New treatment strategy for patients with multiple recurrent Clostridioides difficile infection with bezlotoxumab as first option

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To investigate whether a treatment strategy offering bezlotoxumab before FMT in patients suffering from multiple recurrent CDI results in equal efficacy compared with a treatment strategy with initial FMT. Strategy A includes bezlotoxumab as...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Gastrointestinal infections
Study type	Interventional

Summary

ID

NL-OMON52061

Source
ToetsingOnline

Brief title
Bezlotoxumab versus FMT for multiple recurrent CD (BSTEP)

Condition

- Gastrointestinal infections

Synonym
C. difficile associated diarhea, C. difficile colitis, C. difficile infection

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum

Source(s) of monetary or material Support: bedrijf,Merck Sharp & Dohme (MSD)

Intervention

Keyword: bezlotoxumab, C. difficile, CDI, fecal microbiota transplantation, FMT

Outcome measures

Primary outcome

Global cure of the treatment strategy. Global cure is defined as cure without relapse of CDI within 12 weeks after completion of the treatment strategy in the study arm, i.e. after completion of secondary treatment in case of failure on initial treatment.

Secondary outcome

1. Initial cure after treatment with bezlotoxumab or FMT. i.e. cure assessed two days after completion of the primary CDI treatment in the study arm.

2. Recurrence after initial treatment with bezlotoxumab or FMT. Defined as CDI relapse within 12 weeks, after initial cure.

3. Sustained cure after initial treatment with bezlotoxumab or FMT. i.e. cure without relapse within 12 weeks.

4. Adverse events

5. Development of post-treatment irritable bowel syndrome like symptoms associated with bezlotoxumab treatment or FMT treatment

6. Duration of hospitalization

7. Use of antibiotics

8. Eradication of toxigenic C. difficile

9. Fecal microbiota profile

10. Patient well-being before and after treatment

11. Costs per cured patient (global and sustained cure) and costs per QALY

gained using the EQ-5D-5L health questionnaire

The following data will also be collected:

- Patients* characteristics, i.e. age, medical history, comorbidities,

comedication

- Presence of risk factors for severe and recurrent CDI

- Defecation pattern during treatment and follow-up

Study description

Background summary

The new 2021 European Society for Clinical Microbiology and Infectious Diseases (ESCMID) guideline recommend treating an initial episode of Clostridioides difficile (CDI) infection with vancomycin or fidaxomicin, further referred to as standard CDI antibiotic therapy (CDI ABx). For treatment of a recurrent CDI episode treatment with fidaxomicin, or addition of an intravenous infusion of bezlotoxumab to standard CDI ABx are considered. The optimal treatment for patients with a second or further recurrence of after standard CDI ABx has yet to be established. Indeed, this is identified as a research gap in the updated 2021 ESCMID guidance document for treatment of CDI. Options include addition of bezlotoxumab to standard CDI ABx, or fecal microbiota transplantation (FMT) after standard CDI ABx.

Observational data suggest that bezlotoxumab may prevent FMT in a number of patients with multiple recurrent CDI, though the exact percentage is unknown. A point estimate is needed for effective shared decision making and balancing the risk and benefits of initial bezlotoxumab versus initial FMT for multiple recurrent CDI. Importantly, offering patients initial bezlotoxumab should not negatively impact the outcome of a subsequent FMT in case of bezlotoxumab failure.

We hypothesize that offering patients a treatment strategy with initial bezlotoxumab has no negative impact on the overall outcome, when compared to a strategy with initial FMT. We hypothesize that both treatment strategies (both arms, including rescue therapy) will result in an overall sustained cure of

95%. In addition, we hypothesize that bezlotoxumab result in less AEs and less IBS-like symptoms and diarrhea than FMT, and that FMT results in an increased microbiota diversity post treatment when compared to bezlotoxumab treatment.

Study objective

To investigate whether a treatment strategy offering bezlotoxumab before FMT in patients suffering from multiple recurrent CDI results in equal efficacy compared with a treatment strategy with initial FMT. Strategy A includes bezlotoxumab as ancillary treatment as first option, and FMT in case of failure. Option B includes FMT as ancillary treatment as first option, and antibiotic treatment with fidaxomicin in case of failure. A secondary objective is to provide a point estimate of recurrence after bezlotoxumab for the treatment of multiple recurrent CDI.

Study design

Open label multicentre non-inferiority randomized controlled trial.

Intervention

Patients will be randomized to one of the following treatment strategies (n=33 each):

Strategy A: bezlotoxumab in addition to standard CDI ABx as first option. 14 days antibiotic therapy with oral vancomycin 250* mg QID + one single intravenous infusion of bezlotoxumab 10mg/kg over 60 minutes. In case of treatment failure, i.e. recurrence within 12 weeks, patients will be treated by fecal microbiota transplantation (FMT, i.e. infusion of 198 cc donor feces suspension in the gastroduodenum or colon) after 14 days oral vancomycin 250* mg QID therapy and bowel lavage.

Strategy B: FMT standard CDI ABx as first option. 14 days antibiotic therapy with oral vancomycin 250* mg QID, followed by FMT on day 15. In case of treatment failure, patients will be treated with oral fidaxomicin 200 mg BID for 10 days.

*125 mg vancomycin is administered as suspension, and is also acceptable. 125 mg vancomcyin is considered equally effective as 250 mg tablets in international guidelines.

Study burden and risks

Potential issues of concern
This study concerns and investigational medicinal product (bezlotoxumab) that is approved by the EMA and Dutch CBG for the indication in this study, and an

interventional procedure (FMT). A detailed risk classification can be found in document K6 and is summarized below.

BEZLOTOXUMAB
Bezlotoxumab may result in mild and transient infusion related reactions (1-10%). We will exclude patients with a medical history of congestive heart-failure from the study, due to a potential safety signal in the two phase-3 clinical trials in this group. Due to limited or absent data we will also exclude breastfeeding woman, or patients that are pregnant or have a desire to become pregnant. Potential long-term effects are unknown and are investigated through post-marketing adverse event registration. The lower assumed sustained cure rated of bezlotoxumab (60%) comparted with FMT (81%) means that a proportion of patients in the bezlotoxumab arm do not achieve sustained cure and will have a delay of treatment with FMT; however, the benefit is that a considerable portion of patients in this arm a FMT procedure will be prevented, thereby justifying this trial.

FMT
FMT is an invasive procedure that requires a gastroduodenoscopy or colonoscopy for donor feces infusion. On the day of FMT patients often experience mild self-limiting AEs in 2/3 of patients. During follow up 1/3 of patients reports mild FMT-related (commonly gastro-intestinal) AEs that last for several days. Because these AEs are mild and self-limiting, we think these are acceptable, especially given the high sustained cure rate of FMT.

Although FMT is associated with rehospitalization or prolonged hospitalization (23%) and the occurrence of infections other than CDI (17%), the majority of SAEs is not (definitely) FMT related and/or due to comorbid conditions. Possibly related SAEs include bacterial infections. Cases of transmission of bacteria causing infection in FMT recipients have been described in the US, but can be prevented by adequate screening protocols for donor feces.

Donors and donor feces provided by the NDFB are extensively screened for microbiota perturbating risk factors and infectious pathogens. It is however impossible to screen for unknown pathogens or harmful agents. Therefore, continuous vigilance by donor stool banks is warranted: for example, in the beginning of the COVID-19 pandemic NDFB donor activities were halted and restarted after implementation of SARS-CoV-2 screening. Potential long-term effects of FMT are unknown and are investigated trough long-term follow-up by the NDFB and initiatives to establish (inter)national registries.

To minimize the occurrence of (S)AEs after FMT:
- we used extensively screened donor feces, according to NDFB and international standards
- donor feces will be infused slowly with the patient in the upright position
- patients will be observed after the FMT for at least 2 hours.
- to minimize procedure related risk such as regurgitation and aspiration we

advise to use the coloscopic route for FMT in case of e.g. swallowing problems or delayed gastric emptying.

In general:
- The patient will be instructed to their treating physician or the investigators as soon as possible when experiencing a possible (S)AE.

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

- minimum age is 18 years old
- diarrhea (3 or more unformed stools per 24h for two consecutive days; or >< = 8 unformed stools per 48h)
- positive PCR test for toxin A/B genes and/or positive toxin EIA for current

and previous episodes (low PCR cycle threshold value when only PCR performed)
- a minimum of two prior CDI episodes, at least one of these treated with vancomycin or fidaxomicin
- previous episode is maximum of 3 months prior to the current episode
- the current episode responds well to Standard of Care treatment (vancomycin or fidaxomicin orally).
- Assessment of the severity of the disease will be performed according to the ESCMID recommendations.
- Both mild and severe CDI will be included

Exclusion criteria

- Severe complicated CDI, i.e presence of: hypotension, septic shock, elevated serum lactate, ileus, toxic megacolon, bowel perforation, or any fulminant course of disease.
- ICU admission for underlying disease
- pregnancy or current desire for pregnancy
- breastfeeding
- prolonged use of therapeuric antibiotics (other than for treatment of CDI) during oral standard of care CDI treatment or foreseeable antibiotic use directly after the intervention. Aside from this, there are no specific restrictions on concomitant medication of any kind.
- previous use of bezlotoxumab or fecal microbiota transplantation
- a history of underlying congestive heart failure (potential safety signal phase-III trail bezlotoxumab).
- Diagnosis of inflammatory bowel disease in medical history.
- Any other condition which in the opinion of the investigator would make the patient unsuitable for enrollment or could interfere with the patient participating in and completing the study.

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active

Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	66
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Zinplava
Generic name:	Bezlotoxumab
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	01-11-2021
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	21-04-2022
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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	EUCTR2021-004924-14-NL
CCMO	NL79030.058.21