Efficacy of Bedaquiline in the Treatment of Drug-resistant Tuberculosis: A Systematic Review and Meta-analysis

Ming-Gui Wang
Sichuan University West China Hospital

Shou-Quan Wu
Sichuan University West China Hospital

Jian-qing He (jianqing.he@scu.edu.cn)
Sichuan University West China Hospital

https://orcid.org/0000-0002-4214-2037

Research Article

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Abstract

**Background:** Drug-resistant TB (DR-TB) remains a major public health concern around the world. Bedaquiline, a novel diarylquinoline, was added into WHO recommended all-oral regimen for patients with multidrug-resistant tuberculosis. We undertook a systematic review and meta-analysis to determine the effect of bedaquiline on tuberculosis treatment outcomes.

**Methods:** We searched for relevant studies in the PubMed, Web of Science and EMBASE database for relevant studies published up to 12 Mar 2021. Stata version 16.0 (Stata Corp., College Station, Texas, USA) was used to analyze results of meta-analysis. For randomized controlled trials, were assessed for quality using the Jadad scale, and cohort studies, using the Newcastle–Ottawa scale.

**Results:** Eight studies including 2 randomized clinical trial and 6 cohort studies involving 21,836 subjects were included. When compared with control, bedaquiline treatment was associated with higher rates of culture conversion (Risk Ratio (RR): 1.272 (1.165-1.389), P < 0.001). We found substantial evidence that there was significant reduction in all-cause deaths with relative RR = 1.272 (95% CI: 1.165-1.389, P < 0.001) in bedaquiline treatment group. There was no significant reduction in treatment success with RR = 0.980 (90% CI: 0.948-1.013, P = 0.234).

**Conclusions:** This study demonstrated that the use of bedaquiline has the potential to achieve higher culture conversion rate and lower death risk among drug-resistant tuberculosis cases when compared with controls.

Introduction

Tuberculosis (TB) remains an important global infectious disease, caused by Mycobacterium tuberculosis (MTB), and remains one of the leading causes of infection-related death worldwide. According to the World Health Organization (WHO), there were 10.0 million (range, 8.9–11.0 million) newly TB patients in 2019[1]. Globally, an estimated 1.4 million TB deaths in 2019, including 1.2 million among human immunodeficiency virus (HIV)-negative people, and an additional 208,000 deaths among HIV-positive people[1]. Drug-resistant TB (DR-TB) remains a major public health concern around the world. Rifampicin-resistant TB (RR-TB) requires treatment with second-line drugs and includes multidrug-resistant TB (MDR-TB) that is resistant to both rifampicin and isoniazid (the two most effective anti-TB drugs). Extensively drug-resistant tuberculosis (XDR-TB) defined as MDR-TB plus resistance to a fluoroquinolone and an injectable agent. Globally in 2019, there were 3.3% of new cases and 18% of previously treated cases had MDR/RR-TB. It has estimated 465,000 incident cases of MDR/RR-TB in 2019 and the global proportion of RR-TB cases estimated to have MDR-TB was 78%[1]. The three countries with the heaviest burden of drug-resistant tuberculosis were the India, China and the Russian Federation[1].

A total of 177,099 MDR/RR-TB patients were reported to have received treatment[1], up from 156,205 in 2018. However, the number of people starting MDR-TB treatment was equivalent to 86% of the 206,030 people with MDR/RR-TB were detected and notified in 2019. Treatment outcomes for MDR/RR-TB remain poor even in advanced health systems. Overall, only 57% of MDR/RR-TB patients in the 2017 cohort who successfully completed treatment (cured or treatment completed)[1]. Hence, unsuccessful treatment of MDR-TB is a key problem that cannot be neglected.

The novel diarylquinoline, bedaquiline, was added into WHO recommended all-oral regimen to replaces the injectables[2]. Bedaquiline has been shown to improve the sputum conversion rates in clinical studies[3, 4], and improve the treatment outcome in some observational studies[5–7]. Therefore, it is very important to review and summarize the overall treatment outcomes for MDR-TB under treatment contained bedaquiline in recent years. We conducted this systematic review and meta-analysis to summarize the existing evidence to date of the efficacy of bedaquiline in the treatment of DR-TB.

Methods

This systematic review has been prepared according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines for protocols[8]. Since this was a meta-analysis of existing articles, and no individual patient data were handled, the ethical approval was unnecessary in this study.

Search strategy and study selection

We searched the PubMed, Web of Science and EMBASE database for relevant studies published up to 12 Mar 2021. The search terms were as follows: “bedaquiline”, or “tuberculosis,” or “multidrug resistant tuberculosis” or “extensively drug resistant tuberculosis”, and their synonyms or similar words. Two review authors (MG and SQ) independently screened all citations and abstracts identified by the search strategy for inclusion.

Studies meeting the following criteria were included: (1) patients were aged ≥ 18 years; (2) involving laboratory-confirmed DR-TB; (3) anti-TB therapy containing bedaquiline as intervention; (4) the control group was treated with other drugs or no bedaquiline; (5) culture conversion, or outcomes of success (including cure or treatment completion), failure, and death according to the WHO classification were reported[9]; (6) study was designed as retrospective studies, randomized controlled trials, or prospective cohort studies. When data were duplicated or reported in more than one study, the first published study was included in the meta-analysis. The language was limited to English.

Studies were excluded if: editorial, case-report, conference abstract, animal study, and with a sample size of less than 10.

Assessment of methodological quality

All selected studies in the meta-analysis were assessed for quality and the high-quality studies were then analyzed. For randomized controlled trials (RCTs), two review authors independently used the Jadad scale[10] to assess the methodological quality of each included study by using the following variables: random scheme and allocation concealment, blinding of participants, and follow-up. The maximum score was five points. A score of ≥ 3 was considered high quality.
For cohort studies, we used the Newcastle–Ottawa Assessment Scale (NOS) (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp) to assessed the methodological quality of non-randomized studies. This tool was scored by the three broad perspectives: the selection of the study groups; the comparability of the groups; and the exposure for case-control or cross-sectional studies, or the outcome for cohort studies. The maximum score was nine points. A score of > 7 was considered high quality.

**Data extraction**

Two review authors (MG and SQ) independently extracted data using a data extraction form. The following data were extracted from all included studies: study name (name of the first author with the publication year), country where the trial was undertaken, year in which the study was done, study design, participants (sample size, sex, and age, HIV co-infection), intervention arms and controls (intervention drug and dose, follow-up duration, and anti-TB therapy protocol), and treatment outcomes (culture conversion, treatment success (cure or treatment completed), and death). Where there were disagreements, these were resolved through discussion and consensus.

**Statistical analysis**

Meta-analysis was performed with the Stata version 16.0 (Stata Corp., College Station, Texas, USA). To evaluate the effect of bedaquiline on drug-resistant tuberculosis, we calculated relative risks (RRs) with 95% confidence intervals (95% CIs). Between-study heterogeneity was examined by I² square test. Funnel plots were used to evaluate the publication bias. We interpreted P-values of 25, 50 and 75% were considered to represent low, medium, and high heterogeneity, respectively[11]. To explore the sources of heterogeneity, sensitivity analysis was also performed. Results were considered statistically significant at P < 0.05.

**Results**

**Study flow diagram**

A total of 3484 citations were identified from the scientific literature search. After duplicates removed, 2041 records were screening by titles and abstracts, 80 articles were found relevant for full-text analysis and reference list screening. Then, 72 articles that did not fulfil the inclusion criteria for the review were excluded, 8 studies were identified as eligible for meta-analysis[3–7, 12–14] (Fig. 1).

**Characteristics of included studies**

The characteristics of the studies and the number of cases analyzed in the systematic review and meta-analysis are summarized in Table 1. The 8 studies were conducted in 13 countries across the globe. Per regional distribution, more than half were conducted in South African[3–7, 14] (Table 1). About 75% (n = 6) of studies were published in the last 5 years. Two RCTs was included[3, 4], and the six remaining records consisted of three retrospective cohorts and three prospective cohorts[5–7, 12–14].
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Study design</th>
<th>Country</th>
<th>Recruitment dates</th>
<th>Age (years)</th>
<th>Males</th>
<th>HIV-positive</th>
<th>Follow-up</th>
<th>Duration</th>
<th>Bedaquiline usement</th>
<th>Background regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diacon et al.</td>
<td>2014</td>
<td>Randomized controlled trial</td>
<td>Brazil, India, Latvia, Peru, the Philippines, Russia, South Africa, and Thailand</td>
<td>NA</td>
<td>34 (18–63)</td>
<td>85</td>
<td>19</td>
<td>At 8, 24 and 72 weeks</td>
<td>120-week</td>
<td>400 mg once daily for 2 weeks, followed by 200 mg three times a week for 22 weeks</td>
<td>Ethionamide, pyrazinamide, ofloxacin, kanamycin, and cycloserine</td>
</tr>
<tr>
<td>Kurbatova et al.</td>
<td>2015</td>
<td>Prospective cohort study</td>
<td>Philippines, South Africa, Peru, Russia, South Korea, Latvia, Thailand, Taiwan, and Estonia</td>
<td>January 1, 2005–December 31, 2008</td>
<td>&gt; 18</td>
<td>613</td>
<td>159</td>
<td>monthly</td>
<td>&gt; 18 months</td>
<td>NA</td>
<td>Based on WHO and local treatment guidelines</td>
</tr>
<tr>
<td>Kim et al.</td>
<td>2018</td>
<td>Retrospective cohort</td>
<td>Korea</td>
<td>January 2015 and October 2017</td>
<td>52 (40.5–60)</td>
<td>49</td>
<td>monthly</td>
<td>&gt; 6 months</td>
<td>&gt; 1 month (210 to 237 days)</td>
<td>Based on WHO</td>
<td></td>
</tr>
<tr>
<td>Kempker et al.</td>
<td>2020</td>
<td>Prospective cohort study</td>
<td>Tbilisi, Georgia</td>
<td>December 2015 to May 2017</td>
<td>≥ 16</td>
<td>78</td>
<td>2</td>
<td>monthly</td>
<td>20–24 months</td>
<td>171 (166–190) days</td>
<td>Linezolid, cycloserine, clofazimine, and an injectable agent. Delamanid-based regimen in control.</td>
</tr>
<tr>
<td>Schnippel et al.</td>
<td>2018</td>
<td>Retrospective cohort</td>
<td>South African</td>
<td>July 1, 2014 to March 31, 2016</td>
<td>36 (29–44)</td>
<td>10959</td>
<td>13893</td>
<td>every 2 weeks for the first month, then monthly for 5 months</td>
<td>&gt; 18 months</td>
<td>24 weeks</td>
<td>Kanamycin, moxifloxacin, ethionamide, terizidone, and pyrazinamide</td>
</tr>
<tr>
<td>Zhao et al.</td>
<td>2019</td>
<td>Retrospective cohort</td>
<td>South African</td>
<td>October 2014 to October 2016</td>
<td>&gt; 18</td>
<td>190</td>
<td>233</td>
<td>monthly</td>
<td>12 months</td>
<td>400 mg once daily for 2 weeks, followed by 200 mg three times a week for 22 weeks</td>
<td>Moxifloxacin, pyrazinamide, ethionamide, high-dose isoniazid, ethambutol, and terizidone.</td>
</tr>
<tr>
<td>Olayanju et al.</td>
<td>2018</td>
<td>Prospective cohort study</td>
<td>South African</td>
<td>January 2008 and June 2017</td>
<td>&gt; 18</td>
<td>161</td>
<td>134</td>
<td>monthly</td>
<td>24 months</td>
<td>NA</td>
<td>Para-aminosalicylic acid, clofazimine, capreomycin and second-/fourth-generation fluoroquinolones</td>
</tr>
<tr>
<td>Dooley et al.</td>
<td>2021</td>
<td>Randomized controlled trial</td>
<td>South African and Peru</td>
<td>Aug 26, 2016 and July 13, 2018</td>
<td>34 (20–49)</td>
<td>63</td>
<td>31</td>
<td>every 2 weeks until week 24, then at week 28</td>
<td>&gt; 7 months</td>
<td>400 mg once daily for 2 weeks, followed by 200 mg three times a week for 22 weeks</td>
<td>Capreomycin, cycloserine, ethambutol, ethionamide, pyrazinamide, levofloxacin, isoniazid, terizidone, Linezolid. Delamanid in control.</td>
</tr>
</tbody>
</table>

Totally, 21,836 patients form 8 eligible studies were collected (Table 1), include 1,784 patients treated with bedaquiline and 20,061 not. Nearly 66.3% were HIV positive, and 55.9% were males. Bedaquiline was generally administered at a daily 400 mg for 2 weeks, followed by 200 mg three times a week for 22 weeks.
weeks. The duration of treatment was > 6 months. Sample sizes of the studies included the meta-analysis ranged from 61[12] to 19, 617[7] in the largest study.

Assessment of risk of bias and publication bias

We assessed risk of bias for the included RCTs using the Jadad scale, the two included RCTs were of high quality (≥ 3 score). And, for cohort studies, we assessed the risk of bias using NOS tool, all the included cohort studies were considered high quality. The results of the risk of bias for included studies were summarized in Supplementary Tables 1 and 2.

Begg's and Egger's regression tests were performed to assess publication bias. No substantial publication bias was found either by the Begg's test or the Egger's test. And the Begg's funnel plot is shown in Fig. 2.

Treatment outcomes

Meta-analysis showed that risk of culture conversion was higher in patients receiving bedaquiline contained regimens than those not (Risk ratio (RR): 1.272 (1.165–1.389), P < 0.001) (Fig. 3). However, bedaquiline treatment did not have a statistically significant effect on the outcome of success (RR: 0.980(0.948–1.013), P = 0.234) (Fig. 4). There were significant differences in the proportion of death due to any cause between those who receiving bedaquiline contained regimens versus controls. Patients receiving bedaquiline had lower risk of all-cause mortality compared to those not (RR: 0.529 (0.454–0.616), P < 0.001) (Fig. 5).

Significant heterogeneity was detected between studies in the summary results, with an I² value of 91.4% for culture conversion and 94.8% for treatment successful, and 62.6% for all-cause mortality. Due to the significantly heterogeneity, we did a sensitivity analyses to explore the sources of heterogeneity. We found that the heterogeneity was significantly reduced after the removal of Diacon (2014) (from 62.6–6.2%) for all-cause mortality[4].

Discussion

To our knowledge, this is the first meta-analysis to investigate the effects of bedaquiline on patients with drug-resistant. We analyzed data from 8 studies conducted in 13 countries, included 21, 836 DR-TB patients. The results of this meta-analysis revealed the efficiency of bedaquiline in the treatment of drug-resistant tuberculosis.

For DR-TB, especially MDR/RR-TB and XDR-TB, bedaquiline was always administered in combination with other anti-tubercular drugs. Thus, treatment outcomes may not be entirely attributable to bedaquiline. Nevertheless, since all patients with DR-TB were treated with background regimen, we believe that bedaquiline may be the most important factor affecting the treatment outcome in this study. In this meta-analysis, we found that bedaquiline could increase the culture conversion (RR: 1.272 (1.165–1.389), P < 0.001), and decrease the risk of all-cause mortality (RR: 0.529 (0.454–0.616), P < 0.001). However, the administered of bedaquiline did not increase the treatment success among DR-TB (P = 0.234).

Bedaquiline is a new class of anti-tuberculous drugs, belonging to diarylquinoine compounds. Which contains a quinoline central heterocyclic nucleus with alcohol and amine side chains that play an important role in anti-tuberculosis activity[15]. Studies have shown that bedaquiline is an inhibitor of the mycobacterial ATP synthase, which binds to and perturbs the a-c subunit interface of the Fo and leads to ineffective proton cycle, which is fatal to Mycobacterium[16, 17]. Multicentre study conducted in 25 centres and 15 countries in five continents found that the sputum smear and culture conversion rates in MDR-TB cases were 88.7% and 91.2%, respectively at the end of treatment, and 71.3% achieved treatment success[18]. In another words, bedaquiline-containing regimens achieved high conversion and success rates to treat MDR-TB patients[18]. Another retrospective French cohort study showed that 97% of culture positive TB patients achieved culture conversion at 6 months of bedaquiline treatment[19]. Our study evaluated the efficacy of bedaquiline for the treatment of DR-TB in RCT and cohort study, we found that DR-TB patients can benefit from the use of bedaquiline, with better sputum conversion rate and lower risk of death. The use of bedaquiline may bring dawn for the treatment of DR-TB patients and make corresponding contributions to curb the spread and death of tuberculosis.

Taune, M., et al conducted a retrospective cohort to describe the implementation of bedaquiline and assess the safety and interim effectiveness for MDR-TB patients commenced on bedaquiline, their results found that bedaquiline is a safe and feasible drug with good interim effectiveness[20]. Studies based on children and adolescents with DR-TB also show that bedaquiline containing regimens are effective and well tolerated in children and adolescents, which may provide new ideas for tuberculosis treatment in this group and contribute to the global strategy to end tuberculosis[20–22]. However, we did not evaluate the efficacy of bedaquiline in the treatment of children and adolescent patients with DR-TB, further studies are needed.

There are many adverse reactions in the use of bedaquiline, such as hyperuricaemia, nausea, arthralgia, liver injury and QT prolongation and so on[18–24]. Guglielmetti, L., et al found nearly 20% patients experienced a > 60-ms increase in QT interval, and leading to bedaquiline discontinuation in 6% patients[19]. Multicentre study showed that adverse events presumably due to bedaquiline were 19.4%, and 5.8% patients interrupt bedaquiline due to adverse events[18]. Most patients may have adverse drug reactions during bedaquiline use, and most of them are mild, and do not need to stop the drug[18, 19, 23, 25]. While, fatal arrhythmias can cause death[23].

Our review has some limitations. First, we included studies designed as cohort studies, and RCTs, and this may have leads to heterogeneity. Second, due to the limited data, we failed to evaluate the safety of bedaquiline in the treatment of MDR/RR-TB and XDR-TB, further studies are needed. Third, only eight studies were included in this review, and the sample size of some studies is small. In the future, more randomized controlled trials with larger samples are needed to further evaluate the efficacy and safety of bedaquiline in the treatment of DR-TB.

Conclusion
The use of bedaquiline combined with other active drugs has the potential to achieve higher culture conversion rate and lower death risk among MDR/RR-TB and XDR-TB cases when compared with controls. The use of bedaquiline in DR-TB patients should be more promoted.

Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>TB</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>MTB</td>
<td>Mycobacterium tuberculosis</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>HIV</td>
<td>Human immunodeficiency virus</td>
</tr>
<tr>
<td>DR-TB</td>
<td>Drug-resistant tuberculosis</td>
</tr>
<tr>
<td>RR-TB</td>
<td>Rifampicin-resistant TB</td>
</tr>
<tr>
<td>MDR-TB</td>
<td>Multidrug-resistant TB</td>
</tr>
<tr>
<td>XDR-TB</td>
<td>Extensively drug-resistant tuberculous</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized controlled trial</td>
</tr>
<tr>
<td>NOS</td>
<td>Newcastle–Ottawa Assessment Scale</td>
</tr>
<tr>
<td>RR</td>
<td>Risk ratio</td>
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</tbody>
</table>

Declarations

Acknowledgments

Not applicable.

Ethics approval and consent to participate

Ethics approval for this study was waived.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

Competing interests

The authors declare no conflict of interest.

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Contributions

All authors contributed substantially to the study design, data interpretation, and the writing of the manuscript. Dr. JQH contributed to the study design. MGW and SQW contributed to data collection, completed full text. All authors reviewed the manuscript.

References


Figures
Figure 1
Study flow diagram.

Figure 2
Forest plot of the effect of bedaquiline on culture conversion. (Abbreviations: RR, risk ratio; CI, confidence interval.)

**Figure 3**

Forest plot of the effect of bedaquiline on treatment success. (Abbreviations: RR, risk ratio; CI, confidence interval.)

**Figure 4**

Forest plot of the effect of bedaquiline on all-cause mortality. (Abbreviations: RR, risk ratio; CI, confidence interval.)
Figure 5

Funnel plots for publication bias. (Abbreviations: logor, natural log of odds ratio; s.e. of: logor: standard error of logor)

Supplementary Files

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