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BRIEF REPORT

Clinical Efficacy of Cefixime for the Treatment of Early Syphilis

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Safe and efficacious alternative treatment options for syphilis are necessary. This randomized, 2-arm, noncomparative pilot study evaluated the efficacy of oral cefixime 400 mg in achieving a ≥4-fold rapid plasma reagin titer decrease by 3 or 6 months after treatment. The proportion of cefixime arm participants treated successfully was 87% (95% confidence interval, 69%–100%; 13/15).

Clinical Trials Registration. NCT03752112.

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The public health burden of *Treponema pallidum* subspecies *pallidum*, the etiologic agent of syphilis, is substantial. Left untreated, syphilis can often span decades with multiple stages of infection and can cause serious complications [1]. Early syphilis can also increase the chances of acquiring and transmitting human immunodeficiency virus (HIV) infection by 2- to 5-fold [2, 3]. Syphilis rates have been increasing both in the United States and internationally, with incidence higher among men who have sex with men (MSM) and people living with HIV infection [4, 5].

The currently recommended treatment for syphilis by both the World Health Organization and the Centers for Disease Control and Prevention is injectable benzathine penicillin G (BPG) [6]. More importantly, BPG is the only recommended treatment for syphilis in pregnancy. Doxycycline, tetracycline, and ceftriaxone are recommended alternative treatments [5, 6]. However, there are limitations to their use; tetracyclines cannot be administered during pregnancy or to children, while treatment with ceftriaxone requires multiple daily intramuscular injections or intravenous administration, making treatment adherence potentially challenging. There is a need to identify safe, effective, and convenient antibiotics to treat early syphilis.

Cephalosporins could be good candidates for evaluation; they are β-lactams that inhibit bacterial cell wall synthesis. A study by Norris et al [7] has shown that the minimum inhibitory concentrations of various third-generation cephalosporins for *T. pallidum* are low (ceftriaxone: 0.0007 mg/L, ceftazidime: 0.007 mg/L, cefetamet: 0.04 mg/L). Considering that ceftriaxone, a parenterally administered third-generation cephalosporin, has demonstrated effectiveness for syphilis, we hypothesized that other third-generation cephalosporins could also be effective.

Cefixime is a United States Food and Drug Administration–approved orally administered third-generation cephalosporin. The drug was first approved in 1986 and is currently used for the treatment of respiratory infections and abdominal infections, and is recommended as an alternative for the treatment of gonorrhea [8]. One dose of cefixime 400 mg Cefixime achieves a maximum serum concentration of 4.74 mg/L at 3.9 hours [8], and its half-life is 3.5 hours. The estimated concentration of cefixime after 12 hours is 0.63 mg/L. A dose of 400 mg every 12 hours achieves a peak concentration of 5.7 mg/L with a trough of 0.7 mg/L. Following a twice-daily dosing regimen, we would expect cefixime concentrations higher than 1 mg/L for >20 hours/day (or for >10 hours for every 12 hours).

In this pilot study, we evaluated the efficacy of cefixime 400 mg, taken orally twice a day for 10 days, as treatment for early syphilis.

METHODS

We conducted a randomized, open-label, noncomparative pilot study in men and women diagnosed with primary, secondary, or early latent syphilis. The detailed protocol of the study is available elsewhere [9].

Participants

In brief, the study took place in 5 primary care HIV community clinics of the AIDS Healthcare Foundation in California. Enrollment was conducted between September 2018 and January 2020.

Eligible participants were 18 years of age or older, with clinically or laboratory-confirmed primary, secondary, or early latent syphilis, with a rapid plasma reagin (RPR) (Arlington Scientific RPR test kit, Arlington, Virginia) titer ≥1:8. HIV-infected individuals had a CD4 T-cell count ≥350 cells/μL and

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had to be virologically suppressed (viral load <200 copies/mL) during the past 6 months.

Patients were excluded if they (1) had an allergy to cefixime or penicillin; (2) were pregnant or had a positive pregnancy test; (3) had a serofast RPR titer (prior titer ≥1:8 without a history of 4-fold titer decline); (4) received antimicrobial therapy with activity against syphilis within the past 7 days, namely azithromycin, doxycycline, ceftriaxone or other β-lactam antibiotics (eg, amoxicillin); or (5) had a medical condition or other factors that might affect their ability to follow the protocol.

Randomization and Interventions

Participants were randomized (1:1) to receive either BPG 2.4 MU intramuscularly once or cefixime 400 mg, by mouth, twice daily for 10 days. For those assigned to the penicillin arm, the injection was administered on the day of enrollment. Patients assigned to the cefixime arm received 20 capsules of cefixime 400 mg. On the day of treatment initiation, demographic information, sexual history, and laboratory tests (CD4 count, baseline RPR, and viral load) were collected. Participants were asked to return to the clinic at 3, 6, and 12 months after enrollment for clinical evaluation (sexual history, antibiotic use, symptoms) and repeat RPR titer testing. Participants of the cefixime group were asked to either return to the clinic or participate in a phone call 2 weeks following enrollment to evaluate treatment adherence.

Primary Outcome

The primary outcome was treatment response by the 3- or 6-month follow-up. Treatment response was defined as a ≥4-fold RPR titer decrease from baseline.

Statistical Analysis

The primary analysis for the main outcome was conducted on the per protocol (PP) population. This included participants who satisfied the inclusion and exclusion criteria, completed treatment (ie, received the penicillin injection or reported taking the full 10 days of oral cefixime medication), returned for follow-up visits (3 and 6 months), and had evaluable RPR results.

Sensitivity analysis was conducted on the intent-to-treat (ITT) population, which included all of the participants enrolled in the study, regardless of protocol deviations, loss to follow-up, or study withdrawals. Participants who were lost to follow-up or withdrawn from the study were counted as failing treatment.

We calculated the proportion of participants who achieved a 4-fold RPR titer decrease at 3 or 6 months after treatment in each treatment arm and the exact binomial 95% confidence interval (CI).

To ensure that proper randomization was evident between the 2 treatment arms, χ^2 values were calculated for the relationship between baseline characteristics and the treatment randomization variable. The χ^2 values were evaluated for both levels of analysis (ITT and PP). Analysis was conducted using SAS software, version 9.4 (SAS Institute, Cary, North Carolina).

Human Subject Considerations

The protocol of the study was reviewed and approved by the institutional review boards (IRBs) of WCG IRB (IRB number 20181796) and the University of California, Los Angeles (IRB number 18-000665). The study is registered at ClinicalTrials.gov (identifier NCT03752112).

RESULTS

Participants

In total, 58 participants were enrolled; 27 participants were randomized into the cefixime arm and 31 participants to the penicillin arm. All randomized participants were included in the ITT population. The PP population included 15 participants randomized to the cefixime arm and 15 randomized to the penicillin arm, after excluding protocol deviations, withdrawals, or missed study follow-ups.

All participants of the PP population were male, and the majority identified as MSM. Most of the participants (70%) identified as Hispanic/Latino. All participants were HIV infected, with a median CD4 count of 598 cells/μL in the penicillin arm and 610 cells/μL in the cefixime arm. All but 2 participants were enrolled at an early latent stage of syphilis (Table 1).

Randomization

No significant χ^2 probabilities were observed at the .1 or .05 significance level for all relevant baseline characteristics across analysis levels, showing appropriate randomization to the 2 study groups.

Efficacy of Cefixime and BPG

In the PP analysis, treatment response at 3 or 6 months was achieved by 93% (95% CI, 81%–100%; 14/15) of participants in the penicillin treatment arm and 87% (95% CI, 69%–100%; 13/15) in the cefixime treatment arm. In the ITT analysis, treatment response was achieved by 81% (95% CI, 67%–95%; 25/31) in the penicillin treatment arm and 56% (95% CI, 37%–74%; 15/27) in the cefixime treatment arm.

Three cases of treatment nonresponse (serological failure) were recorded: 2 cases among participants of the cefixime arm and 1 among participants of the penicillin arm. Serological treatment failures are summarized in Table 2. These cases received standard-of-care treatment (2.4 MU injectable BPG) at the 6-month time point.

Cefixime Tolerability

Among the 27 participants who received cefixime, 1 adverse event was recorded. One participant reported a mild skin rash

Table 1. Baseline Characteristics of Per Protocol Population (N = 30) by Treatment Group

Characteristic	Type of Treatment			
	Cefixime (n = 15)		BPG (n = 15)	
Male sex	15	(100)	15	(100)
Age, y, median (IQR)	39	(32.5–52.5)	40	(37.5–52.5)
Race				
Hispanic/Latino or Spanish origin	11	(73.3)	10	(66.7)
Non-Hispanic African American	3	(20)	3	(20)
Non-Hispanic white	1	(6.7)	2	(13.3)
HIV status				
HIV infected	15	(100)	15	(100)
CD4 count, cells/μL, median (IQR)	610	(379–1516)	598	(352–1703)
Stage of syphilis infection				
Primary	1	(6.7)	1	(6.7)
Secondary	0	(0)	0	(0)
Early latent	14	(93.3)	14	(93.3)
Sex of partner(s)				
Male	15	(100)	13	(86.7)
Both	…	…	1	(6.7)
Declined to answer	…	…	1	(6.7)
No. of sex partners in the last 3 mo, median (range)	4	(1–40)	3	(1–750)

Data are presented as No. (%) unless otherwise indicated.
Abbreviations: BPG, benzathine penicillin G; HIV, human immunodeficiency virus; IQR, interquartile range.

within 4 hours of receiving the first dose of cefixime. The participant was advised to stop treatment and was reevaluated at the clinic the following day. The skin rash resolved without additional treatment. The participant was withdrawn from the study and he received a single dose of 2.4 MU BPG, intramuscularly.

DISCUSSION

In this randomized noncomparative clinical study, 87% of participants with early syphilis who received cefixime were treated successfully. The study included an ethnically diverse group of participants with HIV infection who might be less responsive to standard therapy but remain high-risk for new incident syphilis. Although this study had a modest sample size (N = 15), our findings suggest that cefixime is a potentially efficacious treatment for early syphilis. Further investigation of cefixime is warranted in larger randomized trials to demonstrate clinical efficacy.

One of the major benefits of using cefixime is its safety. Common reported adverse reactions include mild gastrointestinal reactions, such as diarrhea, nausea, and vomiting [10]. In our study, participants tolerated well the daily dosage of 800 mg divided into two 400-mg capsules. Only 1 adverse event was reported—a mild rash a few hours after receiving cefixime.

The high response rate of penicillin (94%) was not surprising. Its efficacy has been established through long clinical experience and many previous studies [5]. Because of its high efficacy, BPG remains the cornerstone of treatment for syphilis. Various studies have shown the efficacy of penicillin as being between 90% and 95% [11].

However, there were several limitations to this study. This pilot study was designed as a noncomparative study that utilizes an experimental group and a contemporaneous group; thus, it is not designed or adequately powered to show differences between the 2 groups of the study. Another limitation to this study was the study sample size, which reduces the precision of the efficacy estimates.

The initial results of this pilot study are encouraging. Alternative and easy-to-administer treatment options for syphilis are urgently needed. Larger randomized controlled studies are important next steps toward evaluating the effectiveness of

Table 2. Treatment Failures Among Participants of the Per Protocol Population

Participant Number	Intervention Arm	Baseline RPR Titer	3-mo RPR Titer	6-mo RPR Titer[a]	12-mo RPR Titer
Participant 23	Cefixime	1:64	1:64	1:64	1:2
Participant 33	Cefixime	1:16	1:8	1:8	1:8
Participant 37	Penicillin	1:16	1:8	1:8	1:16

Abbreviation: RPR, rapid plasma reagin.
[a]All participants were treated at the 6-month visit with 2.4 MU benzathine penicillin G, intramuscularly.

cefixime. Two studies are currently underway. A phase 2 randomized trial evaluating cefixime 400 mg, taken orally twice daily for 10 days, is currently enrolling nonpregnant women in Brazil [12]. Our team will conduct a noninferiority randomized controlled trial, comparing cefixime 400 mg to intramuscular BPG. The study protocol and procedures are currently under development, and enrollment is projected to start in 2021.

Notes

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