A prospective, randomized, double dummy, double blind, multinational, multicenter trial comparing the safety and efficacy of sequential (intravenous/oral) moxifloxacin 400 mg once daily to intravenous piperacillin/tazobactam 4.0/0.5 g every 8 hours followed by oral amoxicillin/clavulanic acid tablets 875/125 mg every 12 hours for the treatment of subjects with complicated skin and skin structure infections

Published: 25-09-2006
Last updated: 09-05-2024

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Skin and subcutaneous tissue disorders NEC
Study type	Interventional

Summary

ID

NL-OMON29728

Source
ToetsingOnline

Brief title
RELIEF

Condition

- Skin and subcutaneous tissue disorders NEC

Synonym
infected skin, skin infection

Research involving
Human

Sponsors and support

Primary sponsor: Bayer
Source(s) of monetary or material Support: Bayer

Intervention

Keyword: Intravenous, Moxifloxacin, Oral, Skin infection

Outcome measures

Primary outcome

The primary study parameter for this trial is clinical response at the

Test-of-Cure Visit 14-28 days after last dose of study medication. The blinded

assessment will be considered as the primary evaluation for the clinical

response at the TOC visit.

Secondary outcome

• Clinical response assessed by the investigator on treatment Day 3-5.

• Clinical response assessed by the investigator at the End-of -Therapy (EOT).

• Clinical response assessed by the investigator at the TOC visit.

• Bacteriological response at Day 3-5, at EOT and at the TOC visit.

Study description

Background summary

The selection of the optimal antimicrobal agent for treatment of subjects with cSSSIs can be difficult for clinician because of the paucity of well-designed published clinical trials and the various conditions the subjects may present. A number of IV antibiotics, have been investigated for the management of cSSSI during the last decades. Fluoroquinolones are a relatively new alternative to conventional therapies. Amongst them, moxifloxacin has been shown to be effective in treating cSSSIs with efficacy similar to that of standard therapies such as amoxicillin-clavulanic acid or piperacillin/tazobactam.

Study objective

The primary objective of the study is to reject the Null hypothesis: A 7 to 21 day therapy with moxifloxacin, 400 mg once daily is more than 10 % less effective than a 7 to 21 day therapy with piperacillin/tazobactam three times daily possibly followed by oral amoxicillin-clavulanic acid twice daily, based on clinical success at the Test of Cure visit (14 to 28 days after end of therapy).

Study design

A prospective, randomized, double dummy, double blind trial

Intervention

The Test Treatment is sequential (intravenous/oral) moxifloxacin 400 mg once daily.
The Comparator Treatment is intravenous piperacillin/tazobactam 4.0/0.5 g every 8 hours followed by oral amoxicillin/clavulanic acid tablets 875/125 mg every 12 hours.

Study burden and risks

All medicines can cause side effects. Risks that are associated with all of the antibiotics in this study are:
- Use of antibiotics for a long time may result in a secondary infection
- Antibiotics can rarely cause a severe intestinal condition (pseudomembranous colitis) due to a resistant bacteria and this can happen weeks after the study treatment has stopped.

The main side-effects sometimes seen with Moxifloxacin are nausea, vomiting, headache and dizziness.

Moxifloxacin is a quinolone-type antibiotic and quinolones are known to increase the skin*s sensitivity to light giving rise to rash and possibly itching on sun exposed areas. Up to now there is no evidence that this type of sensitivity has been caused by moxifloxacin.

Piperacilline/Tazobactam; The most commonly reported side effects of the intravenous combination of piperacilline and tazobactam are headache, dizziness, nausea, stomach upset or loose stools. These may occur in the first few days of treatment as the body adjusts to the medication. More severe but rarer side effects are vomiting, diarrhoea, fever, chest pain, anxiety, unusual bleeding or bruising.

Amoxicillin/Clavulanic Acid; The most commonly reported side effects of the oral combination of amoxicillin and clavulanic acid are diarrhoea, nausea or vomiting during the first few days as the body adjusts to the medication.

As the study drug is under development there may be side effects that are not yet known. Also, as it may be the case when taking any kind of medication, unexpected or unknown side effects may occur.

General Risks: Risks associated with drawing blood from the arm or injecting IV medication include pain, bruising, swelling, light headedness, and on rare occasion, infection and nerve damage (some numbness and tingling).

The needle aspiration or the biopsy may cause some pain, bruising, bleeding or infection in the biopsy areas.

Risks for Nursing Mothers, Pregnancy and Children: Risks to pregnant women, the embryo, the foetus and nursing children are unknown. Females who enter this study should not be pregnant nor should they be breastfeeding.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Written informed consent.
2. Men or women of age => 18 years of age with a diagnosis of bacterial skin and skin structure infection that requires
a. Hospitalization
or
b. Initial parenteral therapy for at least 48 hours and
c. Meets at least one of the following criteria:
- Involvement of deep soft tissue (eg, fascial, muscle layers)
- Requirement for a significant surgical intervention including surgical drainage, drainage procedure guided by imaging and/or debridement.
- Association with a significant underlying disease that may complicate response to treatment. An underlying disease is considered significant if it includes any of the following conditions that are present at the time of presentation: cancer (except basal- or squamous-cell cancer of the skin), cardiac (ie, congestive heart disease), diabetes mellitus, hepatic (ie, cirrhosis or another form of chronic liver disease), immunologic, renal disease, respiratory, transplantation or vascular disease.
3. Duration of infection < 21 days.
4. Diagnosis of one of the following skin and skin structure infections that requires hospitalization and initial parenteral antibiotic therapy for at least 48 hours:
a. Major abscess(es) associated with extensive cellulitis, which requires antibiotic therapy in addition to surgical incision and drainage.
b. Diabetic foot infection of mild to severe intensity (PEDIS grade 2-4) in the presence or absence of osteomyelitis. Subjects with osteomyelitis may only be enrolled if the infected bone is completely removed by surgery and if residual infection requiring antibiotics is still present following surgery.
c. Wound infection including: post surgical (surgical incision), post-traumatic, human

bite/clenched fist and animal bite wound and wound associated with injection drug abuse:
- Infections must have occurred within 30 days of a surgical procedure, trauma, animal bite, or human bite, and involve the skin and skin structures at the site of the incision, trauma, or bite.
- In addition, post-surgical/trauma wound infections must meet the following criteria:
* Involvement of deep soft tissues (eg, fascial and muscle layers) of the incision/trauma.
* At least one of the following criteria:
* Purulent drainage from the deep incision/trauma.
* Identification of an infecting organism from an aseptically obtained culture of fluid or tissue from incision/trauma.
* At least one of the following signs and symptoms:
a. Localized pain or tenderness.
b. Fever (see below).;AND ;The incision (in case of post-surgical wound infections) is deliberately opened by a surgeon, unless the culture is negative.
- Abscess or other evidence of infection involving the deep incision/trauma, found on direct examination, during reoperation/operation (in case of trauma), or by histologic or radiologic examination.
- Diagnosis of a deep incisional/post-trauma SSI by a surgeon or attending physician.
- Bite wounds/clenched fist infections and wounds associated with injection drug abuse must meet the criteria defining a cSSSI (see point 2c).
d. Infected ischemic ulcers with at least one of the following conditions:
- Peripheral vascular disease.
- Conditions pre-disposing to pressure sores such as paraplegia, peripheral neuropathy.
5. Presence of at least 3 of the following signs or symptoms:
a. Purulent drainage or discharge.
b. Erythema extending > 1 cm from the wound edge.
c. Fluctuance.
d. Pain or tenderness to palpation.
e. Swelling or induration.
f. Fever, defined as body temperature
- > 37.5°C (axillary).
- > 38°C (orally).
- > 38.5°C (tympanically) or
- > 39°C (rectally).
OR
Elevated total peripheral white blood cell (WBC) count > 12,000/mm3.
OR
> 15 % immature neutrophils (bands) regardless of total peripheral WBC count.
g. C reactive protein (CRP) > 20 mg/L.
6. Specimen obtained for culture from infected area by needle aspiration of obviously purulent material or by tissue biopsy or by curettage of the surface of ulcer within 24 hours prior to the initiation of study drug therapy.
7. Duration of treatment of the skin/skin structure infection is anticipated to be at least 7 days.;Surgical drainage or debridement of infected wounds or abscesses, if necessary, have to have been completed <= 48 hours after the initiation of study drug therapy.

Exclusion criteria

1. Women, who are pregnant or lactating, or in whom pregnancy can not be excluded (Note: a urine pregnancy test has to be performed for all women of childbearing potential before randomization to the study drug).
2. The following skin and skin structure infections:
a. Necrotizing fasciitis including Fournier*s gangrene, ecthyma gangrenosum, streptococcal necrotizing fasciitis and clostridial necrotizing fasciitis.
b. Burn wound infections.
c. Secondary infections of a chronic skin disease (eg, atopic dermatitis).
d. Infection of prosthetic materials (eg, subcutaneous tissue infection related to a central venous catheter or permanent cardiac pacemaker battery pack). Subjects with removal of a prosthetic device involved in an infection should not be included.
e. Infections where a surgical procedure alone is definitive therapy.
f. Subjects with uncomplicated skin and skin structure infections including folliculitis and furunculosis, carbunculosis, simple abscesses and superficial cellulitis.
3. Known hypersensitivity to quinolones and/or any type of beta-lactam antibiotic drugs or any of the excipients.
4. Previous history of cholestatic jaundice/hepatic dysfunction associated with amoxicillin-clavulanic acid.
5. Severe, life threatening disease with a life expectancy of less than 2 months.
6. Immunosuppression including:
a. Known neutropenia (neutrophil count < 1000/*L).
b. Known lymphopenia with absolute CD4+ T cell count < 200/mm3.
c. AIDS-defining event and/or concomitant therapy with HAART.
d. Chronic treatment (>= 2 weeks) with known immunosuppressant therapy (including treatment with > 15 mg/day of systemic prednisone or equivalent).
e. Any other congenital or acquired immune defect or immunosuppression.
7. Known severe hepatic insufficiency (Child Pugh C) or transaminases increase > 5 fold upper limit of normal (ULN).
8. Known renal impairment with a baseline measured or calculated serum creatinine clearance < 40 mL/min).
9. Known prolongation of the QT interval or concomitant use of drugs reported to increase the QT interval (eg, Class IA or Class III antiarrhythmics [eg., quinidine, procainamide, amiodarone, sotalol], neuroleptics [eg., haloperidol], tricyclic antidepressive agents, certain antimicrobials [eg, pentamidine, halofantrine], certain antihistaminics [eg., terfenadine], and other [cisapride, vincamine IV, depridil, diphemanil]).
10. Uncorrected hypokalemia.
11. Clinically relevant bradycardia.
12. Clinically relevant heart failure with reduced left ventricular ejection fraction (ie, below 40%).
13. Previous history of symptomatic arrhythmias.
14. Previous history of tendon disease/disorder with quinolones.
15. Known or suspected concomitant bacterial infection requiring additional systemic antibacterial treatment, eg, underlying septic arthritis.
16. Requiring therapy with probenecid.

17. Treatment with a systemic or topical antibacterial agent for > 24 hours in the previous 7 days preceding study entry unless the subject showed no response or had worsening of clinical signs and symptoms despite 3 or more days of prior therapy and a culture obtained at the time of subject enrollment showed persistence of a pathogen which is susceptible to the study drugs. The prior antimicrobial therapy must not have been a fluoroquinolone or a beta lactam/beta lactamase combination.
18. Infection known to be due to a MRSA, MRSE or VRE as the single isolated pathogen.
19. Previous enrolment in this study.
20. Participation in any clinical investigational drug study within 4 weeks of screening.
21. Previous history of seizure disorders.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	29-05-2007
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Augmentin
Generic name:	amoxicillin/clavulanic acid
Registration:	Yes - NL intended use
Product type:	Medicine

Brand name:	Avelox
Generic name:	Moxifloxacin
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Tazocin
Generic name:	piperacillin/tazobactam
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	25-09-2006
Application type:	First submission
Review commission:	METC Maxima Medisch Centrum (Veldhoven)
Approved WMO Date:	02-02-2007
Application type:	Amendment
Review commission:	METC Maxima Medisch Centrum (Veldhoven)
Approved WMO Date:	23-04-2007
Application type:	Amendment
Review commission:	METC Maxima Medisch Centrum (Veldhoven)
Approved WMO Date:	16-05-2007
Application type:	First submission
Review commission:	METC Maxima Medisch Centrum (Veldhoven)
Approved WMO Date:	18-02-2008
Application type:	Amendment
Review commission:	METC Maxima Medisch Centrum (Veldhoven)
Approved WMO Date:	21-03-2008
Application type:	Amendment
Review commission:	METC Maxima Medisch Centrum (Veldhoven)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2006-001599-18-NL
CCMO	NL13846.015.06