Bedaquiline-containing regimens and multidrug-resistant tuberculosis: a systematic review and meta-analysis

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ABSTRACT

Objective: Multidrug-resistant tuberculosis (MDR-TB) is a life-threatening infectious disease. Treatment requires multiple antimicrobial agents used for extended periods of time. The present study sought to evaluate the treatment success rate of bedaquiline-based regimens in MDR-TB patients. **Methods:** This was a systematic review and meta-analysis of studies published up to March 15, 2021. The pooled treatment success rates and 95% CIs were assessed with the fixed-effect model or the random-effects model. Values of $p < 0.05$ were considered significant for publication bias. **Results:** A total of 2,679 articles were retrieved by database searching. Of those, 29 met the inclusion criteria. Of those, 25 were observational studies (including a total of 3,536 patients) and 4 were experimental studies (including a total of 440 patients). The pooled treatment success rate was 74.7% (95% CI, 69.8-79.0) in the observational studies and 86.1% (95% CI, 76.8-92.1; $p = 0.00$; $I^2 = 75\%$) in the experimental studies. There was no evidence of publication bias ($p > 0.05$). **Conclusions:** In patients with MDR-TB receiving bedaquiline, culture conversion and treatment success rates are high even in cases of extensive resistance.

Keywords: Tuberculosis; Drug resistance; Tuberculosis, multidrug-resistant; Efficacy.

INTRODUCTION

Tuberculosis is a life-threatening infectious disease. In 2020, the WHO estimated a total of 10 million tuberculosis cases, 1,400,000 deaths (including 208,000 deaths among people living with HIV), and 465,000 cases of drug-resistant tuberculosis.[1]

Over the last two decades, the global epidemiology of mycobacterial drug resistance has deteriorated, especially with the emergence and spread of multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB).[1] MDR-TB is caused by *Mycobacterium tuberculosis* strains resistant to at least isoniazid and rifampin. MDR-TB with further resistance to any fluoroquinolone and at least one of the three injectable second-line drugs, i.e., kanamycin, amikacin, and capreomycin, was initially defined as XDR-TB.[2] However, the WHO has recently modified the definition of XDR-TB, focusing on resistance to group A drugs, which include bedaquiline.[3,4] The WHO has also introduced the definition of pre-XDR-TB, i.e., MDR-TB strains with additional resistance to fluoroquinolones.[4]

MDR-TB treatment outcomes are poor, with approximately 50% of patients achieving treatment success. A significant factor contributing to treatment failure in many settings is the lack of effective drugs to manage MDR-TB and XDR-TB.[1] Moreover, MDR-TB treatment is long and expensive. Numerous efforts have been made to shorten the therapeutic courses and develop more effective medications. Thus, several new drugs for tuberculosis treatment have been evaluated, including linezolid and some new drugs with novel mechanisms of action, such as bedaquiline and delamanid.[5]

The WHO has recommended bedaquiline and delamanid for the treatment of MDR-TB.[6] Bedaquiline, a diarylquinoline that inhibits mycobacterial ATP synthase, is the first antituberculosis drug in 40 years to be approved for MDR-TB patients.[7-9]

The 2018 WHO guidelines recommend bedaquiline as the first drug in an all-oral regimen designed to maximize treatment outcomes while minimizing the toxicity of injectable agents.[6]

Over the last few years, several studies have assessed the efficacy of bedaquiline.[3,10,11] However, a

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comprehensive analysis has not yet been performed. Thus, the objective of the present study was to evaluate the treatment success rate of bedaquiline-based regimens in MDR-TB patients.

METHODS

Search strategy

We searched MEDLINE (PubMed), EMBASE, and Cochrane Library for studies reporting the efficacy of individualized regimens containing bedaquiline in patients with culture- and drug susceptibility testing-confirmed MDR/XDR-TB, published up to March 15, 2021. The search terms were as follows: ((tuberculosis(Title/Abstract)) AND (bedaquiline(Title/Abstract)) AND (efficacy(Title/Abstract) OR effectiveness(Title/Abstract))). Only studies written in English were selected. This study was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[12]

Study selection

The records found through database searching were merged, and the duplicates were removed using EndNote X7 (Thomson Reuters, Toronto, ON, Canada). Two reviewers independently screened the records by title/abstract and full text to exclude those unrelated to the study topic. Included studies met the following criteria: (i) patients diagnosed with MDR-TB on the basis of the WHO criteria[1]; (ii) patients treated with bedaquiline-containing regimens; and (iii) treatment success (i.e., culture conversion). Conference abstracts, editorials, reviews, experimental studies on animal models, and articles describing tuberculosis patients recruited without a confirmed bacteriological diagnosis were excluded.

Pre-XDR-TB was defined as tuberculosis caused by *M. tuberculosis* strains that fulfill the definition of MDR-TB/rifampin-resistant tuberculosis and that are also resistant to any fluoroquinolone, whereas XDR-TB was defined as tuberculosis caused by *M. tuberculosis* strains that fulfill the definition of MDR-TB/rifampin-resistant tuberculosis and are also resistant to any fluoroquinolone and at least one additional group A drug.[4]

Treatment outcomes were recorded in accordance with adapted definitions of those given in the WHO guidelines, as follows: treatment success, defined as the combination of the number of patients who were cured and that of those who completed treatment; death, defined as death from any cause while on treatment; and treatment failure, defined as unsuccessful treatment, as determined by positive cultures at the end of the treatment regimen.[13]

Data extraction

Two reviewers designed a data extraction form and extracted data from all eligible studies, with differences being resolved by consensus. The following data were extracted: first author's name; year of publication; study duration; type of study; country or countries where the study was conducted; number of patients with MDR-TB; patient age; treatment protocols (treatment regimens and duration of treatment); HIV history; demographics; adverse effects; drug resistance status; and outcomes.

Quality assessment

Two blinded reviewers assessed the quality of the studies using two different assessment tools (checklists): one for observational studies and one for experimental studies.[14] Items such as study population, measure of exposures, confounding factors, extent of outcomes, follow-up data, and statistical analysis were evaluated.

Data analysis

Statistical analyses were performed with Comprehensive Meta-Analysis software, version 2.0 (Biostat Inc., Englewood, NJ, USA). The pooled success rate with 95% CI was assessed using the random-effects model or the fixed-effect model. The random-effects model was used because of the estimated heterogeneity of the true effect sizes. Between-study heterogeneity was assessed by Cochran's Q test and the I^2 statistic. Subgroup analyses stratified by type of study and treatment regimen (bedaquiline-based regimen, delamanid-based regimen, or both) were performed to minimize heterogeneity. Publication bias was statistically assessed by using Egger's test and Begg's test, as well as funnel plots, a value of $p < 0.05$ being considered indicative of statistically significant publication bias and funnel plot asymmetry being suggestive of bias.[15]

RESULTS

The article selection process is shown in Figure 1. A total of 2,679 articles were found by database searching; after the removal of duplicates, the titles and abstracts of 1,946 articles were screened. Of those, 44 met the inclusion criteria and were selected for a full-text review. After the full-text review, 29 were chosen. The studies[10,11,16-42] were divided into two groups: 25 observational studies, including a total of 3,536 patients, and 4 experimental studies, including a total of 440 patients (Table 1). The earliest study was published in 2014, and the latest studies were published in 2021. The mean age of the patients was 39.0 years.

Quality of the included studies

The checklist for observational studies[14] showed that the included observational studies had a low risk of bias (Table 2). In contrast, the checklist for experimental studies[14] showed that the included experimental studies had a high risk of bias for randomization, group concealment, participant assignment, and assessor blinding (Table 3).

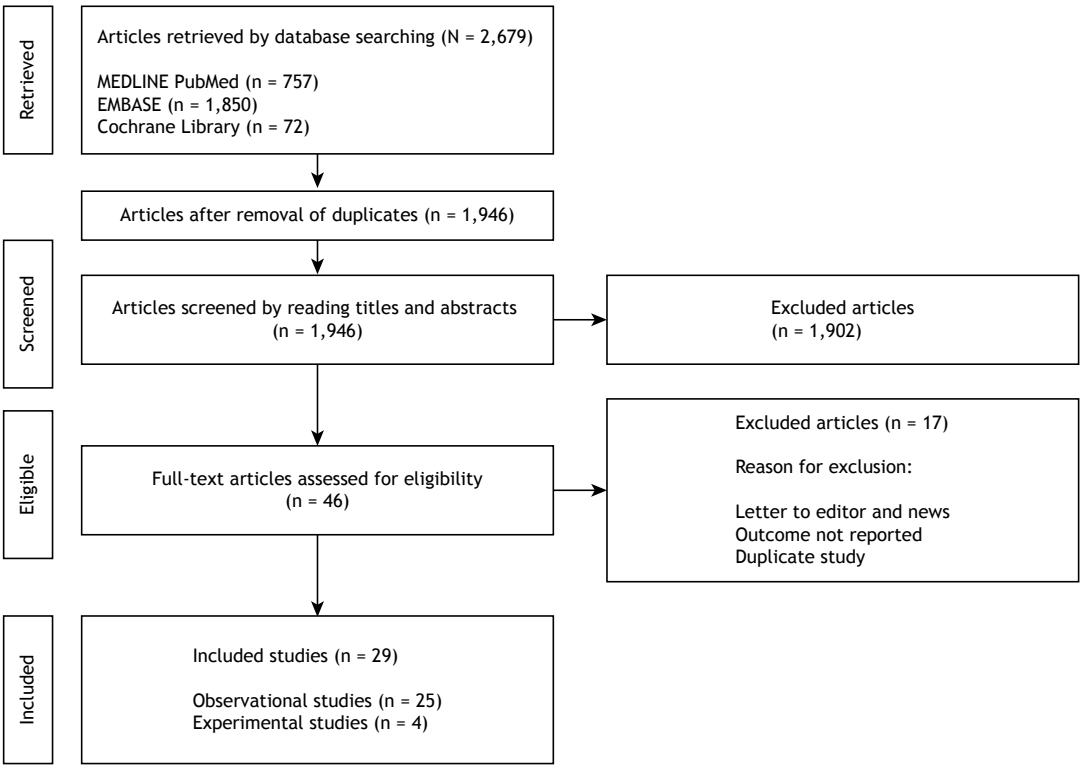

Figure 1. Flow chart of study selection for inclusion in the systematic review and meta-analysis.

Outcomes in the observational studies

The pooled treatment success rate was 74.7% (95% CI, 69.8-79.0; I^2 = 86%; Figure 2). There was no evidence of publication bias (p > 0.05).

The pooled death and treatment failure rates were 9.0% (95% CI, 6.8-12.0; I^2 = 75%) and 5.7% (95% CI, 3.6-8.9; I^2 = 85%), respectively.

Outcomes in the experimental studies

The pooled treatment success rate was 86.1% (95% CI, 76.8-92.1; p = 0.00; I^2 = 75%; Figure 3). There was no evidence of publication bias (p > 0.05).

Mortality rates were reported in 2 studies, and the pooled death rate was 3.6% (95% CI, 0.6-9.2). Only 1 study reported a treatment failure rate, which was 1.8%.

Adverse effects

Most of the adverse events potentially attributed to bedaquiline-containing regimens were gastrointestinal symptoms (15.3%), peripheral neuropathy (13.8%), and hematological disorders (13.6%; Table 4). Although there was limited information on how many patients interrupted bedaquiline treatment because of an increase in the Fridericia-corrected QT interval, 283 of 2,611 patients experienced Fridericia-corrected QT interval prolongation (pooled rate, 10.4%).

Subgroup analysis

Table 5 shows the subgroup analysis of the studies based on the treatment regimen and type of study. The treatment success rate in patients receiving bedaquiline-containing regimens was 74.5%. For patients receiving treatment with bedaquiline and delamanid, the treatment success rate was 73.9%. The treatment success rates in the observational and experimental studies included in the meta-analysis were 74.7% and 86.1%, respectively.

DISCUSSION

Drug-resistant tuberculosis treatment has severe limitations, such as extensive drug resistance limiting the number of effective drugs, a high risk of adverse events, and a high treatment failure rate. In 2020 the WHO introduced a new approach to managing drug-resistant tuberculosis and a new drug classification.[4] According to the WHO recommendations, bedaquiline is the first drug in an all-oral regimen to optimize treatment outcomes while minimizing the toxicity associated with injectable medicines.[6] Although some studies have been conducted on bedaquiline and delamanid to discuss their benefits and drawbacks, no systematic reviews and meta-analyses have recently been published on this topic.

In the current study, we screened 2,679 articles and finally selected 29 studies reporting on 3,929 patients and describing the treatment outcomes of bedaquiline-containing regimens. A pooled treatment success rate of 74.7% was found for bedaquiline-containing regimens in the observational studies. In the experimental studies, the pooled treatment success rate was 86.1%.

Table 1. Observational and experimental studies included in the meta-analysis.

Author	Year	Country	Type of study	Mean/ median age	HIV +, n (%)	Previously treated for TB	TB disease	No. of patients receiving BDQ	Other drugs included in the regimen	Duration of treatment (months)	Outcomes		
											Treatment success	Treatment failure	Death
Koirala et al.[11]	2021	Multicenter	PC	39	27 (5.7)	329	MDR/XDR	383	WHO-recommended regimen	6	284	11	25
Kwon et al.[16]	2021	South Korea	RC	49	0	19	Pre-XDR/ XDR	28	DLM+LZD+CFZ+MEM/CLV+CYC	6	23	2	1
Shi et al.[17]	2021	China	RC	49.8	N/R	186	MDR	72	FLQs+LZD+CFZ+CYC	6	197	4	0
							pre-XDR	78					
							XDR	64					
Gao et al.[18]	2021	China	RC	40	1 (0.6)	168	MDR	39	FLQs+LZD+CFZ+CYC	6	151	23	3
							pre-XDR	56					
							XDR	82					
Barvaliya et al.[19]	2020	India	PC	31	N/R	110	Pre-XDR	87	FLQs+LZD+CFZ	5.5	102	10	14
							XDR	40					
Kashongwe et al.[20]	2020	Congo	RC	32.4	3 (9.4)	23	Pre-XDR	29	FLQs+LZD+CFZ+CYC	20	17	0	15
							XDR	3					
Das et al.[21]	2020	India	RC	Children/ adolescents	0	N/R	Pre-XDR/ XDR	13	DLM+ LZD+CFZ	22	12 or 13	N/R	N/R
Lee et al.[22]	2020	South Korea	RC	49.8	1 (1.4)	49	MDR	13	DLM+FLQs+ LZD+CFZ+CYC	5.5	42	1	4
							Pre-XDR	41					
							XDR	20					
Kim et al.[23]	2020	South Korea	RC	33	9 (3.5)	254	MDR	159	AMGs+FLQs+LZD+CYC	6	139/225	35/225	15/225
							Pre-XDR	51					
							XDR	44					
Mase et al.[24]	2020	USA	RC	43.5	1 (7)	5	MDR	7	WHO-recommended regimen	5.5	12	N/R	1
							Pre-XDR	4					
							XDR	3					
Olayanju et al.[25]	2020	South Africa	PC	33	42 (51)	40	MDR	5	AMGs+FLQs+LZD+CFZ+TRD	6	52	N/R	N/R
							Pre-XDR	10					
							XDR	67					
				34	22 (55)	29	MDR	6	DLM+AMGs+FLQs+LZD+CFZ+TRD	6	27	N/R	N/R
							Pre-XDR	15					
							XDR	19					

Continue...▶

Table 1. Observational and experimental studies included in the meta-analysis. (Continued...)

Author	Year	Country	Type of study	Mean/ median age	HIV +, n (%)	Previously treated for TB	TB disease	No. of patients receiving BDQ	Other drugs included in the regimen	Duration of treatment (months)	Outcomes		
											Treatment success	Treatment failure	Death
Salhotra et al.[26]	2020	India	PC	Range: 18-50	8 (1.3)	600	MDR	524	AMGs+FLQs+CFZ	6	513	N/R	73
							XDR	96					
Chesov et al.[27]	2020	Moldova	RC	37	17 (14.9)	58	MDR	114	AMGs+FLQs+CYC+PZA	6	63	31	10
Kang et al.[28]	2020	South Korea	RC	51.7	0	55	MDR	43	AMGs+FLQs+LZD+CYC	6	86	1	13
							Pre-XDR	47					
							XDR	17					
				47.7	1 (1.5)	47	MDR	8	DLM+AMGs+FLQs+LZD+CYC	6	58	3	3
							Pre-XDR	37					
							XDR	22					
Sarin et al.[29]	2019	India	PC	Range: 21-33	0	N/R	MDR/ Pre-XDR/ XDR	42	DLM+ FLQs+LZD+CFZ+IMP	6	25	N/R	10
Kempker et al.[30]	2019	USA	PC	37.3	2 (3)	8	MDR/XDR	64	FLQs+LZD+CFZ+CYC+IMP	5.5	42	1	0
Taune et al.[31]	2019	New Guinea	RC	39	1 (1.3)	33	MDR	55	AMGs+FLQs+LZD+CFZ+CYC+PZA	6	72	N/R	5
							Pre-XDR	10					
							XDR	12					
Ferlazzo et al.[32]	2018	Armenia, India, South Africa	RC	32.5	11 (39)	4	MDR	2	DLM+ FLQs+LZD+CFZ+IMP	6	22	N/R	1
							Pre-XDR	12					
							XDR	14					
Hewison et al.[33]	2018	Armenia, Georgia	RC	40.5	4 (4.8)	N/R	MDR	6	FLQs+LZD+CFZ+IMP	6	48	6	10
							Pre-XDR	36					
							XDR	40					
Ndjeka et al.[34]	2018	South Africa	PC	34	134 (67)	N/R	Pre-XDR	122	FLQs+LZD+CFZ	6	146	9	25
							XDR	78					
Zhao et al.[35]	2018	South Africa	RC	Range: 35-49	110 (68)	N/R	MDR	162	FLQs+PZA+ETH+hINH+ETM+TRD	6	111/146	7/119	11/145
Kim et al.[36]	2018	South Korea	RC	52	N/R	N/R	MDR/ Pre-XDR/ XDR	39	FLQs+LZD+CFZ	5.6	24	N/R	N/R

Continue...▶

Table 1. Observational and experimental studies included in the meta-analysis. (Continued...)

Author	Year	Country	Type of study	Mean/ median age	HIV +, n (%)	Previously treated for TB	TB disease	No. of patients receiving BDQ	Other drugs included in the regimen	Duration of treatment (months)	Outcomes		
											Treatment success	Treatment failure	Death
Achar et al.[37]	2017	South Africa, Tajikistan, Uzbekistan, Belarus	PC	Children/ adolescents	0	N/R	Pre-XDR/ XDR	23	FLQs+LZD+CFZ+IMP	6	23	0	0
Guglielmetti et al.[38]	2017	France	RC	38	2 (4.4)	34	MDR/ Pre-XDR/ XDR	45	AMGs+FLQs+LZD+CFZ+CYC+PZA+ETH+ETM	6	36	1	3
Borisov et al.[10]	2017	Multicenter	RC	35	94 (22.1)	334	MDR	233	AMGs+FLQs+LZD+CFZ+IMP	5.5	176/247	18/247	33/247
							XDR	195					
Conradie et al.[39]	2020	South Africa	CT	35	56 (51)	N/R	MDR	38	LZD+PMD	6	98	2	7
							XDR	71					
Tweed et al.[40]	2019	South Africa, Tanzania, Uganda	CT	34	25 (42)	N/R	RR	60	FLQs+PZA+PMD	6	58	N/R	0
Pym et al.[41]	2016	Multicenter	CT	32	8 (4)	177	MDR	124	AMGs+FLQs+ CYC+PZA+ETH	6	163	N/R	N/R
							Pre-XDR	44					
							XDR	37					
Diacon et al.[42]	2014	Multicenter	CT	32	5 (8)	N/R	MDR	66	AMGs+FLQs+ CYC+PZA+ETH	6	52	N/R	N/R

PC: prospective cohort; RC: retrospective cohort; CT: clinical trial; BDQ: bedaquiline; DLM: delamanid; FLQs: fluoroquinolones; LZD: linezolid; CFZ: clofazimine; CYC: cycloserine; AMGs: aminoglycosides; MEM/CLV: meropenem-clavulanate; TRD: terizidone; IMP: imipenem; ETH: ethionamide; hINH: high-dose isoniazid; ETM: ethambutol; PZA: pyrazinamide; PMD: pretomanid; MDR: multidrug-resistant; XDR: extensively drug-resistant; RR: rifampin-resistant; and N/R: not reported.

Table 2. Quality assessment of the observational studies included in the meta-analysis.

Author	1	2	3	4	5	6	7	8	9	10	11
Koirala et al.[11]	N/A	N/A	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Kwon et al.[16]	N/A	N/A	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Shi et al.[17]	N/A	N/A	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Gao et al.[18]	N/A	N/A	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Barvaliya et al.[19]	N/A	N/A	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Kashongwe et al.[20]	N/A	N/A	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Das et al.[21]	N/A	N/A	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Lee et al.[22]	N/A	N/A	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Kim et al.[23]	N/A	N/A	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Mase et al.[24]	N/A	N/A	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Olayanju et al.[25]	N/A	N/A	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Salhotra et al.[26]	N/A	N/A	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Chesov et al.[27]	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Kang et al.[28]	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Sarin et al.[29]	N/A	N/A	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Kempker et al.[30]	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Taune et al.[31]	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Ferlazzo et al.[32]	N/A	N/A	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Hewison et al.[33]	N/A	N/A	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Ndjeka et al.[34]	N/A	N/A	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Zhao et al.[35]	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Kim et al.[36]	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Achar et al.[37]	N/A	N/A	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Guglielmetti et al.[38]	N/A	N/A	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Borisov et al.[10]	N/A	N/A	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes

1. Were the two groups similar and recruited from the same population?
2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?
3. Was the exposure measured in a valid and reliable way?
4. Were confounding factors identified?
5. Were strategies to deal with confounding factors stated?
6. Were the groups/participants free of the outcome at the start of the study?
7. Were the outcomes measured in a valid and reliable way?
8. Was the follow-up time reported and long enough for outcomes to occur?
9. Was follow-up complete, and, if not, were the reasons for loss to follow-up described and explored?
10. Were strategies to address incomplete follow-up utilized?
11. Was appropriate statistical analysis used?

Table 3. Quality assessment of the experimental studies included in the meta-analysis.

Author	1	2	3	4	5	6	7	8	9	10	11	12	13
Conradie et al.[39]	No	N/A	N/A	No	No	No	No	Yes	Yes	N/A	Yes	Yes	No
Tweed et al.[40]	Yes	No	Yes	No	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Pym et al.[41]	No	No	N/A	No	No	No	No	Yes	Yes	N/A	Yes	Yes	No
Diacon et al.[42]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes

1. Was true randomization used for assignment of participants to treatment groups?
2. Was allocation to treatment groups concealed?
3. Were treatment groups similar at baseline?
4. Were participants blind to treatment assignment?
5. Were those delivering treatment blind to treatment assignment?
6. Were outcome assessors blind to treatment assignment?
7. Were treatment groups treated identically other than the intervention of interest?
8. Was follow-up complete, and, if not, were differences between groups in terms of their follow-up adequately described and analyzed?
9. Were participants analyzed in the groups to which they were randomized?
10. Were outcomes measured in the same way for treatment groups?
11. Were outcomes measured in a reliable way?
12. Was appropriate statistical analysis used?
13. Was the trial design appropriate and were any deviations from the standard randomized controlled trial design accounted for in the conduct and analysis of the trial?

Study	Event rate	Lower limit	Upper limit	Relative weight
Koirala et al.[11]	0.742	0.695	0.783	5.16
Kwon et al.[16]	0.821	0.636	0.924	2.94
Shi et al.[17]	0.921	0.876	0.950	4.43
Gao et al.[18]	0.853	0.793	0.898	4.68
Barvaliya et al.[19]	0.803	0.725	0.863	4.61
Kashongwe et al.[20]	0.531	0.361	0.694	3.77
Das et al.[21]	0.923	0.609	0.989	1.14
Lee et al.[22]	0.568	0.453	0.675	4.54
Kim et al.[23]	0.618	0.553	0.679	5.08
Mase et al.[24]	0.857	0.573	0.964	1.79
Olayanju et al.[25]	0.648	0.559	0.727	4.81
Salhotra et al.[26]	0.827	0.796	0.855	5.20
Chesov et al.[27]	0.553	0.461	0.641	4.82
Kang et al.[28]	0.828	0.764	0.877	4.75
Sarin et al.[29]	0.595	0.443	0.731	4.03
Kempker et al.[30]	0.656	0.533	0.762	4.36
Taune et al.[31]	0.935	0.853	0.973	3.11
Ferlazzo et al.[32]	0.786	0.598	0.900	3.12
Hewison et al.[33]	0.585	0.476	0.687	4.61
Ndjeka et al.[34]	0.730	0.664	0.787	4.97
Zhao et al.[35]	0.760	0.684	0.823	4.78
Kim et al.[36]	0.615	0.456	0.753	3.93
Achar et al.[37]	0.979	0.741	0.999	0.67
Guglielmetti et al.[38]	0.800	0.658	0.893	3.65
Borisov et al.[10]	0.713	0.653	0.766	5.06
	0.747	0.698	0.790	

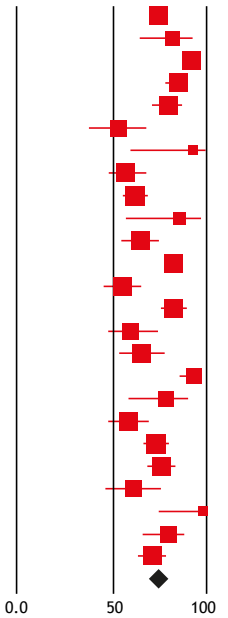

Figure 2. Treatment success rate in the observational studies included in the meta-analysis.

Study	Event rate	Lower limit	Upper limit	Relative weight
Conradie et al.[39]	0.899	0.827	0.943	26.77
Tweed et al.[40]	0.967	0.876	0.992	12.90
Pym et al.[41]	0.795	0.734	0.845	32.81
Diacon et al.[42]	0.788	0.673	0.870	27.52
	0.861	0.768	0.921	

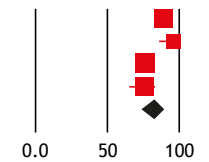

Figure 3. Treatment success rate in the experimental studies included in the meta-analysis.

Previous studies have shown that adding bedaquiline to regimens effectively reduces drug-resistant tuberculosis.[10,43] However, some studies have raised the issue of its potential toxicity, mainly when delamanid and other drugs prolonging the QT interval are prescribed in the regimen (e.g., fluoroquinolones and clofazimine).[10,43]

Two previous systematic reviews on bedaquiline, one published in 2016 and the other in 2018, included a small number of patients. In a systematic review of 2 randomized controlled trials (which were published as 3 articles) including 176 patients, no differences in culture conversion were found between bedaquiline and placebo.[44] Even though the point estimate showed a 33% improvement in the response rate with the use of bedaquiline vs. placebo, this finding was not statistically significant, because of the small sample sizes.[44]

Pontali et al. reported an 81.4% sputum culture conversion rate after 6 months of treatment and a 71.4% treatment success rate in a systematic review including 7 studies investigating 87 adults with drug-resistant tuberculosis treated with delamanid and bedaquiline.[45]

In a phase 2 trial conducted by Diacon et al., 160 patients were randomly assigned to receive either 400 mg of bedaquiline once daily for 2 weeks, followed by 200 mg three times a week for 22 weeks, or placebo, both in combination with a preferred background regimen.[42] The authors demonstrated that adding bedaquiline to a preferred background regimen for 24 weeks resulted in faster culture conversion and a significantly higher culture conversion rate at 120 weeks. The cure rate at 120 weeks was 58% in the bedaquiline group and 32% in the placebo group.[42]

In a cohort study conducted by Mbuagbaw et al. and involving 537 patients treated with bedaquiline, the use of bedaquiline in the treatment regimen for > 6 months was related to positive outcomes, with a culture conversion rate of 78% at 6 months and a treatment success rate of 65.8%.[46] In a retrospective cohort study of 102 patients, the long-term outcome and

Table 4. Adverse effects in the studies included in the meta-analysis.

Author	QTc prolongation	Liver disease/ Elevated liver enzyme	Renal failure/ Increased creatinine levels	Optic neuropathy/ Blurred vision	Ototoxicity/ Hearing loss	Hematological disorders (anemia, thrombocytopenia, eosinophilia)	Gastrointestinal symptoms (diarrhea, vomiting, nausea, abdominal pain)	Peripheral neuropathy	Electrolyte disturbance	Arthralgia	Psychiatric disorder	Dermatological symptoms
Kwon et al.[16]	17	NR	N/R	N/R	N/R	N/R	1	N/R	N/R	N/R	N/R	N/R
Shi et al.[17]	85	59	21	13	10	24	15	16	5	3	9	2
Gao et al.[18]	39	35	9	2	6	15	11	8	11	2	6	N/R
Barvaliya et al.[19]	11	6	N/R	5	4	N/R	33	4	N/R	9	4	18
Kashongwe et al.[20]	3	1	N/R	2	5	14	15	15	N/R	N/R	N/R	15
Das et al.[21]	1	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R
Lee et al.[22]	23	N/R	1	N/R	N/R	N/R	4	N/R	N/R	N/R	N/R	N/R
Kim et al.[23]	7	28	N/R	N/R	N/R	N/R	32	N/R	N/R	34	N/R	8
Mase et al.[24]	6	N/R	N/R	N/R	2	2	4	7	4	N/R	3	3
Olayanju et al.[25]	12	36	N/R	8	59	43	30	30	N/R	20	9	N/R
Salhotra et al.[26]	14	13	4	N/R	8	22	35	26	7	N/R	15	1
Kempker et al.[30]	1	1	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R
Taune et al.[31]	1	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R
Ferlazzo et al.[32]	4	N/R	1	N/R	N/R	N/R	1	1	N/R	N/R	2	N/R
Hewison et al.[33]	12	27	5	1	9	3	34	21	N/R	N/R	N/R	6
Ndjeka et al.[34]	10	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R
Achar et al.[37]	0	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R
Guglielmetti et al.[38]	13	17	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R
Borisov et al.[10]	24/248	N/R	47/413	10/413	N/R	86/412	130/413	96/412	N/R	84/412	29/413	63/412
Conradie et al.[39]	0	17	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R
Tweed et al.[40]	0	4	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R
Efeito aleatório combinado	10.4 (6.2-17.0)	11.7 (6.5-20.0)	4.6 (2.3-8.9)	3.8 (2.4-6.1)	7.8 (2.3-23.0)	13.6 (7.1-24.7)	15.3 (7.5-24.1)	13.8 (9.4-24.0)	4.7 (1.3-15.2)	8.1 (4.3-14.6)	5.1 (3.3-7.9)	7.5 (3.3-16.0)
Heterogeneidade, I^2 (%)	92%	93%	85%	50%	96%	94%	94%	94%	89%	89%	68%	91%
Teste de Begg, p	0.46	0.21	0.13	0.54	0.90	0.71	0.90	0.72	0.65	0.00	0.82	0.22

QTc: corrected QT; and N/R: not reported.

Table 5. Pooled treatment success rates for subgroups of studies.

Subgroup	No. of studies	No. of patients	Treatment success rate (%) (95% CI)	Heterogeneity I^2 (%)	Begg's test value of p
Treatment regimen:					
Regimen containing BDQ	22	3,287	74.5 (67.6-80.3)	91	0.61
Regimen containing BDQ+DLM	7	292	73.9 (62.1-83.0)	72	0.03
Type of study:					
Observational study	25	3,536	74.7 (69.8-79.0)	86	0.18
Experimental study	4	440	86.1 (76.8-92)	75	0.08

BDQ: bedaquiline; and DLM: delamanid.

safety of prolonged MDR-TB treatment with bedaquiline (for > 190 days) was investigated.[38] Outcomes and adverse effects were not significantly different between short-course and prolonged bedaquiline treatment, and most patients on bedaquiline-containing regimens achieved successful outcomes.[38]

Bedaquiline at treatment initiation and as part of an all-oral regimen may preserve good overall treatment outcomes while improving time to culture conversion and minimizing adverse effects, such as hearing loss, associated with the injectable agents.[24]

We found that a proportion of patients had adverse events related to bedaquiline in the studies included in our meta-analysis: 15.3% reported gastrointestinal symptoms, 13.8% had evidence of peripheral neuropathy, and 13.6% reported hematological toxic effects. Although patients taking bedaquiline should be carefully monitored, the adverse effects were manageable in the investigated studies, and adverse events leading to the discontinuation of bedaquiline were uncommon.

Although our study provides updated evidence on bedaquiline efficacy, it has some limitations. It does not evaluate adherence to treatment regimens containing bedaquiline, an important outcome determinant. Other limitations include variability and different patient characteristics across studies.

In conclusion, culture conversion and treatment success rates were found to be high in patients with drug-resistant tuberculosis receiving bedaquiline-containing regimens. Bedaquiline use can be implemented successfully in tuberculosis programs if financial and procurement barriers can be addressed to ensure availability. An efficient monitoring and surveillance system is needed to collect data on patients receiving new drugs and regimens to ensure best practices for the care and treatment of patients with drug-resistant tuberculosis.

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AUTHOR CONTRIBUTIONS

All authors participated in the drafting and revision of the manuscript, as well as in the approval of the final version.

CONFLICTS OF INTEREST

None declared.

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