Bedaquiline versus placebo for management of multiple drug-resistant tuberculosis: A systematic review

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ABSTRACT

Background: Multidrug-resistant tuberculosis (MDR-TB) is associated with significant morbidity and mortality. Bedaquiline is the first drug approved for treating MDR-TB.

Objectives: We performed a systematic review and meta-analysis to summarize the totality of all available evidence on the efficacy of bedaquiline for the management of MDR-TB.

Materials and Methods: We searched the following PubMed and Cochrane Registry of Clinical Trials. Randomized controlled trials (RCTs) with a parallel design comparing bedaquiline versus any treatment for the management of MDR-TB in adults were eligible for inclusion. Data were pooled under a random effects model.

Results: Two trials published as three manuscripts with a total of 207 patients were included. As per the Cochrane risk of bias tool, majority of parameter were labeled as high or unclear risk of bias. Bedaquiline compared with placebo was associated with a statistically significant decrease in time to conversion of positive sputum culture to negative at 8 and 24 weeks with a significant increase in mortality on long-term follow-up. There was no difference in completion rates between bedaquiline and placebo.

Conclusion: Bedaquiline is an effective treatment modality for MDR-TB but needs to be balanced against significant mortality. Future Phase 3 RCTs are needed to make a conclusive recommendation.

KEY WORDS: Bedaquiline, multidrug resistance, sputum conversion, tuberculosis

Introduction

Tuberculosis (TB) is one of the most common infectious diseases associated with significant morbidity and mortality. According to 2013 World Health Organization report, 9 million people were infected with TB and 1.5 million deaths were attributed to TB. There has been significant progress in the management of TB. However, despite these advances, approximately 3.5% of new TB cases and 5% of old TB cases are multidrug-resistant (MDR). In 2013, the estimated new cases of MDR-TB were 480,000. The incidence and prevalence of MDR-TB in some countries are very alarming. According to one estimate, in certain Eastern European and Central Asian countries, around 35% of new cases and 75% of previously treated cases were MDR-TB. At present, majority of MDR TB cases were reported from the India, China, and countries of Russian Federation. MDR TB is difficult to treat due to ineffectiveness of first-line drugs and the decreased efficacy and increased adverse events associated with second-line of treatment. Only 48% cases of MDR-TB are successfully treated which is low resulting in increased mortality and poor quality of life of these patients. There is a constant need for better drugs with novel mechanisms of action to treat MDR-TB effectively with lower chances of drug resistance.

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Bedaquiline is a newer drug approved by US Food and Drug Administration (FDA) in 2012 for MDR-TB. This is the first drug approved for the TB in the last 40 years. Bedaquiline is an adenosine triphosphate (ATP) synthase blocker inhibiting the conversion of adenosine diphosphate to ATP. Bedaquiline is very selective to the Mycobacterium ATP synthase as compared to the eukaryotic ATP synthase found in humans thus reducing the likelihood of adverse events when used in patients with TB.

In 2012, when bedaquiline was approved it was given accelerated approval based on some preliminary results submitted to the FDA by drug manufacturer. Considering the potential for extensive use of this drug and the manner in which it was approved, there is a need for systematic evaluation of all available evidence regarding the efficacy and safety of bedaquiline. Others have recently considered the relevance of bedaquiline in context of four other antibiotics used in the management of MDR-TB, however, the outcomes were limited to only response and dropout rates. Other patient important outcomes such as time to response and occurrence of adverse events was not reported. Hence, this systematic review and meta-analysis was performed with the primary aim of assessing all available data on the efficacy and safety of bedaquiline for the treatment of MDR-TB.

Materials and Methods

Outcomes
The primary outcome of this systematic review was time to conversion of positive sputum to negative sputum culture in patients diagnosed with MDR-TB and treated with bedaquiline versus placebo. Secondary outcomes included rate of conversion of positive sputum to negative culture, mortality, rate of treatment completion, and adverse events.

Search Methods and Identification of Studies
We performed a systematic search in PubMed, Cochrane Clinical Trial Registry, and Google Scholar. Search for relevant studies in PubMed was done in this order - #1-“bedaquiline”, #2-bedaquiline, #3-TMC207, #1-R207910, #5–#1 OR #2 OR #3 OR #4, #6-“tuberculosis, multidrug-resistant” (Mesh), #7-“bedaquiline”, #8-“tuberculosis, multidrug-resistant” (Mesh), #9-“MDR-TB,” #10-“MDR-TB,” #7 OR #8 OR #9, #11–#5 AND #10. We also conducted a hand search for studies of bedaquiline from the FDA website, manufacturer’s website and from Clinical Trial Registry online at www.ClinicalTrials.gov.

Study Selection
All randomized controlled trials (RCTs) assessing the role of bedaquiline compared with any comparator for patients with MDR-TB were eligible for inclusion. Observational studies were not included in this systematic review. Included studies enrolled newly diagnosed adults, regardless of gender, diagnosed with TB resistant to both Isoniazid and Rifampicin regimens. Two review authors (JC and AK) independently reviewed titles and abstracts followed by full text using predefined inclusion criteria. All disagreements about selection of studies were resolved by consensus.

Data Extraction and Management
Two authors (JC and AK) independently extracted and matched data from included trials using a standardized data extraction form. Data were collected on study characteristics (study setting, inclusion criteria, number randomized), patient characteristics (age and gender), treatment characteristics (dose and duration of treatment), risk of bias using Cochrane risk of bias tool, and outcomes (time and rate of conversion of positive spum to negative culture, mortality, treatment completion, and adverse events).

Statistical Analysis
Time to event data was summarized as hazard ratio (HR) with 95% confidence intervals (95% CI) and dichotomous data were summarized as risk ratio (RR) with 95% CI. Data were pooled by outcome using the random effects model. Heterogeneity was assessed using I² values. We set predecided criteria for significant heterogeneity as I² > 50%.

There were only two trials fulfilling the suitability of inclusion hence we did not assess for the publication bias. At least 10 trials are needed for adequate assessment of publication bias.

All data were analyzed using the Review Manager version 5.3 software (Cochrane Collaboration). The systematic review was performed as per the standards of Cochrane Collaboration and reported as per PRISMA standards.

Results

Characteristics of Studies and Risk of Bias
The selection process of eligible studies is shown Figure 1. Of 289 citations, two RCTs published as three manuscripts were included in the final SR. Information about characteristics of studies is summarized in Table 1. While one paper reported data on outcomes with a follow-up of 8 weeks, another paper was the extension of the first study reported the results after the follow-up of 24 weeks and 104 weeks. The second trial reported data with 24 and 120 weeks follow-up.

All included studies enrolled newly diagnosed patients who were infected by MDR-TB (resistant to both isoniazid and rifampicin). Treatment with bedaquiline in both trials was initiated with 400 mg daily for 2 weeks followed by 200 mg daily for rest of the study period. Adult patients of either sex

Figure 1: Flow diagram illustrating the selection process of included studies

- Included in the final analysis
- N=3
- Published as 3 manuscripts
- Included in the final analysis
- N=3
- Published as 3 manuscripts
- Selected for further review
- N=181
- Excluded (n=109)
  - Duplicates - 100
- Included in the final analysis
- N=3
- Excluded (n=159)
  - Reviews articles - 59
  - Basic research/laboratory/cell lines studies - 38
  - Animal studies - 30
  - Drug review - 20
  - View point/comment - 14
  - Editorial - 9
  - Guidelines - 9
  - News - 9
  - Not relevant - 9
  - Case series/case reports - 3
- Excluded (n=159)
  - Reviews articles - 59
  - Basic research/laboratory/cell lines studies - 38
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  - Guidelines - 9
  - News - 9
  - Not relevant - 9
  - Case series/case reports - 3
were included in both trials. Identical looking placebo was given to the control group in both trials. Patients in both arms received standard treatment for MDR-TB (five second-line drugs-fluoroquinolones, aminoglycosides, pyrazinamide, ethionamide, and ethambutol) in addition to either bedaquiline or placebo. Majority of information related to the risk of bias were not reported adequately to make an appropriate judgment on risk of bias. On the basis of reporting, all trials were considered as either high or unclear risk of bias [Figure 2].

**Effects of Interventions**

Results on all outcomes are summarized in Table 2.

**Conversion of positive sputum culture to negative sputum culture at 24 weeks**

Data were extractable from two RCTs enrolling a total of 176 patients [Figure 3].

Bedaquiline compared with placebo was associated with a statistically significant decrease in time to conversion from positive to negative sputum culture (HR = 0.42 [95% CI 0.29 to 0.61; P < 0.00001]), F = 0%. In addition, the number of patients who converted to negative sputum culture at 24 weeks was significantly more in bedaquiline group compared with placebo (two RCTs; 176 patients). (RR = 1.33 [95% CI 1.09–1.62; P = 0.006]), F = 0%.

**Conversion of positive sputum culture to negative sputum culture at 8 weeks**

Data were extractable from one RCT enrolling 44 patients. Bedaquiline was associated with statistically significant decrease in time to conversion of positive sputum to negative sputum compared with placebo. The (HR = 0.09 [95% CI 0.02–0.43; P = 0.003]). The rate of patients converted to negative sputum culture was significantly more in bedaquiline group compared with placebo (one RCT; 44 patients). The (RR = 5.48 [95% CI 1.35–22.17; P = 0.01]).

**Long-term rate of conversion of positive sputum culture to negative**

Data were extractable from two RCTs enrolling 176 patients. Only data related to the rate of conversion from positive to negative culture was extractable. More number of patients was converted from positive to negative sputum culture in bedaquiline group as compared to the placebo but it was not statistically significant. The pooled RR was 1.33 (95% CI 1.00–1.78; P = 0.05), F = 0%.

**Safety of Intervention**

**Mortality long-term**

Data were extractable from two RCTs enrolling 176 patients [Figure 4].

Bedaquiline was associated with significantly higher rates of mortality compared with placebo (RR = 4.72 [95% CI 1.23–18.11; P = 0.02]), F = 0%.

**Adverse events**

The most commonly reported adverse events were nausea and vomiting, arthralgia and extremity pain, and headache. Whereas no significant difference was reported between bedaquiline versus placebo, there was not enough data to pool results.

**Completion of treatment**

Data were extractable from two RCTs enrolling 176 patients [Figure 5].

There was no significant difference in completion rates between bedaquiline and placebo (RR = 1.33 [95% CI 1.00–1.78; P = 0.46]), F = 0%.

**Discussion**

The findings from this systematic review show that bedaquiline significantly shortens the time to conversion to...
**Table 2:**
Summary of findings table for the meta-analysis

**Question:** Should bedaquiline versus placebo be used for management of multiple drug resistant tuberculosis?

| Number of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Bedaquiline (%) | Placebo (%) | Relative (95% CI) | Absolute | Quality | Importance |
|-------------------|--------|--------------|---------------|--------------|-------------|---------------------|----------------|-------------|-----------------|----------|---------|------------|
| **Time to conversion of positive sputum culture to negative (follow-up mean 24 weeks)** |
| 2 Randomized trials | Serious<sup>a</sup> | No serious inconsistency | No serious indirectness | No serious imprecision | None | 0/21 (0) | 0/23 (0) | HR 0.42 (0.29-0.31) | Not estimable<sup>b</sup> | ⊕⊕⊕ | O |

**Conversion of positive sputum to negative (follow-up mean 24 weeks)**

| 2 Randomized trials | Serious<sup>a</sup> | No serious inconsistency | No serious indirectness | No serious imprecision | None | 69/87 (79.3) | 53/89 (59.6) | RR 1.33 (1.09-1.62) | 197 more per 1000 (from 54 more to 369 more) | ⊕⊕⊕ | O |

**Time to conversion of positive sputum to negative (follow-up mean 8 weeks)**

| 1 Randomized trials | Serious<sup>a</sup> | No serious inconsistency | No serious indirectness | No serious imprecision | Reporting bias<sup>c</sup> | 10/21 (47.6) | 2/23 (8.7) | RR 5.48 (1.35-22.17) | 390 more per 1000 (from 30 more to 1000 more) | ⊕⊕ | O |

**Conversion of positive sputum to negative (follow-up mean 8 weeks)**

| 1 Randomized trials | Serious<sup>a</sup> | No serious inconsistency | No serious indirectness | No serious imprecision | Reporting bias<sup>c</sup> | 11/100 (11) | 2/104 (1.9) | RR 4.72 (1.23-18.11) | 72 more per 1000 (from 4 more to 329 more) | ⊕⊕ | O |

**Long term conversion of positive sputum culture to negative**

| 2 Randomized trials | Serious<sup>a</sup> | No serious inconsistency | No serious indirectness | No serious imprecision | None | 32/87 (36.8) | 37/89 (41.6) | RR 0.89 (0.61-1.28) | 46 fewer per 1000 (from 162 fewer to 116 more) | ⊕⊕ | O |

**Mortality at 24 weeks**

| 2 Randomized trials | Serious<sup>a</sup> | No serious inconsistency | No serious indirectness | No serious imprecision | None | 11/100 (11) | 2/104 (1.9) | RR 4.72 (1.23-18.11) | 72 more per 1000 (from 4 more to 329 more) | ⊕⊕ | O |

**Completion of treatment**

| 2 Randomized trials | Serious<sup>a</sup> | No serious inconsistency | No serious indirectness | No serious imprecision | None | 32/87 (36.8) | 37/89 (41.6) | RR 0.89 (0.61-1.28) | 46 fewer per 1000 (from 162 fewer to 116 more) | ⊕⊕ | O |

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*No information reported on methods of randomization sequence generation or allocation concealment. Details on blinding of patients, physicians or outcome assessors are not reported. *Due to non-availability of events we could not calculate the baseline risk. *Wide confidence intervals. *Out of two RCTs, only one reported this outcome. CI=Confidence interval, HR=Hazard ratio, RR=Risk ratio, RCTs=Randomized controlled trials.
from positive culture to negative culture as compared with placebo at 8 weeks and 24 weeks of treatment. Furthermore, more patients converted from positive culture to negative culture in bedaquiline group versus placebo at 24 weeks however at long-term follow-up no statistically significant difference in conversion between bedaquiline and placebo was detected. While the point estimate suggests a 33% improvement in response rate for MDR TB in the long-term with the use of bedaquiline versus placebo, this finding was not statistically significant perhaps due to relatively small sample size in these studies. Primary objectives in both the studies was not the comparison of long-term sputum conversion hence sample size was not calculated based on long-term follow-up.\[^{[12,13]}\]

The results from this systematic review need to be interpreted with caution given the small number of trials and unclear risk of bias as determined according to the reporting. Both trials were Phase 2 trials and industry-sponsored authored by same set of authors. Further studies are necessary to ensure reproducibility. Furthermore, Phase 2 trials are only considered as screening tool for effect of drug and not considered as gold standard for establishing the efficacy of intervention and success in Phase 2 trials does not predict success in Phase 3 trials. That is chances of observing a positive result in Phase 3 trial after positive Phase 2 trials are low.\[^{[14,15]}\] Until now there have been only two trials assessing the efficacy of bedaquiline and both trials are Phase 2 with limited sample size. Therefore, the results obtained in the meta-analysis may be encouraging but cannot be considered definitive. Furthermore, given the high or unclear risk of bias observed in both studies\[^{[16-18]}\] the overall quality of evidence from this systematic review is at best moderate [Figure 2 and Table 2].

One of the key findings of this systematic review is the significant mortality associated with bedaquiline compared to the placebo on long-term follow-up (104 weeks in one trial and 120 weeks in another trial). While no deaths occurred in the first 8 weeks in the treatment or placebo group, the difference in mortality was statistically significant with long-term follow-up. During the 24 weeks follow-up, 1 death was observed in bedaquiline group in both trials. The remaining deaths were observed after 24 weeks in both groups. Excess mortality observed in the bedaquiline group need to be interpreted cautiously. This may be a chance finding, and none of the deaths were considered treatment related according to the study investigators.

There was no difference in completion rates of treatment for both treatments which indirectly measures the tolerability of bedaquiline as compared to the placebo. Comparison of individual adverse effects in the form of meta-analysis except the death was not possible due to differences in reporting of adverse drug reactions in the trials included in this systematic review. However, descriptively, there was an equal chance of having different side effects except nausea which was significantly more in bedaquiline group as compared to the placebo.

**Figure 3:** Forest plot for the comparison of “time to conversion of positive sputum to negative at 24 weeks” between bedaquiline and placebo

**Figure 4:** Forest plot for the comparison of mortality between bedaquiline and placebo

**Figure 5:** Forest plot for the comparison of “number of subjects completed the treatment” between bedaquiline and placebo
This systematic review and meta-analysis is conducted by pooling the data from only two trials, and this is an important limitation. Any systematic review is dependent on the quantity and quality of evidence available for a specific question. After an extensive search, we come to the conclusion that only three publications based on results of two trials are available addressing the question raised in meta-analysis. Hence, on the basis of evidences (clinical trials) available until today, the meta-analysis was done. It is a common practice to re-analysis and modification of results after new trials published, we hope new meta-analysis will be done and published on same questions in the coming years when results of more trials will be available.

**Conclusion**

This systematic review and meta-analysis found that bedaquiline significantly shortens the time to conversion from positive culture negative culture as compared with placebo. However, potential bias in the included clinical trials and availability of less number of clinical trials weakens these findings. Further larger studies are necessary to assess the long-term conversion rates as well as the potential harms associated with the use of bedaquiline for the treatment of MDR-TB.

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**Conflicts of Interest**

There are no conflicts of interest.

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