Pharmacology and Clinical Pharmacy Research
Volume 9 No. 3 December 2024
ISSN:2527-7322 | e-ISSN: 2614-0020
doi: 10.15416/pcpr.v9i3.57368

Effectiveness and Safety of Shorter Treatment Regimen Containing Bedaquiline in Patients with Multidrug-Resistant Tuberculosis

Hardiyono[1], Oki N. Putra[1*], Nur Indah[2], Adi Larasanti[3]

[1]Department of Clinical and Community Pharmacy, Hang Tuah University, Surabaya, Indonesia
[2]Department of Pulmonology, Haji Hospital, Surabaya, Indonesia
[3]Research Unit, Haji Hospital, Surabaya, Indonesia

Abstract

Bedaquiline has been included in the shorter treatment regimen (STR) to treat patients with multidrug-resistant tuberculosis (MDR-TB). This study aims to evaluate the effectiveness and safety of STR-containing bedaquiline. Data were collected retrospectively from medical records of MDR-TB patients receiving STR between January 2020 and December 2021. Sputum culture was evaluated at six months (24 weeks) and the end of treatment. Measurement of renal and liver function tests, serum electrolytes, and uric acid were evaluated to assess safety during six months of treatment. Treatment failure, death, and loss to follow-up were also recorded during the study period. Thirty eligible MDR-TB met the inclusion criteria. Twenty-five (83.3%) had a positive culture at baseline and were enrolled in effectiveness analysis. After treatment completion, 24 of 25 patients (96.0%) had sputum culture conversion. A significant decrease in potassium and calcium serum levels was observed at three months of treatment. Cases of treatment failure and loss to follow-up were 3.3% and 6.6%, respectively. Among MDR-TB patients, shorter treatment regimens containing bedaquiline were associated with highly favorable outcomes at the end of treatment. Based on safety, regimens containing bedaquiline demonstrated a tolerable safety profile without seriuos adverse events. Safety, treatment completion, and culture conversion in this study support use of bedaquiline for the treatment of MDR-TB.

Keywords: Bedaquiline; Effectiveness; MDR-TB; Safety; STR

Corresponding author: Oki Nugraha Putra. Department of Clinical and Community Pharmacy, Hang Tuah University, Surabaya, Indonesia. Email: oki.nugraha@hangtuah.ac.id
Received: 20 August 2024. **Revised**: 29 November 2024. **Published:** 18 December 2024

Introduction

Multidrug-resistant tuberculosis (MDR-TB) is a chronic infectious disease requiring long-term and complex treatment with serious adverse effects. Patients previously treated with antitubercular drugs are a risk factor for developing MDR-TB[1]. The administration of injectable drugs for the treatment of MDR-TB was associated with unfavorable outcomes. Therefore, all-oral regimens with high efficacy and tolerable adverse effects are urgently required. In 2020, WHO announced bedaquiline to replace injectable drugs as part of all-oral regimens to treat MDR-TB patients[2].

Bedaquiline, a novel antituberculosis drug, resulted in promising results in DR-TB patients with shortened treatment time, improved adherence, increased cure, and reduced mortality rates[3]. Bedaquiline was considered a core drug due to its high bactericidal and sterilizing activity and could prevent cross-resistance with other antitubercular drugs during treatment[4]. A meta-analysis by Wang et al., reported that for patients with MDR-TB who received bedaquiline, the culture conversion was higher and the mortality rate was lower than those without bedaquiline[5].

Indonesia is one of the highest-burden countries of MDR-TB in the world. The Indonesia National Tuberculosis Program included bedaquiline in programmatic use for treating MDR-TB, both shorter treatment regimens (STR) and individualized treatment regimens (ITR)[6]. STR has been indicated for patients with MDR-TB without additional resistance to fluoroquinolones and had minimal lung lesions. STR was administered for 9-11 months with seven oral drugs[2]. In addition to effectiveness, drug safety is an important aspect that should be addressed in MDR-TB patients. Two previous studies in Indonesia reported the safety of bedaquiline in MDR-TB patients[7,8]. However, they focused on QTc interval prolongation and did not report sputum conversion during treatment. Meanwhile, several adverse events that might occur during treatment, such as liver and renal dysfunction and electrolyte imbalance, were not reported. Several studies have shown the effectiveness or efficacy of bedaquiline regimens in African[9], Chinese[10], Indian[11], and Korean[12] populations. However, these studies differ regarding the type of TB resistance, co-morbidities, and the regimen co-administered with bedaquiline. The Asian population, primarily the Indonesian, MDR-TB related to bedaquiline, has been poorly studied. WHO claimed oral regimens, including bedaquiline, are safe with minimal adverse effects, resulting in highly favorable outcomes.

Most studies reported the efficacy and safety of bedaquiline in ITR with modifiable drugs. However, studies related to bedaquiline in STR require further exploration. With a shorter treatment time, STR is expected to increase patient compliance in taking medication. Previous studies in Indonesia have reported high treatment failure in MDR-TB patients on regimens containing second-line injectable drugs. However, data are scarce in Indonesia about the effectiveness and safety of STR with all-oral containing bedaquiline to treat MDR-TB patients. Therefore, a retrospective study was conducted to analyze the effectiveness and safety of STR-containing bedaquiline in Indonesian MDR-TB patients. The findings of this study are expected to add to the local literature and enable the National Tuberculosis Control Program to use all-oral regimens containing bedaquiline safely and confidently.

Methods

Eligibility criteria

This was a retrospective study at the Haji Hospital in Surabaya, Indonesia. This study used medical records of MDR-TB patients

who received STR between January 2021 and December 2022. This study was conducted from August to December 2023. This study received approval from the Ethics Committee of Haji Hospital with number 445/40/KOM.ETIK/2023. Written informed consent was unnecessary since this study was retrospective.

MDR-TB patients were defined as resistant to rifampicin alone or both rifampicin and isoniazid. The eligibility of MDR-TB patients to be included in STR was without additional resistance to fluoroquinolones, had no contact with patients with pre-XDR or XDR-TB, and not received first-line antitubercular drugs for ≥ 1 month. The inclusion criteria of this study were as follows:

a. MDR-TB patients aged ≥18 years old
b. Completion of 9-11 months of treatment;
c. GeneXpert/MTB RIF assay showed rifampicin resistance
d. Received seven-all oral shorter treatment regimens including bedaquiline
e. Had a positive sputum culture at baseline.

Drug susceptibility testing was conducted to assess fluoroquinolone resistance. The exclusion criteria were as follows:

a. Renal dysfunction (creatinine clearance < 30ml/min or creatinine serum > 3 x the upper normal limit)
b. Liver impairment (SGOT or SGPT > 3 x the upper normal limit or total bilirubin > 2 x the upper normal limit
c. Incomplete sputum data during the treatment period
d. Switched to individualized treatment regimens
e. Patients with HIV positive at enrollment.

Treatment regimens

STR consists of bedaquiline, levofloxacin, clofazimine, a high dose of isoniazid, pyrazinamide, ethambutol, and ethionamide for the intensive phase during 4-6 months, meanwhile levofloxacin, clofazimine, pyrazinamide, and ethambutol for continuation phase during five months with a total of 9-11 months. The duration of STR was extended to 11 months in case the sputum culture was still positive at the end of the fourth month[6].

The composition of STR cannot be modified. However, regarding adverse effects, ethionamide and levofloxacin could be replaced with protionamide and moxifloxacin. The administration of moxifloxacin should be closely supervised since concomitant use with bedaquiline and clofazimine increases the risk of QTc prolongation. All drugs were administered once daily for every day. Meanwhile, bedaquiline was given daily for the initial two weeks and thrice weekly for the remaining 22 weeks, totaling 24 weeks[6]. All drugs were administered under observation. Patients were first hospitalized for two weeks for the daily administration of all drugs, including bedaquiline, followed by outpatient management at district or primary public health.

Data collection

Demographic, clinical status at diagnosis, and laboratory data to assess treatment effectiveness and safety were recorded from the medical records. Patients underwent several examinations after administration of STR every month from week four and monthly follow-up until treatment was complete. The clinical review included examining sputum culture was used to assess the effectiveness of STR. Renal and liver function test, TSH level, serum electrolytes (potassium, calcium, and magnesium), and hemoglobin level were used to assess the safety of STR[6].

Effectiveness assessment

The initial treatment outcome sputum

ISSN:2527-7322 | e-ISSN: 2614-0020

culture was evaluated at the end of 6 months (24 weeks) of STR. Sputum samples were collected monthly for culture during routine examination until 9-11 months. We restricted patients in this study with positive baseline sputum culture to be included in our analysis. A favorable outcome was culture conversion within 9-11 months in two consecutive, negative cultures collected at least 28 days apart in liquid culture Medium. Unfavorable outcomes, such as death, treatment failure, and loss to follow-up were also recorded during the study period[6].

Safety assessment

Laboratory data, including liver function test (SGOT, SGPT, total bilirubin), renal function test (creatinine serum, BUN), albumin, electrolytes such as potassium, calcium, and magnesium, were measured at baseline and every month to assess safety. Thyroid Stimulating Hormone (TSH) was measured at baseline.6 Since bedaquiline was administered for six months, we evaluated the safety during six months of treatment.

Statistical analysis

Categorical variables were reported as numbers or percentages. Meanwhile, continuous data were expressed as the median and interquartile range (IQR). The rate of sputum culture conversion was reported as a percentage. We used Wilcoxon signed rank test to analyse the differences among continuous data, including renal function (BUN, serum creatinine), liver function (SGOT, SGPT, total bilirubin), electrolytes (potassium, calcium, magnesium), and uric acid, during six months of treatment. Statistical analysis was performed using SPSS version 17.0 (SPSS Inc. Chicago, IL, USA). P-value <0.05 was considered statistically significant.

Result and Discussion

The demographic and clinical characteristics are shown in Table 1. A total of 43 MDR-TB patients received STR between January 2020 and December 2021. Of these, 13 patients were excluded, and only 30 were included in our cohort for further analysis. The median age was 41 (IQR 17-55 years), and half (16/30, 53.4%) were male. Six of 30 (20.0%) patients had diabetes mellitus. All MDR-TB patients had pulmonary TB. Of 30 patients, 25 (83.3%) had positive initial sputum cultures. The flowchart of the included patients is shown in Figure 1.

The cumulative conversion of sputum culture during treatment is shown in Table 2. Two months after treatment, sputum culture conversion and six months (24 weeks) were 80.0% and 96.0%, respectively.

Treatment outcomes, including favorable and unfavorable (treatment failure, death, and loss to follow-up) of STR in MDR-TB patients, were shown in Table 3. We found two cases of loss to follow-up (6.6%) during six months of treatment.

Our study demonstrated that MDR-TB patients treated with a 7-drug-all-oral STR containing bedaquiline, culture conversion was 96.0% at six months (24 weeks) and at the end of nine months, respectively. Compared to the study by Phuong et al., reported in patients with RR-TB who received five drugs of STR (bedaquiline, levofloxacin, linezolid, clofazimine, and/or pyrazinamide), the successful treatment was 95/106 (90%). Meanwhile, unfavorable outcomes, including treatment failure, death, and loss to follow-up, were 4%, 1%, and 6%, respectively[13].

Furthermore, a study by Avaliani et al., demonstrated that in MDR-TB patients in Georgia who received five drugs of STR (bedaquiline, linezolid, levofloxacin, clofazimine, and cycloserine), the treatment

success was 22/25 (88%).14, however, five-drug-all oral STR, including linezolid and or cycloserine, has not been implemented in our hospital since they were included for longer individual regimens. Treatment success of more than 90% in our study was higher than that of Soeroto et al., who reported that 64.5% of successful treatment in Indonesian MDR/RR-TB patients were treated with the second-line injectable-containing 7-drug STR[15].

Regimens containing bedaquiline demonstrated favorable culture conversion at two and four months, 78.6% vs 90.3%, respectively, in DR-TB patients susceptible to fluoroquinolone[16]. Pyrazinamide, one of the STRs for MDR-TB treatment, has excellent sterilizing effect to shorten treatment by diffusing into caseous lessions rather than airway surfaces[17,18]. In addition to bedaquiline, levofloxacin is one of the crucial drugs to manage MDR-TB patients. It has shown excellent penetration into chronic lung lesions in MDR-TB patients. Moreover, its concentration in the blood correlates with the concentration in the lung cavity. Clinically, lung cavitiy in MDR-TB patients delays in sputum conversion, high recurrence rates, and increased acquired drug resistance[19]. A study by Al-Shaer et al., reported median time to culture conversion was significantly shorter in DR-TB patients who received levofloxacin and or moxifloxacin than those with ciprofloxacin and or ofloxacin. Furthermore, those treated with levofloxacin and or moxifloxacin were more likely to have culture conversion. At least, levofloxacin with a dose 1500 to 1750 mg may be needed to achieve maximum effects against M. tuberculosis[20].

A study by Sidamo et al., reported that in MDR-TB patients who received a levofloxacin-based regimen, the treatment success was significantly higher at 81.1% compared to those who received a moxifloxacin-based regimen, 51.2%. The use of bedaquiline was considerably higher in the levofloxacin group compared to moxifloxacin, although the rate of clofazimine use was similar between the two groups[21]. It demonstrates that a levofloxacin-based regimen with bedaquiline and clofazimine provides satisfactory treatment success rates with no relapse after treatment completion[22].

One-fifth of patients in our study had diabetes mellitus (DM). However, the overall sputum culture conversion was satisfactory. A study by Shi et al., reported that sputum conversion at week 24 was 90% and 95%, respectively, in MDR/XDR-TB patients with or without diabetes who received a regimen containing bedaquiline[23]. It indicated that regimens containing bedaquiline provide favorable outcomes in MDR or XDR-TB patients with diabetes. Conversely, in DR-TB patients with DM who received a regimen containing kanamycin, favorable outcomes were 45%. Those with DM were 1.2 times more likely to have unfavorable outcomes[24]. Favorable outcomes in our study can't be separated from the concurrent use of clofazimine. A meta-analysis demonstrated that in DR-TB patients receiving clofazimine-containing regimens, the treatment completion and failure rate were significantly 1.2 times higher and 0.5 times lower than those not receiving clofazimine[25]. However, concurrent use of bedaquiline and clofazimine increases cross-resistance risk. Mutation in Rv0678 was associated with increased MIC and was more likely to develop acquired resistance to bedaquiline and clofazimine. Therefore, regimens containing both drugs should be reconsidered when a mutation is identified to reduce treatment failure[26].

The median (IQR) level of TSH level (mIU/L) at baseline was 0.98 (0.35-3.68).

ISSN:2527-7322 | e-ISSN: 2614-0020

Haemoglobin level was within normal limits during the study period. The median (IQR) level of albumin (mg/dl) at baseline, 3, and 6 months was 3.69 (2.90-4.30), 3.80 (3.10-4.52), and 4.00 (3.41-4.80), respectively. Albumin levels significantly increased from baseline to 6 months and 3 to 6 months (P-value 0.000). The median (IQR) level of uric acid (mg/dl) at baseline, 3, and 6 months was 4.40 (2.60-7.10), 7.00 (3.40-10.20), and 6.40 (2.70-12.20), respectively. Uric acid levels significantly increased from baseline to 3 months and baseline to 6 months (P-value 0.000).

Prolonged and abnormal QTc intervals increase the risk of potentially life-threatening ventricular arrhythmias, known as Torsade de Pointes (TdP). Although bedaquiline was associated with QTc prolongation, the severity grade was low and no TdP or death-related cardiac arrhythmias.11,27-28. Intracellular concentrations of M2 were higher than bedaquiline and it was responsible for QTc prolongation[29].

Although we did not analyze the QTc interval due to lack of data, arrhytmia or TdP was not observed during this study. Interestingly, our study found a significantly lower potassium and calcium level at three months, as shown in Figure 2. The median (IQR) level of potassium, calcium, and total magnesium at baseline, 3, and 6 months was 4.30 (3.10-5.40), 3.90 (2.00-4.40), and 4.00 (2.70-5.00); 9.40 (7.90-10.10), 9.00 (8.10-10.70), and 9.10 (8.00-15.70); 2.00 (1.10-2.40), 1.90 (1.30-2.40), and 2.00 (1.50-2.40), respectively. A significantly reduced median potassium and calcium level was observed from baseline to month 3. Meanwhile, the median magnesium level significantly increased from baseline to 6 months of treatment (p-value < 0.05).

The magnesium level was within the normal limit during six months of treatment. Electrolyte disturbance, mainly potassium, was associated with QTc prolongation. Hypokalaemia is a risk factor for QTc prolongation. The M2 metabolite of bedaquiline prolongs the QTc interval by inhibiting the human ether-a-go-go gene (hERG), which causes potassium rectifier (Ikr) repolarization. Hypokalemia decreases IKr by increasing the inactivation of sodium competitive barriers, ultimately leading to prolonging the QTc interval. Therefore, periodic monitoring of potassium levels is necessary to prevent potential prolongation of the QTc interval[9].

A study by Li et al., demonstrated when the QTc interval was prolonged in patients who received bedaquiline, serum potassium levels decreased by 10.71%, and sodium levels increased by 1.07% from baseline.30 Tang et al., reported that hypocalcemia was associated with QTc prolongation. Hypocalcaemia may induce QTc prolongation through a calcium-dependent inactivation of the L-type calcium channel (LTCC) and lead to early depolarization[31]. Therefore, coadministration with other drugs that induce lower potassium and calcium levels should be considered to reduce the risk of QTc prolongation in MDR-TB patients.

Discontinuation of bedaquiline due to QTc prolongation was not observed during this study. A study by Kusmiati et al., reported in DR-TB patients who received the second line injectable-containing 7-drug STR, including kanamycin and moxifloxacin, 18.5% and 28% of them experienced moderate (471-500ms) and severe QTc prolongation (>500ms), respectively[32]. It indicated replacing second-line injection with bedaquiline is relatively safe, particularly in QTc intervals.

Renal function tests, including serum

creatinine and BUN during six months of treatment, are shown in Figure 3. The median (IQR) level of BUN (mg/dl) at baseline, 3, and 6 months was 9.00 (3.90-17.00), 8.00 (4.10-17.00), and 9.00 (3.00-22.40), respectively. The median (IQR) level of serum creatinine (mg/dl) at baseline, 3, and 6 months was 0.75 (0.50-1.30), 0.80 (0.52-1.56), and 0.90 (0.60-1.70), respectively. The median level of BUN did not significantly increase during six months of treatment. Meanwhile, serum creatinine levels significantly increased from baseline to 6 months (p-value < 0.05).

We found a significant increase in serum creatinine within six months of treatment for the renal function test. Creatinine is the end product of muscle metabolism and is widely used to assess renal function. Levofloxacin, one of the drugs in STR, 80% of its dose is excreted unchanged in the urine. Elevated serum creatinine is associated with acute interstitial nephritis (AIN). The study by Sidamo et al., reported that significantly increased serum creatinine was found in patients receiving moxifloxacin-based regimens compared to levofloxacin[21]. Although we found a significant increase in serum creatinine in our study, it was still within the normal range.

Liver function tests during six months of treatment are shown in Figure 4. Median (IQR) level of SGOT, SGPT, and total bilirubin at baseline, 3, and 6 months was 21.00 (12.00-48.00), 24.00 (17.50-75.00), and 23.00 (14.50-122.60); 20.00 (7.00-84.00), 23.00 (8.00-127.00), and 21.00 (7.00-179.00); 0.49 (0.19-0.99), 0.53 (0.21-1.70), and 0.59 (0.24-1.16), respectively. The median level of SGPT and total bilirubin were not statistically significant during the administration of STR. Meanwhile, the median level of SGOT significantly increased from baseline to 6 months of treatment (p-value < 0.05).

We found a median increase in SGOT, SGPT, and total bilirubin for liver function tests within six months of treatment, although not statistically significant, except for baseline and sixth month. However, we found that no patients had symptoms of hepatotoxicity, such as jaundice and malaise, during the study period. In STR, the antituberculosis drugs that contribute to the risk of hepatotoxicity are isoniazid and pyrazinamide . Bedaquiline is thought to have hepatotoxic effects due to its high lipophilicity and leads to phospholipidosis. However, increased hepatotoxic effects of bedaquiline are more commonly found in elderly patients, hepatitis, hypoalbumin, and the use of other drugs that induce hepatotoxicity. A study by Aslam et al., reported that the incidence of hepatotoxicity in MDR-TB patients receiving regimens containing bedaquiline in Pakistan was 9.7%.4 Hepatotoxicity is the most common cause of discontinuation of drugs related to rifampicin, isoniazid, and pyrazinamide. Data regarding the incidence of hepatotoxicity in MDR-TB patients who received STR is scarce. A study in Indonesia reported that in MDR-TB patients who received STR, the incidence of hepatoxicity was 41/129 (31.78%), with the majority of onset > 14 days.33 Compared to drug-sensitive TB, the incidence of hepatotoxicity was lower, 7.9%34 and 9.7%[35].

The median uric acid level was significantly increased at baseline to 3 months and at baseline to 6 months. Pyrazinamide increases uric acid levels by inhibiting its excretion in the renal proximal tubular and thus leading to hyperuricemia. A decrease in uric acid clearance was associated with hyperuricemia after the administration of pyrazinamide. Patients who received a regimen containing bedaquiline had more hyperuricemia than those without bedaquiline, 65.71% vs 39.71%, respectively[16]. A study by Louthrenoo et al.,

demonstrated a significant increase at baseline to four months in serum uric acid in patients who received pyrazinamide for six months[36]. However, the incidence was reversible and had no significant effects on renal function.

This study had several limitations. First, since it was retrospective, only some clinical patient complaints can be found in the medical record. Second, we did not classify the severity of side effects due to limited information. Third, the sample size was relatively small, so it cannot be generalized to MDR-TB patients. A further prospective study is urgently needed to increase the number of patients and obtain more comprehensive data regarding the safety and effectiveness of STR in MDR-TB patients.

Conclusion

A shorter treatment regimen with all seven oral drugs containing bedaquiline achieved favorable sputum conversion at 6 months (24 weeks) and at the of treatment. It was relatively safe to manage MDR-TB patients. Unfavorable outcomes were low during the STR period.

Acknowledgement

We thank all of the medical staff who provided and supported the study.

Funding

We did not find any funding from other parties.

Conflict of Interest

We declare there was no conflict of interest during this study.

References

1. Panford V, Kumah E, Kokuro C, Adoma PO, Baidoo MA, Fusheini A, et al. Treatment outcomes and associated factors among patients with multidrug-resistant tuberculosis in Ashanti Region, Ghana: a retrospective, cross-sectional study. *British Medical Journal Open*. 2022; 12:e062857. https://doi.org/ 10.1136/ bmjopen-2022-062857
2. World Health Organization. Consolidated Guidelines on Tuberculosis Treatment. Module 4: Treatment - Drug-Resistant Tuberculosis Treatment. Geneva, Switzerland: World Health Organization; 2020. *https://www.who.int/publications/i/item/9789240007048.* (Accessed 25.11.2022)
3. Sarathy JP, Gruber G, Dick T. Re-understanding the mechanisms of action of the anti-mycobacterial drug bedaquiline. *Antibiotics*. 2019;8:261. https://doi.org/ 10.3390/antibiotics8040261
4. Aslam H, Omar A, Fatima R, Rasool U, Yaqoob A, Ullah W, et al. Treatment outcomes and adverse drug reactions among patients with drug-resistant tuberculosis receiving all-oral, long-term regimens: first record viewing report from Pakistan. *Asian Pacific Journal of Tropical Medicine*. 2023;16(2):58-64
5. Wang MG, Wu SQ, He JQ. Efficacy of bedaquiline in the treatment of drug-resistant tuberculosis: a systematic review and meta-analysis. *BMC Infectious Disease*. 2021;21(1):970. https://doi.org/10.1186/s12879-021-06666-8
6. Ministry of Health of Indonesia Republic. Techinal guide. Management of drug resistant tuberculosis in Indonesia. Indonesia. Ministry of Health of Indonesia Republic. 2020. *https://tbindonesia.or.id/pustaka/pedoman/tb-ro/petunjuk-teknis-penatalaksanaan-tuberkulosis-resistan-obat-di-indonesia*. (Accessed 28.11.2022)
7. Darmayani IG, Ascobat P, Institay I, Sugiri YJR, Sawitri N. Bedaquiline effect on QT interval of drugs-resistant tuberculosis patients: Real world data. *Acta Medica Indonesiana*. 2022;54(3):389-396
8. Primadana V, Yovi I, Estiningsih DS. Bedaquiline correlation to QT interval

prolongation in DR-TB patients. *Journal of Respirology*. 2022;8(3):140–146. https://doi.org/10.20473/jr.v8-I.3.2022.140-146
9. Brust JCM, Gandhi NR, Wasserman S, Maartens G, Omar S v., Ismail NA, et al. Effectiveness and cardiac safety of bedaquiline-based therapy for drug-resistant tuberculosis: A prospective cohort study. *Clinical Infectious Diseases*. 2021;73(11):2083–2092. https://doi.org/10.1093/cid/ciab335
10. Gao M, Gao J, Xie L, Wu G, Chen W, Chen Y, et al. Early outcome and safety of bedaquiline-containing regimens for treatment of MDR- and XDR-TB in China: a multicentre study. *Clinical Microbiology and Infection*. 2021;27(4):597–602. https://doi.org/ 10.1016/j.cmi.2020.06.004
11. Salhotra VS, Sachdeva KS, Kshirsagar N, Parmar M, Ramachandran R, Padmapriyadarsini C, et al. Effectiveness and safety of bedaquiline under conditional access program for treatment of drug-resistant tuberculosis in India: An interim analysis. *Indian Journal of Tuberculosis*. 2020;67(1):29–37. https://doi.org/10.1016/j.ijtb.2019.10.002
12. Kim CT, Kim TO, Shin HJ, Ko YC, Choe YH, Kim HR, et al. Bedaquiline and delamanid for the treatment of multidrug-resistant tuberculosis: A multicentre cohort study in Korea. *European Respiratory Journal.* 2018;51(3):1702467. https://doi.org/ 10.1183/13993003.02467-2017
13. Phuong NTM, Minh LTH, Merle CSC, Pedrazzoli D, Linh NN, Decroo T, et al. Effectiveness and safety of bedaquiline-based, modified all-oral 9-11-month treatment regimen for rifampicin-resistant tuberculosis in Vietnam. *International Journal of Infectious Diseases*. 2023;126:148-154. https://doi.org/10.1016/j.ijid.2022.11.007
14. Avaliani T, Sereda Y, Davtyan H, Tukvadze N, Togonidze T, Kiria N, et al. Effectiveness and safety of fully oral modified shorter treatment regimen for multidrug-resistant tuberculosis in Georgia, 2019-2020. *Monaldi Archives for Chest Disease*. 2021;91(1):4-9. https://doi.org/10.4081/monaldi.2021.1679
15. Soeroto AY, Nurhayati RD, Purwiga A, Lestari BW, Pratiwi C, Santoso P, et al. Factors associated with treatment outcome of MDR/RR-TB patients treated with shorter injectable based regimen in West Java Indonesia. *PLoS One*. 2022;17(1):e0263304. https://doi.org/10.1371/journal.pone.0263304
16. Fu L, Weng T, Sun F, Zhang P, Li H, Li Y, et al. Insignificant difference in culture conversion between bedaquiline-containing and bedaquiline-free all-oral short regimens for multidrug-resistant tuberculosis. *International Journal of Infectious Diseases*. 2021;111:138–147. https://doi.org/10.1016/j.ijid.2021.08.055
17. Irwin SM, Prideaux B, Lyon ER, Zimmerman MD, Brooks EJ, Schrupp CA, et al. Bedaquiline and pyrazinamide treatment responses are affected by pulmonary lesion heterogeneity in mycobacterium tuberculosis infected C3HeB/FeJ Mice. *ACS Infectious Diseases Journal*. 2016;2(4):251–67. https://doi.org/10.1021/acsinfecdis.5b00127
18. Sun F, Li Y, Chen Y, Guan W, Jiang X, Wang X, et al. Introducing molecular testing of pyrazinamide susceptibility improves multidrug-resistant tuberculosis treatment outcomes: A prospective cohort study. *European Respiratory Journal*. 2019;53(3):1801770. https://doi.org/10.1183/13993003.01770-2018
19. Kempker RR, Barth AB, Vashakidze S, Nikolaishvili K, Sabulua I, Tukvadze N, et al. Cavitary penetration of levofloxacin among patients with multidrug-resistant tuberculosis. *Antimicrobial Agents and Chemotherapy*. 2015;59(6):3149–3155.

https://doi.org/10.1128/AAC.00379-15
20. Al-Shaer MH, Alghamdi WA, Alsultan A, An G, Ahmed S, Alkabab Y, et al. Fluoroquinolones in drug-resistant tuberculosis: Culture conversion and pharmacokinetic/pharmacodynamic target attainment to guide dose selection. *Antimicrobial Agents and Chemotherapy*. 2019;63(7):e00279-19.https://doi.org/10.1128/AAC.00279-19
21. Sidamo T, Shibeshi W, Yimer G, Aklillu E, Engidawork E. explorative analysis of treatment outcomes of levofloxacin- and moxifloxacin-based regimens and outcome predictors in Ethiopian MDR-TB patients: A prospective observational cohort study. *Infection and Drug Resistance* 2021;14:5473–5489. https://doi.org/10.2147/IDR.S342964
22. Anh LTN, Kumar AMV, Ramaswamy G, Htun T, Thi TTH, Nguyen GH, et al. High levels of treatment success and zero relapse in multidrug-resistant tuberculosis patients receiving a levofloxacin-based shorter treatment regimen in Vietnam. *Tropical Medicine and Infectious Disease*. 2020;5(1):43. https://doi.org/10.3390/tropicalmed5010043
23. Shi L, Gao J, Gao M, Deng P, Chen S, He M, et al. Interim effectiveness and safety comparison of bedaquiline-containing regimens for treatment of diabetic versus non-diabetic MDR/XDR-TB patients in China: A multicenter retrospective cohort study. *Infectious Diseases and Therapy*. 2021;10(1):457–70. https://doi.org/10.1007/s40121-021-00396-9
24. Soedarsono S, Kusmiati T, Permatasari A. Effect of diabetes mellitus on renal and audiology toxicities in patients with drug-resistant pulmonary tuberculosis. *Archives of Clinical Infectious Diseases*. 2021;16(2);e99260. https://doi.org/10.5812/archcid.99260
25. Zheng H, He W, Jiao W, Xia H, Sun L, Wang S, et al. Molecular characterization of multidrug- resistant tuberculosis against levofloxacin, clofazimine, and delamanid in southwest of China. *BMC Infectious Disease*. 2021;21(1):330. https://doi.org/10.1186/s12879-021-06024-8
26. Ghodousi A, Rizvi H, Baloch Q, Ghafoor A, Khanzada M. Cross acquisition of cross-resistance to bedaquiline and clofazimine following treatment for tuberculosis in Pakistan. *Antimicrobial Agents and Chemotherapy.* 2019;63(9):e00915-19. https://doi.org/ 10.1128/AAC.00915-19
27. Dooley KE, Rosenkranz SL, Conradie F, Moran L, Hafner R, von Groote-Bidlingmaier F, et al. QT effects of bedaquiline, delamanid, or both in patients with rifampicin-resistant tuberculosis: a phase 2, open-label, randomised, controlled trial. *Lancet Infectious Diseases*. 2021;21(7):975–83. https://doi.org/10.1016/S1473-3099(20)30770-2
28. Nihlah NA, Almattin BN, Wicaksono IA. Adverse events of bedaquiline drug use in the treatment of multidrug-resistant tuberculosis (MDR-TB) patients: A Review. *Pharmacology and Clinical Pharmacy Research*. 2024;9(1):11-27
29. Ngwalero P, Brust JCM, van Beek SW, Wasserman S, Maartens G, Meintjes G, et al. Relationship between plasma and intracellular concentrations of bedaquiline and its m2 metabolite in South African patients with rifampin-resistant tuberculosis. *Antimicrobial Agents and Chemotherapy*. 2021;65(11):e0239920. https://doi.org/10.1128/AAC.02399-20
30. Li J, Yang G, Cai Q, Wang Y, Xu Y, Zhang R, et al. Safety, efficacy, and serum concentration monitoring of bedaquiline in Chinese patients with multidrug-resistant tuberculosis. *International Journal of Infectious Diseases.* 2021;110:179–186. https://doi.org/ 10.1016/j.ijid.2021.07.038
31. Tang JKK, Rabkin SW. Hypocalcemia-

induced QT interval prolongation. *Cardiology*. 2022;147(2):191–195. https://doi.org/10.1159/000515985
32. Kusmiati T, Devina Suci Y, Purnama Dewi K. QTc interval prolongation in drug resistant-tuberculosis patients treated with shorter treatment regimen. *Medico-legal Update*. 2021;21(2):1208-1215. https://doi.org/10.37506/mlu.v21i2.2855
33. Azis FDA, Nurlaila H. Early detection of elevated liver function test in drug-resistant tuberculosis with short term therapy and individual therapy. *Bali Medical Journal.* 2022;11(1):324–327. https://doi.org/10.15562/bmj.v11i1.3113
34. Molla Y, Wubetu M, Dessie B. Anti-tuberculosis drug induced hepatotoxicity and associated factors among tuberculosis patients at selected hospitals, Ethiopia. *Hepatic Medicine*. 2021;13:1–8. https://doi.org/10.2147/HMER.S290542
35. Raj Mani S, Iyyadurai R, Mishra A, Manjunath K, Prasad J, Lakshmanan J, et al. Predicting antitubercular drug-induced liver injury and its outcome and introducing a novel scoring system. *The International Journal of Mycobacteriology*. 2021;10(2):116–121. https://doi.org/ 10.4103/ijmy.ijmy_15_21
36. Louthrenoo W, Hongsongkiat S, Kasitanon N, Wangkaew S, Jatuworapruk K. Effect of antituberculous drugs on serum uric acid and urine uric acid excretion. *Journal of Clinical Rheumatology*. 2015;21(7):346–348. https://doi.org/10.1097/RHU.0000000000000297

Table 1. Demographic and clinical characteristics of MDR-TB patients treated with STR (n=30).

Patient characteristics	Number (%) or median (IQR)
Sex	
Male	14 (46.6)
Female	16 (53.4)
Age (years)	41 (17-55)
BMI (kg/m2)	20.0 (15.5-29.3)
Prior anti-TB treatment	8 (26.6)
Pulmonary TB	30 (100.0)
Diabetes mellitus	6 (20.0)
Sputum culture positive at baseline	25 (83.3)

Table 2. Sputum culture of MDR-TB patients during STR.

Period	Culture (n=25)		% Conversion
	Positive	Negative	
Baseline	25	0	0
Month 1	10	15	60.0
Month 2	5	20	80.0
Month 3	3	22	84.0
Month 4	1	24	96.0
Month 5	1	24	96.0
Month 6	1	24	96.0
Month 7	2	23	92.0
Month 8	1	24	96.0
Month 9	1	24	96.0

Table 3. Treatment outcomes of STR for MDR-TB patients

Favorable Outcomes	n=25, (%)	Unfavorable Outcomes	n=30, (%)
Negative sputum culture at 24 weeks	24 (96.0)	Treatment failure	1 (3.3)
Negative sputum culture at 9 months	24 (96.0)	Loss to follow-up	2 (6.6)

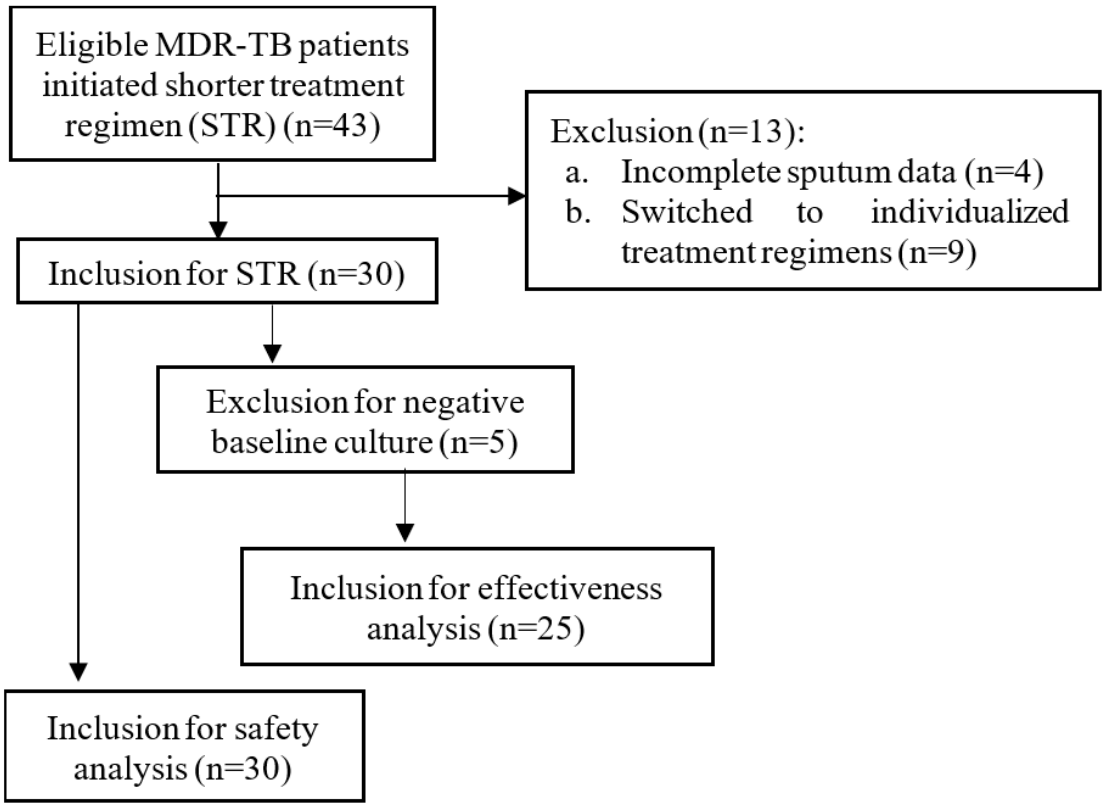

Figure 1. Overview of the study cohort.

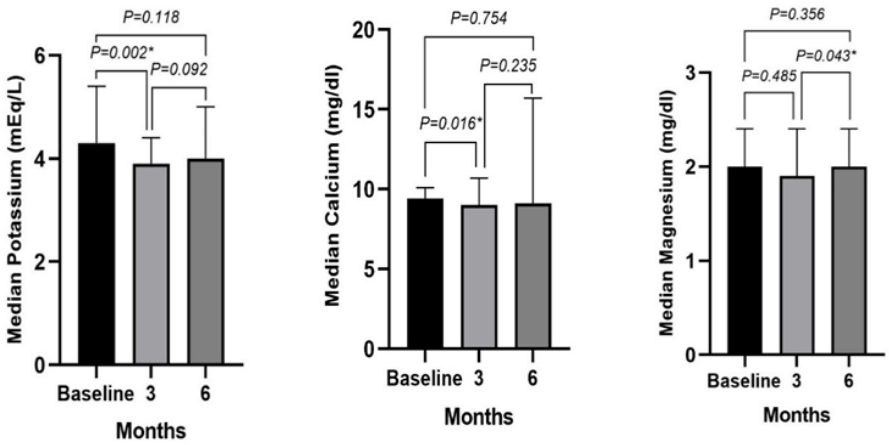

Figure 2. Electrolytes level during 6 months of treatment. Potassium (left), calcium (centre), and magnesium (right)

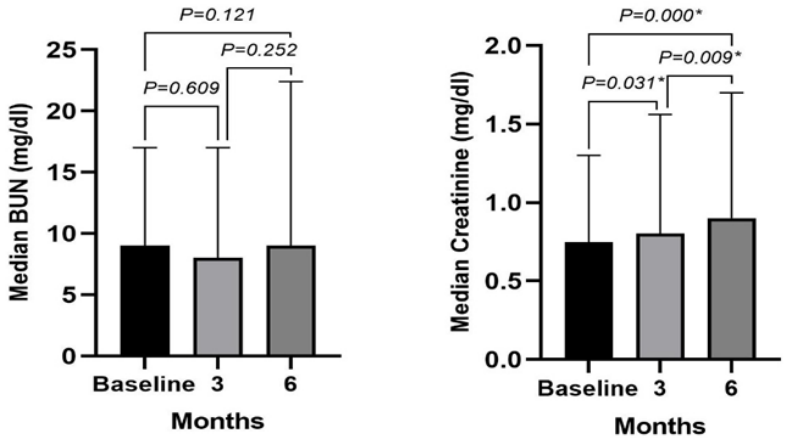

Figure 3. Renal function test during 6 months of treatment. BUN (left) and serum creatinine (right).

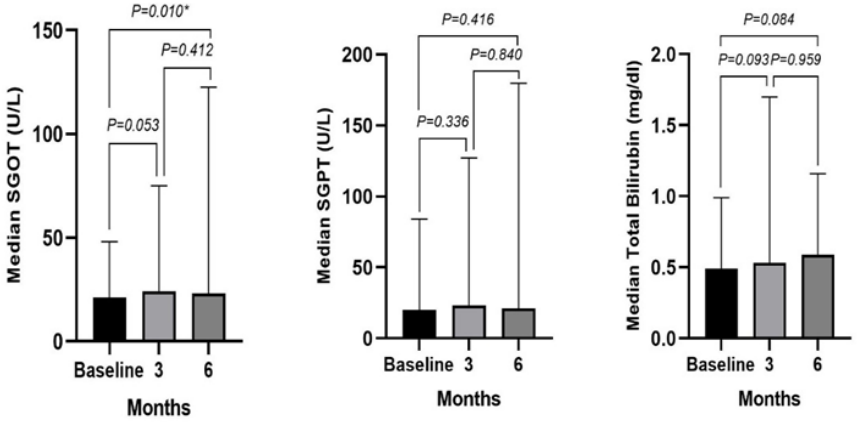

Figure 4. Liver function test during 6 months of treatment. SGOT (left), SGPT (centre), and total bilirubin (right).