FOsfomycin Randomised controlled trial for E.coli Complicated urinary tract infections as Alternative Stepdown Treatment

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To demonstrate non-inferiority of oral fosfomycin-trometamol compared to oral ciprofloxacin as a step-down treatment for E.coli AF-UTI in women for the cumulative incidence of survival and clinical cure (resolution of symptoms) 6-10 days post-...

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

Summary

ID

NL-OMON47265

Source
ToetsingOnline

Brief title
FORECAST
FORECAST-ECO (substudy)
FORECAST-FAR (substudy)

Condition

- Bacterial infectious disorders

Synonym
ascending urinary tract infection, Complicated urinary tract infection

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Antibiotic therapy, Enterobacteriaceae, Fosfomycin, Urinary tract infection

Outcome measures

Primary outcome

The primary endpoint is the cumulative incidence ofclinical cure (resolution of symptoms, incl. survival)) 6-10 days post-treatment

Secondary outcome

Secondary endpoints:

1. The cumulative incidence of microbiological cure 6-10 days post-treatment

2. The cumulative incidence of survival AND clinical cure (resolution of symptoms) AND microbiological cure 6-10 days post-treatment

3. The cumulative incidence of acquired fosfomycin resistance, ciprofloxacin resistance or ESBL-producing bacteria in urine culture 6-10 days post-treatment

4. The cumulative incidence of survival and clinical cure (resolution of symptoms) 30-35 days post-treatment

5. The cumulative incidence of mortality for any reason or related to UTI or study medicines within 30-35 days post-treatment

6. The cumulative incidence of ICU admissions for any reason or related to UTI or study medicines within 30-35 days post-treatment

7. The cumulative incidence of readmissions for any reason or related to UTI or study medicines within 30-35 days post-treatment

8. The cumulative incidence of relapses within 30-35 days post-treatment

9. The cumulative incidence of reinfections within 30-35 days post-treatment

10. The cumulative incidence of additional antibiotic use for UTI within 30-35 days post-treatment

11. The cumulative incidence of early discontinuation of study medicines because of adverse events OR because of loss of complaints

12. Total days of hospitalisation and Intensive Care Unit stay within 30-35 days post-treatment

13. The cumulative incidence of absenteeism within 30-35 days post-treatment

14. The cumulative incidence of study protocol related and unrelated adverse events, within 30-35 days post-treatment

15. Patient characteristics associated with the primary or secondary outcomes in both study arms (Charlson comorbidity index, Diabetes Mellitus y/n, indwelling catheter y/n, age
y/n, treatment restrictions at randomisation y/n, renal stones y/n)

16. Disease related characteristics associated with the primary or secondary outcomes in both study arms (systemic symptoms, ICU admission before iv-oral switch, local symptoms, bacteraemia y/n, time being afebrile before iv-oral switch, CRP, kreatinin, WBC at admission)

17. Treatment related characteristics associated with the primary or secondary outcomes in both study arms (duration of oral treatment, compliance, duration, name and dose empirical intravenous antibiotic treatment)

FORECAST-ECO: Classical culture and whole-genome sequencing of the feces on

different time points in the blinded treatment of either fosfomycin or

ciprofloxacin.

FORECAST-FAR: Plasma en urine concentrations of participants on pre-defined

timepoints after intake of blinded studymedication

Study description

Background summary

Difficulties arise in the treatment of common infections due to antibiotic resistance and
the lack of new antibiotics. The high level of resistance to oral available antibiotics is worrisome and encourages the exploration of alternative antibiotic options (1).

Urinary Tract Infections (UTI) are the most common bacterial infections needing antibiotic treatment in the western world (2). Complicated urinary tract infections (cUTI) are defined upon the presence of systemic symptoms - Acute Febrile-Urinary Tract Infections - (AF-UTI) or upon the susceptibility of the host for a complicated course (3). Systemic symptoms include fever, rigors, delirium or hemodynamic instability. Examples of AF-UTI, pyelonephritis, urosepsis, are difficult to distinguish at first presentation (4). Host factors associated with a complicated course in women are pregnancy, anatomical or functional abnormalities of the urinary tract, presence of a urinary catheter, renal diseases (polycystic kidney disease, renal stones, renal transplant patients), and immunocompromising diseases such as diabetes (3).

Dutch national guidelines recommend to treat AF-UTI with a 10-14 day course of antibiotics (3). The recommended empirical treatment is with intravenous antibiotics in the majority of cases followed by oral stepdown antibiotics. The Dutch national guideline for antibiotic stewardship recommends stepdown to an oral agent after 48 hours of therapy on the basis of the clinical condition and when oral treatment is feasible. The choice of oral antibiotics should be based on documented bacterial antibiotic susceptibility, if available (5).
Often used oral antibiotics as stepdown treatment of AF-UTI are amoxicillin, amoxicillin + clavulanic acid, ciprofloxacin and trimethoprim-sulfamethoxazole.

Unfortunately, antibiotic resistance increasingly complicates oral treatment. cUTI are mainly caused by Enterobacteriaceae. Escherichia coli (E.coli) is the

causative organism in around 70-75% of cUTI (6,7). In 2015, E. coli was the most frequently isolated pathogen (43%) in inhospital non-Intensive Care Unit (ICU) departments in the Netherlands followed by Klebsiella pneumoniae (7%) and Proteus mirabilis (7%) (1). The resistance of Enterobacteriaceae for currently used antibiotics is worrisome. In 2015, resistance proportions of inhospital (non-ICU) E. coli isolates in the Netherlands were 13% for ciprofloxacin, 25% for trimethoprim-sulfamethoxazole and 21% for amoxicillin + clavulanic acid. For K. pneumoniae these proportions were 6%, 13% and 11%, respectively, and for P. mirabilis 9%, 27% and 24%, respectively (1). Among Enterobacteriaceae derived from patients visiting urology departments the resistance level for ciprofloxacin is even higher, about 25% in the Netherlands (3). As fluoroquinolone use is associated with the development of fluoroquinolone resistance and Extended Spectrum Beta-Lactamase (ESBL) production, a goal of antibiotic stewardship in many Dutch hospitals has become the reduction of fluoroquinolone use (eg. ciprofloxacin) (3). For cUTI caused by bacteria resistant to all oral antibiotic drugs, only intravenous antibiotics remain. This implies that patients need to receive the entire course intravenously, either in the hospital or provided at home by specialized personnel. This may require an extra week of hospitalisation with an additional risk of complications and added healthcare costs.

Fosfomycin is a phosphoenolpyruvate analogue, produced by Streptomyces spp., but also produced synthetically (8). The only treatment indication for oral fosfomycin in the Netherlands is uncomplicated UTI in women. Oral fosfomycin-trometamol is a promising antibiotic for cUTI. It has high bactericidal activity against Enterobacteriaceae, especially to E. coli. The resistance rate to fosfomycin in inpatient -non ICU - E.coli isolates is currently <1% in the Netherlands without co-resistance to other antibiotics such as ciprofloxacin, trimethoprim-sulfamethoxazole and/or cephalosporins (1). Its bio-availability is up to 40% with good tissue penetration in urine and urine bladder (9*14). Oral fosfomycin-trometamol has been effective as treatment of cUTI and as prophylaxis before prostate biopsy (14*19). Oral fosfomycin-trometamol was non-inferior in comparison to carbapenems in observational studies considering cUTI*s (20,21). Oral fosfomycin-trometamol has a good tolerability and little side effects; it is used extensively with a good safety profile (22).

As cUTI are two distinct entities in women and men, accociated with different treatment durations, different outcomes and different etiologies, it is impossible to consider it as one group. Stratifying for men would not provide enough participants and therefore gives not enough power to prove non-inferiority. Therefore, in first instance, this trial will investigate the efficacy only in women. If fosfomycin-trometamol would be non-inferior in women.

In conclusion, oral fosfomycin-trometamol has great potential as stepdown antibiotic treatment for AF-UTI. Clinical evidence from randomised studies is

lacking. In this *real practice* randomised controlled, double blind, non-inferiority, multicentre investigator initiated trial, we aim to provide evidence for the use of fosfomycin-trometamol in the stepdown therapy of AF-UTI.

FORECAST-ECO:
The FORECAST trial provides the perfect opportunity to evaluate the development of resistance of Enterobacteriaceae, especially of E. coli after oral ciprofloxacin or fosfomycin use. This is the first blinded randomised controlled trial that investigates the development of Enterobacteriaceae resistance during fosfomycin-trometamol therapy using classical culture methods and metagenomics analysis. A comparison between these arms provides useful information and have implications for the future employability of these antibiotics.The FORECAST-ECO substudy will determine the direct and late effect of oral ciprofloxacin and fosfomycin therapy on gut microbiota diversity and development of antibiotic resistance in Enterobacteriaceae For this, stool samples will be collected on different time points before, during and after study treatment. This study will give insights on the ability of bacteria to develop resistance to the drug fosfomycin. This is of great importance because of possible prospective applications of fosfomycin.
Additionally, in case of newly found forms of Enterobacteriacea resistance, we will seek for identification of direct mutants to baseline urinary E. coli.

FORECAST-FAR:
The FORECAST study investigates the clinical and microbiological efficacy of fosfomycin-trometamol in the stepdown treatment of complicated Urine Tract Infections (cUTI). The FORECAST-FAR study is a sub-study of the larger FORECAST study and focuses on the pharmacokinetic profile of fosfomycin-trometamol and oral ciprofloxacin. With the emergence of Enterobacteriaceae resistance, only few oral available antibiotics exist for the treatment of cUTI.
Fosfomycin-trometamol has been used as a single-dose preparate for uncomplicated cystitis. Little is known about the pharmacokinetic properties of fosfomycin-trometamol; the few available studies in this topic are performed on healthy individuals who received a single-dose of fosfomycin-trometamol. In the FORECAST study fosfomycin will be used in a heterogenous patient population with a cUTI, in a dosage of 3 gram every 24 hours for 5-8 days. This design provides the opportunity to measure plasma and urine concentrations of both fosfomycin and ciprofloxacin in order to determine and compare the pharmacokinetic properties of both antibiotics and relate these with the clinical and microbiological outcome.

Study objective

To demonstrate non-inferiority of oral fosfomycin-trometamol compared to oral ciprofloxacin as a step-down treatment for E.coli AF-UTI in women for the cumulative incidence of survival and clinical cure (resolution of symptoms) 6-10 days post-treatment.

FORECAST-ECO: To describe the effect of using oral fosfomycin-trometamol or ciprofloxacin on the composition of Enterobacteriacea and the resistance to fosfomycin, ciprofloxacin and ESBL-production in the gut microbiota.

FORECAST-FAR: To determine the pharmacokinetic profile of fosfomycin-trometamol (dosed 3 gram every 24 hours for 5 till 8 days) and oral ciprofloxacin (dosed 500mg every 12 hours for 5-8 days) and to relate these concentrations with the clinical and microbiological outcome.

Study design

The FORECAST study is a randomized, controlled, multi-center, double-blind, double-dummy investigator initiated trial.

The non-inferiority of fosfomycin-trometamol will be compared to the current standard of care, ciprofloxacin. After patients are assessed for eligibility and written IC is obtained, participants will be randomized to one of the two treatment arms. Physicians, participants and investigators are blinded for the content of study medication.

The FORECAST FAR and FORECAST ECO will be performed on participants of the FORECAST study.

Intervention

Active treatment in the study arm consists of oral fosfomycin-trometamol 3000mg every 24 hours. In the Netherlands, this is commercially available as Monuril 3000, granules for suspension. One sachet contains 5,631 gram fosfomycin-trometamol (1:1) corresponding with 3 gram fosfomycin. It is combined with trometamol in order to improve absorption and therefore bio-availability. Active treatment in the standard of care arm consists of oral ciprofloxacin 500mg, in the Netherlands manufactured as ciprofloxacin tablets or granules/dissolvent for suspension. The ciprofloxacin tablets are generally used in daily practice and will therefore be used in our study. It is impossible to equalize the fosfomycin-trometamol granules to the ciprofloxacin granules. Therefore a double dummy design is chosen and a placebo will be used for both active substances. The placebo for fosfomycin will be manufactured as sachets containing granules for suspension, indistinguishable from fosfomycin with an identical color, composition and taste and based on the same formulation except for the active (antibiotic) ingredients. Placebo for encapsulated ciprofloxacin tablets will be manufactured as capsules with an identical color, composition and taste, based on the same formulation except that it does not contain the active (antibiotic) ingredients.

Study burden and risks

We consider the risk to participate in the FORECAST trial low if compared to the current standard of care for the following reasons.

First, fosfomycin has a good safety profile and the current available evidence gives rise to a good efficacy for this purpose. We estimate that fosfomycin-trometamol will be well tolerated in dosages of 3 gram every 24 hours. Fosfomycin is safe when used intravenously in high dosages. Animal studies report no hazardous effects concerning fertility, teratology, mutagenicity or carcinogenicity. Fosfomycin-trometamol has been registered and extensively used for the treatment of a uncomplicated urinary tract infection in women with good results. The efficacy is comparable to alternative antibiotic options. The pharmacokinetic profile favors it use for cUTI with high bio-availability, reaching high levels in urine and bladder wall and sufficient levels in plasma to eradicate E.coli; this has also been investigated in observational studies for cUTI leading to good efficacy rates. This is summarized in the IB.

Secondly, our entry criteria are designated to reflect daily practice with regard to the safety of the participants.
* Only consenting women are included. Patients with a delirium at the moment of randomisation, which could be a sign of systemic infection, will therefore be excluded. Patients are included if they have a presumptive diagnosis of AF-UTI and if AF-UTI is the main reason for hospitalisation. This prevents inclusion of patients hospitalised for another diagnosis, for instance myocardial infarction, who have a AF-UTI as an ancillary finding. As the incentive to start intravenous therapy is usually different in such patients they are not considered representative for patients with AF-UTI. Patients are included if they are adequately treated *48 hours with intravenous antibiotics. The isolated pathogen has to be susceptible for the used intravenous antibiotics. Furthermore, patients are only allocated for an iv-oral switch if they are candidates for an safe intravenous to oral switch. As a result, patients will not be severely ill at the moment of randomisation.
* Exclusion criteria: Patients with a known allergy to one of the study medications will be excluded. Pregnant and lactating women will be excluded. Patients with a glomerular filtration rate * 30ml/min are excluded. Patients that use concomitant antibiotic treatment are excluded as it would be impossible to determine which antibiotic effect is measured. Specific patient groups with comorbidity or (suspected) bacterial complications which require an alternate antibiotic strategy and for which other endpoints are constructed will be excluded.

Third, the first administration of study medication will occur in the hospital, allowing monitoring (rare) type 1 allergic reactions. Furthermore the majority of patients, except vital and non ill patients, will be discharged 24-hours after the iv-oral switch in order to evaluate the clinical effect.

All patients will receive oral and written information on the trial, including

possible risks of participating. For questions, patients receive the contact information of the local principle investigator and of an expert physician who has no conflicts of interest in the study.

The in- and exclusion criteria are set-up to optimize patient safety and reflect the daily clinical practice. In conclusion, the benefits of this trial for future purposes outweighs the low risks involved.

FORECAST-FAR: This will be the first randomized controlled trial involving the use of oral fosfomycin-trometamol for more than a single dose. In the nearby future, fosfomycin could be used as an alternative antibiotic option for cUTI and other purposes. This requires information about the pharmacokinetic profile. This study is a unique opportunity to evaluate not only pharmacokinetics after single oral dose fosfomycin but also to evaluate after multiple administrations of oral fosfomycin. Carrying out this substudy is neccesary for defining the use of fosfomycin-trometamol and ciprofloxacin in the future daily practice. The risks of participating to this study as a result of venapunction are negligible. However participants need to visit the hospital for an extra day and undergo venapunction, which could be a burden.

FORECAST-ECO: Due to the emergence of resistance in Enterobacteriaceae, limited antibiotics are available for the stepdown treatment of AF-UTI. This aims for the exploration of new purposes for existing antibiotics, in this case fosfomycin-trometamol. The benefit is to be expected for future patients with AF-UTI involving Enterobacteriaceae with multidrug resistance but susceptible to fosfomycin. The FORECAST trial could provide the required evidence for the stepdown switch to oral fosfomycin, allowing (earlier) hospital discharge. However, it is necessary to directly evaluate the effects of fosfomycin use on microbiological resistance. If the use of fosfomycin leads to an unexpected rise of carriage of fosfomycin resistent Enterobacteriaceae or ESBL-producing Enterobacteriaceae, this has great implications for its implementation, and could be a limitation for its future use. Therefore the FORECAST-ECO substudy is an essential substudy of the FORECAST study. There are no risks involved to participating in this study. The collection of feces could be a burden.

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

Inclusion criteria:
-Hospitalised
-Competent women (*18 years), able to give informed consent
-AF-UTI as presumptive diagnosis and primary reason for hospitalisation*
-Adequate intravenous antibiotic therapy for *48 - *120 hours**
-Candidate for safe iv to oral switch as judged by the attending physician
-Urine (*104 CFU/ml) OR blood culture obtained within 24 hours before or after admission: Escherichia coli , ciprofloxacin S AND fosfomycin S***;* Acute Febrile Urinary Tract Infections (AF-UTI) are UTI with at least one of the forthcoming systemic symptoms/signs: fever or low temperature (*38.0 C * or <36 C *), rigors, delirium or hemodynamic instability as a result of sepsis requiring intravenous fluids, increase in CRP (*30mg/L) or leucocytes (*10*109/L) AND at least one of the following local symptoms: lower abdominal pain, low back pain, flank pain or costo-vertebral angle pain or tenderness on physical examination, any of the following symptoms of UTI (dysuria, urinary urgency, urinary frequency, suprapubic/pelvic discomfort, macroscopic hematuria, new urinary incontinence or worsening of pre-existing incontinence). Local symptoms are not required in case the urine and blood culture are positive for a phenotypically matched E.coli. The local study investigator determines the presumptive diagnosis as the primary reason for hospitalization with consultation of the attending physician.
**Amoxicillin+/-clavulanic acid / 2nd or 3rd cephalosporin/ aminoglycoside/ carbapenem/ fluoroquinolones/ trimethoprim-sulfamethoxazole OR a combination AND in vitro

susceptibility of the causative E.coli to at least one of the used agents
*** If a participating microbiological laboratory only processes urine cultures * 10*5 CFU/ml, only these will be included. If an urine or blood culture results in another non-E.coli bacteria that requires antibiotic treatment, the patient should be excluded. In case of presence of non-E.coli-type Enterobacteriaceae in urine culture (*103 CFU/ml), the patient should be excluded automatically.;FORECAST-FAR/ECO: All participants that are eligible for the FORECAST study, are automatically eligible for the FAR and ECO substudy.

Exclusion criteria

Exclusion criteria
-Pregnant or nursing women
-Glomerular filtration rate < 30 ml/min/1,73 m3 or renal replacement therapy
-Concomitant systemic antibacterial treatment #
-Ascertained or presumptive hypersensitivity to the active compounds and/or any excipient of the products or to any quinole
-Participation to any trial with an investigational product involved in the 30 days before the screening visit
-Every other laboratory result, clinical condition, disease or treatment that, in investigator*s opinion, make the subject non suitable for the study
-Specific comorbidity or diagnosis##
-Contraindications/interactions for any of the active compounds or medication ###
-Patients with inadequate understanding of the study risks or its requirements or unwilling to plan a follow-up visit;# If prophylactic antibiotic therapy could not be paused during study therapy, the patient should be excluded Except for continuation of prophylactic antibacterial therapy
Renal transplant patients, polycystic kidney disease, neutropenia (<500 /*l), paraplegia, long-term indwelling catheters, (placed *24 hours before admission), urostomy, ileal loops, suspicion/presence of renal abscess, suspicion of septic metastatic foci/endocarditis, long-term urinary catheter (placed *24 hours before admission), e.g. double-J catheter, nephrostomy catheter, suprapubic catheter, suspicion/presence of renal abscess, suspicion of septic metastatic foci/endocarditis
Concurrent use of Tizanidin, Clozapin or Theophylline. If pausing or conversion of this medicine disadvantages the participant, she will be excluded. Patients with a history of tendon disease/disorder related to quinolone treatment. Patients with known risk factors for prolongation of the QT interval. Glucose-6-phosphate dehydrogenase deficiency

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):	22-11-2017
Enrollment:	240
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Ciprofloxacin
Generic name:	Ciprofloxacin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Monurol
Generic name:	Fosfomycin-trometamol
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	14-08-2017
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

Approved WMO

Date:	19-09-2017
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

Approved WMO

Date:	03-10-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	01-02-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	08-03-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	02-05-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	02-08-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	17-10-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	21-01-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	13-02-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

ID: 22782
Source: NTR
Title:

In other registers

Register	ID
EudraCT	EUCTR2016-004486-37-NL
CCMO	NL60186.041.17
OMON	NL-OMON22782