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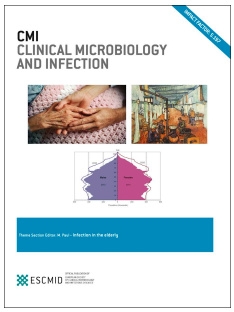

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Clofazimine improves clinical outcomes in multidrug-resistant tuberculosis: a randomized controlled trial

Running Title: Treatment of MDR-TB with CFZ in China

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Abstract

Objectives: We carried out a randomised multicenter study in China to investigate whether the clofazimine (CFZ) would improve the efficacy of the standardised regimen in multidrug-resistant tuberculosis (MDR-TB) patients.

Methods: MDR-TB patients managed in 17 TB specialised hospitals in China between September 2009 and September 2011 were randomly assigned to the treatment groups at enrolment. In the intervention group 100 mg CFZ per day was added to the standardised regimen. The primary outcome was the proportion of patients with successful outcomes.

Results: From the 156 patients that were screened, 74 were assigned to the control group and 66 to the CFZ group. Of the 66 cases analysed for clinical outcome in the CFZ group, 36 patients were cured, and 7 completed treatment, yielding a favourable outcome rate of 65.1%. The proportion of patients with favourable outcomes among control regimen was 47.3% (35/74), which was significantly lower than that in the CFZ group (*P*=0.034, RR=0.661, 95%CI: 0.243-0.949).

Conclusions: The addition of clofazimine to the standard regimen improved the treatment of MDR-TB.

Keywords: multidrug-resistant tuberculosis; clofazimine; treatment; China; adverse events

Introduction

Multidrug-resistant tuberculosis (MDR-TB), defined as resistance to at least rifampicin (RIF) and isoniazid (INH), is a major public health threat that jeopardizes the progress in TB control worldwide [1, 2]. According to an estimation by the World Health Organization (WHO), in 2016 490,000 MDR-TB cases emerged globally, and of these 240,000 died as a result of MDR/RIF-resistant (RR)-TB [1]. Among new and previously treated TB cases, the proportions of MDR/RR-TB cases were 4.1% (95% confidence interval [CI]: 2.8%-5.3%) and 19% (95% CI: 9.8%-27%), respectively [1].

China has the third largest number of TB patients worldwide [1]. Despite the steady decline in the overall TB notification rate [3], the MDR-TB epidemic emerges as the greatest challenge facing TB control in this country [4], with estimated rates of 7.1% and 24% among new and previously treated TB cases, respectively [1]. More importantly, only a small proportion of affected individuals are actually diagnosed and can access proper treatment in China[5], contributing to increasing treatment failures and ongoing transmission within communities.

Treatment of patients with MDR-TB is more complicated than those with drug-susceptible TB due to the limited efficacy of second-line drugs, an increased number of adverse events associated with the drugs, and the long duration of therapy [6, 7].The treatment outcome of MDR-TB is generally poor, and only 48% of MDR-TB cases worldwide achieve a favourable outcome [8]. We need novel TB drugs that are

active against drug-resistant bacteria [7]. Given the costly and lengthy process of new drug discovery, repurposing existing drugs has emerged as an alternative strategy to provide accessible anti-TB drugs for patients infected with MDR-TB [7]. Among these candidate drugs, clofazimine (CFZ), a member of riminophenazine antibiotic class, probably improves outcomes of MDR-TB and is classified by WHO as a group C drug [9]. In 2010, a clinical trial conducted in Bangladesh revealed that a 9-month treatment regimen including CFZ could cure nearly 90% of patients with MDR-TB [10], indicating the potential role of CFZ for improving the treatment outcome of this serious form of TB. The finding was subsequently confirmed by several observational studies from other researchers [11, 12].

To provide further evidence on the use of CFZ in the treatment of MDR-TB cases, we carried out a randomised multicentre study in China focused on the potential of adding CFZ to the standardised regimen. The adverse events associated with CFZ were analysed to evaluate its safety in Chinese population.

Methods

Ethic statement

The study was approved by the Medical Research Ethics Committee, Beijing Chest Hospital, Capital Medical University (2009-28). Eligible participants infected with MDR-TB were required to provide written informed consent. Patients could withdraw from the trial at their own request. This study was registered after its completion with the Chinese Clinical Trial Registry (ChiCTR, www.chictr.org.cn) under identifier ChiCTR1800014800.

Study design

A multicentre, randomized trial was conducted among MDR-TB patients who registered in 17 TB specialized hospital between September 2009 and September 2011.The study consisted of 3 phases: (1) screening; (2) treatment of intensive phase (6 months); (3) treatment of consolidation phase (18 months).

Participants were randomized (1:1) to control or experimental group at enrolment. Randomization was conducted by using a computer-generated random-number table, statistical staff generated the random allocation sequence. Clinical doctors enrolled participants. All participants and clinicians involving in this study were unblinded to the treatment allocation. Patients in the control group received amikacin (capreomycin), levofloxacin, pyrazinamide, ethambutol, para-aminosalicylic acid (protionamide), and amoxicillin/clavulanate for 6 months; and then were subsequently administered a baseline regimen of levofloxacin, pyrazinamide, ethambutol, para-aminosalicylic acid (protionamide), and amoxicillin/clavulanate for 18 months. The dose of drugs was listed in Table S1. Patients in the CFZ group received 100 mg of CFZ per day in addition to the baseline regimen within the whole 24-month treatment period. Patients and clinicians were unblinded to the treatment received throughout the trial. At enrolment, data were collected on demographic and clinical characteristics, including age, sex, body mass index (BMI), anti-TB treatment duration, and co-morbidity. No changes were made to study methods after commencement of the trial.

Participants

Patients were recruited from 17 hospitals in China (Table S2). Eligible patients were at least 18 years of age, not pregnant, had sputum smear-positive pulmonary TB, and

had MDR-TB confirmed by conventional drug susceptibility testing. Reasons for exclusion included: (i) XDR-TB (MDR-TB strains with additional resistance to any fluoroquinolone and one injectable second-line drug); (ii) patients infected with non-tuberculous mycobacteria; (iii) severe comorbidity (Table S3); (iv) previous anti-tuberculosis treatment with clofazimine.

Assessment

Sputum smears and solid culture were performed monthly during 2-year study period. Drug susceptibility testing (DST) for four first-line anti-TB drugs (rifampicin, isoniazid, ethambutol, and streptomycin) and 6 second-line drugs (amikacin, capreomycin, ethionamide, para-aminosalicylic acid, ofloxacin, and levofloxacin) was performed using the proportional agar method on Löwenstein–Jensen (L-J) medium [14]. In addition, routine blood counts, biochemical tests, and urinalysis were assessed monthly to monitor the occurrence of adverse events. Skin discoloration was defined as the visible presence of reddish discoloration/pigmentation and ichthyotic changes of the skin. Hepatic damage was defined as the elevation of serum transaminases to at least three times the normal levels in the presence of gastrointestinal symptoms, or serum transaminases to at least five times the normal levels without symptoms. Renal damage was defined as the elevation of creatinine to at least 1.3 times the normal levels. Adverse events were graded according to an adaptation of the AIDS Clinical Trials Group Table for Grading Adverse Experiences [15]. Study regimen was temporarily discontinued for all patients with grade 3 or 4 adverse events, defined as serious adverse event.

The primary outcome was the proportion of patients with successful outcomes. The clinical outcomes were assessed by the local investigator without blinding. The

following treatment outcome definitions were adapted from WHO guidelines. Cure was defined by at least 3 consecutive negative cultures and no positive culture during the last 18 months of treatment. Treatment completion was defined by bacteriological conversion through the end of treatment but fewer than three consecutive negative culture. Death was defined as death for any reason during the course of MDR-TB treatment. Default was defined as treatment interruption for 2 or more consecutive months for any reason without medical approval. Treatment failure was defined as persistence of two or more positive cultures of the five cultures recorded in the final 12 months, persistence of one or more positive cultures of the final three months, or early treatment termination because of poor clinical or radiological response or adverse events. Successful outcome included cure and treatment completion, while adverse outcome included any death, default, and treatment failure [16]. There were no changes to trial outcomes after the trial commenced.

Sample size calculation

By reviewing previous studies [10, 13] , we estimated that the rates of patients with favourable outcomes at the end of treatment were 50% for the control group and 80% for the CFZ group. The sample size calculation determined that 51 subjects per treatment arm would provide a power of 80% to show the difference of the CFZ intervention to the control regimen, assuming a one-side type I error of 0.05. In addition, we estimated that 10% of the MDR patients in each study group would have XDR-TB and that 20% would be loss of follow-up or default. Hence, a sample of 65 subjects per arm was recruited during the study period.

Data analysis

The original data of treatment records were entered into a computer by a double data entry method using Epidata-Entry (http://www.epidata.dk/). We used SPSS 20.0 for analysis. We used Chi-square analysis to investigate the clinical outcomes, occurrence of adverse events of patients randomly assigned in the control and experimental groups. Student's t-test were conducted for continuous variables. In addition, univariate analysis and multivariate analysis were conducted to assess the potential risk factors associated with a poor clinical outcome, respectively. The Kaplan–Meier curve was generated to describe and compare the overall rate of bacteriological conversion over a two-year period. The difference was declared as significant if the *P* value was less than 0.05.

Results

Participants

Between September 2009 and September 2011, a total of 156 patients were screened, and 140 underwent randomisation in this study, where 74 and 66 patients were assigned to the control and CFZ groups, respectively. All recruited patients had a negative test result for the human immunodeficiency virus (HIV). The trial ended on the date of the final follow-up of the patient who was last randomised. During the study period, 39 patients discontinued their treatment (Fig. 1). The principal reason for discontinued treatment was a failure to follow-up (*n*=19), followed by treatment modification due to self-reported intolerable adverse events (*n*=8) and early treatment termination due to serious adverse events (*n*=8). The demographic and clinical characteristics of the patients were similar in the two study groups. Approximate 95% (132/140) of patients had a previous tuberculosis treatment history, with a median

previous treatment duration of 18 months and 24 months for control and CFZ group, respectively. One tenth of patients had comorbidity (Table 1).

Treatment efficacy

Of the 66 cases analysed for clinical outcome in the CFZ group, 36 patients were cured, and 7 achieved treatment completion who had documented bacteriological conversion through the end of treatment but fewer than three consecutive negative culture, yielding a favourable outcome rate of 65.1%. Out of 23 patients meeting the criteria of adverse outcome, 4 died, 10 defaulted, and 9 failed the treatment in the CFZ group. The proportion of patients with favourable outcomes among those receiving the control regimen was 47.3% (35/74, 26 cured and 9 treatment completion), which was significantly lower than that in the CFZ group (P=0.034, RR=0.661, 95%CI: 0.243-0.949) (Table 2).

Of the 140 study patients, 101 with culture results were included in Kaplan–Meier analyses. As shown in Fig. 2, MDR patients in the CFZ group had conversion to culture-negative status sooner than those in the control group by using mycobacterial culture with L-J medium (P=0.031) (Fig. 2).

Adverse events

A total of 44 adverse events occurred in 44 patients in this study, including 14 in the control group and 30 in the CFZ group. There was a significant difference in the incidence of adverse events between the two groups (P=0.001). Data on the adverse events is detailed in Table 3.

Nine patients (9/44, 20.5%) had serious adverse events, including 3 in the control and 6 in the CFZ groups, respectively (Table 3 & Table S4). Anti-TB treatment in the control grouped was stopped and not restarted due to a gastrointestinal reaction and an occurrence of anaemia. Also, the adverse effect of the patient suffering gastrointestinal reaction was resolved by stopping treatment, and the initial regimen was reused after one-month of interruption. In the CFZ group, 6 different reactions (two of hepatic damage, two of gastrointestinal reaction, one of renal damage, and one of leukocytopenia) caused serious adverse events; thus, treatments were discontinued and not restarted.

Discussion

In this study involving 140 MDR-TB patients, we found that the addition of clofazimine to the treatment regimen significantly improved outcomes among MDR-TB patients. Similar results were observed in the prospective cohort studies from Norway (86.9%) [17] and Bangladesh (87.1%) [10] and were higher than those from Brazil (65.2%) [18], Shanghai (62.9%) [12] and Peru (59.9%) [19]. The discrepancy across various reports may be related to the study's population and treatment regimen [18]. The individuals enrolled in this study had MDR-TB instead of XDR-TB, which may explain the greater treatment success rate in our study. This difference may also be due to longer treatment duration of clofazimine during the whole 24-month treatment period. There is evidence that an extended duration of treatment is associated with favourable outcomes [20, 21]. In addition to the significant benefit effect on the clinical outcomes, the cost of CFZ is more affordable compared with other second-line drugs. This further highlights its use as an important candidate drug against MDR-TB, especially in low-resource settings.

Despite exhibiting promising efficacy against MDR-TB, several major concerns regarding the application of CFZ should be taken into consideration in clinical practice. For instance, cross-resistance to bedaquiline and clofazimine has been noted by some researchers [24, 25], where prior exposure to clofazimine could cause resistance to both drugs due to sharing the same efflux pump system [25]. The abuse of clofazimine may facilitate the emergence of bedaquiline resistance, thereby resulting in the rapid loss of this new drug. Therefore, the evaluation of *in vitro* CFZ resistance is essential before its clinical application. Furthermore, the critical concentration of CFZ has not yet to be established by WHO [14]; thus, there is an urgent need to develop the accurate and reproducible DST method for CFZ.

The beneficial effect of clofazimine was tempered, as expected, by the high rates of drug-related adverse events. While skin discoloration is the most common adverse event associated with the administration of CFZ [12], previous studies demonstrated that lowering the dose of clofazimine to 100 mg every other day could help manage the side effects of skin discoloration [12]. However, the effect of decreased exposure to CFZ on clinical outcomes remains unknown. Moreover, hepatic damage (according to our definition) was observed more often patients assigned to the CFZ group compared with patients in the control group, though the difference did not reach statistical significance due to the small sample size. Our findings indicate that routine determination of hepatic enzyme levels should be performed in patients administered the CFZ-containing regimen to avoid the occurrence of severe hepatic injury.

Our study has several limitations. First, we limited our analysis to the primary outcome of treatment success rate at the end of the treatment course, while the long-term effect of CFZ on relapse among this cohort of MDR-TB cases was not evaluated. Second, due to lack of a reliable DST method for the detection of CFZ resistance, we could not assess the correlation of *in vitro* DST results of CFZ with clinical response to treatment. Likewise, the acquired resistance following exposure to CFZ was not collected in this clinical trial. Third, all patients enrolled in this study had MDR-TB, which means that it was not possible to determine whether CFZ exhibits promising efficacy for patients with XDR-TB. Fourth, although great efforts were focused on patient follow-up, 19 out of 140 study patients failed to show for follow-up visits, which increases the risk of statistical bias. Despite these limitations, our findings echo the increasing evidence that the addition of CFZ is more effective in achieving favourable outcomes for individuals infected with MDR-TB.

In conclusion, our data demonstrate that the addition of clofazimine to the routine treatment regimen exhibits promising efficacy for the treatment of MDR-TB. The high incidences of CFZ-related skin discoloration and hepatic dysfunction highlight the need to conduct routine examination to avoid the occurrence of serious adverse events.

Conflicts of interest None declared.

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Author contributions NC and SX designed the study. HD, XC, ZL, YP, WJ, TX participated in data analysis. HD, XC, ZL, PY and WJ wrote the manuscript. PL, TW, CC, JS, ZQ, HY, CQ, CL, YX, WC, ZY, ZL, GC, SW, YL, LC, MZ, QW, JW, YD and JW participated in data collection and patients' follow-up. All authors approved the final version of the paper.

Access to to the full data: Tao Xu

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Figure Legends

Figure 1 Enrolment and follow-up of the study patients.

Figure 2 Time to sputum-culture conversation in the control and experimental groups

Table 1 Demographic and clinical characteristics of MDR-TB patients enrolled in this study

Characteristic	Experimental group (*N*=66)	Control group (*N*=74)
Age--years		
Mean	36.8	36.4
Range	19~65	18~61
Male sex--no.(%)	44(66.7)	44(59.5)
Body mass index--kg/m^2		
Mean	19.9	19.8
Range	15.0~27.3	14.0~25.7
Treatment history		
New cases--no.(%)	3 (4.5)	5 (6.8)
Previously treated--no.(%)	63 (95.5)	69 (93.2)
Treatment duration of previously treated patients--months		
Mean	29.9	23.0
Range	1~140	1~120
Co-morbidity--no.(%)		
Diabetes	2 (3.0)	2 (2.7)
COPD[a]	2 (3.0)	2 (2.7)
Cardiopathy	1 (1.5)	1 (1.4)

[a]COPD, chronic obstructive pulmonary disease.

Table 2 Treatment outcomes of patients with multidrug-resistant tuberculosis

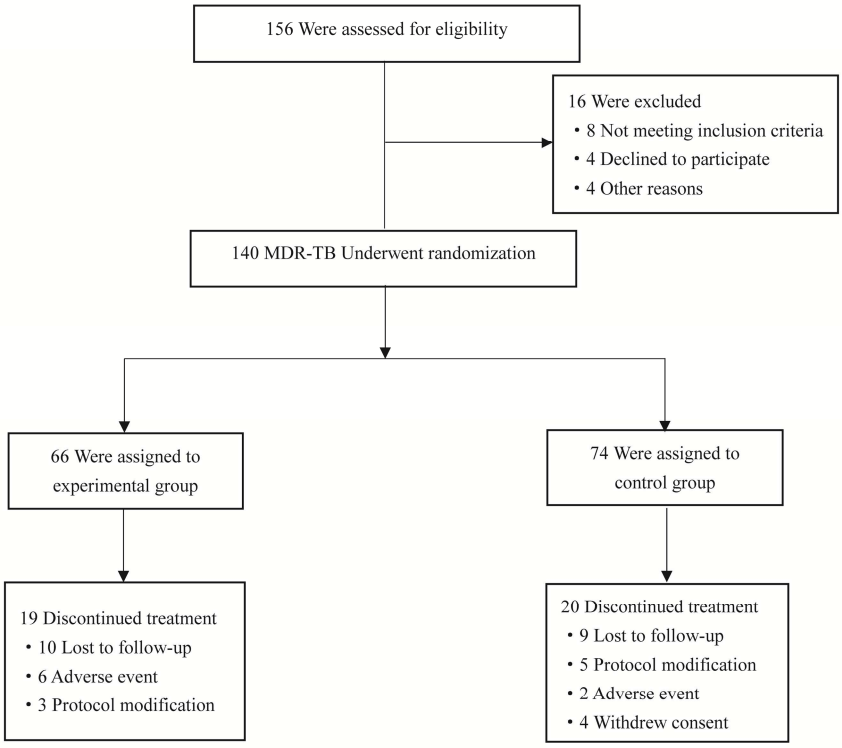
Treatment outcome	No. of patients (%)		*P* value
	Experimental group (*N*=66)	Control group (*N*=74)	
Favorable outcome			0.034
Cure	36 (54.5)	26 (35.1)	
Treatment completion	7 (10.6)	9 (12.2)	
Adverse outcome			
Treatment failure	9 (13.6)	24 (32.4)	
Death	4 (6.1)	2 (2.7)	
Default[a]	10 (15.2)	13 (17.6)	

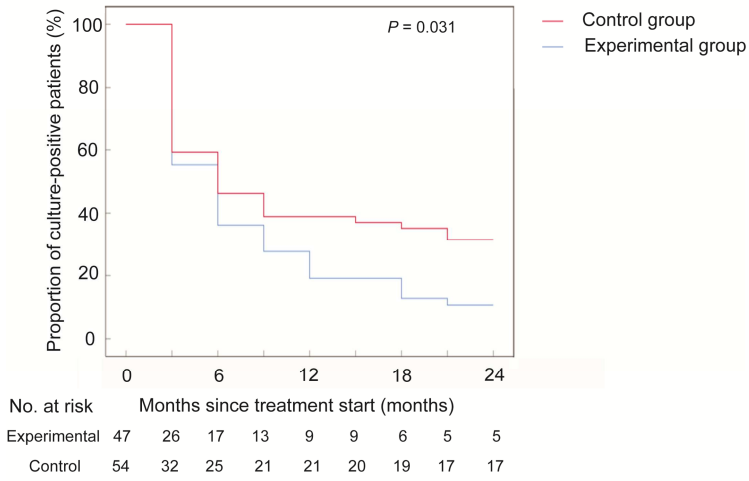
[a]Four patients withdrawing consent due to in control group are classified into default category.

Table 3 Adverse events during 24-month treatment among patients enrolled in this study

Adverse event	No. of patients (%)		*P* value
	Experimental group (*N*=66)	Control group (*N*=74)	
Skin discoloration	8 (12.1)	0 (0.0)	0.002
Hepatic damage	8 (12.1)	2 (2.7)	0.046
Hyperuricemia	3 (4.5)	2 (2.7)	0.667
Gastrointestinal reaction	3 (4.5)	5 (6.8)	0.722
Others[a]	8(12.1)	5 (6.8)	0.275

[a]Other adverse events include renal damage, rash, leukocytopenia, anemia, arthralgia and hearing loss.





No. at risk									
Experimental	47	26	17	13	9	9	6	5	5
Control	54	32	25	21	21	20	19	17	17