New Antibiotic Treatment Options for Uncomplicated Anogenital Gonorrhoea infections

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Primary objectivesTo determine the bacterial eradication capacity of ertapenem, fosfomycine and gentamicine compared to the reference treatment (ceftriaxone) in uncomplicated anogenital gonococcal infections (at one included infection site) by...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Bacterial infectious disorders
Study type	Interventional

Summary

ID

NL-OMON49273

Source
ToetsingOnline

Brief title
NABOGO

Condition

- Bacterial infectious disorders

Synonym
Gonorrhea, Neisseria gonorrhoeae

Research involving
Human

Sponsors and support

Primary sponsor: AMC dermatologie
Source(s) of monetary or material Support: ZonMW

Intervention

Keyword: Gonorrhoea, Neisseria gonorrhoeae, RCT, Treatment

Outcome measures

Primary outcome

- Bacterial eradication of Ng-infection at the included infection site, based on a test of cure (TOC) using an RNA-based NAAT (Aptima Combo 2 assay) at the follow-up visit 7-14 days after treatment (T7), or

- Meet the criteria for treatment failure as described in the protocol (7.1.1.)

Secondary outcome

1. Bacterial eradication of Ng-infection at the included infection site, based on TOC using an RNA-based NAAT 7-28 days after treatment.

2. Bacterial eradication of Ng-infection at any infected site(s) not included in the primary endpoint analysis, based on a TOC using an RNA-based NAAT 7-28 days after treatment.

3. Any adverse events (type, frequency and severity) occurring during 7-14 days following the start of treatment, and during 1 month after treatment.

4. In vitro MICs of all Ng-strains for all study antimicrobials, determined by e-test on culture at inclusion (before treatment, T0) and at the TOC follow-up visit (T7).

5.

a. Symptoms (such as pain, irritation/itch, redness, any discharge, bleeding, changed defecation pattern and/or swelling) from treatment to TOC visit (7-14 days).

b. Time (in days) from the start of treatment to disappearance of symptoms.

c. Signs (such as mucosal fragility, redness, discharge, bleeding and/or

swelling) assessed at physical examination if indicated, at T0 and T7.

6. Pharmacokinetic characteristics of study drugs in peripheral blood up to 24

hours after administration.

Study description

Background summary

Antimicrobial resistant gonorrhoea is a growing worldwide problem. Resistance and treatment failures to the last evidence-based treatment option, ceftriaxone, have been reported In several European countries, including the Netherlands. It is feared that ceftriaxone resistance will become widely prevalent, making this last resort treatment obsolete, and gonorrhoea once again an untreatable disease causing frequent and severe chronic complications. In the short term, no new antibiotics are expected. Yet existing antibiotics could form promising new treatment modalities, but
these need to be evaluated first in patients with gonorrhea. If there is sufficient clinical efficacy, these agents can be considered
first line alternative options for the future treatment of ceftriaxone resistant gonorrhoea.

On October 2, 2018, the fosfomycin treatment arm of the NABOGO trial was dropped. From this moment, fosfomycin and oral placebo was not administered to participants anymore. This decision was based on the advice of the Data Safety Montoring Board (DSMB) following the predefined stopping rules after on a pre-arranged interim analysis.

Study objective

Primary objectives
To determine the bacterial eradication capacity of ertapenem, fosfomycine and gentamicine compared to the reference treatment (ceftriaxone) in uncomplicated anogenital gonococcal infections (at one included infection site) by molecular test of cure 7-14 days after treatment.

Secondary objectives
1. To determine the bacterial eradication capacity of the experimental treatment options (ertapenem, fosfomycine and gentamicine) compared to the reference treatment (ceftriaxone) in uncomplicated anogenital gonococcal infections by molecular test of cure after 7-28 days.

2. To determine the bacterial eradication capacity of experimental treatment options compared to the reference treatment at infection sites other than the included infection site (also pharyngeal gonorrhoea) by molecular test of cure after 7-28 days.
3. To determine the type, frequency and severity of adverse events of the experimental treatment options compared to the reference treatment.
4. To determine the in vitro antimicrobial susceptibility (in MIC) of the experimental and reference treatment in all Ng-strains collected at all infected anatomical sites of each participant at inclusion and in case of a positive test of cure.
5. To determine the time to disappearance of symptoms at the included infection site in the first 14 days after treatment, for the experimental treatment compared to the reference treatment.
6. To determine the clinical and demographic predictors for treatment failure (see chapter 7 for definition).
7. To determine the population pharmacokinetics of ceftriaxone, gentamicin and ertapenem administered intramuscularly, and fosfomycin administered orally.

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Study design

A double-blind randomized non-inferiority trial with three experimental arms and one reference arm.

The project consists of two parts:
1. Clinical- and microbiological efficacy and side effects of ertapenem, gentamicin, and fosfomycin,
2. A Monte Carlo simulation model based on pharmacokinetic- and antimicrobial susceptibility data of N. gonorrhoeae strains to
predict the future treatment failure rate under various antimicrobial resistance prevalence conditions.

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Intervention

- Reference treatment: single dose ceftriaxone 500 mg IM, dissolved in 2 ml

lidocaine 1% supplemented with 0.9% NaCl until 10 ml (2 x 5 ml).
- Experimental arm 1: single dose ertapenem 1000 mg IM, dissolved in 3.2 ml lidocaine 1% supplemented with 0.9% NaCl until 10 ml (2 x 5 ml).
- Experimental arm 2: gentamicin 5 mg/kg IM injection once (solution 40 mg/ml), if indicated supplemented with 0.9% NaCl until 10 ml (2 x 5 ml).
- Experimental arm 3: fosfomycin 6 gram trometamol oral once.
- Placebo intramuscular injection: 10 ml (2 x 5 ml) 0.9% NaCl.
- Placebo oral suspension: orange lemonade.

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Volunteers participating in the PK substudy will not receive gentamicin.

Study burden and risks

Considering the development pattern of resistance to previous first line treatment regimes for gonorrhoea on one side and, the emergence of Ng-strains with decreased susceptibility or even resistance to ESCs on the other side, it is expected that gonorrhoea becomes untreatable in the near future. For this reason, there is an urgent need to find alternative treatment options. Previous research suggests that ertapenem, fosfomycin and gentamicin might be effective and safe options. However, this is not yet proven by well-designed and robust trials in uncomplicated anogenital gonorrhoea cases. The most important risk for participants in this study is thus inefficacy of one of the treatment options, and therefore treatment delay. To minimize this risk, we will install a DSMB to perform an interim analysis on treatment efficacy. In the case of disproportional numbers of treatment failure in one treatment arm, we will preliminary terminate this arm. Furthermore, there is always a risk of adverse events in medication trials. Since ceftriaxone, ertapenem, fosfomycin and gentamicin are registered and safely used for several indications for decades, we expect the risk of serious adverse events to be minimal. However, nephro- and ototoxicity are known side effects of gentamicin, in particular among patients receiving multiple (high) dosages of gentamicin and among patients with renal impairment. Although the effects of a single dose of gentamicin are never structurally investigated, we do expect this risk to be low in our relatively healthy study population receiving a single dose intramuscular dose. The consequences of nephro- and ototoxicity are considered serious, therefore we will examine the renal function (by performing a point of care serum creatinine test) and symptoms of ototoxicity (by questionnaire) before and after the admission of treatment. We will exclude patients with renal impairment defined by an eGFR<50mL/min (Cockroft-Gault). A disadvantage for participation is the administration of an additional intramuscular injection and an oral suspension. Albeit the risk of pain/bleeding/infection at injection

site is very low, it is increased as a result of two IM injections instead of one. In conclusion, the most important benefit for participants, as well as for anyone else at risk for STIs, is the aim to assure treatment options for gonorrhoea in the near future. A benefit for participants in particular is a TOC and thus assurance of bacterial eradication.

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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

18 years old and older
Anorectal, cervical, urethral or vaginal gonorrhea; confirmed by positive gram stain and NAAT / culture
Willing to return for test of cure
Willing to abstain from sex or use condoms until follow-up visit
Provide informed consent

Exclusion criteria

Complicated gonorrhea
Genital ulcer at inclusion visit
Known Chlamydia trachomatis infection
Pregnant or breastfeeding
Unable to read Dutch or English
Newly diagnosed HIV infection
CD4+ cell count <200 cells/ul
Known allergy to the study antibiotics
History of renal impairment, liver cirrosis and/or heart failure
Concurrent use of any of the following: systemic antibiotics/immunosuppressives/valproic acid
Previous enrolment in the study
Current participation in other non-observational medical research

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	18-09-2017
Enrollment:	406
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Gentamicin
Generic name:	Gentamicin
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Invanz
Generic name:	Ertapenem
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Monuril
Generic name:	Fosfomycin
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Rocephin
Generic name:	Ceftriaxone
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	21-06-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-08-2017
Application type:	First submission

Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-03-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-03-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-03-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-05-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-06-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2017-000176-28-NL
ClinicalTrials.gov	NCT03294395
CCMO	NL60555.018.17