ORIGINAL ARTICLE

Resistance Profile of *Mycobacterium tuberculosis* to Isoniazid, Quinolone, Bedaquiline, Clofazimine, Linezolid, and Second-line Injection Drug

Andriansjah Rukmana[1], Ariyani Kiranasari[1], Fadilah[2]

[1] Department of Microbiology, Medical Faculty, Universitas Indonesia. Jalan Pegangsaan Timur No 16, Jakarta, 10320.
[2] Department of Medical Chemistry, Medical Faculty, Universitas Indonesia. Jalan Salemba Raya no 6, Jakarta, 10430.

ABSTRACT

Introduction: Tuberculosis (TB) due to infection of the *Mycobacterium tuberculosis* has become a concern since this disease has been suffered by most of the world's population and causes death in large numbers. The increasing number of TB patients has increased our vigilance to reduce the spread of this disease. One of the efforts to provide effective treatment for cases of infection by this bacterium is to determine the proper anti-tuberculosis drug. **Methods:** This study tested *M. tuberculosis* isolates against several tuberculosis drugs, such as isoniazid, quinolone (ofloxacin and moxifloxacin), kanamycin, capreomycin, bedaquiline, linezolid, and clofazimine in MGIT liquid medium. The isolates used were bacterial stock belonging to the Department of Microbiology, Medical Faculty, Universitas Indonesia. All isolates used had a resistance phenotype to the anti-tuberculosis drug rifampicin determined by the GeneXpert MTB/Rif method. **Results:** From all the isolates tested, the percentage of anti-tuberculosis resistance was as follows: low-dose isoniazid 70.4%, high-dose isoniazid 66.7%, ofloxacin 9.9%, low-dose moxifloxacin 9.9%, high-dose moxifloxacin 2.5%, and bedaquiline 5.1%. There was no resistance to linezolid and clofazimine among the tested isolates. This study also found that 57 isolates were multi-drug resistant (MDR) strains, six isolates were pre-extensively drug resistance (XDR), and one isolate was an XDR strain. **Conclusion:** This study presented an overview of the resistance profile of *M. tuberculosis* to several first-, second-line and new tuberculosis drugs *in vitro*. The results of this study can be used by stakeholders in the health sector to develop policies for better management of tuberculosis.

Keywords: *M. tuberculosis*, Resistance, Anti-tuberculosis drugs

Corresponding Author:
Andraiansjah Rukmana, M.Biomed.
Email: andriansjah.ms@ui.ac.id
Tel: +62 21 3160491

INTRODUCTION

Tuberculosis (TB) is a severe health problem facing the world, especially in Indonesia. With a high population, Indonesia ranks third, with the highest amount of TB globally after China and India (1). Based on World Health Organization (WHO) data, in 2018, there were around 10 million new infection cases, with 8.7 million (87%) patients living in countries with a high incidence of TB, including Indonesia. It is estimated that the death rate from this disease reaches 1.3 million deaths per year (1,2). Globally, the incidence of TB has decreased slowly by around 1.6% per year, which is far from the WHO's End TB target strategy estimate of 4–5% per year, although the mortality rate has decreased to 4.1% per year (3). Although TB has infected 1.7 million people globally, only some have developed active TB (4). The bacterium *M. tuberculosis* complex is acid-fast, non-motile, aerobic, and short rod-shaped (5). TB infection generally attacks the productive age of humans, while the clinical symptoms are fever, sweating when asleep at night, losing weight due to loss of appetite, and frequent coughing and phlegm (6). In addition, TB can be transmitted through droplets released from the patient and inhaled by other people and can develop into active TB depending on the patient's immune status (7). Economically, TB infection has a significant impact on the economy. The research results in Indonesia show that infection with this disease dramatically affects the household economy level; as many as 36% of households are economically affected by 282 cases of drug-sensitive TB and 64 cases of multi-drug resistant (MDR) TB (6).

The burden of TB is to be challenging, with elevated cases of *M. tuberculosis* showing resistance to first-line drugs. Since 2016, it is estimated that there have been 490,000 cases of MDR TB infection (8). Some TB-resistant patients have experienced treatment failure,

either due to the lack of effectiveness of the drug or side effects. The WHO has included a group of five antibiotics, including thiacetazone, high-dose isoniazid, clofazimine, linezolid, amoxicillin plus clavulanate, macrolides, carbapenem, and thioridazine in the regimen for resistant TB to overcome this resistance problem (9). Indonesia has implemented a standard treatment and drug regimen for tuberculosis patients, such as bedaquiline, levofloxacin/moxifloxacin, clofazimine, ethionamide, high-dose isoniazid, pyrazinamide, and ethambutol for short-term treatment of drug-resistant TB (10). However, not all drugs have standardized susceptibility culture testing. In the national TB control programme, only low/high dose isoniazid, low/high dose moxifloxacin, ofloxacin, kanamycin, and capreomycin must be laboratory tested to determine the phenotypic profile (10).. Therefore, laboratory data are needed regarding the resistance profile of several anti-tuberculosis drugs outside of those routinely carried out.

Knowing the profile of *M. tuberculosis* resistance to antibiotic drugs is very important for understanding the epidemiology and control of this disease. In this study, we tried to analyse the resistance profile of *M. tuberculosis* to the first-line and second-line tuberculosis drugs that have been routinely tested for susceptibility in the laboratory and other drugs in group A (bedaquiline, linezolid) and group B (clofazimine) that have not been included in the testing panel. Although the number of bacteria tested in this report is small, the information presented is essential. This can be a starting point for understanding the spread of tuberculosis resistance and practical guidance for implementing national TB control in Indonesia.

MATERIALS AND METHODS

Isolates

The samples were stock isolates belonging to the Tuberculosis Laboratory of Unit Kerja Khusus Laboratorium Mikrobiologi Klinik (UKK LMK), Department of Microbiology, Medical Faculty Universitas Indonesia. All isolates were *M. tuberculosis* bacteria with a genotypic profile of resistance to rifampicin through testing using the Genexpert method. The bacterial isolates were from patient samples taken from a district hospital in Bogor, West Java, from March to May 2021.

Species determination

The stock isolates used in this study were regrown in Lowenstein–Jensen medium. The bacteria that grew were then tested for correctness as species of the *M. tuberculosis* complex using the SD MPT64 TB Ag Kit (Standard Diagnostic) and growth in Lowenstein-Jensen-P-nitrobenzoic acid (LJ-PNB) medium. Bacteria that grew in the LJ medium but did not grow in the LJ-PNB medium and gave a positive band in the SD MPT64TB Ag test were continued for drug susceptibility testing.

Drug susceptibility testing

In this study, the control isolates were *M. tuberculosis* H37Rv (ATCC 27294) or *M. tuberculosis* H37Ra (ATCC 25177) strains, which were susceptible to all types of anti-tuberculosis antibiotics. The drugs used for the susceptibility test were low- and high-dose isoniazid 0.1 µg/ml and 0.4 µg/ml, moxifloxacin low- and high-dose 0.25 µg/ml and 1 µg/ml, ofloxacin 2 µg/ml, capreomycin 2.5 µg/ml, kanamycin 2.5 µg/ml, bedaquiline 1 µg/ml, linezolid 1 µg/ml, and clofazimine 1 µg/ml in Mycobacterium Growth Indicator Tube (MGIT) 960 medium (Becton Dickinson). Antibiotic concentration calculation was based on the protocol from the National Reference Laboratory for the culture test of Balai Besar Laboratorium Kesehatan (BBLK) Surabaya. In the step for bacteria preparation, all isolates were sub-cultured on LJ medium before being tested with anti-tuberculosis drugs. A drug susceptibility test was carried out on bacteria 3–4 weeks old. The bacterial suspension was carried out until it reached McFarland 0.5 (11). A solution with a serial concentration of 1 ml of the bacterial suspension was then transferred to a tube containing 4 ml dH2O. Finally, 100 µl of bacterial suspension was transferred into a tube containing 10 ml of dH2O. For the susceptibility test, 500 µl of suspension was transferred into a prepared drug and control labelled MGIT tube. The control MGIT tube and the tube containing the drug are inserted into the MGIT machine. The results of the examination are obtained from the machine after incubation of 5–19 days (12).

RESULTS

Phenotypic profile of DST results

The results of drug susceptibility testing on several anti-tuberculosis drugs are shown in Table I. For first-line anti-tuberculosis drugs represented by isoniazid, the number of resistant strains was 66.7% for a high dose of isoniazid and 70.4% for a low dose. Although it was only 3.7% different between the low and high doses, these data showed that 29.6% of isolates from MDR patients based on the Genexpert method were still sensitive to isoniazid.

For the second-line injectable drugs, namely kanamycin and capreomycin, the number of sensitive isolates was higher than the resistant ones. The sensitive isolates for kanamycin and capreomycin were 96.3% and 95.1%, respectively. Similar values were also obtained for quinolone anti-tuberculosis drugs, such as ofloxacin and moxifloxacin. The number of isolates sensitive to ofloxacin, low-dose moxifloxacin, and high-dose moxifloxacin was 90.1%, 90.1%, and 95.1%, respectively.

In drug susceptibility testing for the other group A and group B, it was seen that almost all drugs still showed high sensitive values. However, bedaquiline, as the drug of choice, showed that 5.1% of the tested isolates were

Table I: Drug susceptibility testing results for anti-tuberculosis drugs

Anti-tuberculosis drug	concentration	n	resistant n (%)	sensitive n (%)
Isoniazid	0,4 mg/ml (high dose)	81	54 (66,7)	27 (33,3)
	0,1 mg/ml (low dose)	81	57 (70,4)	24 (29,6)
Kanamycin	2,5 mg/ml	81	3 (3,7)	78 (96,3)
Capreomycin	2,5 mg/ml	81	4 (4,9)	77 (95,1)
Ofloxacin	2 mg/ml	81	8 (9,9)	73 (90,1)
Moxifloxacin	1 mg/ml (high dose)	81	2 (2,5)	79 (97,5)
	0,25 mg/ml (low dose)	81	8 (9,9)	73 (90,1)
Bedaquiline	1 mg/ml	79	4 (5,1)	75 (94,9)
Clofazimine	1 mg/ml	79	0 (0)	79 (100)
Linezolid	1 mg/ml	40	0 (0)	40 (100)

resistant. Meanwhile, clofazimine and linezolid showed that 100% of isolates were sensitive to the tested drug. Due to the limited available drugs, only 40 isolates were tested for the linezolid anti-tuberculosis drug.

Distribution of MDR and extensively drug resistant (XDR) based on isoniazid's phenotypic profile

Under the Indonesian national TB programme, patients suspected of having MDR-TB will be sampled for the first time using the Genexpert method and an MTB/rif cartridge. The use of this cartridge only provides an assessment of resistance to rifampicin as an MDR marker. A positive result on Genexpert examination with rifampicin resistance will recommend that the patient undergo MDR TB treatment. This often makes clinicians have doubts about eliminating the use of isoniazid in the treatment of TB. In Table II, it can be seen that if MDR TB treatment is only based on the Genexpert results, there is a 29.6–33.3% chance that patients can get isoniazid treatment.

Table II: Percentage of MDR-TB

Anti-tuberculosis drug	concentration	MDR by Rifampicin and Isoniazid resistant assessment* n (%)	MDR only by Genexpert assessment (Isoniazid sensitive) n (%)
Isoniazid	0.4 mg/ml (high dose)	54 (66.7)	27 (33.3)
	0.1 mg/ml (low dose)	57 (70.4)	24 (29.6)

*Rifampicin resistant by genexpert method, Isoniazid resistant by MGIT drug susceptibility culture

We also calculated the number of pre-XDR and XDR in the tested samples, especially from the MDR samples, by determining the results of Genexpert methods and drug susceptibility testing at a low dose of isoniazid. The results in Fig. 1 show that at least six isolates are pre-XDR and one isolate is of the XDR strain.

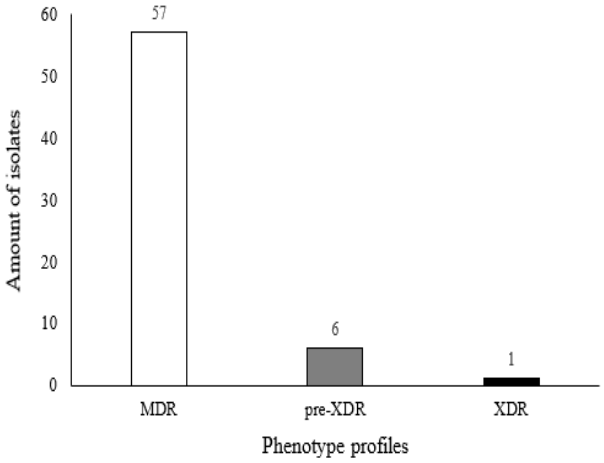

Figure 1: Amount of MDR and pre-XDR from isolates tested. White box, MDR determined by rifampicin resistant (Genexpert method) and low-dose isoniazid resistant (drug susceptibility testing method); Grey box, amount of pre-XDR; Black box, amount of XDR.

DISCUSSION

The resistance of *M. tuberculosis* to anti-tuberculosis medicine is a severe problem due to the limited availability of anti-tuberculosis drugs, especially for first-line drugs, which have potential and mild side effects. Rifampicin is a first-line drug and a potential drug of choice for drug-sensitive TB patients besides other anti-tuberculosis drugs, such as isoniazid, ethambutol, and pyrazinamide (13). The trend of increasing MDR TB cases in which the antibiotic rifampicin can no longer be given to patients demands second-line anti-tuberculosis or additional drugs. Several second-line and additional anti-tuberculosis drugs have been implemented in Indonesia, such as quinolones (levofloxacin, moxifloxacin), second-line injectable drugs (capreomycin, kanamycin), and additional drugs, such as bedaquiline, linezolid, and clofazimine (10).

The results of our study showed that several second-line or additional anti-tuberculosis drugs still had a high level of susceptibility, even though resistant *M. tuberculosis* was already evident. At least more than 50% of the isolates are resistant to isoniazid; this is not surprising because the isolates used are resistant to rifampicin. Rifampicin is a marker of MDR TB; as an MDR marker, studies in several countries state that rifampicin monoresistance is estimated to be less than 1% in European countries and 3.2% in Zambia for new TB cases (14,15). These data indicate that rifampicin resistance is common with other anti-tuberculosis resistance, including that of isoniazid. Isoniazid is one of the anti-tuberculosis drugs used together with rifampicin or as a single drug to prevent tuberculosis infection or prevent latent TB from becoming active TB (16). The data in Table II show that 29.6% and 33.3% of isolates are sensitive to low-dose and high-dose isoniazid, respectively. These data show that MDR TB patients undergoing second-line treatment based on Genexpert results will partially respond to isoniazid. However, in most MDR-TB patients, especially those receiving a short-term regimen, isoniazid administration is of little benefit (10).

Meanwhile, for the second-line injection drugs, kanamycin and capreomycin still showed *M. tuberculosis*

susceptibility values above 90%. Kanamycin is the second-line injectable drug that has become the standard of therapy in Indonesia (17), while capreomycin is the primary choice for second-line injection (18). These data indicate that second-line injectable drugs are still effective for patients. Indonesia has also implemented a rapid diagnosis, namely the Line Probe Assay (HAIN Lifescience), which looks for the genotypic profile of the quinolone group and second-line injectable drugs. The results of this method are one way to determine whether TB patients can follow short-term treatment (10). This report did not compare the phenotypic profile based on culture susceptibility testing with the genotypic profile based on LPA results.

The results of drug susceptibility testing for the quinolone group showed that the susceptibility to *M. tuberculosis* was still above 90%. Low doses of ofloxacin and moxifloxacin showed relatively the same percentage of sensitive isolates. In laboratory diagnosis in Indonesia, ofloxacin is a marker to determine the resistance profile of levofloxacin. A study conducted to compare the effectiveness of levofloxacin compared with moxifloxacin found that high-dose moxifloxacin was more effective than high-dose levofloxacin in mice that were both sensitive and resistant to *M. tuberculosis* (19). However, both anti-tuberculosis drugs are still given to patients with MDR TB in the short- and long-term regimens (10).

In the absence of rapid diagnosis for drugs such as bedaquiline, clofazimine, and linezolid, culture susceptibility testing is an alternative to determine the susceptibility of *M. tuberculosis* to these drugs (20). Using a liquid culture method such as MGIT would be an efficient way of guiding the treatment of TB patients, as reported for the anti-tuberculosis drug bedaquiline (21,22). From our research data, it appears that all of these anti-tuberculosis agents still have a low level of *M. tuberculosis* resistance. Only 5.1% of *M. tuberculosis* in this study were resistant to bedaquiline. Bedaquiline has activity against replicating and non-replicating mycobacterium cells (23). The use of bedaquiline as a novel regimen for MDR TB patients has shown encouraging results, where the study results showed a cure rate of 58% compared to 32% of placebo (24). Bedaquiline therapy also accelerates the conversion of sputum to negative within six months (25,26). Proper administration of antibiotics will suppress the increasing number of *M. tuberculosis* strains that are resistant to bedaquiline. Meanwhile, two other anti-tuberculosis drugs, linezolid and clofazimine, still showed a susceptibility value of 100%. Clofazimine is given to patients in short-term treatment, whereas in long-term treatment, clofazimine and linezolid can both be given (10). Although the success rate of clofazimine administration is the same as that of pyrazinamide, the mortality rate of TB patients given clofazimine is higher than that of those given pyrazinamide. The use of clofazimine still indicates its effectiveness and safety (27). As for linezolid, this drug has excellent effectiveness for MDR and XDR TB (28), although it has high toxicity and is relatively expensive (29).

The problem of TB infection by MDR strains has received much attention due to the more extended treatment period and lesser drug effectivity than drug-sensitive TB. Some of these MDR TB strains have undergone further mutations with resistance to quinolone anti-tuberculosis drugs and drugs classified in group A; these strains are known as pre-XDR or XDR strains (30, 31). Although Indonesia had recently used group A anti-tuberculosis in the treatment of TB patients without laboratory examination for bedaquiline, clofazimine, and linezolid when the study started, the data of this study supported that pre-XDR TB and XDR TB strains already exist, especially in the area where patient samples come. The emergence of these strains needs to be a concern for TB control programme implementers in Indonesia, considering that these strains are hazardous. Because MDR and especially XDR strains are resistant to many potent anti-tuberculosis drugs, TB treatment becomes less effective, has more severe side effects, is more expensive, and leads to death. XDR TB is of particular concern when infecting people with HIV or immunosuppressed patients (32,33).

A comparison of data regarding the phenotype profile of *M. tuberculosis* against anti-tuberculosis drugs is significant in determining the spread of resistant *M. tuberculosis* in Indonesia. We observed that the information on the resistance profile of this bacteria is not well informed through scientific articles; as a result, it is challenging to compare resistance levels in other areas in Indonesia. In addition, we believe that this in vitro study of bedaquiline, linezolid, and clofazimine is a new occurrence in Indonesia. These data are expected to serve as a reference for other similar studies.

The results of this research are intriguing. However, this study has limitations in that the results may only describe the conditions of the sample's origin. In addition, this study focuses only on in vitro phenotypic profiles and does not involve patient status, so there is no discussion between clinical response and related bacterial phenotypes.

CONCLUSION

Some anti-tuberculosis drugs, especially second-line, group A and group B, from the results of this study still show a high susceptibility percentage. The low rate of resistance to these drugs gives hope that their use can increase cure cases in MDR TB patients, especially in Indonesia. Caution and adequacy in the administration of anti-tuberculosis drugs will reduce the rate of *M. tuberculosis* resistance. However, pre-XDR and XDR strains based on WHO updated definitions were found,

albeit in low percentages.

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