A randomised controlled trial comparing FMT (fecal microbiota transplantation) after budesonide or placebo in patients with active ulcerative colitis: ;Acronym: the FECBUD trial

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To study the effect size of FMT after a 3 weeks course of budesonide as induction therapy in patients with active ulcerative colitis despite previous therapy. The purpose of the pre-treatment is to reduce active inflammation prior to donor feces...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Gastrointestinal inflammatory conditions
Study type	Interventional

Summary

ID

NL-OMON49003

Source
ToetsingOnline

Brief title
FMT for ulcerative colitis after initiation of budesonide

Condition

- Gastrointestinal inflammatory conditions

Synonym
inflammatory bowel disease, ulcerative colitis

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: De studie wordt mogelijk gemaakt door een onderzoeksubsidie van Vedanta een biotechnologie bedrijf in Boston USA. ,Vedanta

Intervention

Keyword: budesonide, FMT, microbiota, ulcerative colitis

Outcome measures

Primary outcome

The primary outcome is engraftment of donor microbiota at 1,2, 4 and 8 weeks

after the last FMT in patients pretreated with budesonide or placebo assessed

with metagenomics/deep sequencing of the gut microbiota.

Secondary outcome

Secondary endpoints

a. clinical response at 4 and 8 weeks after FMT

b. donor dependent efficacy c. safety

- Partial response is defined as reduction of disease activity at 4 weeks and 8

weeks after the 4th donor feces infusion.

- Activity is defined as the occurrence (or recurrence) of symptoms in

combination with increasing fecal calprotectin levels and distinctive

radiological or endoscopic findings.

- Remission is defined as absence of symptoms, and at endoscopy mucosal healing

or minimal focal inflammation (Mayo 0-1).

- Non-response (failure) is described as absence of response.

- Sigmoidoscopy will be performed at 8 weeks after the 4th FMT (t=13 weeks), or

earlier in case of clinical suspicion of persistent or recurrent activity.

- In addition, salivary samples of patients will be studied for microbiota

composition and comparison to gut microbiota composition.

Study description

Background summary

Despite an increasing number of active drugs against Inflammatory Bowel Disease (IBD) (ulcerative colitis and Crohn*s disease), treatment results are disappointing for a subset of patients. In general, patients with ulcerative colitis are treated with with mesalazine (with or without prednisolone as induction). If mesalazine alone appears insufficient, a thiopurine (azathioprine or purinethol) is added as maintenance treatment. In a subset of patients, treatment with biologicals is required. Investigations of dysbiosis of the gut microbiota in patients with IBD may guide the development of new therapeutic strategies. IBD is characterized by a disturbed gut microbiota. Importantly, fecal microbiota transplantation (FMT) is able to induce remission in a small subset of patients with active ulcerative colitis (1-4). Interestingly, certain donors may be more effective, and patients with a response after FMT showed a change of their microbiota profile towards that of their donor, pointing to the potential benefit of careful donor selection (1). So far, FMT was been studied as induction therapy in patients with active inflammation without pre-treatment with antiinflammatory medication. The active inflammation may in part explain the side effects of FMT described in IBD patients, such as fever, increased CRP and bacteraemia. Furthermore, the active inflammation may negatively influence engraftment of donor microbiota, which could possibly explain the limited efficacy of FMT in IBD patients.

Our hypothesis is that the efficacy of FMT in patients with active ulcerative colitis can be increased by:

1. Pre treatment with budesonide (cortiment, which is a standard treatment approach in patients with activity of ulcerative colitis) to enhance engraftment of donor microbiota in the recipient
2. Rational donor selection increases the effectiveness of FMT in patients with FMT

Study objective

To study the effect size of FMT after a 3 weeks course of budesonide as induction therapy in patients with active ulcerative colitis despite previous

therapy. The purpose of the pre-treatment is to reduce active inflammation prior to donor feces infusion, possibly enhancing engraftment of donor microbiota. The initiation of budesonide is a standard treatment approach in patients with activity of ulcerative colitis.
Donor selection is based on the microbiota profile of the donor and in vivo assessment of the capacity of donor derived bacteria to induce regulatory T cells in germ free mice as performed by Vedanta Biosciences.
The study is designed as a pilot study and the results may guide the initiation of a larger randomized study investigating the effects of FMT after pre-treatment with budesonide in combination with rational donor selection as therapy in patients with IBD.

Study design

Multi center double-blind randomized placebo-controlled pilot study investigating different strategies with regard to timing of FMT (before or after initiation of standard induction therapy)

Intervention

Intervention Patients with active ulcerative colitis (n=24) will be randomized to a 3 weeks course of budesonide 9 mg once a day or placebo, followed by 4 infusions of a donor feces solution produced by the NDFB. The first FMT will be scheduled immediately after cessation of budesonide or placebo (t=3 weeks) and is delivered by a nasoduodenal tube. Three subsequent FMTs are scheduled weekly. Each individual patient receives donor feces infusion of one donor. Patients are treated with bowel lavage one day prior to the first FMT. Bowel lavage is not given prior to the 2nd, 3rd and 4th FMT. Sigmoidoscopy will be performed 8 weeks after the 4th FMT, or earlier in case of clinical suspicion of persistent or recurrent activity.

Randomized studies suggest a donor dependent effect of FMT. Initially, two donors will be selected (donor A and donor B), and patients are randomized to receive donor feces suspensions from either donor A or donor B. Previous randomized controlled trials have shown modest effectivity of FMT in patients with active ulcerative colitis using different treatment schedules with 3; 6 and 40 (repeated) infusions of donor feces suspensions (1-3). The study which offered only three infusions of donor feces did not show a statistically significant improvement (2). Therefore, the current study protocol consists of 4 infusions of donor feces suspensions after short induction treatment with budesonide

Donor selection:
Donors are healthy volunteers, carefully selected by the Netherlands Donor Feces Bank (5). Donor screening consists of questionnaires addressing potential risk factors for transmittable diseases, and risk factors for diseases

associated with a disturbed gut microbiota. Subsequently, extensive blood and stool testing for the presence of pathogens is performed (5). Donor stool is diluted in isotonic NaCl with the addition of glycerol as cryoprotectant and stored in -80 Celsius. After negative results during retesting of the donor, the donor feces solution can be used for FMT.

Donor feces of several potential donors will pre-screened by conducting metagenomic sequencing to determine the nature and abundance of Clostridia cluster IV, XIVa and XVIII organisms in the donor microbiota. In addition, culturable bacteria isolated from each donor will be evaluated for their capacity to induce regulatory T cells in inoculated germfree mice.

Study burden and risks

- participants need to collect their stools at home and deliver the feces to the hospital.
- Lack of effectivity of FMT, causing delay of initiation of other therapies
- Progression of activity during placebo treatment. Patients continue maintenance treatment. In case of serious progression, patients will not continue the study treatment.
- Theoretical long term and unknown side effects of FMT
- FMT is delivered through a nasoduodenal tube, which is placed by endoscopy. The risks for bleeding or perforation are neglectable. In general, local anesthesia is offered.
- Subjects will be seen in the hospital for 8 study visits (outpatient).
- sigmoidoscopy is performed to assess treatment outcome. Sedation and analgesia will be offered using midazolam and/or fentanyl according to local (standard) procedures. Complications of colonoscopy are perforation and bleeding, which occur in about 0.1 % of patients undergoing diagnostic colonoscopies. Substantially fewer complications occur after sigmoidoscopy.
- additional blood sampling will be performed.

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

patients > 18 years old (n<=24) with mild or moderate activity of ulcerative colitis despite previous maintenance therapy (mesalazine, or thiopurine, or anti-TNF, or vedolizumab) with a MAYO endoscopic subscore of I or II and with written informed consent.

Exclusion criteria

amongst others: pregnancy, need for (continuous) antibiotic treatment, previous prednisolon or budenofalk resistant inflammation

Study design

Design

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):	07-05-2019
Enrollment:	24
Type:	Actual

Medical products/devices used

Generic name:	Fecal Microbiota Transplantation
Registration:	No
Product type:	Medicine
Brand name:	cortiment
Generic name:	budesonide
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	05-11-2018
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	26-10-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	18-12-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)

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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	EUCTR2018-001812-31-NL
CCMO	NL65976.098.18

Study results

Date completed:	13-05-2021
Actual enrolment:	24