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ORIGINAL RESEARCH

Safety and Tolerability of Contezolid Versus Linezolid for Short-Term Treatment of Rifampicin-Resistant Pulmonary Tuberculosis: A Randomized Controlled Study

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Purpose: Linezolid is a core drug used to treat rifampicin-resistant tuberculosis (RR-TB) and multidrug-resistant tuberculosis (MDR-TB). However, adverse events (AEs) have limited its clinical application. Safer alternatives to linezolid are needed to address the safety concerns.

Patients and Methods: A total of 27 patients with RR-TB (including MDR-TB) were randomly assigned to receive either contezolid (n=14) or linezolid (n=13) in combination with standardized background anti-TB regimens, that is, linezolid-bedaquiline (pyrazinamide)-levofloxacin (moxifloxacin)-cycloserine-clofazimine or contezolid-bedaquiline (pyrazinamide)-levofloxacin (moxifloxacin)-cycloserine-clofazimine. The dosage was 600 mg q12h for linezolid, and 800 mg q12h for contezolid. AE data were collected during the 2-month treatment period to analyze the characteristics, severity, onset time, duration, drug relatedness, management, and outcome of the adverse drug reactions.

Results: The median (range) age of contezolid- and linezolid-treated patients was 40.9 (26–65) and 36.7 (18–65) years, respectively. The incidence of AEs was 14.3% (2/14) in contezolid-treated patients and 92.3% (12/13) in linezolid group. All drug-related AEs in contezolid group were gastrointestinal reactions (nausea and vomiting one case each). No peripheral neuropathy or myelosuppression AEs were observed. The AEs in linezolid group included anemia (30.8%, 4/13), peripheral neuropathy (53.8%, 7/13), and gastrointestinal reactions (23.1%, 3/13). Dose reduction or discontinuation was required for linezolid in 84.6% (11/13) of patients. The anti-TB efficacy of contezolid and linezolid was comparable in terms of sputum culture conversion rate and imaging-confirmed lesion absorption rate after treatment for 2 months.

Conclusion: Contezolid may be a safer alternative to linezolid based on AE incidence in the treatment of multidrug-resistant tuberculosis for two months.

Clinical Trial Registration: This study was registered at https://www.chictr.org.cn (identifier: ChiCTR2300074234).

Keywords: contezolid, linezolid, safety, multidrug-resistant tuberculosis, peripheral neuropathy, anemia

Introduction

Tuberculosis (TB) is a chronic respiratory infectious disease that seriously threatens human health and the quality of life. According to the Global Tuberculosis Report 2023, approximately 10 million new TB cases were reported worldwide, of which 748000 were in China, making China a country with high TB and rifampicin-resistant tuberculosis (RR-TB) /multidrug-resistant TB (MDR-TB) burden.[1] Long-term treatment is usually required to manage TB patients, which makes them prone to treatment noncompliance and drug resistance. The introduction of new drugs, such as bedaquiline

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and delamanid, into clinical practice has contributed to the control of MDR-TB,[2] but more innovative drugs are still required to further improve the management of MDR-TB.

Linezolid is the first generation of oxazolidinone drug and is mainly used for gram-positive bacterial infections. Linezolid also has good efficacy in the treatment of MDR-TB.[3] Therefore, both the WHO Consolidated Guidelines on Drug-resistant Tuberculosis Treatment and Chinese expert consensus on the all-oral treatment of drug-resistant pulmonary tuberculosis have adopted linezolid as a core drug for the treatment of drug-resistant TB since 2019.[4,5] In particular, the Nix-TB study published in the New England Journal of Medicine in 2020 confirmed that the treatment success rate of the new drug regimen, including linezolid, pretomanid, and bedaquiline, reached 90% for the treatment of MDR-TB.[6] However, a high percentage of patients had adverse events (AEs) related to linezolid in the Nix-TB trial. Myelosuppression (anemia, leukopenia, and thrombocytopenia) was reported in 49% of the patients, and peripheral neuropathy was reported in 81% of the patients receiving linezolid-containing anti-TB regimen; only 15% of the patients completed the 26-week course of linezolid without interruption or a reduction of 1200 mg/day,[6] which severely limits the long-term use of linezolid. About 29% of patients discontinued linezolid due to adverse drug reactions in real-world settings. Linezolid-related myelosuppression frequently occurs within the first 2 months of treatment in most cases. Findings from programmatic experience in field conditions have also demonstrated similar results. A recent study conducted under programmatic conditions focused on a WHO-endorsed bedaquiline-containing all-oral regimen for MDR-TB treatment. Linezolid, serving as a key component of this regimen, was associated with adverse drug reactions in 42.45% of patients. Among these, 93.33% experienced peripheral neuropathy - an agonizing adverse reaction for people with MDR-TB in field conditions, often compromising their treatment outcomes.[7] Therefore, there is an urgent need to develop safer drugs and regimens to address MDR-TB.

Contezolid is a new generation of oxazolidinone antibiotics originally developed and approved in China.[8] Contezolid has shown good in vitro activity against *M. tuberculosis* strains (MIC_{50}/MIC_{90} = 0.5/1 mg/L).[9,10] Additionally, the good antimicrobial activity is maintained and the safety profile is optimized for contezolid by improving its structure-activity relationship. Short-term treatment clinical trials also suggest a better safety profile than that observed with linezolid.[11] However, safety information on clinical use of contezolid is still limited. We conducted a randomized, active-controlled trial of contezolid vs linezolid in combination with other anti-TB drugs for the treatment of drug-resistant TB to characterize the safety and tolerability of contezolid treatment for two months.

Patients and Methods

Study Design

This study was designed as a randomized, active-controlled trial in patients with RR-TB who were treated at the Tuberculosis Department of Beijing Chest Hospital Affiliated to Capital Medical University from August 1, 2023, to March 31, 2024. The study protocol and informed consent form were reviewed and approved by the Institutional Review Board for Human Investigation of Beijing Chest Hospital of Capital Medical University (approval no. YJS-2021-022). This study was registered at https://www.chictr.org.cn (identifier: ChiCTR2300074234) on August 1, 2023. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Patients

All participants voluntarily participated in this study. Enrolled patients were randomized using a randomization table based on block randomization after signing an informed consent form. The inclusion criteria included 18–65 (inclusive) years of age and diagnosis of RR-TB based on molecular biology methods, and admission to the hospital to receive initial anti-TB treatment or retreatment. The patient did not show fluoroquinolone resistance based on a line probe assay (LPA). An acid-fast bacteria (AFB) smear was positive (at least 1+) in sputum samples. Patients receiving treatment with other anti-TB drugs were willing to discontinue all anti-TB drugs and agreed to undergo a 7-day wash-out period. The patients were closely monitored to address the concerns regarding potential disease progression or worsening symptoms during the 7-day wash-out.

Subjects were excluded if they met any of the following criteria: (1) A history of allergy to the study drug or any of its components, or an effective treatment plan was not available; (2) complicated with severe comorbidities such as respiratory failure, cardiac insufficiency, or liver and kidney dysfunction (serum creatinine level, ALT and/or AST levels higher than three times the upper limit of normal [ULN]); (3) significant electrocardiogram abnormalities (QT interval prolongation > 430 ms for males, or > 450 ms for females); (4) severe cardiovascular or cerebrovascular diseases; (5) pregnant or lactating women; (6) participation in any other clinical trial within three months before initiation of this study; and (7) positive for HIV antibody or AIDS patients.

Anti-TB Regimens

Patients were randomly assigned to receive linezolid or contezolid in combination with other background anti-TB drugs, such as linezolid-bedaquiline (pyrazinamide)-levofloxacin (moxifloxacin)-cycloserine-clofazimine or contezolid-bedaquiline (pyrazinamide)-levofloxacin (moxifloxacin)-cycloserine-clofazimine. Anti-TB drugs were purchased from the same manufacturer and provided in the same dosage form and strength. The specific dosage was linezolid 600 mg q12h, contezolid 800 mg q12h, bedaquiline 400 mg/d for 2 weeks, adjusted to 200 mg three times per week, moxifloxacin 400 mg/d, levofloxacin 600 mg/d, cycloserine 250 mg bid, and clofazimine 100 mg/d.

Safety Assessment

All patients were closely monitored during the treatment period for the occurrence and progression of AEs, including clinical symptoms, vital signs, electrocardiogram findings, and laboratory test abnormalities. Hematology tests, urinalysis, and biochemical assays, including liver and kidney function tests, were performed for all patients every two weeks. The clinical characteristics, severity, onset time, duration, management, and outcome of AEs were documented and drug relatedness was evaluated. The risk factors for AEs were also analyzed. The frequency of dose reduction or discontinuation owing to AEs was also evaluated.

All AEs were coded and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.[12] Grade 1 AE was defined as mild, asymptomatic, or mild symptoms; clinical or diagnostic observations only; and intervention not required. Grade 2 AE was defined as moderate, minimal, local, or noninvasive intervention indicated and limiting age-appropriate instrumental activities of daily living. Grade 3 AE was defined as severe or medically significant but not immediately life-threatening, hospitalization or prolongation of hospitalization indicated, disabling, and limiting self-care activities of daily living. Grade 4 AE was defined as life-threatening consequences and urgent intervention was indicated. Grade 5 AE was defined as death related to AE.

Anti-TB Efficacy Monitoring

Anti-TB efficacy was analyzed in terms of microbiology diagnostic testing and imaging examinations. All patients underwent monthly sputum smear tests for AFB and sputum cultures for *Mycobacterium tuberculosis*. Chest CT scan was scheduled for all the patients at the end of the second month of treatment.

Statistical Analysis

Sample size calculation was based on superiority study design. The patients were randomly assigned to contezolid or linezolid group at a ratio of 1:1. Contezolid is expected to be safer than linezolid. The sample size was calculated using the following formula:

Set $\alpha = 0.05$, $1- \beta = 0.80$,

$$n = \frac{(Z_{1-\alpha} + Z_{1-\beta})^2 \left[p_1(1-p_1) + p_2(1-p_2)\right]}{(\varepsilon - \delta)^2}$$

In our experience, the expected incidence of AEs was 2.5% in contezolid group and 49% in linezolid group, based on the safety profiles of such regimens. At least 10 evaluable cases were required in contezolid and linezolid groups to test the superiority of contezolid, assuming two-sided $\alpha = 0.05$, $\beta = 0.2$, superiority threshold $\delta = 15\%$, and a 20% dropout rate.

Statistical analyses were conducted using SPSS 24.0 software. Data are expressed as mean ± standard deviation (SD) and compared between groups using Student's *t* test or Wilcoxon's signed rank test. The incidence of AEs was compared between groups using Chi-square test or Mehta's modification of Fisher's exact test.

Results

Baseline Patient Characteristics

A total of 35 smear-positive RR-TB patients were screened, and 29 patients were enrolled and randomized to receive treatment at Beijing Chest Hospital from August 1, 2023 to March 31, 2024. Of the 15 patients treated with contezolid, one patient was excluded from the analysis due to rifampicin-susceptible TB. One of the 14 patients in linezolid group was excluded from the analysis because of withdrawal of informed consent. Finally, 14 patients in contezolid group and 13 patients in linezolid group completed the study and were included in the safety analysis (Figure 1).

The median (range) age was 40.9 (26–65) years for the patients in contezolid group, and 36.7 (18–64) years for the patients in linezolid group. The baseline characteristics of the two groups of patients were comparable (Table 1).

AE Profiles of Contezolid Versus Linezolid

Overall, the incidence of treatment-emergent AEs (TEAEs) was 14.3% (2/14) in contezolid-treated patients and 92.3% (12/13) in linezolid group ($P < 0.05$). The most common TEAEs were peripheral neuropathy, myelosuppression, and gastrointestinal reactions in linezolid group, but only gastrointestinal reactions in contezolid-treated patients (Table 2).

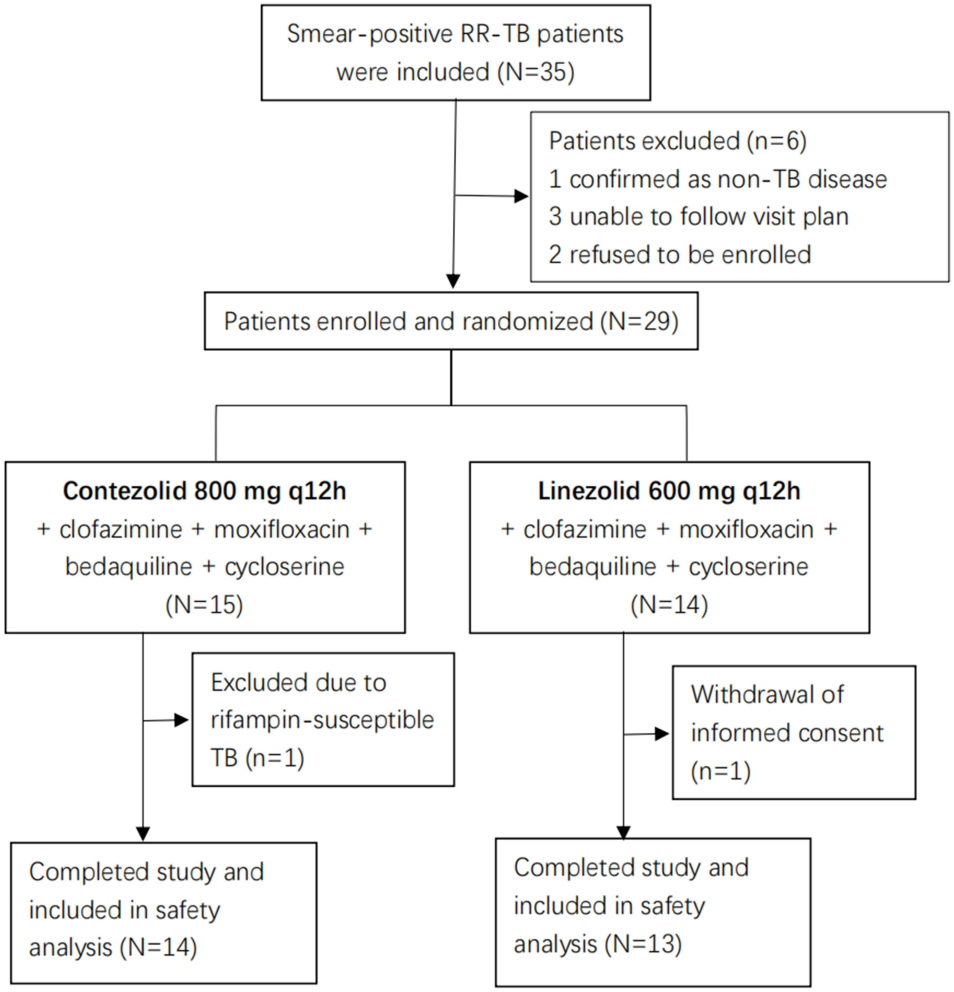

Figure 1 Disposition of the patients in the study.
Abbreviation: RR-TB, rifampicin-resistant tuberculosis.

Table 1 Demographic and Clinical Characteristics of Rifampicin-Resistant Tuberculosis Patients Receiving Contezolid or Linezolid for Anti-TB Treatment

Characteristic	Contezolid (n =14)	Linezolid (n =13)	*P* value
Age (years)	40.9 (26–65)	36.7 (18–64)	0.99
Male	11 (78.6)	8 (61.5)	0.33
Body mass index (kg/m^2)	18.9 (12.9–25.4)	21.2 (12.5–26.8)	0.19
History of anti-TB treatment			
Treatment-naïve	4 (28.6)	3 (23.1)	0.73
Prior anti-TB treatment	10 (71.4)	10 (76.9)	
Prior anti-TB treatment duration (month)	23.5 (1–55)	24.96 (1–66)	0.19
Comorbidity			
Diabetes mellitus	3 (21.4)	2 (23.1)	0.69
Liver disease	2 (14.3)	1 (7.7)	
Chronic obstructive pulmonary disease	2 (14.3)	1 (7.7)	
Cardiovascular disease	1 (7.1)	0	
TB duration before randomization (years)			
≤ 1	4 (28.6)	3 (23.1)	0.73
>1 to 3	2 (14.3)	1 (7.7)	
> 3	8 (57.1)	9 (69.2)	
Resistance to anti-TB drugs			
Isoniazid	14 (100.0)	13 (100.0)	
Rifampicin	14 (100.0)	13 (100.0)	
Ethambutol	11 (78.6)	10 (77.0)	0.93
Ofloxacin	0	0	
Amikacin	5 (35.7)	7 (53.8)	0.35
Background anti-TB drugs			
Bedaquiline	13 (92.9)	13 (100.0)	0.33
Levofloxacin or moxifloxacin	14 (100.0)	13 (100.0)	
Cycloserine	14 (100.0)	13 (100.0)	
Pyrazinamide	1 (7.1)	0	
Clofazimine	14 (100.0)	13 (100.0)	

Notes: Data are presented as number (%) or mean (range) unless otherwise specified.
Abbreviation: TB, tuberculosis.

Table 2 Treatment-Emergent Adverse Events of Contezolid and Linezolid During Anti-TB Treatment for 2 months

Treatment-Emergent Adverse Event	No. of Patients (%)		
	Contezolid (n = 14)	Linezolid (n = 13)	*P* value
Anemia			
Grade 1	0	0	
Grade 2 or higher	0	4 (30.8)	0.023
Peripheral neuropathy	0		
Grade 1	0	0	
Grade 2 or higher	0	7 (53.8)	0.002
Gastrointestinal reaction			
Grade 2	2 (14.3)	3 (23.1)	0.56

Patients in contezolid group did not experience any AEs related to bone marrow suppression (anemia, neutropenia, or thrombocytopenia) during the 2-month treatment period. AEs related to bone marrow suppression (anemia) were observed in 4 patients in linezolid group (30.8%), all of which were Grade 2 or higher (hemoglobin levels reduced from 132 to 48 g/L, 112 to 86 g/L, 142 to 59 g/L, and 128 to 89 g/L, respectively). Specifically, 2 cases (15.3%) of Grade

Table 3 Anti-Tuberculosis Effect of Contezolid-Containing Versus Linezolid-Containing Regimens for Rifampicin-Resistant Tuberculosis Patients

Anti-TB Effect	No. of Patients (%)		*P* value
	Contezolid (n = 14)	Linezolid (n = 13)	
Time to sputum culture conversion			
1 month	7/14 (50.0)	7/13 (53.8)	0.82
2 month	13/14 (92.9)	12/13 (92.3)	0.95
Time to imaging-confirmed lesion absorption			
2 month	12/14 (85.7)	11/13 (84.6)	0.94

2 anemia completely resolved after linezolid dose reduction to 600 mg/day. One case of Grade 3 anemia occurred in a patient after linezolid treatment for one month. The patient discontinued linezolid and received blood transfusion. The remaining one case of Grade 4 anemia (hemoglobin level reduced from 132 g/L to 48 g/L) developed two months after linezolid treatment. The patient was managed with blood transfusion and permanent discontinuation of linezolid.

Peripheral neuropathy was not observed in any patient who received contezolid. Peripheral neuropathy (numbness and/or tingling in the limbs) was observed in 7 patients in the linezolid group (53.8%). Most of these cases (6/7) were Grade 2 AEs and the remaining one case was Grade 3. Two of these patients discontinued linezolid treatment due to concurrent Grade 4 and Grade 3 anemia, respectively. The peripheral neuropathy of these two patients was also resolved after discontinuation of linezolid. The peripheral neuropathy AE in three patients were not relieved, even after linezolid dose was reduced to 600 mg qd. Linezolid dose was reduced to 600 mg/day in one patient because of gastrointestinal reactions after treatment for 20 days. One month later, this patient experienced finger numbness. The symptoms did not resolve during treatment at this dose. One patient (7.7%) developed Grade 3 AE one and half months after linezolid treatment. The symptoms were partially resolved after permanent discontinuation of linezolid.

Two patients (14.3%) in contezolid treatment group developed Grade 2 gastrointestinal AEs. All symptoms were resolved completely after the dose was reduced to 400 mg q12h. Three patients (23.1%) in linezolid group experienced Grade 2 gastrointestinal AEs. All symptoms were resolved completely after the linezolid dose was reduced to 600 mg/day.

In summary, contezolid showed significantly lower incidence rates than linezolid for myelosuppression and peripheral neuropathy but not for gastrointestinal AEs. Furthermore, dose reduction or discontinuation owing to AEs was observed for linezolid in most patients (84.6%, 11/13).

Sputum Smear Conversion After 2-month Treatment

Both contezolid-containing and linezolid-containing anti-TB regimens showed good clinical efficacy. Overall, the sputum negative conversion rate was 92.9% (13/14) in contezolid group and 92.3% (12/13) in linezolid group. The imaging-confirmed lesion absorption rate was 85.7% (12/14) in contezolid group and 84.6% (11/13) in linezolid group. The clinical efficacy was similar between contezolid-containing and linezolid-containing regimens (Table 3).

Discussion

Contezolid is an innovative drug of a new generation of oxazolidinone antibiotics. It is derived from structural modification of linezolid to form a non-coplanar structure between the B ring and the A and C rings, which makes the structure-activity relationship of contezolid more favorable in terms of safety and efficacy. Structural modification enables contezolid with enhanced binding to bacterial target and so reduced risk of drug resistance, leading to more efficient antimicrobial activity.[13] The optimized structure of contezolid is associated with lower somatic and mitochondrial permeability, and thus, the normal function of mitochondria is not damaged, which may effectively reduce the side effects of bone marrow suppression. The National Medical Products Administration of China approved contezolid in 2021 for the treatment of infections caused by susceptible pathogens after pivotal Phase III clinical trials in China provided favorable and supporting data.[14–17]

Shoen et al demonstrated that contezolid was similar to linezolid in the in vitro and in vivo anti-TB activities in mouse infection models against drug-sensitive and drug-resistant *M. tuberculosis*.[9] However, the safety and efficacy of contezolid treatment for MDR-TB patients have not yet been evaluated in China at present time. The Nix-TB trial targeting MDR-TB has shown that most of the adverse reactions of linezolid occur after treatment for approximately 8 weeks.[18] Therefore, linezolid was used as the control group in this study to monitor the occurrence of any AEs during the 2-month anti-TB treatment with contezolid- or linezolid-containing regimens.

In this study, during the 2-month anti-TB treatment period, TEAE was reported in 12 of 13 subjects receiving linezolid treatment (92.3%). All AEs were considered to be related to linezolid treatment. Eleven of the 12 patients underwent dose reduction or discontinuation of linezolid owing to adverse drug reactions. Only one patient continued to complete 2-month treatment with linezolid at a dose of 600 mg q12h. Linezolid-related AEs included anemia, peripheral neuropathy, and gastrointestinal reactions. All AEs occurred 1–2 months after the initiation of linezolid treatment. In contrast, AE was reported in 14.3% (2/14) of the patients receiving contezolid. All AEs were gastrointestinal reactions, one case each of nausea and vomiting. Both AEs were related to contezolid and occurred within one month after the initiation of contezolid treatment. The symptoms were resolved after reducing the contezolid dose to 400 mg q12h. Contezolid was associated with a significantly lower incidence of bone marrow suppression and peripheral neuropathy AEs compared with linezolid. Our data support the good safety of contezolid in the treatment of patients with TB. These findings are consistent with those of previous reports on contezolid regimens for the treatment of TB patients.[19–23]

The results of this study indicated that the sputum negative conversion rate (92.9%) after treatment with contezolid-containing regimens for two months was comparable to that in patients treated with linezolid-containing regimens (92.3%). Contezolid-containing anti-TB regimens and linezolid-containing regimens showed similar clinical efficacy in terms of sputum negative conversion rate and imaging-confirmed pulmonary lesion absorption rate.

This study has some limitations, such as the small sample size, single-center design, relatively short treatment duration of anti-TB regimens, potential selection bias, and the effect of background anti-TB drugs. Especially, the dosage of linezolid used in this study (600 mg q12h) exceeds the current WHO recommended dose of 600 mg/day for MDR-TB treatment. Following the Nix-TB trial, the ZeNix trial demonstrated that reducing both the dose and duration of linezolid to 600 mg/day for 26 weeks was associated with statistically significant treatment success. The higher dose used in this study may have contributed to the elevated adverse drug reaction rate (92.3%) observed in the linezolid group.[24,25] These limitations could impact the generalizability of the study conclusion. Therefore, adequate-designed multi-center clinical trials are needed to confirm the utility of contezolid versus linezolid for the long-term treatment of MDR-TB.

Conclusion

Preliminary data in this randomized controlled study further support that contezolid has a safer safety profile than linezolid in combination with other background anti-TB drugs for a 2-month treatment of patients with MDR-TB. Both drugs showed similar anti-TB efficacy. However, the long-term safety beyond the 2-month window is unclear yet. Contezolid is safer based on the body of evidence available even though small sample size in this study may weaken the robustness and generalizability of the conclusion. Adequate-designed multicenter long-term clinical trials are required to confirm our findings.

Data Sharing Statement

The original data have been included in this article. Further inquiries can be directed to the corresponding author.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of Beijing Chest Hospital of Capital Medical University (approval no. YJS-2021-022). Informed consent was obtained from all participants.

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Disclosure

The authors declared no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

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