidence exists on the effects of implementing the STR in the medium and long term. Information is missing on the regimen's efficacy under programmatic conditions, the durability of its effectiveness (eg, no additional drug resistance generated), and its potential to increase numbers of patients who are ineligible for treatment because of additional resistance.[6] No studies have reported the number of MDR/RR-TB patients who switched their regimen from STR to longer regimen. This study was conducted to evaluate the factors that caused switch STR to a longer regimen.

Material and Methods

A study conducted from October 2017 to December 2019 in Dr. Soetomo Hospital Surabaya, Indonesia. Based on the medical records, all RR-TB cases both new cases and previously treated cases diagnosed based on geneXpert included in this study. MDR-TB was defined as resistant to rifampicin and isoniazid. RR-TB was defined as resistant to rifampicin based on geneXpert and as the first diagnosis of MDR-TB. As most rifampin-resistant isolates are also resistant to isoniazid, rifampicin-resistant can be used as a marker for MDR *M. tuberculosis*[7] and as the program policy for all RR-TB were directly treated with MDR regimens without waiting for the results of 1st line TB DST. Patient's medical history, laboratory, chest X-Ray, and phenotypic DST results to the constituent drugs were analyzed to determine their eligibility for a shorter treatment regimen. Patients who switch their regimen during treatment were analyzed and determine the factors cause of switching STR to a longer regimen.

Findings

There were 224 MDR/RR-TB patients who received STR in this study with a mean age of 44.61 years old. There were 134 men and 90 women in this study as presented in table 1.

Table 1. Profile of MDR / RR-TB patients receiving STR (n=224)

	Switch regimen (n=40)	STR (n=184)	Total (n=224)
Men (n=134)	19 (48%)	115 (62%)	134
Women (n=90)	21 (52%)	69 (38%)	90
Age	44.05 ± 11.35 (19-63)*	44.73 ± 13.15 (14-74)*	44.61 ± 12.82 (14-74)*

*mean ± SD (range)

STR for MDR-TB patients consisted of 52/224 (23%) new cases and 172/224 (77%) previously treated cases. Recurrence cases were dominant with 94/224 (42%) in patients who received STR. This result was presented in table 2.

Table 2. MDR / RR-TB patients who received STR based on previous treatment history

Previous History of TB treatment	Count (n=224)
Chronic/ failures of the WHO category II regimen	2 (0.9%)
Patients with positive smears at 3rd month of the WHO category II regimen	4 (1.8%)
History of using anti-TB drugs of poor or unknown quality	2 (0.9%)
Failures of the WHO category I regimen	32 (14%)
Patients with positive smears at 2nd or 3rd month of the WHO category I regimen	12 (6%)
Recurrence	94 (42%)
Returns after default	23 (10%)
Contact of MDR-TB cases	2 (0.9%)
TB HIV co-infection	1 (0.5%)
New case	52 (23%)

Of the 224 MDR/RR-TB patients who received STR, 40 (18%) were switch their regimen to longer regimen because of the presence of prolonged QT, resistance to ofloxacin (Ofl), resistance to kanamycin (Km), resistance to amikacin (Amk), adverse effect of increased serum creatinine, intolerance to Km and Cm, and adverse effect of hepatitis as presented in table 3.

Table 3. The reason for switch STR to a longer regimen

Reason for switch	Count (n=40)
Resistance to Ofloxacin	17
Prolonged QT	16
Resistance to Kanamycin and or Amikacin	3
Adverse effect of increased serum creatinine	2
Intolerance to Km and Cm	1
Adverse effect of hepatitis	1

Of the 16 MDR/RR-TB patients who switch their regimen caused by prolonged QT, it was found that the average of potassium level was decreased, 4.06 mmol/l at the baseline test to 2.92 mmol/l when presence prolonged QT. This was presented in table 4.

Table 4. Average of potassium and natrium level in patients who switch their regimen due to prolonged QT (N=16)

No	Baseline test (K and Na)		K and Na along with prolonged QT	
	K (mmol/l)	Na (mmol/l)	K (mmol/l)	Na (mmol/l)
Average	4.06	135.68	2.92	135.81

Adverse effects of shorter regimen caused switch to longer regimen also occurred in some patients, 2/224 (0.9) switched their regimens because of increased serum creatinine and 1/224 (0.5%) because of hepatitis. Intolerance to Kanamycin and Capreomycin also caused the switch to longer regimen in 1/224 (0.5%) patient. This result suggested that allergy test before determining shorter regimen is critical to prevent the switch of regimen.

Table 5. Suspect criteria in switch STR patients caused by resistance to fluoroquinolone and or 2nd line injection (n=20)

Suspect criteria	Total (n=20)
History of using anti-TB drugs of poor or unknown quality	1
Failures of the WHO Category I regimen	4
Patients with positive smears at 2nd or 3rd month of the WHO category I regimen	3
Relapse	7
Returns after default	1
New case	4

Based on the history of previous TB treatment, of the 20 patients who switch to a longer regimen caused by the presence of resistance to Ofl, Km, and Amk, 4 (20%) were new cases and 16 (80%) were previously treated cases. This was presented in table 5.

Discussion

There were 224 MDR/RR-TB patients who received STR in this study, consisted of 134 men and 90 women. In Indonesia, TB is significantly more common among men than among women.[8] Previously treated cases was 172/224 (77%) and new cases was 52/224 (23%) in this study. Previous anti-TB treatment was by far a strong predictor of drug resistant.[9] Globally at the world level, it is estimated that there are 484,000 RR-TB cases in 2018 with a composition of 3.4%, new cases and 18% previously treated cases. In Indonesia, the percentage of new cases of MDR/ RR-TB is 2.4% and previously treated cases are 13%.[1] At the Dr. Soetomo hospital since the programmatic management drug-resistant (PMDT) was implemented from 2009 to April 2019 there were 1,080 MDR/RR-TB patients with 94 (8.6%) new cases and 995 (91.4%) previously treated cases.[10] Previously treated TB patients were 8.1 times more likely to develop an MDR-TB infection compared with newly diagnosed TB patients.[11]

MDR/RR-TB patients from recurrence cases was found higher with 94/224 (42%) in this study. Recurrence cases terminology was used due to an uncertain whether it was re-infection or relapse cases. According to several studies, recurrent TB patients are defined as patients who have previously been treated for TB, were declared cured or treatment completed at the end of their most recent course of treatment, and are now diagnosed with a recurrent episode of TB (either a

true relapse due to reactivation of the disease or a new episode of TB caused by a new strain of *Mycobacterium tuberculosis* or reinfection).[12,13] Bacteriological relapse is defined as the reappearance of bacterial activity in a patient who has followed and completed a correct treatment and, therefore, been cured of TB. However, there can be a certainty that a patient has completed all their medication only when treatment administration is directly observed. If the treatment was not supervised, the authenticity of a relapse can be questioned. A study by Shen et al., 2017 conducted in China reported that there were 5.3% (710/13,417) of successfully treated cases had a recurrence and among 141 recurrent cases that had paired isolates, 59 (41.8%) were indicating reinfection and 82 (58.2%) were relapsed.[14]

Our study found 40/224 (18%) MDR/RR-TB patients who switched their regimens from shorter regimen to longer regimen. 20/224 (9%) MDR/RR-TB patients switched their regimens caused by the presence of resistance to fluoroquinolon (FQ) and or 2nd line injection drug (SLID). Resistance to Ofloxacin were 17/224 (7.6%) and resistance to Kanamycin and or Amikacin were 3 (1.3%). These patients were diagnosed with pre-XDR/XDR-TB according to drug susceptibility test (DST). Extensively drug-resistant TB (XDR-TB) defined as MDR-TB plus resistance to a fluoroquinolone and at least one 2nd line injectable agent: amikacin, kanamycin and/or capreomycin, pre-XDR-TB defined as MDR-TB plus resistance to a fluoroquinolone or one 2nd line injectable agent: amikacin, kanamycin or capreomycin.[2] Pre-XDR/XDR-TB patients were not eligible to receive STR because STR was recommended by WHO only for MDR-TB patients. Of the 20 patients who switch their regimen due to resistance to FQ and or SLID, 16/20 (80%) of them were previously treated cases. WHO guideline (2016) stated that until more evidence is available, WHO recommends that the shorter MDR-TB regimen not be used in patients who have been previously treated with 2nd line drugs for more than one month or who have documented or are likely to have strains resistant to medicines in the regimen. Preferably, resistance to at least fluoroquinolones and the injectable agent used in the regimen is excluded before starting treatment by in vitro testing. In the absence of such testing, patients who are highly unlikely to be infected with resistant strains based on history of exposure, use of 2nd line medicines at country level or recent representative surveillance data may also be eligible for the shorter MDR-TB regimen.[3]

There were 16/224 (7%) MDR/RR-TB patients switched their regimens because of the presence of prolonged QT. Moxifloxacin (Mfx), one of drug in STR was considered to cause prolonged QT. There is evidence that Mfx is more likely to cause both QTc prolongation and a longer QTc prolongation than the other fluoroquinolones (FQs), although it is also the FQ likely to be most effective against MDR-TB. The risk of QTc prolongation with the FQs is higher when there are electrolyte abnormalities and when other QTc prolonging medications are used.[15]

However, the previous study reported that in adults with pulmonary TB without any cardiac risk factors, Mfx 400 mg given daily for up to 4 months did not cause an increase in the QTc interval. The study indicates that Mfx, at a dose of 400 mg given once daily, is well tolerated and without any adverse cardiac events.[16] In this study, Mfx was given as national program: bodyweight <30 kg with 400 mg, 30-50 kg with 600 mg, and >50 kg with 800 mg. A study of clinical trial reported that moxifloxacin was well tolerated and not associated with increased risk of adverse reactions including prolonged QT. The study suggests that moxifloxacin could be safely used for even longer periods, though this needs to be confirmed in additional studies that are large enough to detect small but important rates of toxicity.[17] A study in London also reported that Mfx is well tolerated in treating TB.[18]

The mean value of potassium level at the baseline test in patients who switch their regimen caused by prolonged QT was 4.06 mmol/l. This level decreased to 2.92 mmol/l along with incidence of prolonged QT. This result showed that most of patients who experienced prolonged QT were also experienced hypokalemia. Hypokalemia was defined as serum potassium level of <3.5 mmol/l. A study in France reported that hypokalemia seems to be one of the most important risk factors for QT prolongation.[19]

Conclusion

There are 40/224 (18%) MDR/RR-TB patients who switched their regimen from shorter regimen to longer regimen. The major cause of switching in this study

is due to the presence of resistance to fluoroquinolone and 2nd line injection drugs and incidence of prolonged QT with 20/224 (9%) and 16/224 (7%), respectively. A diagnostic rapid test such as the line probe assay 2nd line TB drugs is absolutely a screening tool to determine MDR-TB patients, pre-XDR-TB or XDR TB as soon as the regimen is given. Monitoring and efforts to overcome prolonged QT side effects are also needed to prevent switch regimens that can affect the patient's psychological condition as a result of treatment, which must be started again using the longer regimen.

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References

1. World Health Organization. WHO global tuberculosis report. Geneva, Switzerland: WHO, 2019.
2. World Health Organization. Multidrug and extensively drug-resistant TB (M/XDR-TB): Global report on surveillance and response. Geneva, Switzerland: WHO, 2010.
3. World Health Organization. WHO Treatment Guidelines for Drug-Resistant Tuberculosis: 2016 Update. Geneva, Switzerland: WHO, 2016.
4. National Tuberculosis Control Program of Pakistan. Protocol for Treating MDR-TB/RR-TB with Shorter Treatment Regimen (STR). 2017. National Tuberculosis Control Program of Pakistan: Pakistan: National Tuberculosis Control Program of Pakistan, 2017.
5. World Health Organization. Rapid Communication: Key Changes to Treatment of Multidrug- and Rifampicin-Resistant Tuberculosis (MDR/RR-TB). Geneva, Switzerland: WHO, 2018.
6. Sotgiu G, Migliori GB. Effect of the short-course regimen on the global epidemic of multidrug-resistant tuberculosis. *Lancet Respiratory Medicine*. 2017; **5:** 159-61.
7. Helb D, Jones M, Story E, Boehme C, Wallace E, Ho K, et al. Rapid detection of *Mycobacterium tuberculosis* and rifampicin resistance by use of on-demand, near-patients technology. *Journal of Clinical Microbiology*. 2010; **48**: 229-37.
8. Indonesia Ministry of Health. The Joint External TB Monitoring Mission (JEMM TB) Indonesia 2017. Indonesia: Indonesia Ministry of Health, 2017.
9. Hafez SA, Elhefnawy AM, Hatata EA, El Ganady AA, Ibrahiem MI. Detection of extensively drug resistant pulmonary tuberculosis. *Egyptian Journal of Chest Diseases and Tuberculosis*. 2013; **62**: 635-46.
10. Indonesia Ministry of Health. E-TB manager: tuberculosis management information system. 2019. Cited April 22th 2019. Available on http://etbmanager.sitb.id.
11. Eshetie S, Gizachew M, Dagnew M, Kumera G, Woldie H, Ambaw F, et al. Multidrug resistant tuberculosis in Ethiopian settings and its association with previous history of anti-tuberculosis treatment: a systematic review and meta-analysis. *BMC Infectious Diseases.* 2017; **17**: 219.
12. Gadoev J, Asadov D, Harries AD, Parpieva N, Tayler-Smith K, Isaakidis P, et al. Recurrent tuberculosis and associated factors: a five-year countrywide study in Uzbekistan. *Plos One.* 2017; **12**: e0176473.
13. Zong Z, Huo F, Shi J, Jing W, Ma Y, Liang Q, et al. Relapse versus reinfection of recurrent tuberculosis patients in a national tuberculosis specialized hospital in Beijing, China. *Frontier Microbiology*. 2018; **9**: 1858.
14. Shen X, Yang C, Wu J, Lin S, Gao X, Wu Z, et al. Recurrent tuberculosis in an urban area in China: Relapse or exogenous reinfection?. *Tuberculosis*. 2017; **103**: 97-104.
15. Harausz E, Cox H, Rich M, Mitnick CD, Zimetbaum P, Furin J. QTc prolongation and treatment of multidrug-resistant tuberculosis. *International Journal of Tuberculosis and Lung Diseases*. 2015; **19**: 385-91.
16. Nair D, Velayutham B, Marimuthu M, Navaneethapandian PGD, Chinnaiyan P, Jawahar MS, et al. Effect of moxifloxacin on QTc interval in adults with pulmonary tuberculosis. *National Medical Journal of India*. 2018; **31**: 58-9.
17. Conde MB, Efron A, Loredo C, Souza G, Graca NP, Cezar MC, et al. Moxifloxacin in the initial therapy of tuberculosis: a randomized, phase 2 trial. *Lancet*. 2009; **373**: 1183-9.

18. Erik S, Graham B. Adverse effects of moxifloxacin during tuberculosis treatment. European Respiratory Society: Annual Congress 2012. Cited April 22th 2019. Available at https://erj.ersjournals.com/content/erj/40/Suppl_56/4291.full.pdf.
19. Trojak B, Astruc K, Pinoit JM, Gelinier JCC, Ponavoy E, Bonin B, et al. Hypokalemia is associated with lengthening of QT interval in psychiatric patients on admission. *Psychiatry Research*. 2007; **169**: 257-60.