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Randomized control study of the use of faropenem for treating patients with pulmonary tuberculosis

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ABSTRACT

Objectives: Faropenem has antituberculosis activity *in vitro* but its utility in treating patients with tuberculosis (TB) is unclear.
Methods: We conducted an open-label, randomized trial in China, involving newly diagnosed, drug-susceptible pulmonary TB. The control group was treated with the standard 6-month regimen. The experimental group replaced ethambutol with faropenem for 2 months. The primary outcome was the treatment success rate after 6 months of treatment. Noninferiority was confirmed if the lower limit of a 95% one-sided confidence interval (CI) of the difference was greater than −10%.
Results: A total of 227 patients eligible for the study were enrolled in the trial group and the control group in a ratio of 1:1. Baseline characteristics of participants were similar in both groups. In the modified intention-to-treat population, 88.18% of patients in the faropenem group achieved treatment success, and 85.98% of those in the control group were successfully treated, with a difference of 2.2% (95% CI, −6.73-11.13). In the per-protocol population, treatment success was 96.04% in the faropenem group and 95.83% in the control group, with a difference of 2.1% (95% CI, −5.31-5.72). The faropenem group showed

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noninferiority to the control group in the 6-month treatment success rates. The faropenem group had significantly fewer adverse events (P <0.01).

Conclusions: Our study proved that oral faropenem regimen can be used for the treatment of TB, with fewer adverse events. (Chinese Clinical Trial Registry, ChiCTR1800015959).

Introduction

Tuberculosis (TB) remains a major global challenge to human health. In 2020, there were about 9.90 million new cases and approximately 1.3 million deaths from TB worldwide [1]. Despite the decline in incidence, the milestone of the End TB Strategy—a 35% reduction in TB incidence in 2020 compared to 2015—is still far from being met [1]. Most of the world's TB burden originates from drug-susceptible *Mycobacterium tuberculosis* (*Mtb*) strains. Few new classes of drugs have been approved for drug-susceptible TB since the introduction of the standard 6-month treatment regimen (isoniazid, rifampicin, pyrazinamide, and ethambutol) in the 1970s [2]. Despite the standard regimen achieving a treatment success rate of about 85% [1], the treatment is challenging mainly due to lengthy therapy, which can cause nonadherence and drug intolerance or toxicities. It has been shown that merely minor degrees of nonadherence or missed doses significantly increased the risk of unfavorable outcomes of TB treatment [3]. Several pivotal trials evaluating short-course regimens containing moxifloxacin, gatifloxacin, and linezolid all failed to meet the noninferiority margins compared with the standard first-line regimen in patients with pulmonary TB [4–6]. Developing a new drug from preclinical to clinical is costly, and TB drug development typically lacks the commercial interest from pharmaceutical industry compared with cancer therapies. Therefore, repositioning the existing clinically approved agents is a valid alternative in this context [7]. There is recent interest in the development of β-lactams, including carbapenems, by pharmaceutical companies and academic institutions as promising TB drugs [8]. Carbapenems have demonstrated potent anti-TB activity [9–11] and excellent tolerability in Multidrug-resistant Tuberculosis/Extensively Drug-resistant Tuberculosis treatment and are listed by the World Health Organization (WHO) as group C anti-TB agents [12,13]. Currently, injectable drugs are being replaced by oral agents in TB chemotherapy [13], and the repurposing of oral carbapenems can be considered in constructing effective alternative anti-TB regimens.

Faropenem is a new oral β-lactam antibiotic belonging to the penem group, which is structurally similar to the carbapenems but distinguished by a sulfur atom at position 1 instead of a carbon atom. The special chemical structure of faropenem provides its unique property in terms of broad antibacterial spectrum, β-lactamase stability, clinical safety, and good oral bioavailability [14–16]. Faropenem has recently been considered a potential anti-TB drug based on *in vitro* studies [17–19]. Faropenem has good activity in causing rapid cytolysis of *Mtb* and has synergy with rifampin *in vitro* [20–22]. Faropenem has been shown to have reasonable activity in a mouse study [23], but it has not been formally evaluated as a TB drug clinically. In this study, we conducted a randomized clinical trial to determine whether faropenem is an effective replacement for ethambutol in treating drug-susceptible TB.

Methods

Study design and participants

This multicenter, randomized, open-label trial was launched in 2018 to examine the effect of replacing ethambutol with an oral agent, faropenem, in the standard treatment regimen for drug-susceptible TB. A total of 13 hospitals in China participated in the study and all TB laboratories were licensed by and followed the standard procedures of the Tuberculosis Control Institute of the China Centre for Disease Control and Prevention. Patients aghed ≥18 years with Xpert MTB/RIF (Cepheid, Sunnyvale, CA, USA) from May 2018 to January 2020 were eligible for inclusion. Patients were excluded with concomitant nontuberculous mycobacteria (NTM) infection, extrapulmonary TB, history of active TB, baseline laboratory abnormalities (white blood cell <4.0 × 109, hemoglobin <120 g/l [for male]/< 110 g/l [for female], alanine transaminase >40 U/l, aspartate transaminase >40 U/l, serum creatinine >133 μmol/l), HIV infection, pregnant or lactating females, and patients who participated in any other clinical study. Given that the GeneXpert assay and the Biochip assay were been taken as the quick TB diagnosis tool and NTM differential diagnosis tool, the participants enrolled in the trial did not need to receive the standard treatment previously. All the participants were informed and signed written informed consent forms. The privacy rights of participants always be protected.

Randomization and treatment

Eligible participants were randomly assigned to the trial group and the control group in a ratio of 1:1. The statistics staff performed the randomization by using random number tables and allocated them through sealed envelopes to the study centers. Enrolled patients were sequentially assigned a sealed envelope that contained a unique study number and one of the corresponding treatment regimens. The control group involved 8 weeks of a once-daily dose of isoniazid (H), rifampicin (R), pyrazinamide (Z), and ethambutol (E), followed by 16 weeks of isoniazid and rifampicin (2 months HRZE/4 months HR) according to WHO [24]. For the faropenem group, ethambutol was replaced by faropenem (F ,200 mg, thrice a day) for 8 weeks, followed by 16 weeks of isoniazid and rifampicin (2 months HRZF/4 months HR). The details of dosing information are shown in Table 1.

Study procedures

All patients underwent baseline clinical examinations before treatment initiation including complete blood counts, liver function tests, renal function tests, chest computed tomography (CT), sputum specimen examination, and visual acuity test. Two sputum specimens were required for acid-fast bacilli (AFB), Xpert MTB/RIF

Table 1
Dosages of study medications adjusted by body weight.

Drug	Dose (<50 kg)	Dose (≥50 kg)
Isoniazid (H)	300 mg/d	300 mg/d
Rifampicin (R)	450 mg/d	600 mg/d
Pyrazinamide (Z)	1500 mg/d	2000 mg/d
Ethambutol (E)	750 mg/d	1000 mg/d
[a]Faropenem (F)	200 mg/ thrice a day	200 mg/thrice a day

[a] Faropenem sodium is commercially available in China for upper-and lower-respiratory tract and genitourinary infections.

(Cepheid, Sunnyvale, CA, USA), and liquid culture in Mycobacteria Growth Indicator Tube system (Becton Dickinson, MD, USA). The initial isolates were subjected to the Biochip assay to confirm *Mtb* infection [25], and drug susceptibility tests were performed using the Mycobacteria Growth Indicator Tube 960 system to exclude first-line TB drug resistance. The sputum specimen evaluations were performed at weeks 1, 2, and 4 and then every month until 6 months, which included AFB smear, liquid culture, and Xpert MTB/RIF. Chest CT was evaluated at 0 week, 4 weeks, 8 weeks, 16 weeks, and 24 weeks, according to the treatment schedule. Post-treatment follow-ups after treatment success were continued for 12 months, with sputum smear, culture, and CT every 6 months. The results of the longitudinal CT scans will be reported in our subsequent paper. All laboratory staff were blinded to the regimen assignments.

Safety

Adverse events were closely monitored and managed during the entire study course. At each follow-up schedule, the patients' subjective symptoms that may be associated with drug side effects were asked by investigators. Study data were timely recorded by study nurses in electronic case report form according to the Common Terminology Criteria for Adverse Events Version 5.0 [26]. An independent safety monitoring committee reviewed the records of each follow-up visit and made a recommendation on whether to continue the study.

Study outcomes

The primary outcome was defined as the proportion of patients who reported 6-month treatment success without relapse and was assessed 12 months after the completion of treatment. The secondary outcomes included negative Xpert MTB/RIF conversion time in different regimen assignments and the proportion of patients who had sputum culture and AFB conversion at each scheduled visit and a 6-month cure rate. The negative conversion was defined as two consecutive negative results at different visits or no sputum specimen collection after at least one negative sputum evaluation. The date of negative conversion was defined as the collection date of the first negative sputum specimen in two consecutive negative results. Treatment success was determined according to the WHO definitions and reporting frameworks for TB [27]. Cure was defined as bacteriological negative conversion and radiological resolution (closure of pulmonary cavities, complete absorption of infectious lesions, or merely residual fibrous calcification lesions) after 6 months of anti-TB treatment. The safety outcome was defined as the frequency of adverse events. Subgroup analysis was performed according to baseline AFB results and CT lesion extent.

Statistical analysis

It was assumed that the new regimen was not inferior to the standard regimen. Taking the noninferiority margin of −10%, setting one-side $\alpha = 0.05$, and $(1\text{-}\beta) = 0.8$, we estimated that the sample size was 105 for each group. The primary outcome and secondary outcome were analyzed in the modified intention-to-treat (mITT) population. Per-protocol (PP) population analyses were performed secondarily. In the mITT population, we included patients who met the inclusion and exclusion criteria and took at least one trial regimen. In the PP population, we included patients who took the whole planned trial dose. For the primary outcome analysis, the faropenem group had confirmed noninferiority if the lower limit of a 95% one-sided confidence interval (CI) of the difference was greater than −10% in treatment success rate. In addition, the median time to Xpert MTB/RIF conversion was analyzed with Kaplan-Meier curves and compared by the log-rank test between the groups in the mITT population and PP population. The cure rates and frequencies of adverse events were analyzed using Fisher's exact test. The criterion for statistical significance was set at 0.05. All analyses were performed with SAS software (version 9.3, SAS Institute, Cary, NC, USA).

Results

Study participants

A total of 236 patients with newly diagnosed TB who had not received any TB treatment previously were screened, and nine patients were excluded before randomization (two with extrapulmonary TB, three with rifampin resistance, four confirmed NTM infection). Of 227 patients who were eligible for the study, 114 were in the faropenem group, and 113 were in the control group. However, 10 patients who did not take the trial drug were excluded from the mITT analyses. Thus, a total of 217 patients were included in the mITT analyses. The faropenem group comprised 110 patients, and 68 were male (61.82%) and the median age was 37 years (interquartile range [IQR: 25-52]). The control group comprised 107 patients, and 69 were male (64.49%) and the median age was 39 years (IQR: 26-54). A total of 197 patients were included in the PP analyses (Fig. 1). The most common cause of exclusion from the PP analysis of the two groups was lost to follow-up, followed by adverse events and withdrawal of informed consent for nonmedical reasons. The baseline clinical characteristics of all patients were similar in the two groups (Table 2).

Treatment outcomes

In the mITT population, 88.18% of patients in the faropenem group achieved treatment success, and 85.98% of those in the control group were successfully treated, with a difference of 2.2% (95% CI, −6.73-11.13). In the PP population, treatment success rate was 96.04% in the faropenem group and 95.83% in the control group, with a difference of 2.1% (95% CI, −5.31-5.72). The faropenem group showed noninferiority to the control group in the 6-month treatment success rate. In the mITT analyses, the Kaplan-Meier curves and the log-rank test showed that the median time to Xpert conversion was 29 days (IQR: 19-56) in the faropenem group and 30 days (IQR: 17-66) in the control group ($P = 0.14$, Fig. 2).

In addition, we compared the sputum examination results at each follow-up point between the groups with no significant difference. In the mITT population, 90 (81.81%) patients in the faropenem group and 84 (78.50%) in the control group reached culture conversion by the end of 8 weeks ($P = 0.61$). In the PP analysis, culture conversion by 8 weeks was observed in 86 (85.15%) in the faropenem group and 80 (83.33%) in the control group ($P = 0.84$). Although there was an overall trend that the faropenem group had slightly higher culture conversion rates than the control group at different time points (Fig. 3), they did not reach statistical significance. In terms of AFB results (Fig. 4), 93 (84.54%) pa-

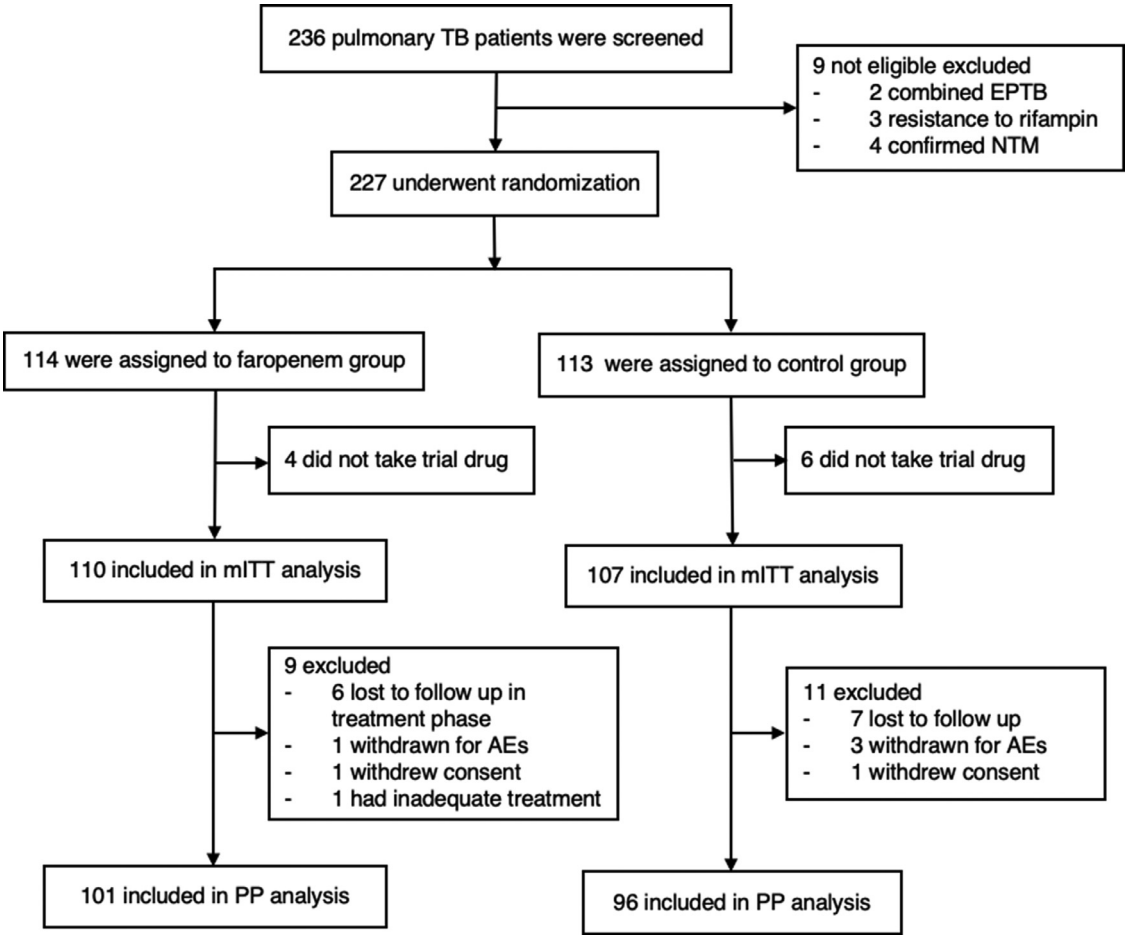

Fig. 1. The study flowchart. mITT included all participants except those patients who failed to meet eligibility criteria or did not take trial drugs.; PP excluded patients in the mITT population who took the whole planned trial dose. AE, adverse event; NTM, nontuberculous mycobacteria; EPTB, extrapulmonary TB; mITT, modified intention-to-treat population; PP, per-protocol population; TB, tuberculosis.

Table 2
Baseline clinical characteristics.

Characteristics	Faropenem group (n = 110)	Control group (n = 107)
Gender		
Male	68 (61.82)	69 (64.49)
Female	42 (38.18)	38 (35.51)
Age (median, interquartile range)	37.00 (25.00-52.00)	39 (26.00-54.00)
Smoking	20 (18.18)	25 (23.36)
Body mass index (kg/m^2)	19.59 (17.92-21.75)	19.81 (18.22-22.46)
Acid-fast bacilli positive	89 (80.91)	90 (84.11)
1+	43 (39.09)	45 (42.06)
2+	23 (20.91)	20 (18.69)
3+	13 (11.82)	13 (12.15)
4+	10 (9.09)	12 (11.21)
Computed tomography scan		
Unilateral	50 (45.45)	50 (46.73)
Bilateral	60 (54.55)	57 (53.27)
TB symptom score[a]		
0-5	88 (80.00)	87 (81.31)
6-10	21 (19.09)	19 (17.76)
11-15	1 (0.91)	1 (0.91)

TB, tuberculosis

[a] TB symptoms include cough, sputum, hemoptysis, fever, shortness of breath, malaise, and night sweats, each of which is scored 1-3, according to the severity of symptoms. The TB symptom score is the sum of each symptom score.

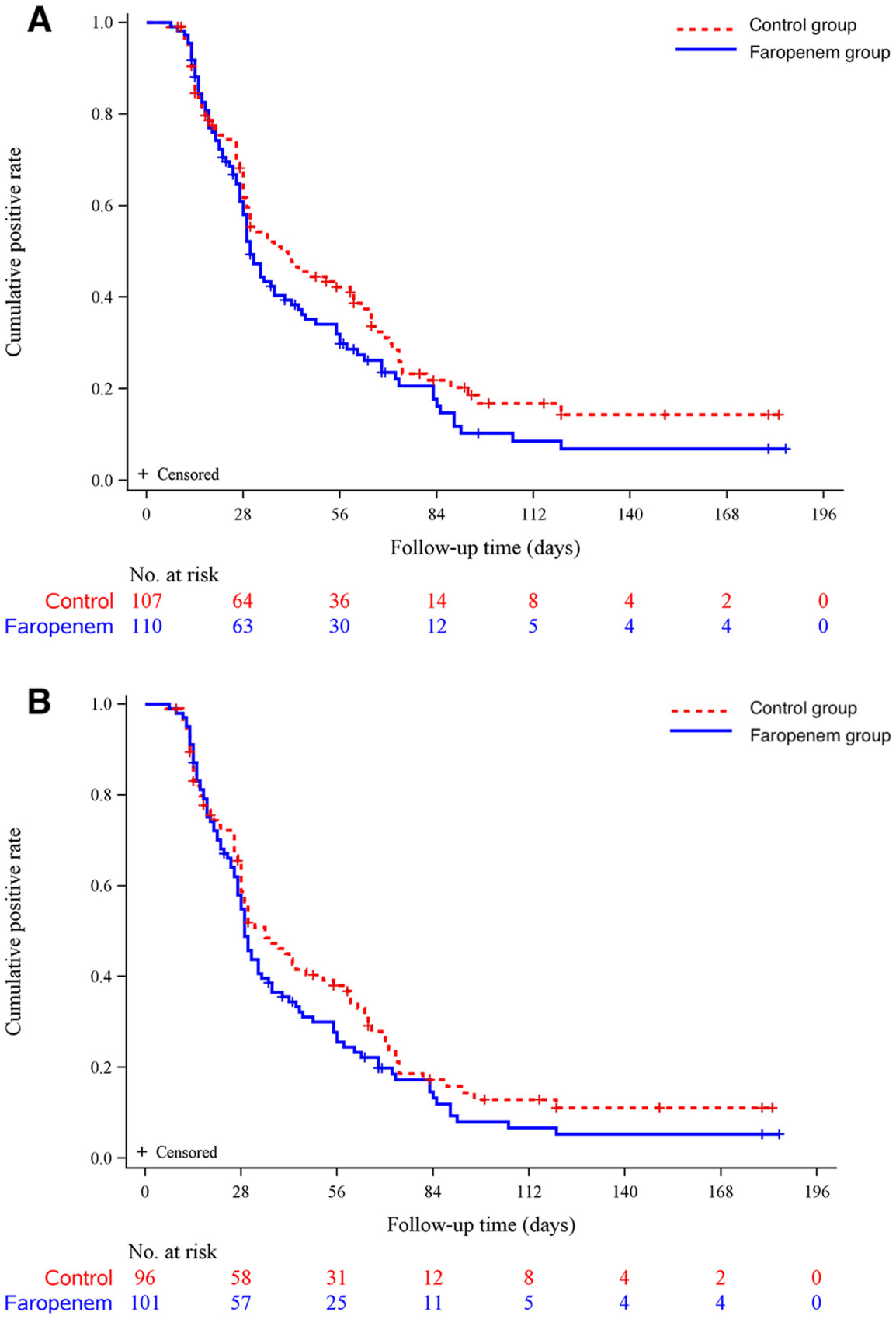

Fig. 2. Kaplan-Meier analyses of the time to Xpert negative conversion in mITT analyses. (a) In the mITT analyses, the faropenem group and the control group had a comparable median Xpert negative conversion time ($P = 0.14$). (b) In the per-protocol analyses, the faropenem group and the control group had a comparable median Xpert negative conversion time ($P = 0.17$). mITT, modified intention-to-treat population.

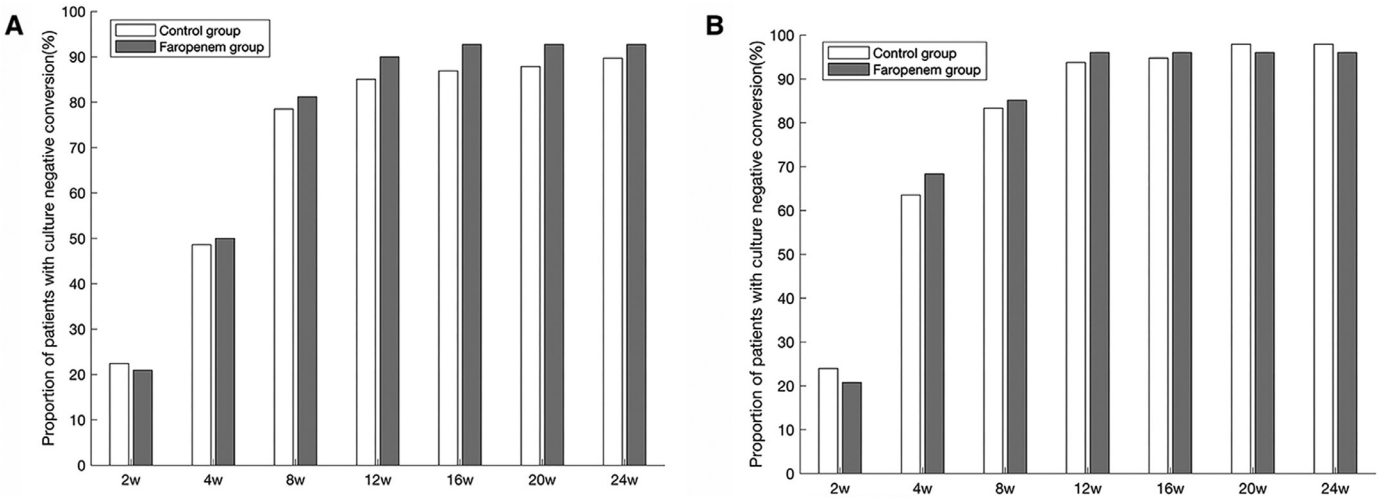

Fig. 3. Proportion of patients with culture negative conversion. (a) Proportion of patients with sputum culture negative conversion at each visit schedule in the modified intention-to-treat analyses. (b) Proportion of patients with sputum culture negative conversion at each visit schedule in the per-protocol analyses. There were no significant differences between the study groups in sputum culture censored at each visit schedule.

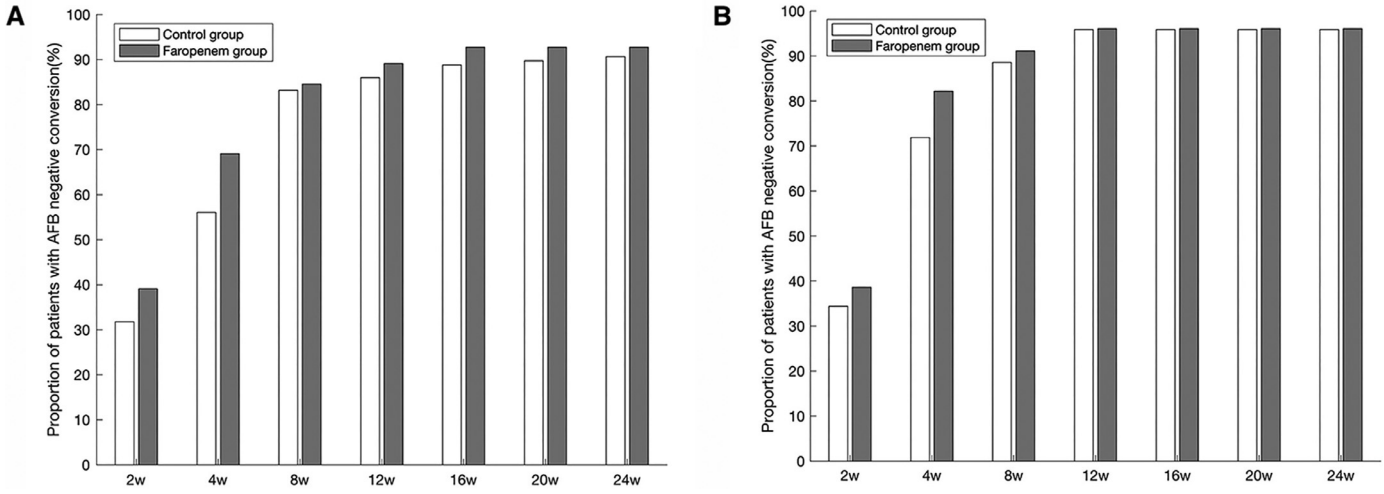

Fig. 4. Proportion of patients with AFB smear negative conversion. (a) Proportion of patients with sputum AFB smear negative conversion at each visit schedule in the modified intention-to-treat analyses. (b) Proportion of patients with sputum AFB smear negative conversion at each visit schedule in the per-protocol analyses. There were no significant differences between the study groups in sputum AFB smear censored at each visit schedule. AFB, acid-fast bacilli.

tients in the faropenem group and 89 (83.18%) in the control group reached AFB conversion by the end of 8 weeks in the mITT population ($P = 0.85$). In the PP analysis, AFB conversion by 8 weeks was observed in 92 (91.09%) in the faropenem group and 85 (88.54%) in the control group ($P = 0.64$).

In the mITT analyses, at 6 months, cure was reported in 87 (79.09%) of 110 patients in the faropenem group. As a comparison, a total of 76 (71.03%) of 107 patients in the control group reported cure ($P = 0.21$). In the PP analyses, cure was reported in 87 (86.14%) of 101 patients in the faropenem group and 76 (79.17%) of 96 patients in the control group ($P = 0.26$). In the faropenem group, three patients without negative conversion reported treatment failure at the end of 6 months of treatment. One reported TB relapse at the 12-month post-treatment follow-up. In the control group, two patients who did not achieve negative conversion reported treatment failure at the end of 6 months of treatment, one reported TB relapse at the post-treatment follow-up, and one relapsed with rifampin-resistant TB at post-treatment follow-up, with extended chest CT scan lesions (Table 3).

Subgroup analysis

No evidence was found of a difference in the efficacy between the faropenem group and the control group in the prespecified subgroup analyses, including AFB results and CT lesions extent (Table 4).

Safety analysis

No deaths and grade IV or greater adverse events were reported during the study course. 31.81% (35/110) of patients in the faropenem group reported adverse events, whereas 49.53% patients (53/107) in the control group ($P < 0.01$) reported adverse events (Table 5). Three patients in the faropenem group and five patients in the control group reported grade 3 adverse event hepatotoxicity. Almost all the hepatotoxicity events occurred at the early stages of treatment but the treatment did not stop. We found that nine (8.18%) participants in the faropenem group reported loss of appetite, and seven of nine participants also had hepatotoxicity. A

Table 3
Treatment outcome analysis.

Treatment outcome	Modified intention-to-treat population		Per-protocol population	
	Faropenem group (n =110)	Control group (n = 107)	Faropenem group (n =101)	Control group (n = 96)
8w acid-fast bacilli conversion	93 (84.54)	89 (83.18)	92 (91.09)	85 (88.54)
8w culture conversion	90 (81.81)	84 (78.50)	86 (85.15)	80 (83.33)
Treatment success (%)	97 (88.18)	92 (85.98)	97 (96.04)	92 (95.83)
Cure	87 (79.09)	76 (71.03)	87 (86.14)	76 (79.17)
Treatment completed	10 (9.09)	16 (14.95)	10 (9.90)	16 (16.67)
Difference in rate of treatment success	2.2 (-6.73-11.13)	Ref	2.1 (-5.31-5.72)	Ref
Unfavorable outcome (%)				
Death	0 (0)	0 (0)	0 (0)	0 (0)
Treatment failure	3 (2.73)	2 (1.87)	3 (2.97)	2 (2.08)
Relapse	1 (0.91)	2 (1.87)	1 (0.99)	2 (2.08)

The primary outcome was defined as the proportion of patients who reported treatment success after 6 months treatment. Cure was defined as bacteriological negative conversion and radiological complete resolved after 6 months of treatment. Treatment failure was defined as sputum smear or culture positive at 5 months or later or emergence of a multidrug-resistant strain at any time during the treatment. Relapse was defined as a positive sputum smear or culture result after cure at any point of time during 12-month post-treatment follow-up.
Ref: reference.

Table 4
Subgroup analysis.

	Faropenem group	Control group	Unadjusted difference (95% confidence interval)
Acid-fast bacilli result			Interaction p = 0.55
Negative	19/21 (90.48%)	14/17 (82.35%)	8.12 (-13.92-3.02)
Positive	78/89 (87.64%)	78/90 (86.67%)	0.91 (-8.83-10.78)
Computed tomography lesion extent			Interaction *P* = 0.37
Unilateral	46/50 (92.00%)	47/50 (94.00%)	2.0 (-11.99-7.99)
Bilateral	51/60 (85.00%)	45/57 (78.95%)	6.05 (-7.86-19.97)

Table 5
Safety analysis.

Adverse event	Faropenem group (n=110)	Control group (n =107)	*P*-value
Any adverse event	35 (31.81)	53 (49.53)	<0.01
Grade 3 adverse event	3 (2.72)	5 (4.55)	0.49
Grade 4 adverse event	0 (0)	0 (0)	NA
Details of symptom			
Hepatotoxicity	21 (19.09)	23 (21.50)	0.66
Diarrhea	2 (1.82)	3 (2.80)	0.63
Nausea and vomiting	1 (0.91)	5 (4.67)	0.09
Loss of appetite	9 (8.18)	13 (12.15) (11.2)	0.37
Rash	1 (0.91)	4 (3.74)	0.15
Leukopenia	5 (4.55)	6 (5.61)	0.72
Anemia	1 (0.91)	1 (0.93)	0.98
Thrombocytopenia	0(0.00)	1 (0.93)	0.31
Visual impairment	0 (0.00)	5 (4.67)	0.02
Numbing	2 (1.82)	2 (1.87)	0.98
Hypogeusia	0 (0.00)	1 (0.93)	0.31
Creatine increase	0 (0.00)	1 (0.93)	0.31

The safety analysis includes all patients who underwent randomization and received at least one dose of a study regimen.

total of 13 (12.15%) patients in the control group reported loss of appetite, 12 of them had hepatotoxicity. The significant difference between the groups was the incidence of visual impairment, a side effect of ethambutol. Visual impairment was not identified in any patient in the faropenem group, whereas, in the control group, five patients (4.67%) experienced visual impairment ($P = 0.02$).

Discussion

In this prospective study, we found that the substitution of ethambutol with faropenem in the first-line background regimen has shown noninferiority in the 6-month treatment success of TB and has significantly fewer adverse events. The reason that the faropenem group had a similar cure rate to the control group may be due to the strong bactericidal effect of faropenem or the presence of a synergistic batericidal effect of faropenem with other drugs, such as rifampin [21,22]. It is of interest to note that faropenem has been shown to be active against nonreplicating *Mtb in vitro* [19], and drugs with activity against nongrowing dormant persisters are considered important for shortening the treatment [28,29]. Thus, the activity of faropenem against both growing and nongrowing *Mtb* may be related to the ability of the faropenem regimen to achieve a similar treatment effect to the control regimen with ethambutol. Our study reveals the potential of faropenem in the treatment of TB and provides some basis for further study. However, there is no other large-scale, multicenter randomized controlled trial study to support our conclusion; thus, more clinical experience needs to be accumulated for the appli-

cation of faropenem in anti-TB treatment. Replacing ethambutol in the standard regimen with faropenem may also present some drawbacks, such as the lack of a fixed dose combination and the impact of widespread use of a broad-spectrum antibiotic on pressure for drug resistance developing in the community.

In our regular clinical treatment practice, the GeneXpert of most patients with pulmonary TB turned negative within 2 or 3 months of treatment, which is used as auxiliary information to judge the efficacy in clinical practice. Therefore, the GeneXpert result was used as additional supporting evidence for the classical outcome parameter AFB smear and culture in this study, but it is not a conventional parameter in previous clinical trials. It is known that the persistence of Xpert signal and positive result on treatment are not indicative of viable bacilli, and it is not known whether it is reliable as a surrogate marker for the efficacy of a treatment regimen.

An interesting observation of the study is that the faropenem group had a significantly fewer total number of adverse events than the control regimen. Previous studies demonstrated that oral faropenem for upper respiratory tract infections and urinary tract infections was safe and well tolerated. Almost all the hepatotoxicity events occurred within the first month of treatment and the patients experienced mildly elevated transaminases, which reverted back to normal after glycopyrrolate treatment. The ethambutol-related ocular toxicity has been a concern for physicians, especially in patients with risk factors, such as old age, low weight, and kidney disease [30]. Our findings that replacing ethambutol with faropenem can not only achieve a comparable therapeutic effect on TB but also avoid ethambutol-associated ocular toxicity with fewer side effects are highly significant. It is worth noting that the proportion of visual impairment in our study with ethambutol was 4.67% (five cases) higher than the optic neuropathy expected, which is about 1%, at a dose of 15 mg/kg ethambutol. The reason for the relatively high visual impairment was that patients with subjective symptoms, such as blurred vision, reduced visual acuity, visual fatigue, and eye dryness but no objective ophthalmologic abnormalities, were included in the adverse event reports for safety concerns. Also, the dosage of ethambutol was adjusted according to body weight (15-20 mg/kg), which is higher than the dose of 15 mg/kg.

This study has some limitations. First, the sample size was limited and this open-label study with strict exclusion criteria for patients may introduce selection bias. Second, we did not perform pharmacokinetic analysis of faropenem for the faropenem group. A better understanding of the optimal dose of faropenem and its concentration in plasma and in pulmonary sites is needed in future studies. Third, the study was conducted in one country, which may lead to bias due to the differences in resources and experience. These potential drawbacks may limit the generalizability to programmatic roll-out outside of a clinical access program. In addition, this study was conducted in patients with drug-susceptible TB and the nature of the study design may not allow the beneficial effects of oral faropenem used only in the intensive phase of the treatment to fully manifest. Future studies with longer treatment duration and optimal dosage will be needed to demonstrate the value of this promising oral agent for treating both drug-susceptible and drug-resistant TB.

Conclusion

Faropenem combined with the other three standard treatment drugs (isoniazid, rifampicin, pyrazinamide) has shown noninferiority to the first-line standard regimen containing ethambutol for drug-susceptible pulmonary TB, with fewer adverse events during treatment.

Declaration of competing interest

The authors have no competing interests to declare.

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Ethics approval

Ethics approval was obtained from the institutional review board of the First Affiliated Hospital, School of Medicine, Zhejiang University (Approval No. 20180351).

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Author contributions

Kaijin Xu, Ying Zhang, Lanjuan Li, Yanwan Shangguan, Cheng ding conceived the study and participated in the design of the study. Yanwan Shangguan, Wanru Guo, Xuewen Feng, Jiafeng Xia, Xiaomeng Li, Wenjuan Hu and Ming Hu wrote and revised the manuscript. Zhifen Pan, Yunzhen Shi, Jichan Shi, Xiaodong Tao, Yuyin Zhu, Xiaoqiang Zhang, Zebao He, Lingxiao Jin, Xinming Zhu, Qun Song, Xiuyuan Jin, Shujuan Huang, Liangxiu Jiang, Tiantian Wu, Dan Cao participated in data collection. Ding Chen, Zhongkang Ji, Chengjie Zhao, Yuecui Li, Lin Zheng, Yuping Wang and Yanwan shangguan performed the data analysis. No one who was not an author contributed to the writing of the manuscript. All the authors read and approved the final version of the manuscript.

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