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Nine months of bedaquiline, linezolid, levofloxacin, clofazimine, and cycloserine chemotherapy for rifampicin/multidrug-resistant tuberculosis: a multicenter, randomized, open-label non-inferiority trial in China

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Abstract

Background We concurrently developed a prospective study to assess clinical outcomes among patients receiving 9-month bedaquiline (BDQ)-containing regimens, aiming to provide valuable data on the use of this short-course regimen in China.

Methods This open-label, randomized, controlled, multicenter, non-inferiority trial was conducted at sixteen hospitals, and enrolled participants aged 18 years and older with pulmonary rifampicin/multidrug tuberculosis. Participants were randomly assigned, in a 1:1 ratio. Individuals within the standard-regimen group received 6 months of BDQ, linezolid, levofloxacin, clofazimine, and cycloserine plus 12 months of levofloxacin, and any three potentially effective drugs from clofazimine, cycloserine pyrazinamide, ethambutol and protionamide, whereas individuals within shorter-regimen group received 9 months of BDQ, linezolid, levofloxacin, clofazimine and cycloserine. The primary outcome was the percentage of participants with a composite unfavorable outcome (treatment failure, death, treatment discontinuation, or loss to follow-up) by the end of the treatment course after randomization in the modified intention-to-treat population. The noninferiority margin was 10%. This trial was registered with www.chictr.org.cn, ChiCTR2000029012.

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Results Between Jan 1, 2020, and Dec 31, 2023, 264 were screened and randomly assigned, 132 of 264 participants were assigned to the standard-regimen group and 132 were assigned to the shorter-regimen. Thirty-three (12.55%) of 264 participants were excluded from the modified intention-to-treat analysis. As a result, 231 participants were included in the modified intention-to-treat analysis (116 in the standard-regimen group and 115 in the shorter-regimen group).In the modified intention-to-treat population, unfavorable outcomes were reported in 19 (16.5%) of 115 participants for whom the outcome was assessable in the shorter-regimen group and 26 (22.4%) of 116 participants in the standard care group (risk difference 5.9 percentage points (97.5% CI − 5.8 to 17.5)). One death was reported in the standard-regimen group. The incidence of QTcF prolongation in the shorter-regimen group (22.6%, 26/115) was similar to the standard-regimen group (24.1%, 28/116).

Conclusions The 9-month, all-oral regimen is safe and efficacious for the treatment of pulmonary rifampicin/multidrug-resistant tuberculosis. The high incidence of QTc prolongation associated with the use of BDQ highlights the urgent need of routine electrocardiogram monitoring under treatment with BDQ-containing regimens in the Chinese population.

Keywords Multidrug-resistant, Tuberculosis, Efficacy, Safety, RCT trial

Background

Despite the continued decline in incidence over past decades, tuberculosis (TB) continues to exert a major public health concern worldwide, with an estimated 10.60 million incident TB cases and 1.3 million TB deaths in 2022 [1]. The emergence of drug-resistant TB, especially multidrug-resistant TB (MDR-TB, defined as resistance to at least the most effective anti-TB drugs, isoniazid and rifampicin), is especially alarming. In China, 501,261 participants with tuberculosis were notified in 2022. It is noteworthy that the treatment of MDR-TB patients required a prolonged duration of second-line drugs. Conventionally, the World Health Organization (WHO) endorsed an 8-month intensive phase and a total duration of ≥ 20 months of therapy for clinical management of MDR-TB patients; however, the results of a previous individual patient data meta-analysis including more than 9000 MDR-TB patients from 32 observational studies found that only 54% of them achieved successful outcomes [2]. Notably, it confirmed that treatment success was associated with the use of later-generation fluoroquinolones [3], emphasizing the clinical efficacy of newer agents in short-duration therapy. The lack of response to anti-TB treatment would facilitate the transmission of MDR-TB in the community. This global threat calls for the collaborative action to develop new drugs.

Shortening the treatment duration could make an important contribution to improving treatment adherence of MDR-TB patients. In a previous study conducted in Bangladesh, a 9-month fluoroquinolone-based regimen showed a relapse-free cure rate of 87.9% among 206 multidrug/rifampicin-resistant tuberculosis (MDR/RR-TB) patients. Subsequently, the replacement of injectables with bedaquiline (BDQ), an oral diarylquinoline, resulted in an excellent treatment response and was associated with a lower risk of death [4–7], which facilitate the use of WHO-endorsed 9-month, all-oral, BDQ-containing regimens in patients affected by MDR/RR-TB. The 9-month regimen is also currently being evaluated in cohort studies in high TB-burden countries. Given that the majority of studies were conducted in Africa, more evidence is required to recommend the regimen for widespread programmatic use in other countries.

China has a serious epidemic of drug-resistant tuberculosis, especially MDR-TB, associated with inadequate antibiotic treatment. With support from various agencies, the Chinese Food and Drug Administration (FDA) approved BDQ as part of therapeutic regimens for adults afflicted with MDR/RR-TB. In China, the treatment of MDR/RR-TB patients follows the recent WHO's guidelines and Chinese guidelines [7, 8]. For patients with fluoroquinolone-susceptible isolates, short treatment regimens (9–11 months) are endorsed, whereas the extended regimens (18–20 months) are used for patients with fluoroquinolone-resistant isolates. Due to the inaccessibility to BDQ, pretomanid, and linezolid (BPaL)/BPaL plus moxifloxacine (BPaLM) treatment regimen is not used in China. In view of the limited options for anti-TB drugs, a universal short-course regimen was urgently required for the clinical management of MDR/RR-TB patients in China. Therefore, we concurrently developed a prospective, observational study to assess clinical outcomes among patients receiving 9-month BDQ-containing regimens, aiming to provide valuable data on the use of this short-course regimen in this country.

Methods

Study design

The aim of this study was to compare, in a noninferiority design, the efficacy and safety of a 9-month regimen based on the WHO-recommended standard of regimen. 16 TB-specialized hospitals were included in the

present study, including Beijing Chest Hospital, Anhui Chest Hospital, Chengdu Public Health Clinical Center, Changsha Central Hospital, Wuhan Pulmonary Hospital, Kunming Third People's Hospital, Chongqing Public Health Medical Center, Fuzhou Pulmonary Hospital of Fujian, Hangzhou Red Cross Hospital, Shenyang Tenth People's Hospital, Tuberculosis Hospital of Jilin Province, The Forth People's Hospital of Taiyuan, Shaanxi Provincial Tuberculosis Prevention and Control Hospital, Henan Provincial Infectious Diseases Hospital, Hebei Chest Hospital, and Lanzhou Pulmonary Hospital. The eligibility criteria included (i) MDR-/RR-TB confirmed by drug susceptibility testing; (ii) adults aged 18–65 years; and (iii) patients who had no previous exposure to the second-line anti-TB therapy or had previous exposure to the second-line anti-TB therapy of less than 3 months. Reasons for exclusion included (i) patients with additional resistance to FQ by drug susceptibility testing; (ii) pregnant or breast-feeding; (iii) history of allergy to any agents or their derivatives in the regimens; (iv) QT interval of more than 450 ms; (v) a history of risk factors for prolonged QT interval; and (vi) concomitant serious illness.

Participants with pulmonary tuberculosis meeting the inclusion criteria were enrolled in study pilots. Eligible participants with MDR/RR-TB confirmed by phenotypic (Lowenstein-Jensen medium for isolation) or genotypic drug susceptibility testing (DST). This trial was approved by institutional review boards for all sites and was done in accordance with the ethical principles of the Declaration of Helsinki. All participants provided written informed consent before any trial-related procedures were initiated.

CProcedures

Participants were randomly assigned to treatment groups at enrolment. In the shorter-regimen group, BDQ, linezolid, levofloxacin, clofazimine, and cycloserine were administered for 9 months. The dose of each drug was as follows: BDQ initiated at a dose of 400 mg once a day for 2 weeks and reduced to 200 mg three times a week in the third week; linezolid (300–600 mg once a day); levofloxacin (400–600 mg once a day); clofazimine (100 mg once a day); cycloserine (500–1000 mg twice or three times a day). In the standard-regimen group, patients received 18-month anti-TB therapy, comprising 6 months of BDQ, linezolid, levofloxacin, clofazimine, and cycloserine plus 12 months of levofloxacin, and any three potentially effective drug from clofazimine, cycloserine pyrazinamide, ethambutol and protionamide, as listed in Additional file 1: Table. S1.

Study assessment

After inclusion, clinical visits were guaranteed at baseline, weeks 2 and 4, and every 4 weeks since week 4. At each visit, two specimens were collected from each patient for acid-fast bacilli microscopy and liquid culture using the BACTEC MGIT 960 (MGIT; BD Microbiology Systems. Drug susceptibility testing on Mycobacterium tuberculosis (MTB) isolates was done for first-line and second-line drugs according to the WHO guidelines in each pilot. For phenotypic DST, the pilot laboratories used their routine methods to determine the drug susceptibilities of MTB isolates to four first-line anti-TB drugs (rifampicin, isoniazid, ethambutol, and streptomycin) and four second-line anti-TB drugs (ofloxacin, levofloxacin, kanamycin and amikacin), including the proportion method on Löwenstein-Jensen (L-J) medium, the BACTEC MGIT 960 system, and the microtiter plate method on Middlebrook 7H9 medium (BASO Company, Zhuhai, China). The susceptibilities of MTB isolates to BDQ, linezolid, and clofazimine were not detected due to the lack of commercial kits. For genotypic DST, Xpert MTB/RIF assay (Cepheid, Sunnyvale, CA, USA) and MeltPro assay (Zeesan Biotecheh, Xiamen, China) were performed to determine rifampicin or/and isoniazid resistance following the manufacturer's instruction. If the patients were diagnosed as MDR/RR-TB, the MeltPro assay was subsequently used to detect fluoroquinolone susceptibility. All laboratories used standardized protocols and passed the external quality assurance held by the Innovation Alliance on Tuberculosis Diagnosis and Treatment since 2018. In addition, safety assessments included physical examinations, routine blood counts, biochemical tests, urinalysis, and an electrocardiogram. We employed the AIDS Clinical Trials Group Table for Grading Adverse Experiences to grade the severity of adverse events.

Outcome

The primary efficacy endpoint was the treatment success rate at the end of the treatment course. The treatment outcome definitions followed WHO guidelines [4]. Participants who were "cured" and "treatment completed" were defined as treatment success. Unfavorable outcomes included treatment failure (including adverse events), death, and loss to follow-up. Participants who withdrew from the trial because of pregnancy were also excluded from the primary outcome analysis. Cure was defined by at least two consecutive negative cultures with an interval of at least 28 days, and no positive culture during the last 12 months of treatment. Treatment completion was defined as the patients with culture conversion through the end of treatment but who did not meet all the criteria of cure. Treatment success included cure and treatment

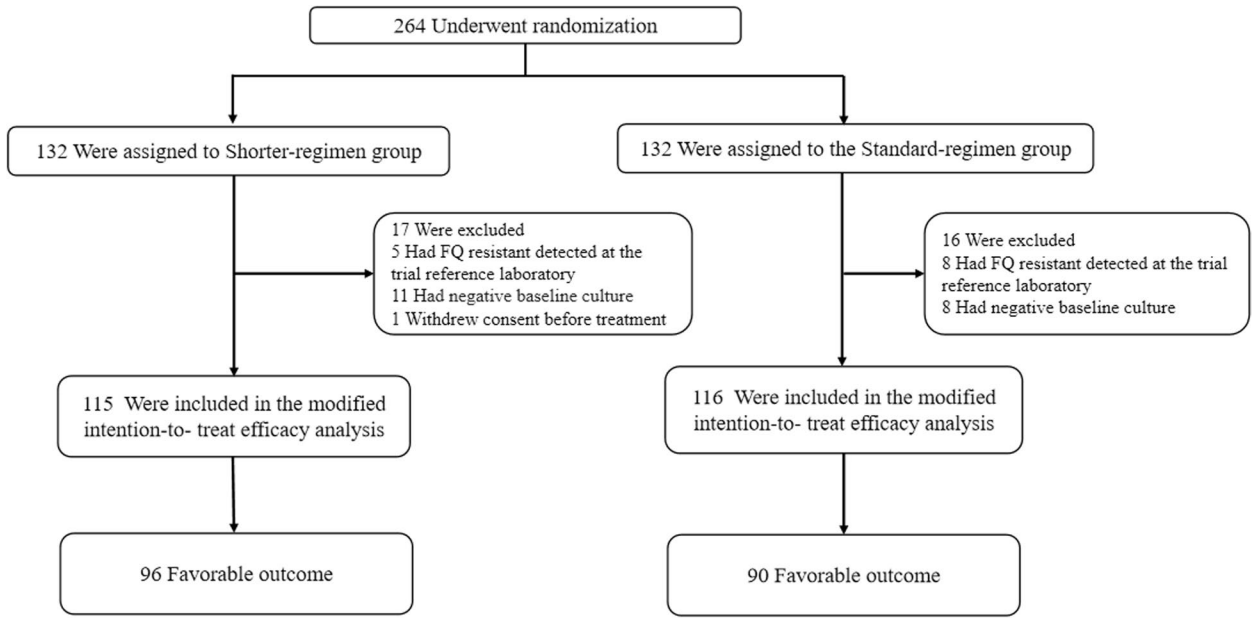

Fig. 1 Participant enrollment

completion. The secondary efficacy endpoint were permanent discontinuation because of an adverse drug reaction and any grade 3 or 4 drug-related adverse effects.

Sample size calculation

The sample size calculation is based on a non-inferiority comparison for a composite unfavorable outcome at the end of treatment (assumed to be 80% in the long regimen and 85% in the short regimen). Using $\alpha = 0.025$ for significance (one-sided test), power of 80%, and a less than 10% difference in treatment success rates as a non-inferiority margin, 101 participants per group would be required. Additionally, expecting a rate of fluoroquinolone-sensitive multidrug-resistant tuberculosis among participants of 20% and anticipating, the final number of participants was calculated as 127 participants per group (254 in total).

Statistical analysis

The original data of treatment records were entered using the Electronic Data Capture System (https://itrial.chinaiatb.org/user/login). The results of this trial for efficacy outcomes were analyzed according to both modified intention-to-treat approaches with a primary consideration for the modified intention-to-treat results. The modified intention-to-treat group included participants who were randomly assigned after satisfying the eligibility criteria and who received a predefined regimen at least one time. The non-inferiority of the shorter regimen was confirmed if the lower limit of the 97.5% one-sided CI of the difference of treatment success rate at the end of treatment after the initiation of treatment between two groups (the short-regimen group minus the control group) was greater than the non-inferiority margin of −10%. All analyses were performed using the R software package (version 4.3.2). This study was registered with www.chictr.org.cn, ChiCTR2000029012.

Results

Between Jan 1, 2020, and Dec 31, 2023, the patients were diagnosed with multidrug-resistant tuberculosis or rifampicin-resistant tuberculosis in the 16 participating hospitals (Fig. 1). A total of 271 patients with multi-drug-resistant tuberculosis were successfully screened for participation in this study. However, 7 patients declined to sign the informed consent form, resulting in 264 being screened and randomly assigned. 132 of 264 participants were assigned to the standard-regimen group and 132 were assigned to the shorter-regimen group. Thirty-three (12.55%) of 264 participants were excluded from the modified intention-to-treat analysis. The most common reasons for the exclusion were negative baseline culture (19 participants) and fluoroquinolone resistance (13 participants). As a result, 231 participants were included in the modified intention-to-treat analysis (116 in the standard-regimen group and 115 in the shorter-regimen group), Among the 231 participants included in the modified intention-to-treat analysis, 149 (64.5%) were men, and the mean age was 37.9 years (Table 1). One hundred eleven (48.1%) of 231 participants had

histories of previous tuberculosis, and 17 (7.4%) had diabetes. Pulmonary cavities were present for 104 (45.0%) of 231 participants at the baseline visit. Among the 231 participants included in the modified intention-to-treat analysis, favorable outcome was reported in 90 (77.6%) of 116 participants in the standard-regimen group and 96 (83.5%) of 115 participants in the shorter-regimen group (Table 2). The between-group difference in the treatment success rate at the end of treatment was 5.9% (97.5% one-sided CI − 5.8% to 17.5). The most common reasons for unfavorable outcomes were adverse events (12 in the standard-regimen group and 9 in the shorter-regimen group; Table 2) and default (11 in the standard-regimen group and 7 in the shorter-regimen group). The proportion of participants who experienced adverse events that were possibly, probably, or related to the study drugs did not differ between the control group (81 (69.8%) of 116 participants) and the shorter-regimen group (71 (61.7%) of 115 participants).

A total of 322 adverse events were recorded among 231 patients, with 157 occurring in the short-term treatment group and 165 in the standard treatment group. The most prevalent adverse reactions centered around QT interval prolongation, Hematologic, and hepatic disorder (Additional file 2: Table. S2). The proportions of participants who experienced grade 3 or more adverse events, serious adverse events, or death also did not differ between the groups (Table 3). In one (0.86%) of 116 participants in the standard-regimen group, the cause of death was shortness of breath. None died in the shorter-regimen group. The most common grade 3 or more adverse events were the QTcF prolongation (28 in the standard-regimen group and 26 in the shorter-regimen group) and hematologic events (7 in the control group and 5 in the shorter-regimen group; Table 3).

Table 1 Baseline characteristics of the participants in the population

Characteristic	Shorter-regimen group (*N* = 115)	Standard-regimen group (*N* = 116)	Total (*N* = 231)
Male sex—no. (%)	67 (58.3)	82 (70.7)	149 (64.5)
Age year—mean ± SD	37.1 ± 12.6	38.7 ± 12.6	37.9 ± 12.6
Age—no. (%)			
< 40	77 (67.0)	66 (56.9)	143 (61.9)
40–59	28 (24.3)	42 (36.2)	70 (30.3)
≥ 60	10 (8.7)	8 (6.9)	18 (7.8)
BMI, kg/m^2—mean ± SD	21.0 ± 3.0	21.2 ± 3.1	21.1 ± 3.1
Low BMI—no. (%)	27 (23.5)	23 (19.8)	50 (21.6)
Previous treatment for tuberculosis no. (%)	48 (41.7)	63 (54.3)	111 (48.1)
Diabetes no. (%)	8 (7.0)	9 (7.8)	17 (7.4)
Pulmonary cavities no. (%)			
Present	54 (47.0)	50 (43.1)	104 (45.0)
Absent	61 (53.0)	66 (56.9)	127 (55.0)
QTcF interval mean ± SD	404.4 ± 22.0	408.6 ± 23.3	406.5 ± 23.2
QTcF interval—no. (%)			
< 400 ms	50 (43.5)	47 (40.5)	97 (42.0)
400–449 ms	65 (56.5)	69 (59.5)	134 (58.0)

Discussion

We firstly reported a clinical trial of treatment outcomes for MDR/RR-TB patients who were treated with 9-month regimens in China. Our results demonstrate

Table 2 Primary outcome (treatment success rate) by treatment group in the modified intention-to-treat analyses

Variable	Modified intention-to-treat population		
	Shorter-regimen group	Standard-regimen group	Total
Disposition of the participants			
Underwent randomization—no	132	132	264
Were included in primary outcome analysis—no	115	116	231
Outcome			
Attained favorable outcome—no. (%)	96 (83.5)	90 (77.6)	186 (80.5)
Difference versus the control group (97.5% one-sided CI)	5.9 (− 5.8–17.5)[a]	1 (ref)	
Had an unfavorable outcome—no. (%)	19 (16.5)	26 (22.4)	45 (19.5)
Death	0 (0.0)	1 (0.9)	1 (0.4)
Early discontinuation			
Adherence issues	7 (6.1)	11 (9.5)	18 (7.8)
Adverse event	9 (7.8)	12 (10.3)	21 (9.1)
Withdrew consent during treatment	3 (2.6)	2 (1.7)	5 (2.2)

[a] 97.5% one-sided CI for non-inferiority test

Table 3 Summary of safety outcome

Outcome	Shorter-regimen group (*N* = 115)	Standard-regimen group (*N* = 116)	Total (*N* = 231)
Grade 3 to 5 adverse event—no.(%)	40 (34.8)	49 (42.2)	89 (38.5)
Serious adverse event—no.(%)	3 (2.6)	8 (6.9)	11 (4.8)
Death—no.(%)	0 (0.0)	1 (0.9)	1 (0.4)
Related to tuberculosis	0 (0.0)	0 (0.0)	0 (0.0)
Other or uncertain	0 (0.0)	1 (0.9)	1 (0.4)
Grade 3 to 5 adverse events according to the three most common—no. (%)			
QT prolongation	26 (22.6)	28 (24.1)	54 (23.4)
Hematologic	5 (4.3)	7 (6.0)	12 (5.2)
Hepatic disorder	2 (1.7)	7 (6.0)	9 (3.9)

The primary safety outcome in the trial was a grade 3 to 5 adverse event at any point during the treatment

that an oral 9-month regimen is non-inferior in efficacy to the 18-month control regimen in participants with MDR/RR-TB. 96 (83.5%) of patients achieved favorable outcomes by the completion of 9-month therapy compared with 90 (77.6%) in the control group. In recent years, a series of clinical trials have been conducted to assess the efficacy of BDQ-containing regimens, yielding a pooled treatment success rate of 74.7% [9]. Our results are comparable to those in studies [10, 11], in which approximately 80% of MDR/RR-TB patients were successfully treated with BDQ-containing regimens, whereas our success rate was significantly higher than the other trials (58%) [12]. In another previous trial by our group assessing outcomes of MDR-TB patients receiving 9-month clofazimine-containing regimens, only 70% of MDR-TB patients had a favorable outcome [13]. This great difference in clinical efficacy is undoubtedly attributed to the excellent bactericidal activity of BDQ. In addition to BDQ, the usage of linezolid may also contribute to improved outcomes in our cohort. In line with our hypothesis, a previous clinical trial evaluating linezolid-containing regimens for pre-XDR-TB patients demonstrated that 79% of patients experienced favorable outcomes [14], which was higher than that in the MDR-TB cohort treated with clofazimine-containing regimens. Taken together, these data emphasize that the future use of BDQ and linezolid as part of an all-oral regimen may preserve good overall treatment outcomes. Recently, the NIX-TB trial reported favorable outcomes in 90% of MDR-TB patients not responding to therapy using an all-oral 6-month regimen of BPaL regimen [11]. Comparable favorable outcomes (88%) were also noted in MDR-TB patients prescribed the BPaLM regimen, which was slightly higher than our report. This difference may be attributed to the addition of pretomanid in the therapy regimens [15].

Despite yielding comparable clinical efficacy, the drug safety associated with the prolonged use of BDQ is another major concern that should be taken into consideration. Fortunately, the prolonged use of BDQ under programmatic conditions seems safe, and the majority of QTc prolongation was noted within 24 weeks, of which the extension of QTc associated with BDQ peaked between weeks 8 and 12 of treatment. Our findings are in line with pooled data from 5 cohorts of patients treated with BDQ, which indicates an absence of effect of exposure to BDQ for > 6 months on QTc prolongation [16]. In a prospective cohort study in China, the prolonged use of BDQ for 9 months did not yield a statistical increase in the incidence of QTc prolongation among MDR/RR-TB patients [17]. Evidence from a cohort of people infected with pre-XDR also suggests that extension of BDQ use was associated with culture conversion in populations who had delayed culture conversion, whereas the safety parameters were comparable to those who received standardized 24 weeks of BDQ [18]. Therefore, the study results add to the existing data, supporting the efficacy and safety of BDQ for up to 9 months of use.

Although no significant increase in adverse events associated with the extended use of BDQ was recorded in our analysis, the QTc prolongation, the primary safety concern with BDQ, remains the most frequently observed adverse event in our Chinese cohort. Our findings are similar to those observed in other large multicenter studies in China and Korea [19, 20], whereas skin adverse events and neurological abnormalities were the most common from studies in India and the USA [21, 22]. These findings may reflect racial diversity in the vulnerability to BDQ and other anti-TB drugs. Further genetic studies are warranted to identify major susceptibility genes and the mechanism involved in QTc prolongation associated with BDQ use in the Chinese population, to assist in the development of better methods for targeted early interventions.

Another important finding of this report is that the overall mortality for patients on BDQ was 0.4%, as compared with previously reported mortality rates ranging from 6.8% in France to 20% in South Africa [23, 24]. Our lower mortality rate may reflect the low proportion of TB patients coinfected with HIV in this study, since HIV infection is the major predictor of TB patient mortality [25]. In addition, BDQ pilot studies completed to date were conducted in tertiary care hospitals that lacked resources and clinicians to monitor and support BDQ patients during outpatient follow-up. Such support

would improve patient access to better medical care for preventing or responding to multiple adverse events, leading to the improved survival observed in this study.

Despite evidence of the efficacy of BDQ when used in the Chinese population, we must acknowledge that the treatment interruption due to adverse events was the major cause of poor clinical outcomes of MDR-TB patients in this analysis. Conversely, nearly all patients receiving BDQ therapy achieved culture conversion irrespective of the presence of treatment interruption. This provides several important hints for the clinical management of MDR-TB. On the one hand, the significant decrease in bacterial burden was attributed to the promising bactericidal efficacy of BDQ against tubercle bacilli, and also reduce the risk of transmission of this deadly infection within the community. On the other hand, more attention should be paid to conducting routine electrocardiogram monitoring under treatment with BDQ-containing anti-TB regimens.

We also acknowledged several obvious limitations to the present study. First, WHO has endorsed the programmatic use of a 6-month BDQ, pretomanid, and linezolid-based regimen in individuals with MDR/RR-TB as a shorter alternative to a 9-month regimen [7]. However, pretomanid is still unapproved by the Chinese Food and Drug Administration; therefore, we were unable to validate the therapy efficacy of this 6-month regimen in MDR/RR-TB patients. Second, the present study conducted a 12-month follow-up to monitor the recurrence of drug-resistant TB patients. However, the lack of long-term follow-up after the termination of treatment may underestimate the true relapse rate in this population. Third, considering that the regimen modification of the short-course regimen was the use of BDQ for an additional 3 months, more attention was paid to monitor the efficacy and tolerability of the prolonged BDQ use rather than other effective drugs. Fourth, despite yielding favorable outcomes, an unignored question is raised as to whether the prolonged terminal elimination half-life of BDQ may lead to the development of drug resistance given the absence of any efficacious active agents by the end of 9-month therapy. Monitoring longitudinally the in vitro antimicrobial susceptibility among relapse cases is urgently required to interpret it.

Conclusions

Our data demonstrate that all oral 9-month regimens are non-inferior in efficacy to the 18-month control regimen in participants with MDR/RR-TB. The high incidence of QTc prolongation associated with the use of BDQ highlights the urgent need for routine electrocardiogram monitoring under treatment with BDQ-containing regimens in the Chinese population.

Abbreviations

BDQ	Bedaquiline
DST	Drug susceptibility testing
FDA	Food and Drug Administration
L-J	Löwenstein-Jensen
MDR	Multidrug-resistant
MTB	Mycobacterium tuberculosis
RR-TB	Rifampicin-resistant tuberculosis
TB	Tuberculosis
WHO	World Health Organization

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-024-03633-3.

Additional file 1: Table. S1 Dosage and usage of anti-tuberculosis drugs in the Regimen.

Additional file 2: Table. S2: Safety analysis.

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Authors' contributions

MG and YP conceived and designed the study. YS, YP, JD, GW, HW, LM, LX, ZK, XW, RL, HC, HL, QG, LN, ZL, XH, ML, MJ, XC, QC, WC, YL1, YM, YT, YC, SG, QZ and YL2 collected clinical information and samples. WS, FM, FL and YP analysed and interpreted the data. YS, WS, YP, JD, GW, HW wrote the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Beijing Chest Hospital, Capital Medical University, ID: (2019) Clinical Review (86).

Consent for publication

None declared.

Competing interests

The authors declare no competing interests.

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