Pharmacokinetics, pharmacodynamics, and safety of single- and multiple-dose intravenous ceftobiprole in healthy Chinese participants

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Background: Ceftobiprole is a novel β-lactam cephalosporin with activity against Gram-positive and -negative bacteria. The aim of the present study was to investigate the pharmacokinetics (PK), pharmacokinetics/pharmacodynamics (PK/PD), safety and tolerance of ceftobiprole in Chinese participants, to evaluate this dosage regimen for the treatment of community-acquired pneumonia (CAP) and hospital-acquired pneumonia (HAP) in China.

Methods: The use of ceftobiprole was investigated in a single-center, open-label, single- and multiple-dose study using 12 healthy Chinese participants (6 males and 6 females). Ceftobiprole plasma and urine concentrations were analyzed using a validated liquid chromatography-tandem mass spectrometry assay. The PK/PD characteristics of 500 mg ceftobiprole every 8 h at 1.5-, 2-, 3-, or 4-h infusion time were analyzed by Monte Carlo simulations (MCS).

Results: The maximum plasma concentration of ceftobiprole was observed 2 h after dosage; its terminal half-life was about 3 h. Ceftobiprole was predominantly eliminated in urine, and the cumulative excretion in 24 h was >90%. There was no accumulation after multiple dosing. Both single and multiple doses were well tolerated, with no severe or serious adverse events (AEs). PK/PD analysis indicated that Staphylococcus pneumoniae (S. pneumoniae) and Staphylococcus aureus (S. aureus) were sensitive to ceftobiprole. About half of extended-spectrum β-lactamase (ESBL) non-producing Enterobacteriaceae are sensitive to ceftobiprole, according to PK/PD results of ceftobiprole. For Pseudomonas aeruginosa (P. aeruginosa), no regimen was found to be effective against strains.

Conclusions: The PK/PD results indicated that 500 mg ceftobiprole every 8 h at 2-h infusion time is expected to achieve good microbiological efficacy in the treatment of CAP and HAP in China.

Keywords: Ceftobiprole; pharmacokinetic/pharmacodynamic analysis (PK/PD analysis); Monte Carlo simulation (MCS)

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Introduction

Ceftobiprole is the active metabolite of ceftobiprole medocaril, which is a fifth-generation cephalosporin with bactericidal activity against broad-spectrum pathogens. The most prominent feature is that ceftobiprole binds tightly to penicillin-binding proteins (PBPs), that are resistant or insensitive to conventional β-lactam antibiotics, including PBP2a of methicillin-resistant Staphylococcus aureus (MRSA) and PBP2x of penicillin-resistant pneumococci (PRP) (1,2). These pharmacological mechanisms are responsible for the broad-spectrum bactericidal activity of ceftobiprole. It has potent activity against Gram-positive bacteria, including MRSA and penicillin-resistant Staphylococcus pneumoniae (PRSP) (3), as well as in vitro activity against most of common Gram-negative bacteria, including Escherichia coli, Klebsiella pneumonia, and Pseudomonas aeruginosa. However, it does not have clinical activity against extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae (4,5). Ceftobiprole was approved by the European Medicines Agency in 2013 for the treatment of adult patients with community-acquired pneumonia (CAP) and hospital-acquired pneumonia (HAP), with the exception of ventilator-associated pneumonia.

Pneumonia, including CAP and HAP, is the leading cause of morbidity and mortality worldwide (6). In general, Streptococcus pneumoniae (S. pneumoniae) is the most common pathogen of CAP, followed by Haemophilus influenzae, Mycoplasma pneumoniae, Staphylococcus aureus (S. aureus), and another microorganism (7-9). There are significant differences in the composition of the HAP pathogen spectrum in China, which is different from that in Europe and the USA. Gram-negative bacteria such as Enterobacteriaceae is considered to be the main cause of HAP (10-12).

The microbial etiology of CAP and HAP is changing due to the widespread use of antibiotics. According to the data of the China Antimicrobial Surveillance Network (CHINET), the isolation rate of MRSA was 37.3% in 2017 in China. The prevalence of penicillin-non-susceptible S. pneumoniae was reported to be between 4.6% and 8.2% in adults from 2015 to 2017 (13). Because the causative organism is typically unknown early on, the timely administration of empirical antibiotics is a cornerstone of pneumonia management (6). Antibiotic recommendations for the empirical treatment of CAP and HAP are based on the selection of agents that are effective against the major pathogens of infectious diseases (8). Therefore, it is necessary to choose antibacterial drugs with a broad spectrum and high safety for clinical practice.

In the present study, we report the pharmacokinetic (PK) parameters of 500 mg ceftobiprole after single- and multiple-dose regimens in healthy Chinese participants. The safety and tolerability of ceftobiprole were also assessed. Although the PK of ceftobiprole has previously been reported, the literature may be due to the fact that the information is relatively incomplete and outdated after a long time. Considering the changes in bacterial resistance and the differences in the composition of pathogens of infectious diseases in different regions, the pharmacokinetics/pharmacodynamics (PK/PD) could be used to evaluate the clinical application of the current administration regimen approved in Europe for the treatment of CAP and HAP indications in China. To the best of our knowledge, the present study is the first to investigate PK and PK/PD of ceftobiprole in a Chinese population. We present the following article in accordance with the MDAR reporting checklist (available at http://dx.doi.org/10.21037/atm-21-588).

Methods

Participants

A total of 12 healthy men and women (male: female =1:1) aged 18–45 years (inclusive) with a body mass index of 18–26 kg/m² (inclusive) were enrolled in the present study. Baseline hematological and clinical biochemical laboratory parameters were within normal limits for all participants. Individuals were excluded if they had any of the following conditions: clinically relevant history of allergies or hypersensitivity (including penicillin, cephalosporin, or other β-lactams); a previous history of nephrolithiasis, urinary obstruction, or difficulty in voiding; history of chronic disease of any major organ or system; viral hepatitis or human immunodeficiency virus (HIV); corrected QT interval (QTc) prolongation on 12-lead electrocardiogram (ECG); clinically significant abnormality, as shown in laboratory tests; a history of drug allergies; substance abuse; participation in another clinical study in the past 3 months; and pregnancy.

Study design

The present study was a single-center, open-label, and single- and multiple-dose study carried out with 12 eligible participants. A single-dose was defined as 500 mg...
ceftobiprole for 2 h on day 1. A multiple dose was defined as 500 mg ceftobiprole every 8 h on days 4–8, with the last administration on day 9. The study was performed at the Phase I Unit of Huashan Hospital, China, in accordance with the principles of the Declaration of Helsinki (as revised in 2013). The research protocol and informed consent form were reviewed and approved by the Ethics Committee of Huashan Hospital, Fudan University (No. 2019-014). All participants provided written informed consent to participate in the study.

**Bioanalytical assay**

Ceftobiprole was isolated from K2 ethylene diamine-tetra acetic acid (K₂EDTA) human plasma or urine (with citric acid) by solid-phase extraction protein precipitation (Oasis®HLB µElution Plate 30 µm; Waters Co., Milford, MA, USA). The concentrations of ceftobiprole were determined using validated liquid chromatography-tandem mass spectrometry assay. Monitoring of selected reactions was performed on a SCIEX (Triple Quad 5500; AB Sciex Co., Foster City, CA, USA) mass spectrometer operated in the positive ionization detection mode. The transition ions at m/z 535.2–264.1 and m/z 539.3–312.3 were monitored for ceftobiprole and its internal standards, respectively. The method was validated over a ceftobiprole concentration range of 0.05–25 µg/mL in plasma and 0.4 to 200 µg/mL in urine matrices. Quality control (QC) samples at three levels (low QC, medium QC, and high QC) were prepared and tested in each run of the study.

**PK study**

On days 1 and 9, blood samples for the PK analysis were collected prior to administration and at 0.5, 1, 2, 2.17 (10 min after intravenous infusion), 2.5, 3, 4, 6, 8, 12, 14, 18, and 24 h after the start of infusion. K₂EDTA blood was treated with citric acid to stabilize ceftobiprole. On days 4–8, blood was collected before the first dose (−3 h to 0 h) and 2 h and 10 min after the start of intravenous infusion. Subsequently, urine samples were collected during the following collection periods: −12 to 0, 0−2, 2−4, 4−8, 8−12, 12−18, and 18−24 h after the start of infusion on days 1 and 9. The urine container was protected against sunlight to prevent degradation of ceftobiprole; urine sample containers were pretreated with citric acid. Because 4 female participants violated the requirements of the program in urine sample collection, the urine sample data of the above 4 participants were excluded, and a total of 8 participants (6 males and 2 females) were included in the pharmacokinetic analysis of urine samples.

**Statistical analysis**

Descriptive statistics for quantitative variables, such as means, standard deviations, medians, and maximum and minimum. PK parameters were derived from non-compartmental and 3-compartmental methods with WinNonlin 8.0. To evaluate whether there was accumulation of ceftobiprole after multiple doses and whether there were sex differences in PK of ceftobiprole.

**PK/PD targets of ceftobiprole against Gram-positive and -negative bacteria**

The PK/PD targets were derived from an *in vivo* PK/PD study of ceftobiprole in a neutropenic murine thigh infection model. The median target values of the static dose and 2-log reduction in colony counts were used for the PK/PD analysis (14).

**PK/PD analysis**

Monte Carlo simulations (MCS) were performed by Excel add-in macros (written in Visual Basic for Applications) and MATLAB (version 7.0.1; Mathworks, Natick, Massachusetts, USA). On the basis of the PK results calculated by the 3-compartmental model in healthy Chinese participants, according to the reported PK/PD targets, the probability of target attainment (PTA) was estimated under different administration regimen (1.5-, 2-, 3-, or 4-h infusion time) of ceftobiprole 500 mg every 8 h. The MCS to perform MCS 5,000 times and calculated the PTA. PTA was defined as the probability that at least a specific value of a PK/PD index is achieved at a certain minimum inhibitory concentration (MIC). A PTA of 90% was considered effective. The upper limit of the MIC range was taken as the PK/PD breakpoint when PTA >90%.

**Safety and tolerability**

All 12 participants were included in the safety analysis. The safety of the participants was evaluated by physical examination, vital signs, and safety laboratory tests, such as hematological tests, urinalysis, serum biochemical tests, and a 12-lead ECG.
Table 1 Demographic data of the healthy Chinese participants (n=12)

| Characteristics          | Participants          |
|--------------------------|-----------------------|
| Sex, n (%)               |                       |
| Male                     | 6 (50.0)              |
| Female                   | 6 (50.0)              |
| Age (years)              |                       |
| Mean (SD)                | 30 [5]                |
| Range                    | 23–39                 |
| Race, n (%)              |                       |
| Asian                    | 12 (100.0)            |
| Height (cm)              |                       |
| Mean (SD)                | 165.0 (9.0)           |
| Range                    | 150.7–178.5           |
| Weight (kg)              |                       |
| Mean (SD)                | 60.1 (7.2)            |
| Range                    | 47.5–69.8             |
| Body mass index (kg/m²)  |                       |
| Mean (SD)                | 22.0 (1.4)            |
| Range                    | 20.1–24.0             |
| Ccr (mL/min)             |                       |
| Mean (SD)                | 117.5 (13.7)          |
| Range                    | 94.8–141.4            |

Ccr, creatinine clearance rate; SD, standard deviation.

**Results**

**Participants' demographic and baseline characteristics**

Twelve healthy participants, including 6 men and 6 women, were enrolled in the study. All participants were healthy and none had a medical history or current conditions that would have interfered with the distribution, metabolism, or excretion of the study drug (Table 1).

**PK results**

Figure 1 shows the mean plasma concentration profiles of the active drug ceftobiprole after single and multiple doses for 2-h in 12 participants. The peak levels of ceftobiprole in plasma were observed at the end of the 2-h infusion.

Table 2 presents the corresponding PK parameters on days 1 and 9. Systemic exposure on days 1 and 9 were comparable. Elimination half-life was approximately 3 h on day 1 and remained unchanged following multiple infusions, whereas distribution volume decreased from days 1 to 9. The accumulation index approximated unity, indicating minimal accumulation from days 1 to 9; ceftobiprole was primarily excreted in urine.

**PK/PD analysis of ceftobiprole at different regimens**

**PTA**

Figure 2 demonstrates the PTA of each regimen to Gram-positive bacteria with diverse MICs. For *S. pneumoniae*, to
achieve a PK/PD target of time that drug concentration exceeds MIC (T>MIC) =18.8, all administration regimens could achieve a PTA of 100% against strains with MIC ≤ 8 mg/L. To achieve a PK/PD target of T>MIC =25.8, if the MIC ≤ 4 mg/L, each administration regimen could exceed the PTA of 97.9%. For \textit{S. aureus}, to achieve a PK/PD target of T>MIC =21.1, either infusion time was effective against strains with MIC ≤ 2 mg/L, with a PTA of 100%. To achieve a PK/PD target of T>MIC =29.3, if the MIC ≤ 4 mg/L, each administration regimen could exceed the PTA of 97.9%.

\textit{Figure 3} shows the PTA of each regimen to Gram-negative bacteria with diverse MICs. For \textit{Enterobacteriaceae} (ESBL non-producing), to achieve a PK/PD target of T>MIC =40.8, 500 mg ceftobiprole administered every 8 h at 2-, 3-, a 4-h infusion time could achieve a PTA of ≥94.5% against strains with a MIC ≤ 4 mg/L. To achieve a PK/PD target of T>MIC =64.5, 3 or 4 h infusion time could achieve a PTA of ≥94.3% against strains with MIC ≤ 1 and MIC ≤ 2 mg/L. For \textit{P. aeruginosa}, to achieve a PK/PD target of T>MIC =46.7, all infusion times could achieve a PTA of ≥93.8% against strains with MIC ≤ 2 mg/L. An infusion time of 3 or 4 h could achieve a PTA of ≥94.5% against strains with MIC ≤ 8 mg/L; all the regimens achieved the PTA. For \textit{Enterobacteriaceae} and \textit{P. aeruginosa}, the current regimen could reach the PTA of 98.0% and 95.7% with MIC ≤ 2 mg/L. To achieve 2-log kill-dose target, ceftobiprole was effective against \textit{S. pneumoniae} with MIC ≤ 8 mg/L. And for \textit{S. aureus}, PTA could be achieved 90% with MIC ≤ 8 mg/L in all administration regimens, except for 1.5-h regimen which could achieve PTA of 97.9% with ≤ 4 mg/L. For \textit{Enterobacteriaceae}, an infusion time of ≥ 2 h could reach the PTA of ≥91.1%, with MIC ≤ 1 mg/L. For \textit{P. aeruginosa}, the regimen could not exceed a PTA of 90%.

\textbf{PK/PD breakpoints}

\textit{Table 3} shows the PK/PD breakpoints for the 4 bacteria.
under each different regimen (infusion time). For both *S. pneumoniae* and *S. aureus*, PK/PD breakpoints for all regimens achieved a European Committee on Antimicrobial Susceptibility Testing (EUCAST; version 10.0, http://www.eucast.org) suggested breakpoint (0.5 mg/L for *S. pneumoniae*, 2 mg/L for *S. aureus*). Compared with the EUCAST breakpoint for *Enterobacteriaceae*, PK/PD breakpoints of either infusion time also reached 0.25 mg/L. For *P. aeruginosa*, prolonged infusion time was not effective.

**Safety and tolerability**

The adverse events (AEs) of ceftobiprole were mild and transient, and no serious or severe AEs were observed (Table 4).

Headache was the most common AE in the present study. One male and 3 females experienced AEs that were considered to be related to ceftobiprole. All AEs occurred with multiple doses of ceftobiprole. All participants with AEs recovered spontaneously without treatment. The participants showed good tolerability to 500 mg ceftobiprole every 8 h at 2-h infusion time for 5 consecutive days.

**Discussion**

CAP and HAP are associated with mortality, morbidity, and high cost. The incidence of pneumonia is estimated to be between 1.5 and 14.0 cases per 1,000 person-years (15). Appropriate antibiotic therapy is closely related to the
prognosis of infectious diseases. Therefore, early and effective empirical treatment is necessary to reduce antibiotic resistance and side-effects (6,15,16).

Ceftobiprole has wide spectrum activity against Gram-positive and -negative bacteria. Compared with conventional β-lactams, it has outstanding activity against MRSA and PRSP, which led to ceftobiprole being classified as a 5th-generation cephalosporin (17,18). The approval of ceftobiprole for CAP and HAP is based on 2 phase 3 randomized controlled trials (19,20). According to a previously published study, for the empirical treatment of CAP and HAP, ceftobiprole is considered a suitable option for the following reasons: (I) its broad spectrum of activity; (II) its activity against MRSA; and (III) its good safety profile (21).

Both CAP and HAP are common clinical diseases that require anti-infection treatment in China. However, the results of a number of domestic adult CAP and HAP epidemiological investigations have indicated that the composition of CAP and HAP pathogens in China is different from that in other countries (9,11). We conducted a PK study of ceftobiprole in healthy Chinese participants to evaluate the current administration regimen from the perspective of PK/PD and safety, so as to provide more references for the choice of antibiotic for clinical infectious diseases.

Figure 3 PTA of different regimens to Gram-negative bacteria. (A) PTA of ceftobiprole in terms of T>MIC following different intravenous infusion time to Enterobacteriaceae. (B) PTA of ceftobiprole in terms of T>MIC following different intravenous infusion time to P. aeruginosa. ivgtt: intravenously guttæ; P. aeruginosa, Pseudomonas aeruginosa; PTA, probability of target attainment; q8h, every 8 h; S. pneumoniae, Staphylococcus pneumoniae; S. aureus, Staphylococcus aureus; T>MIC, time that drug concentration exceeds MIC.
Figure 4 PTA of different regimens to *S. pneumoniae*, *S. aureus*, *Enterobacteriaceae* and *P. aeruginosa*. (A) PTA of ceftobiprole in terms of static-dose target following different intravenous infusion time to bacteria. (B) PTA of ceftobiprole in terms of 2-log kill-dose target following different intravenous infusion time to bacteria. ivgtt: intravenously guttae; *P. aeruginosa*, *Pseudomonas aeruginosa*; PTA, probability of target attainment; q8h, every 8 h; *S. pneumoniae*, *Staphylococcus pneumoniae*; *S. aureus*, *Staphylococcus aureus*; T>MIC, time that drug concentration exceeds MIC.
The prodrug ceftobiprole medocaril can be rapidly converted to the active drug ceftobiprole. It minimally binds to plasma proteins (16%). Systemic exposure of ceftobiprole was comparable after single and multiple doses. Accumulation was negligible (accumulation ratio: 1:29) after multiple-dose administration. More than 90% of ceftobiprole was recovered from urine after a single-dose administration. In short, the results of a single- and multiple-dose study of ceftobiprole in Chinese participants showed that ceftobiprole has stable PK characteristics, small inter-individual variability, and no sex differences. Our PK data are in good agreement with those of previously published studies (22-25). A small amount of ceftobiprole is metabolized into open-ring metabolites without antimicrobial activity. In participants with normal renal function, the systemic exposure of open-ring metabolites was found to be much lower than that of ceftobiprole, accounting for about 4% of the parent drug exposure (25). In the present study, the systemic exposure of the open-ring metabolite was about 5.7% following single dose administration, which is similar to that reported in the literature (4). Elimination half-life of the open-ring metabolite was approximately 5 h. The accumulation ratio was approximately 1:80, indicating slight accumulation. Approximately 6.6% of open-ring metabolites are excreted in urine following single-dose administration. Our PK data of open-ring metabolites are in accordance with those of previously published studies (4). Our findings also indicate that there were no PK differences between Asians and non-Asians at the standard dose of 500 mg ceftobiprole every 8 h as a 2-h infusion.

| Strain           | Target            | PK/PD breakpoint (500 mg, q8h) | ≤S  | R>  |
|------------------|-------------------|--------------------------------|-----|-----|
|                  |                   | 1.5 h | 2 h | 3 h | 4 h |     |     |
| S. pneumoniae    | Static dose       | 18.8  | 8   | 8   | 8   | 0.5 | 0.5 |
|                  | 2-log kill dose   | 25.8  | 8   | 8   | 8   | 2   | 2   |
| S. aureus        | Static dose       | 21.1  | 8   | 8   | 8   | 2   | 2   |
|                  | 2-log kill dose   | 29.3  | 4   | 8   | 8   | 1   | 2   |
| Enterobacteriaceae | Static dose     | 40.8  | 2   | 4   | 4   | 0.25| 0.25|
|                  | 2-log kill dose   | 64.5  | 0.5 | 1   | 1   | 2   |     |
| P. aeruginosa    | Static dose       | 46.7  | 2   | 2   | 4   | 4   | IE  |
|                  | 2-log kill dose   | 98.8  | NA  | NA  | NA  | NA  |     |

IE, insufficient evidence; NA, not applicable; P. aeruginosa, Pseudomonas aeruginosa; PD, pharmacodynamics; PK, pharmacokinetics; q8h, every 8 h; R, resistance; S, susceptible; S. pneumoniae, Staphylococcus pneumoniae; S. aureus, Staphylococcus aureus.

### Table 4 Number (%) of participants with ceftobiprole-related adverse events in the pharmacokinetic study

| Adverse event                        | No. (%) of participants with indicated adverse events |
|--------------------------------------|------------------------------------------------------|
|                                      | Male | Female | Total |
| Abnormal laboratory assay            |      |        |       |
| White blood cell count decreased     | 0 (0)| 2 (33.3)| 2 (16.7)|
| lymphocyte count decreased           | 0 (0)| 1 (16.7)| 1 (8.3)|
| Percentage of eosinophils increased  | 0 (0)| 1 (16.7)| 1 (8.3)|
| neutrophils count decreased          | 0 (0)| 2 (33.3)| 2 (16.7)|
| Clinical disorder                    |      |        |       |
| Headache                             | 1 (16.7)| 1 (16.7)| 2 (16.7)|

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According to the neutropenic murine thigh model (14), for *S. pneumoniae*, *S. aureus* (including MRSA), *Enterobacteriaceae*, and *P. aeruginosa*, the PK/PD parameter best correlating with efficacy was T>MIC, as with other β-lactam antimicrobial agents. The recommended clinical dose regimen for ceftobiprole is 500 mg administered every 8 h as a 2-h intravenous infusion. The PK/PD analysis of ceftobiprole was conducted at different infusion times. The ceftobiprole PK were best described by a 3-compartmental model in the present study. In the context of the bactericidal (2-log kill) exposure targets, a PTA >90% was all reached in simulations for *S. pneumoniae* and *S. aureus* with MIC ≤4 mg/L. For *Enterobacteriaceae*, a PTA of 90% was only reached in simulations of dosing regimens with prolonged infusion to 4 h, with MIC ≤2 mg/L. For *P. aeruginosa*, the PTA was below 90% in all simulations.

Based on breakpoints of the EUCAST, the suggested breakpoint of *S. pneumoniae* and *S. aureus* were 0.5 and 2 mg/L, which were lower than the breakpoints of PK/PD in the present study. For *Enterobacteriaceae*, the breakpoints of PK/PD were also higher than the EUCAST breakpoint. There is no recommended breakpoint for *P. aeruginosa*. In general, the breakpoints of ceftobiprole for Gram-positive and -negative bacteria also indicated that ceftobiprole is effective against *S. pneumoniae* and *S. aureus* (26-28). Although ceftobiprole is not active against ESBL-producing strains of *Enterobacteriaceae*, it has potential activity against ESBL-non-producing bacteria and *P. aeruginosa*; therefore, more clinical trial data are needed to support the application of ceftobiprole in Gram-negative bacterial infections.

The administration regimen of 500 mg ceftobiprole every 8 h at 2-h infusion is well tolerated, with no severe or serious local or systemic AEs, and with no ECG abnormalities or adverse changes in vital signs. Its safety information is similar to the clinical results reported in previous phase I studies aboard (23). Two cases of drug-related AEs were reported during the multiple-dose administration as headache, which is a common but mild and predictable adverse reaction of β-lactam antibiotics (29,30).

**Conclusions**

The PK characteristics of ceftobiprole in the Chinese population are consistent with those previously reported abroad. There is no sex difference, and its safety and tolerance are good. Our PK/PD findings indicated that the dosing regimen of 500 mg every 8 h as a 2-h infusion is suitable for CAP and HAP infections in China.

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**Footnote**

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**Ethical Statement:** The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethical Committee of Huashan Hospital (No. 2019-014). Written, informed consent was obtained from all participants. This trial is registered at Chinese Clinical Trial Registry (CTR20190655).

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