Determining the causative agent and optimal duration of antibiotic therapy in persons with diabetes and foot osteomyelitis: BonE BiOPsy (BeBoP) trial

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Ethische beoordeling	Positief advies
Status	Werving gestart
Type aandoening	-
Onderzoekstype	Interventie onderzoek

Samenvatting

ID

NL-OMON26089

Bron
NTR

Verkorte titel
BeBoP

Aandoening

diabetes mellitus, osteomyelitis

Ondersteuning

Primaire sponsor: VU University Medical Center, Amsterdam, The Netherlands
Overige ondersteuning: Dutch Diabetes Research Foundation (Diabetes Fonds) number 2017.82.014

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

The primary objective is to prospectively compare outcomes of subjects with diabetic foot osteomyelitis treated with antibiotic agents targeted based on culture and antibiotic sensitivity results from bone biopsy versus results from ulcer bed tissue sampling.

Toelichting onderzoek

Achtergrond van het onderzoek

Rationale: In persons with diabetes and osteomyelitis of the foot, the optimal strategy to determine the causative organism and the optimal empiric duration of antibiotic therapy is currently unknown.
Objectives:
The primary objective is to prospectively compare outcomes of subjects with diabetic foot osteomyelitis treated with antibiotic agents targeted based on culture and antibiotic sensitivity results from bone biopsy versus results from ulcer bed biopsy sampling.
Secondary Objectives:
1.To evaluate disease activity after 3 and 6 weeks of treatment using a repeated bone biopsy, imaging (FDG-PET/CT and MRI) and laboratory biomarkers and to investigate the role of these repeated tests in up to 12 months follow up of diabetic foot osteomyelitis.
2.To evaluate if imaging, laboratory systemic inflammatory biomarkers and microbiological data, including molecular techniques, can predict clinical remission of osteomyelitis after cessation of therapy, and after 6 and 12 months.
3.To compare microbiological data, including molecular techniques and culture, in bone biopsy specimens and wound bed biopsy specimens.
4. To assess the effect of long-term systemic antibiotic treatment on faecal microbiota.
5. To assess change in quality of life and to compare this between diagnostic groups.
Study design: Randomized clinical trial, combined with observational study
Study population: Eighty subjects with diabetes and foot osteomyelitis.
Intervention: All subjects with suspected DFO will undergo plain X-rays, ulcer bed biopsy, and percutaneous bone biopsy, before initiation of empiric antibiotic therapy as part of standard treatment. Standard treatment will include metabolic control of serum glucose levels, ensuring effective biomechanical pressure offloading of the affected foot (e.g. total contact cast), assessment of arterial vascular supply of the affected foot and to ensure interventions to improve arterial blood flow.
Forty subjects will receive an antimicrobial regimen based on culture results of the bone biopsy specimen, the other forty based on culture results of a ulcer bed specimen. In an observational part of the study, up to forty of eighty subjects will undergo a FDG-PET at baseline and a follow-up FDG-PET/CT scan, MRI and repeated bone biopsy for culture, next generation sequencing (PCR of 16S region in genetic material of bacteria)/IS-pro and histology at 3 weeks; the other half will undergo these procedures at 6 weeks after initiation

of antibiotic therapy to evaluate inflammatory activity. All subjects will be treated with guided antibiotic therapy for 6 weeks. After 6 weeks antibiotic therapy will be stopped and the subjects will enter the follow-up phase of the study. If there is a need to continue therapy, cessation of antimicrobial therapy will be pragmatically determined at weekly intervals.
Main study parameters/endpoints: The primary outcome measure will be remission of osteomyelitis at 12 months. Outcome measures to determine remission will be: healing of any overlying soft tissue ulcer, time to ulcer healing, occurrence of ulcer relapse, change in ulcer size, presence of signs of soft tissue inflammation, markers of systemic inflammation (e.g. erythrocyte sedimentation rate, C-reactive protein) need for surgical intervention at the infection site (including bone resection or amputations), evidence of bone healing on plain x-rays, adverse events of antimicrobial treatment, duration of antimicrobial treatment, quality of life and survival.
Nature and extent of the burden and risks associated with participation, benefit and group relatedness:
Most of the diagnostic and therapeutic interventions are standard interventions in patients with osteomyelitis of the foot. These include standard blood tests, plain X-ray, (percutaneous) bone biopsy, deep wound tissue specimens, antibiotic treatment, biomechanical pressure offloading and regular wound care (including debridement, and revascularization in case of critical limb ischemia) and in selected subjects MRI, FDG-PET/CT.
The additional burden due to the study is that both bone biopsy and soft tissue samples are taken at the start of the study, while usually only one of these tests is performed (preferably bone biopsy). At week 3 or 6 weeks, FDG-PET/CT, MRI and a repeated bone biopsy are performed in up to half of the subjects (i.e., 40 patients). In standard care, these studies are usually only performed at baseline. At follow up, these are only performed in selected groups of patients, e.g. those who do not respond well to treatment. These studies, however, are necessary to evaluate inflammatory activity in order to gain knowledge concerning adequate treatment duration of diabetic foot osteomyelitis. Additional risk for the subjects is small. The questionnaires filled out at inclusion and 6 and 12 months follow up are also additional to standard care. We will collect rectal swab samples before and after antibiotic treatment.

Doel van het onderzoek

We hypothesize that outcomes will be better in subjects treated based on bone biopsy cultures compared with those treated based on deep wound soft tissue samples, that imaging will predict outcomes of antibiotic therapy when taken at three weeks after initiation of targeted antibiotic therapy, that laboratory and microbiological data can predict outcomes of antibiotic therapy and that there will be great overlap between specimen cultures and molecular biology results at 6 and 12 months after intiation of therapy.

Onderzoeksopzet

2019 February 14th: Medical Ethical Committee approval, start inclusion
2019: obtain study approval in other participating centers
2022 treatment and data collection of final subject
2022 start data analysis and writing reports

Onderzoeksproduct en/of interventie

One arm: treatment based on bone biopsy culture results. Control arm: treatment based on ulcer bed tissue samples

Contactpersonen

Publiek

Amsterdam UMC, location VUmc
Edgar Peters

+31 20444 4444

Wetenschappelijk

Amsterdam UMC, location VUmc
Edgar Peters

+31 20444 4444

Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

1 Type 1 or 2 diabetes mellitus
2 Infected wound, that extends at least to the anatomical plane of the fascia, muscle, tendon or bone (International Working Group on the Diabetic Foot (IWGDF) infection grade 3 or 4).[24]
3 Osteomyelitis, defined as presence of such a wound with at least one of the following criteria:
- Positive probe to bone test [25]
- Abnormalities on plain X-ray suggestive for osteomyelitis
- Erythrocyte sedimentation rate ≥70 mm/hr (with no other explanation for the elevated sedimentation rate than osteomyelitis)
- Signs of osteomyelitis on MRI
- Signs of osteomyelitis on FDG-PET/CT
- Positive culture, PCR, or histology of a bone biopsy

4 Able and willing to comply with the research protocol.

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

- Likely to undergo complete surgical bone debridement or amputation. Subjects that (are likely to) undergo surgery within 72 hours after enrollment for other reasons, e.g. abscesses, compartment syndrome, partial bone resection) are not excluded.
- Presence of uncorrectable critical limb ischemia. Subjects that (are likely to) undergo surgical or percutaneous revascularization are not excluded
- Severely immunocompromised (as judged by the treating physician, e.g. neutropenia due to chemotherapy, hiv infection with CD4-count of < 200 /ul)
- Pregnant or lactating
- Unable to give informed consent
- Unlikely to live at least one year
- Unable or unwilling to follow protocol requirements (with exception of rectal swabs)
- Received systemic antimicrobial therapy within one week before enrollment
- General contraindications for MRI if included in the observational part of the study

Onderzoeksopzet

Opzet

Type:	Interventie onderzoek
Onderzoeksmodel:	Parallel
Toewijzing:	Gerandomiseerd
Blindering:	Dubbelblind
Controle:	N.v.t. / onbekend

Deelname

Nederland

Status:	Werving gestart
(Verwachte) startdatum:	14-02-2019
Aantal proefpersonen:	80
Type:	Verwachte startdatum

Voornemen beschikbaar stellen Individuele Patiënten Data (IPD)

Wordt de data na het onderzoek gedeeld: Nee

Ethische beoordeling

Positief advies

Datum:	05-03-2019
Soort:	Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

ID: 52791
Bron: ToetsingOnline
Titel:

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL7582
CCMO	NL66106.029.18
OMON	NL-OMON52791

Resultaten