Clofazimine for the Treatment of Multidrug-Resistant Tuberculosis: Prospective, Multicenter, Randomized Controlled Study in China

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Background. Clofazimine (Cfz) has shown activity against Mycobacterium tuberculosis, including multidrug-resistant (MDR) strains in vitro and in animal studies. Here we evaluate the clinical efficacy and tolerability of using Cfz to treat MDR tuberculosis in China.

Methods. We enrolled 105 patients who had sputum culture–positive MDR tuberculosis in 6 major tuberculosis specialty hospitals in China. Patients were randomly assigned to either the Cfz therapy group (n = 53) or control group (n = 52). Patients in the 2 groups were given 21 months of individual-based chemotherapy regimens based on medication history and drug susceptibility test results. The Cfz therapy group regimens incorporated 100 mg of Cfz once daily for 21 months.

Results. Three patients in each group discontinued therapy because of side effects or other reasons. Sputum culture conversion to negative was earlier in patients who received Cfz compared with controls (P = .042 by log-rank test). Chest computed tomography showed cavitary changes in 46 patients in the Cfz therapy group and 45 in the control group. Cavity closure was earlier in patient who received Cfz compared with controls (P = .047 by log-rank test). The treatment success rate in the Cfz group was 73.6%, higher than that in control group (53.8%; P = .035). Side effects in skin only occurred in the Cfz group. The rates of skin discoloration and ichthyosis were 94.3% and 47.2%, respectively.

Conclusions. Using Cfz to treat MDR tuberculosis promotes cavity closure, accelerates sputum culture conversion, and improves treatment success rates.

Keywords. clofazimine; multidrug-resistant tuberculosis; efficacy; tolerability.

The increasing incidence of multidrug-resistant (MDR) tuberculosis, defined as resistance to at least isoniazid and rifampin, is a major concern for tuberculosis control programs worldwide [1, 2]. China is one of the 27 countries with the highest burden of MDR tuberculosis.

The prevalence of both tuberculosis and drug-resistant tuberculosis is very high [3, 4]. According to a national survey of drug-resistant tuberculosis in China, 5.7% of new cases and 25.6% of previously treated cases had MDR tuberculosis [5]. Effective treatment of MDR tuberculosis requires prolonged use of multiple second-line antituberculosis drugs, which are more expensive and toxic than first-line drugs, yet less efficacious [6].

Clofazimine (Cfz) is a fat-soluble riminophenazine dye used in the treatment of leprosy worldwide. Although it was first synthesized as an antituberculosis drug by Berry et al in 1954 and has activity against MDR tuberculosis strains in vitro and in vivo [7, 8], inconsistent results in animal models have hindered its use against tuberculosis [9, 10].
Potent activity against hypoxic, nonreplicating *Mycobacterium tuberculosis* led to suggestions that Cfz may have potential as a sterilizing drug [11]. The minimum inhibitory concentration of Cfz against *M. tuberculosis* ranged from 0.06 to 2.0 µg/mL, with a suggested susceptibility breakpoint of 1 µg/mL [7]. In mice, a 20 mg/kg daily dose gave mean plasma concentrations of 0.55 µg/mL at steady state, but concentrations in tissues such as liver and lung were much higher [7,12]. At this dose, Cfz monotherapy showed bactericidal activity [13]. Another study indicated that Cfz possesses significant bactericidal activity against *M. tuberculosis* persisters, both in vitro and in vivo, and there were no severe side effects even when administered at high doses and long treatment duration in mice [14]. Using a mouse model of MDR tuberculosis, Grosset et al found that compared to its Cfz-free counterpart, a Cfz-containing regimen was significantly more active in achieving culture conversion and preventing relapse [15]. Although the exact mechanisms of Cfz-mediated antimicrobial activity remain to be established, it has shown efficacy and low toxicity against drug-resistant tuberculosis strains in vivo including against MDR and extensively drug-resistant (XDR) strains [16]. XDR tuberculosis is defined as tuberculosis with resistance to at least isoniazid, rifampin, a fluoroquinolone, and 1 of 3 injectable second-line drugs (amikacin, kanamycin, or capreomycin).

Recently Cfz has been suggested by the World Health Organization (WHO) for use as a group 5 drug in the treatment of tuberculosis [17, 18]. A series of studies evaluated the efficacy, safety, and tolerability of the Cfz-containing regimens for treating MDR tuberculosis cases; however, these were restricted mainly to case reports, a retrospective analysis, and small case series [19–21]. Van Deun et al reported an effective treatment regimen that required a minimum of 9 months of treatment with gatifloxacin, Cfz, ethambutol, and pyrazinamide throughout the treatment period supplemented by prothionamide, kanamycin, and high-dose isoniazid during an intensive phase with a minimum duration of 4 months. It gave a relapse-free cure of 87.9% (95% confidence interval [CI], 82.7%–91.6%) among 206 patients [21]. Another study showed that an aggressive, comprehensive management program in which most patients (97.7%) received Cfz cured >60% of patients with XDR tuberculosis who had received numerous unsuccessful antituberculosis treatments [22]. In a systematic review, Gopal et al identified 9 observational studies and found that after treatment with Cfz, 65% (95% CI, 52%–79%) of those with MDR tuberculosis and 66% (95% CI, 42%–89%) of those with XDR tuberculosis experienced favorable treatment outcomes [23]. However, another meta-analysis suggested that Cfz might have only a limited role in the treatment of XDR tuberculosis or fluoroquinolone-resistant MDR tuberculosis treated with linezolid-containing regimens [24].

Thus, although Cfz is currently recommended for use in combination with other drugs in the second-line treatment of drug-resistant tuberculosis [17, 25], the available evidence is not clear-cut and clinical studies with Cfz in MDR tuberculosis, particularly prospective randomized clinical trials, are scarce. The aim of this study was to evaluate the clinical efficacy and tolerability of Cfz in treating patients with MDR tuberculosis at 6 large-scale tuberculosis specialty hospitals in China using a prospective, multicenter, randomized study.

**METHODS**

**Study Patients**

From August 2010 to November 2011, we enrolled all suitable patients aged 18–64 years, who were sputum culture positive with an MDR tuberculosis strain and had not had a satisfactory response to any available chemotherapeutic option during the previous ≥6 months. Exclusion criteria: (1) allergy to Cfz; (2) severe cardiovascular, liver, kidney, or blood system diseases or other serious illnesses; (3) psychiatric illness, regardless of severity; (4) pregnant or lactating women; (5) a positive test result for human immunodeficiency virus (HIV); (6) XDR tuberculosis. We excluded patients with a history of psychiatric illness whether the condition was stable or not, because there had been reports of suicide from depression caused by skin discoloration, which is an adverse effect of Cfz.

**Study Design**

This multicenter, prospective, randomized, controlled and open study was conducted in 6 large-scale tuberculosis specialty hospitals in China. The study was designed as a superiority test. Assuming a 48% treatment success rate under control MDR tuberculosis regimens and 78% success rate in a test group that included Cfz [17, 18], 52 patients were required per arm for discrimination at the 95% level. Patients were randomly assigned to either the Cfz therapy group or control group. Patients in the 2 groups were assigned to 21 months of individual-based chemotherapy. Directly observed therapy at least once per month throughout the treatment period supplemented by prothionamide, kanamycin, and high-dose isoniazid during an intensive phase.

**Exclusion Criteria**

1. Sputum smear positive for acid-fast bacilli
2. AMDR and extensively drug-resistant (XDR) tuberculosis
3. History of psychiatric illness
4. Pregnant or lactating women
5. Allergy to Cfz
6. History of suicide
7. Human immunodeficiency virus (HIV) positive
8. Other serious illnesses
9. History of psychiatric illness

**Study Patients**

The study was approved by the ethics committees of the 6 hospitals. Individual participants gave written informed consent before enrollment in the study. The trial was performed...
in accordance with the Good Clinical Practice guidelines, and was monitored by an independent data and safety monitoring committee. All the patients’ information was routinely collected and recorded by attending physicians.

**Study Procedures**

**Microbiological Assessments and Outcome Measures**

Morning sputum specimens were obtained at least once every month during the first 3 months, and after that at least once every 3 months during the treatment period. Sputum samples were routinely tested by smear fluorescence microscopy and by culture on Lowenstein–Jensen medium and in the Bectec MGIT 960 System (Becton Dickinson Diagnostic Systems, Sparks, Maryland). Drug susceptibility testing of positive cultures was performed by using the MGIT 960 System according to WHO guidelines [26]. All the tests were performed at the tuberculosis reference laboratory, and quality control was routinely performed.

Treatment outcomes were defined according to the WHO and International Union Against Tuberculosis and Lung Disease guidelines [17, 18, 27]. “Cured” was defined as a patient who had completed treatment according to program protocol and had been consistently culture negative (with at least 5 results) for the final 12 months of treatment for tuberculosis. “Completed treatment” was defined as a patient who had completed treatment according to program protocol but did not meet the definition for cure because of lack of bacteriological results. The “died” category included any patient who died for any reason during the course of tuberculosis treatment. “Treatment failure” included any patient for whom 2 or more of the 5 cultures recorded in the final 12 months of therapy were positive, or if any 1 of the final 3 cultures was positive. “Defaulter” was defined as a patient whose tuberculosis treatment was interrupted for ≥2 consecutive months for any reason. Additionally, cured and completed treatment categories were combined as “treatment success,” whereas others were combined as “poor treatment outcome.” Outcome was assigned for each patient at the time of completion of treatment. Relapse beyond the 21-month treatment period was not assessed.

**Imaging Evaluation**

Chest radiographs and computed tomography (CT) scans were obtained at least once every month during the first 3 months, and subsequently at least once every 3 months during the treatment period. All images were evaluated by 2 physicians and a radiologist, all of whom were highly experienced in identifying cavitation and cavitary collapse.

In this study, “cavity closure” was defined as cavity closed and remaining closed on the chest radiograph or CT scan. “Cavity closure rates” were calculated by dividing the number of patients who had cavity closure by the number of patients found to have cavitary lesions in each group.

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**Figure 1.** Enrollment, study-drug assignments, follow-up, and assessment of patients. Between August 2010 and November 2011, a total of 135 patients were assessed for eligibility and 105 underwent randomization. Fifty-three patients were included in the clofazimine (Cfz) therapy group and 52 in the control group. Three patients in the Cfz group and 3 patients in the control group discontinued because of adverse events.
Safety Assessments

Patients underwent monthly baseline and serial safety evaluations. Leukopenia was defined as white blood cell count $<4.0 \times 10^9$/L. Anemia was defined as hemoglobin $<9$ g/dL. Thrombocytopenia was defined as a platelet cell count $<100 \times 10^9$/L. Adverse events were recorded daily, and immediately reportable events and clinically significant abnormal laboratory results were evaluated as appropriate.

Statistical Analysis

All statistical analyses were performed using SPSS 14.0 software, version 14.0 (IBM SPSS, Chicago, Illinois). Comparisons of...
categorical variables were performed using the Pearson $\chi^2$ test or Fisher exact test to compare different groups. We used the log-rank test to compare the time to event Kaplan–Meier curves between patients in the study arm and control arm for both sputum culture conversion and cavity closure. Statistical significance was set at $P < .05$.

RESULTS

Study Patients

In total, 135 patients with MDR tuberculosis were assessed for eligibility. Thirty patients were not included in the study. Sixteen of them did not meet inclusion criteria (6 were excluded because of respiratory failure, 2 because of severe heart failure, 4 because of severe blood disease, and 4 because of severe liver injury); 14 declined to participate in the study. The remaining 105 patients were assigned treatment at random, with 53 assigned to the Cfz group and 52 to the control group (Figure 1). Mean age was 42 years, and no significant differences in demographic or baseline clinical characteristics between the 2 groups were identified (Table 1). All patients had received antituberculosis treatment for >6 months before their admission to the study. Results from a total of 572 sputum culture surveillance samples from the control group and 583 from the Cfz group were available for analysis. Three patients in the Cfz group and 3 patients in the control group discontinued therapy because of side effects.

Figure 2. Kaplan–Meier plots of the proportion of patients with positive sputum cultures and time to conversion. Sputum culture conversion to negative was earlier in patients who received clofazimine (Cfz) vs controls ($P = .042$ by log-rank test).

Figure 3. Kaplan–Meier plots of the proportion of patients having cavity and time to cavity closure. Cavity closure was earlier in patients who received clofazimine (Cfz) vs controls ($P = .047$ by log-rank test).

Table 2. Treatment Outcomes

<table>
<thead>
<tr>
<th>Treatment Outcomes</th>
<th>Cfz Group (n = 53), No. (%)</th>
<th>Control Group (n = 52), No. (%)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment success</td>
<td>39 (73.6)</td>
<td>28 (53.8)</td>
<td>.04</td>
</tr>
<tr>
<td>Cure</td>
<td>27 (50.9)</td>
<td>20 (38.5)</td>
<td>.20</td>
</tr>
<tr>
<td>Treatment completion</td>
<td>12 (22.6)</td>
<td>8 (15.4)</td>
<td>.34</td>
</tr>
<tr>
<td>Poor treatment outcomes</td>
<td>14 (26.4)</td>
<td>24 (46.2)</td>
<td>.04</td>
</tr>
<tr>
<td>Death</td>
<td>4 (7.5)</td>
<td>4 (7.7)</td>
<td>1</td>
</tr>
<tr>
<td>Failure</td>
<td>6 (11.3)</td>
<td>15 (28.8)</td>
<td>.03</td>
</tr>
<tr>
<td>Default</td>
<td>4 (7.5)</td>
<td>5 (9.6)</td>
<td>.74</td>
</tr>
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</table>

Abbreviation: Cfz, clofazimine.

Sputum Conversion

Sputum culture conversion to negative was earlier in patients who received Cfz compared with controls ($P = .042$ by log-rank test; Figure 2).

Cavity Closure

Chest CT showed cavitary changes in 46 patients in the Cfz therapy group, and in 45 of the control group. Cavity closure was earlier in patients who received Cfz compared with controls ($P = .047$ by log-rank test; Figure 3).

Treatment Outcomes

The treatment success rate in the Cfz group was 73.6%, higher than that in the control group (53.8%; $P = .035$; Table 2). Four patients in the Cfz group died, 1 from massive hemoptysis and
the others from respiratory failure. Meanwhile, 3 patients in the control group died of respiratory failure, and 1 patient died from massive hemoptysis.

**Adverse Events**

Side effects in skin only occurred in the Cfz group. The rates of skin discoloration and ichthyosis were 94.3% and 47.2%, respectively. Other side effects including liver injury and gastrointestinal adverse events were similar between the 2 groups (Table 3).

### DISCUSSION

Our results indicate efficacy of Cfz against MDR tuberculosis, as the proportion of sputum culture conversions in the Cfz group by culture was significantly higher than that in the control group. Cavity closure was earlier in patients who received Cfz compared with controls. Furthermore, the treatment success rate in the Cfz group was 73.6%, significantly higher than that in the control group (53.8%; \(P = .035\)). Our findings are consistent with the results of most studies [21–23], in showing that Cfz-containing regimens can have excellent efficacy in treating MDR tuberculosis [28].

The adverse effects of Cfz are reportedly seen primarily in the skin, eyes, and gastrointestinal tract [23, 24, 29]. Patients enrolled in the Cfz group had all adhered to the regimen and no patient discontinued therapy because of side effects from Cfz. The study thus indicated good tolerance and low toxicity of Cfz in these regimens. Gastrointestinal tract side effects reportedly may be mild to moderate (abdominal/epigastric pain, nausea, diarrhea, vomiting, gastrointestinal intolerance) or, less frequently, severe (splenic infarction, bowel obstruction, bleeding), and occasionally fatal [23, 24, 29], but were not evident in this study. The reddish-brown discoloration seen in skin and conjunctiva were gradually reversible on cessation of therapy, as reported [12]. However, Dey et al [30] noted that patients suffered from depression due to skin discoloration. Therefore, depending on the extent of the skin discoloration, it might be prudent to provide additional psychosocial support to patients undergoing Cfz treatment.

In previous studies, the dose and duration of Cfz treatment were diverse. Most researchers used 100 mg once daily [23, 24]. The minimum was 25 mg once daily and the maximum was 600 mg once daily [22], but there has been no comparison between different dosages. In early 2012, a WHO consultation group on the diagnostic definition and treatment options for so-called totally drug-resistant tuberculosis concluded, based on expert opinion, that Cfz (at a daily dose of 100 mg) and linezolid were likely to be the most effective in the group 5 category of second-line antituberculosis drugs for the treatment of XDR tuberculosis [31]. Administration by the oral route of 100, 300, or 400 mg Cfz daily to leprosy patients resulted in average plasma levels of 0.7, 1.0, and 1.41 mg/L, respectively [32]. In our study, Cfz was used at a dose of 100 mg daily and patients had good tolerance. However, the proper dosage of Cfz for treatment of MDR tuberculosis should be further investigated.

Our study has several limitations. First, it was limited by the relatively small number of patients with MDR tuberculosis, and impact on mortality was not assessed; larger studies with post-treatment follow-up are needed. Second, we did not undertake drug susceptibility testing for Cfz, so resistance of the bacteria to this drug may have contributed to treatment failure. Third, we did not compare different doses of Cfz to identify the optimum; better or worse results might be obtained with higher doses. Fourth, HIV-infected patients, a clinically important group, were excluded because they must be transferred to specialized hospitals in China and this might affect the generalizability of conclusions. Fifth, no placebo was given and there was no blinding of treatment. Because the Cfz treatment group received 1 more drug than the control group, we do not know if knowledge of the number of drugs taken influenced the results. Finally, the potential effect of different coadministration drugs, such as traditional Chinese medicines, to reduce liver toxicity was not studied.

Despite these limitations, to our knowledge, this may be the first prospective, multicenter, randomized study on efficacy, safety, and tolerability of Cfz for treating MDR tuberculosis. Our study demonstrated that Cfz-containing chemotherapy for treatment of MDR tuberculosis can promote cavity closure, accelerate sputum culture conversion, and improve treatment success rates. Cfz appears to be associated with a lower incidence of serious adverse effects compared with other second-line therapeutics, suggesting that Cfz could potentially be considered as

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<th>Table 3. Adverse Events</th>
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<tr>
<td><strong>Adverse Events</strong></td>
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<tr>
<td>Anemia</td>
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<tr>
<td>Thrombocytopenia</td>
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<tr>
<td>Leukopenia</td>
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<tr>
<td>Nausea/vomiting</td>
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<tr>
<td>Peripheral neuropathy</td>
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<td>Optic neuropathy</td>
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<tr>
<td>Liver injury</td>
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<tr>
<td>Tinnitus or hearing loss</td>
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<tr>
<td>Rash or pruritus</td>
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<tr>
<td>Arrhythmia</td>
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<tr>
<td>Hypokalemia</td>
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<tr>
<td>Pink to brownish-black discoloration of skin</td>
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<tr>
<td>Ichthyosis</td>
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Abbreviation: Cfz, clofazimine.
an additional therapeutic agent for the treatment of MDR tuberculosis. We suggest that Cfz be recommended for the treatment of MDR tuberculosis.

Notes

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Author contributions. S. T. designed the study. All authors participated in the implementation of the study and in data collection and management. S. T., L. Y., X. H., Y. L., and Z. Z. participated in data analysis. S. T., L. Y., X. H., and Y. L. wrote the initial draft of the report, and all authors revised and approved the final report.

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Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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