Clinical Efficacy of Cefixime for Treatment of Early Syphilis

NCT:03660488

August 10, 2020

Clinical Trial Protocol to Evaluate the Efficacy of Cefixime in the Treatment of Early Syphilis

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Abstract

Background: Syphilis rates have been increasing both in the US and internationally with incidence higher among men-who-have-sex-with-men and people living with human immunodeficiency virus (HIV) infection. Currently, benzathine penicillin is the recommended treatment for syphilis in all patients. Global shortages and cost increases in benzathine penicillin call for alternative treatment options. This study evaluates the efficacy of oral cefixime for the treatment of early syphilis.

Methods: We are conducting a randomized, multisite, open-label, non-comparative clinical trial in Los Angeles and Oakland, California. Eligible participants are ≥18 years old, with primary, secondary or early latent syphilis (Rapid Plasma Reagin [RPR] titer ≥1:8). Patients with HIV infection must have a viral load ≤200 copies/mL and CD4+ T cell count ≥350 cells/µl during the past 6 months. Participants are randomized to receive either 2.4M IU benzathine penicillin G intramuscularly once or cefixime 400mg orally twice a day for 10 days. Participants return at 3, 6, and 12 months post-treatment for follow-up RPR serological testing. The primary outcome is the proportion of participants who achieve ≥4-fold RPR titer decrease at 3- or 6-months post-treatment.

Discussion: Clinical trials evaluating the efficacy of alternative antibiotics to penicillin are urgently needed.

Trial Registration: Clinicaltrials.gov, NCT03660488. Registered September 4, 2018,

https://clinicaltrials.gov/ct2/show/NCT03660488

Keywords

Clinical Trial, Cefixime, *Treponema pallidum*, penicillin, early syphilis, syphilis

Administrative information

Title {1}	Clinical Trial Evaluating the Clinical Efficacy of Cefixime in Treatment for Early Syphilis
Trial registration {2a and 2b}.	ClinicalTrials.gov Identifier: NCT03660488 (1)
Protocol version {3}	Version 9; 11.20.2019
Funding {4}	AIDS Healthcare Foundation research grant (Grant #20181796)
Author details {5a}	1. Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, CA/United States of America 2. Department of Medicine, AIDS Healthcare Foundation, Los Angeles, CA/United States of America 3. Public Health Division, AIDS Healthcare Foundation, Los Angeles, CA/ United States of America
Name and contact information for the trial sponsor {5b}	AIDS Healthcare Foundation

Role of sponsor {5c}	The sponsor played no part in study design; and will play no part in the collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication.

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Introduction

Background and rationale {6a}

Syphilis rates have been increasing both in the US and internationally, with incidence higher among men-who-have-sex-with-men and people living with human immunodeficiency virus (HIV) infection (2-4). Currently, benzathine penicillin is the recommended treatment for syphilis in all patients, including those living with HIV infection. Doxycycline and tetracycline are available alternative treatments for non-pregnant patients who are allergic to penicillin (5-8). Injectable daily ceftriaxone is another alternative treatment that may be considered and is safe in pregnancy, as a recent review from our team showed (9).

Existing alternative treatment recommendations are based on clinical experience, a limited number of small clinical trials, and case series (5-7, 10). However, each regimen poses clinical challenges. Doxycycline/tetracycline require 14 days of treatment by mouth, with tetracycline requiring four daily doses. Ceftriaxone is administered intramuscularly, just like penicillin, but it requires daily injections for 10-14 days, making adherence potentially problematic. In pregnancy, only benzathine penicillin is recommended due to potential toxic effects of the alternatives or due to insufficient efficacy data (WHO). Shortages of benzathine penicillin worldwide have led to the use of unproven non-penicillin alternatives (10-12).

Considering the high cost and time required for developing and approving new antibiotics that can treat syphilis in patients with and without HIV infection, a new approach for identifying new, safe, and efficacious antibiotic treatments for syphilis is necessary. Previously Food and Drug Administration (FDA)-approved antibiotics, that are safe and efficacious in other infections and have a favorable pharmacologic profile suggesting activity against *Treponema pallidum,* may be effective alternatives for treating syphilis.

Cefixime is an FDA-approved orally administered third-generation cephalosporin with spectrum of activity and pharmacokinetic profile similar to that of ceftriaxone, a drug which has been used for the

treatment for syphilis (13). Cefixime is clinically used for uncomplicated urinary tract infections, upper respiratory tract bacterial infections and in the treatment of uncomplicated *Neisseria gonorrhoeae* genital infection (14). To our knowledge, it has never been studied as a treatment for early syphilis.

Cefixime has a well-studied pharmacokinetic profile (14-19). Unlike other alternatives for syphilis, adverse event profiles are favorable with cefixime in non-pregnant as well as pregnant patients (20, 21) . Nearly 40-50% of the dose is absorbed when it is given orally, whether administered with or without food. Peak concentrations occur between 2 and 6 hours following oral administration of a single 400mg tablet. A single 400mg tablet produces an average peak concentration of approximately 3.7μg/mL (range 1.3-7.7μg/mL). Typical blood levels of cefixime after a single dose of cefixime 400 mg by mouth are 4.84 μg/ml maximum at 4 hours and above 1.0 μg/ml at 12 hours. Serum protein binding is concentration independent with a bound fraction of approximately 65%. Cefixime is moderately distributed into extracellular water/tissue pools. Its half-life averages to 3-4 hours but may range up to 9 hours in healthy volunteers. Approximately 50% of the absorbed dose is excreted unmodified in the urine within 24 hours and nearly 10% is excreted in bile (10).

We therefore believe that cefixime's pharmacokinetic similarity to ceftriaxone and its safety in the treatment of pregnant women could potentially make it a viable option in the treatment of early syphilis.

Objective {7}

The primary objective of our study is to determine the efficacy of cefixime 400mg, taken orally two times a day (BID) for 10 consecutive days. Our hypothesis is that cefixime would be an efficacious treatment for early syphilis.

Trial design {8}

This is a randomized, open-label, non-comparative pilot clinical trial. Participants will be randomly assigned (1:1 allocation) to receive either the standard of care benzathine penicillin injection or 10-days of oral cefixime. The study will require 2 years to be completed and each participant will be part of the study for one year.

Methods: Participants, interventions and outcomes

Study setting {9}

The study will take place in 3 primary care HIV healthcare clinics and 1 wellness center of the AIDS Healthcare Foundation in Los Angeles and Oakland, California. Healthcare clinics offer HIV and sexually transmitted infection (STI) primary care services while wellness centers are walk-in comprehensive sexual health clinics that offer HIV/STI screening services, STI treatment and other prevention services.

Eligibility criteria {10}

The inclusion criteria are:

1) Clinically or laboratory confirmed new cases of early syphilis (primary, secondary, early latent syphilis) with a plasma Rapid Plasma Reagin (RPR) ≥ 1:8
2) 18 years of age or older, capable of providing informed consent
3) HIV infected individuals must have CD4 T cll count≥350 cells/mm^3 and be virologically suppressed (viral load < 200 copies/mL) during the past 6 months
4) Able to travel to clinic once a day or be available for phone calls or receive text message for at least 7-10 days

The exclusion criteria are:

1) Allergy to cefixime or penicillin
2) Pregnancy or a positive pregnancy test

3) Serofast RPR titer (prior titer ≥1:8 without history of 4-fold titer decline)
4) Recent (within the past 7 days) or concomitant antimicrobial therapy with activity against syphilis, namely azithromycin, doxycycline, ceftriaxone or other beta lactam antibiotics (e.g. amoxicillin)
5) A medical condition or other factor that might affect their ability to follow the protocol

Who will take informed consent? {26a}

Patients must provide written, informed consent before any study procedures occur (randomization, blood sample collection, treatment). Consent will be obtained by a study team member in a private examination room.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

Patients will also sign a Health Insurance Portability and Accountability Act (HIPAA) release form allowing access to clinical and laboratory data, including their HIV test results.

Interventions

Explanation for the choice of comparators {6b}

This is a pilot, non-comparative clinical trial designed to collect preliminary efficacy data. It includes an "experimental arm" of participants receiving cefixime and a contemporaneous "control arm" of participants receiving benzathine penicillin. The study was not designed to be adequately powered to show a statistically significant difference in the efficacy between the penicillin and cefixime arms.

Intervention description {11a}

Eligible participants who provide their consent are randomized to the two arms of the study. Initially, the study team collects demographic (age, gender, race, ethnicity, contact, sexual orientation) and clinical information (most recent RPR titer, CD4 T cell count, HIV viral load). A venipuncture blood sample is collected by trained clinic staff and it is sent to the laboratory for testing. Testing is conducted on serum using the Arlington scientific RPR test kit (Arlington, Virginia) (22). Participants are randomly assigned to the two treatment groups. Participants assigned to the penicillin arm will receive 1 dose of 2.4M IU benzathine penicillin G on the day of enrollment. Participants who are assigned to the cefixime arm will be given 20 capsules of oral cefixime 400mg on the day of enrollment to take for the following 10 days. Study staff observed receipt of the first dose. Subjects in the cefixime arm will then be asked to return for a clinical assessment or have a phone call assessment with the study team member 2 weeks following enrolment.

Study staff will follow up with all participants at 3, 6, and 12 months. In each follow up, participants are asked questions regarding symptoms, antibiotic use in the past 3 months and number of sex partners with whom they had condom-less sex in the past 3 months. A new venipuncture blood sample is also collected for RPR testing

Criteria for discontinuing or modifying allocated interventions {11b}

Participants may request to leave the study or they may be withdrawn due to study-related adverse events. If a subject is discontinued from study participation due to an adverse event, they will be evaluated by the study clinicians for the need of additional treatment for syphilis. Safety data will be collected on any subject who is withdrawn from the study.

Participants in both study groups may receive additional treatment with penicillin, if they show no response to treatment (stable or absence of 4-fold decline at 6 months).

Strategies to improve adherence to interventions {11c}

To ensure retention of participants, follow-up visits will be scheduled to coincide with routine clinic appointments for HIV care or preventive sexual health appointments, which occur every three months. In addition, study staff will contact participants, either over the phone or via text message, before their scheduled follow-up appointment. Finally, participants will receive reimbursement for their time and transportation in the form of a gift card.

Relevant concomitant care permitted or prohibited during the trial {11d}

Usual HIV care and treatment for the participant will continue throughout the trial. Concomitant antibiotic use during the participation in the study duration of the trial will be recorded.

Provisions for post-trial care {30}

Once participants complete the study, they will be able to continue receiving clinical care from the clinics. Participants study records will be reviewed and if necessary, additional treatment for syphilis will be administered according to the standard of care protocol.

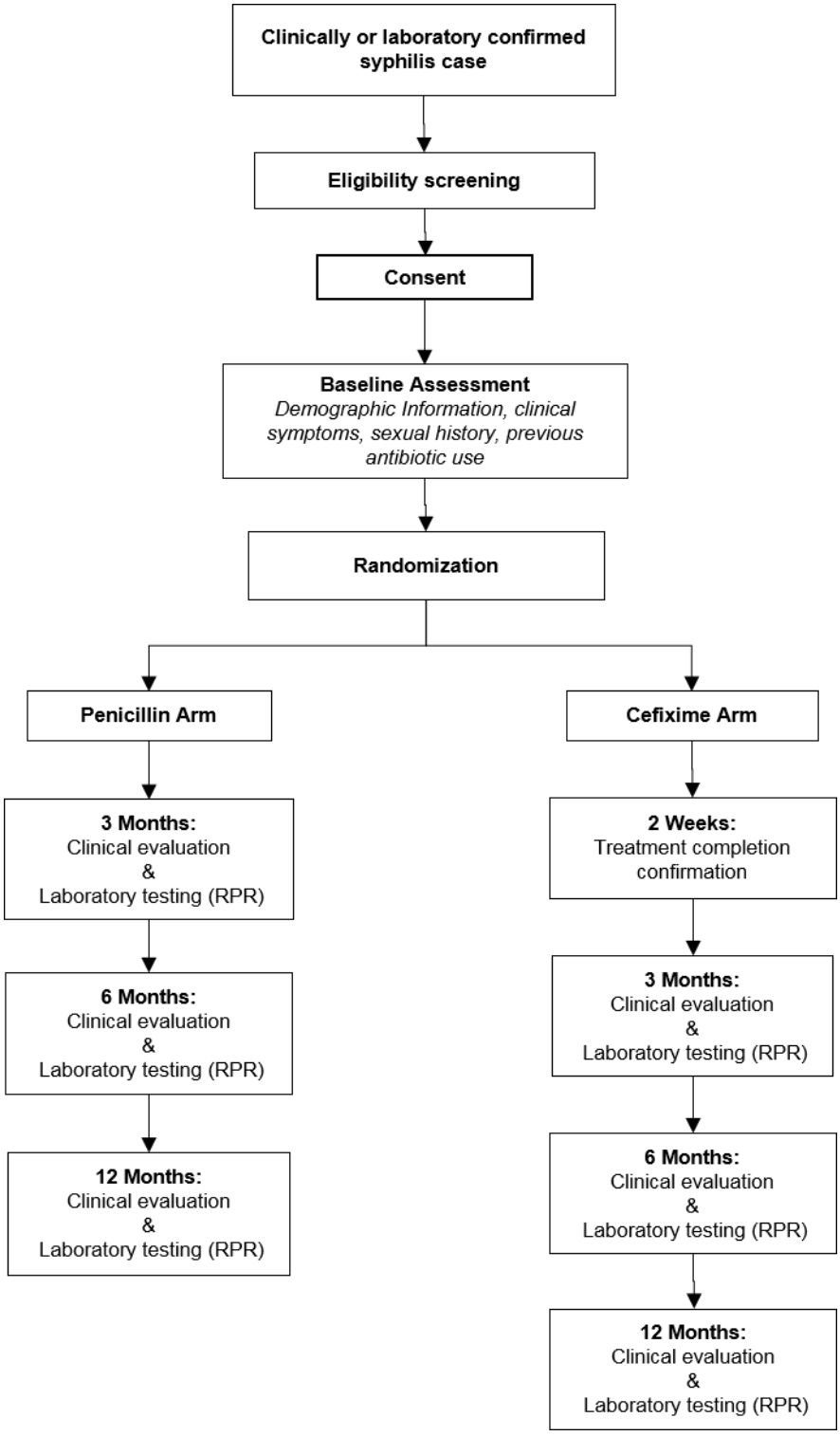
Outcomes {12}

The primary outcome is the successful treatment of early syphilis by the 3-, or 6-month follow-up. The participants' RPR titer will be used as the primary measure of outcome. Successful treatment is defined as an equal or greater than 4-fold RPR titer decrease, from baseline to 3 or 6 months after treatment.

Participant timeline {13}

Participants will be part of the study for 12 months. Study evaluations will occur at 3, 6- and 12-months post-treatment. See Figure 1 for the participant timeline for the trial.

Figure 1: Participant Enrollment and Follow-Up Schedule



Sample size {14}

The primary analysis will compute the proportion of subjects with a 4-fold decrease (from study entry RPR) in RPR titer from baseline at 6 months in the per protocol analysis population. If we assume a sample size of 40 and the proportion of subjects with a 4-fold decrease in RPR from baseline at 6 months to be 0.9 (90%), we would have a 95% confidence interval of (0.76, 0.97). To calculate the number of subjects required to enroll to reach 40 evaluable subjects in the PP analysis population, the assumptions that 20% of subjects will be excluded from the PP analysis population (due to loss to follow-up or non-compliance with study medication schedule). Under that assumption, enrolling 50 subjects will provide 40 subjects in the PP analysis population.

Recruitment {15}

Participant recruitment will occur in 4 AIDS Healthcare Foundation (AHF) Clinics based in Los Angeles, California and Oakland, California. Study clinicians will review the medical and laboratory records of syphilis cases returning for treatment before the scheduled clinical visit and if the participant fulfils the eligibility criteria, they will be invited to participate in the study.

Assignment of interventions: randomization

Sequence generation {16a}

After consent, participants are randomly assigned to the study arms with a 1:1 allocation. We will use a simple randomization method with a shuffled deck of sealed envelopes that contain a card with the assigned treatment. The cards are created before the enrollment period and distributed to each of the study sites. No other factors will be taken into consideration for randomization.

Concealment mechanism {16b}

The envelopes containing the randomization cards are sealed, thus the team member conducting enrollment does not know the content of the envelope.

Implementation {16c}

The study staff will ask the participant to select a sealed envelope from the shuffled deck. After selecting the envelope, the participant will reveal the treatment to themselves and the study staff.

Assignment of interventions: Blinding

Who will be blinded {17a}

This is an open label clinical trial, while neither the participants nor the study staff will be blinded to the assigned treatment, staff performing statistical analyses will be masked to treatment assignment.

Procedure for unblinding if needed {17b}

Not applicable.

Data collection and management

Plans for assessment and collection of outcomes {18a}

A venipuncture blood sample will be collected at 3, 6, and 12 month visits and it will be tested for RPR titer.. Study data collected on baseline include basic demographic information, sexual history, laboratory tests (CD4 count, viral load, RPR titer). On each follow up visit, sexual history, antibiotic use, symptoms and the RPR titer will be collected. Data will be collected on paper data collection forms and will be entered into Research Electronic Data Capture (REDCap) (23, 24).

Plans to promote participant retention and complete follow-up {18b}

Study follow-up visits are scheduled to coincide with routine clinic appointments within AHF. Study staff will send participants a 1 month, 2 week, and 1 day notification prior to their follow-up appointment.

Data management {19}

Participant data will be collected on paper data collection forms and entered into RedCap. Data that will be entered into RedCap include participant information (name, date of birth, medical record number, contact information) and laboratory results.

Confidentiality {27}

Redcap servers are encrypted, HIPAA-compliant, password protected and accessible only by designated study members. Hard copy data collection forms will be stored into a locked cabinet with limited access only to designated members.

Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

There are no plans in this trial to evaluate or store biological specimen for genetic or molecular analysis for future use.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

The primary analysis for the main outcome will be conducted on the "Per Protocol" (PP) population. This will include participants who satisfy the inclusion and exclusion criteria, completed treatment (i.e. received the penicillin injection or received all of the cefixime pills), report no adverse events, returned for follow-up visits (3 and/or 6 months) and have an evaluable RPR result.

For each treatment group, we will calculate the proportion of PP participants who achieved a 4-fold RPR titer decrease at 3, or 6-months post-treatment and the exact binomial 95% confidence interval.

Interim analyses {21b}

A summary of the enrollment progress, treatment success proportions, adverse events and protocol deviations will be provided to the Data Safety Monitoring Board members.

Plans to give access to the full protocol, participant level-data and statistical code {31c}

The protocol of the study is publicly available on clinicaltrials.gov (NCT03660488). Deidentified data will be available upon request to the study Primary Investigator.

Oversight and monitoring

Composition of the coordinating center and trial steering committee {5d}

The immediate study research team based in the University of California of Los Angeles meet on a weekly basis. The immediate team is joined by a wider team of AHF study clinicians, based in study clinics, who also meet on a weekly basis.

Composition of the data monitoring committee, its role and reporting structure {21a}

The Data and Safety Monitoring Board (DSMB) will be composed of a physician, biostatistician, regulatory affairs specialist/ethicist and will oversee the study throughout the 2-year study period. They will review study activities every 6 months. The committee will review safety data and clinical efficacy reports and report their decision to the Primary investigator.

Adverse event reporting and harms {22}

The study site investigators will report serious adverse events and adverse events to the responsible IRB for that study site in accordance with respective IRB policies and procedures. Follow-up

information to a reported adverse event will be submitted to the IRB as soon as the relevant information is available.

Frequency and plans for auditing trial conduct {23}

The trial and individual clinic sites will be audited at least once during the duration of the study by the study sponsor (AIDS Healthcare Foundation).

Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees) {25}

Amendments will be submitted to the IRB according to policies and guidance. Any protocol changes will be promptly communicated to the IRB, the DSMB and the study team.

Dissemination plans {31a}

We plan to disseminate study results through peer-reviewed journal publications and conference presentations. Study findings will also be shared with relevant clinical and scientific groups.

Discussion

This is a randomized, non-comparative, pilot study evaluating the efficacy of daily oral cefixime 400mg for 10 days for the treatment of early syphilis. To our knowledge, this is the first study assessing the efficacy of cefixime for early syphilis. As syphilis rates increase and penicillin shortages continue to occur in the United States and worldwide, alternative treatments that are efficacious for both pregnant and non-pregnant populations, regardless of HIV status are needed (6-8). Already approved and antibiotics in clinical use with favourable pharmacokinetic profile, such

as cefixime, should be clinically evaluated for alternative treatment options.

Data from this pilot study could be used as a foundation to assess the clinical effectiveness for cefixime in early syphilis treatment. Currently, our study is being conducted among non-pregnant individuals. However, subsequent clinical studies should also include women and pregnant women to address the gap in the treatment of maternal syphilis.

Trial status

Recruitment was initiated in September 16th, 2018 and is currently ongoing. The current protocol version is version 9 (11/20/2020).

Declarations

Authors' contributions {31b}

SM led the writing of the manuscript. CS led the proposal and protocol development and contributed to the writing of the manuscript. DT, PB, CO, and CM contributed to clinical and logistical aspects of protocol development. JDK led the proposal and protocol development and developed the treatment algorithm for the protocol. All named authors adhere to the authorship guidelines of Trials. All authors have approved the final manuscript and agreed to publication.

The database for this study was supported by NIH National Center for Advancing Translational Science (NCATS) UCLA CTSI Grant Number UL1TR001881.

Funding {4}

The trial is funded by AHF (Grant #20181796). The funding body had no role in the design of the study, collection of data or the writing of this paper, nor will the funding body have a role in analysis, interpretation of data or in writing future manuscripts.

Availability of data and materials {29}

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate {24}

The study was approved by Western IRB (IRB# 20181796) and UCLA IRB (IRB# 18-000665).

Consent for publication {32}

Not applicable

Competing interests {28}

The authors declare that they have no competing interests.

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