Personalized AZithromycin/metronidAZole, in combination with standard induction therapy, to achieve a fecal microbiome community structure and metagenome changes associated with sustained remission in pediatric Crohn*s Disease (CD): a pilot study

Published: 04-02-2020
Last updated: 10-04-2024

The primary objective is to evaluate the potential efficacy of personalized adjunctive antibiotic therapy in maintaining clinical remission in pediatric subjects undergoing SOC induction therapy for mild to moderate Crohn*s disease who have a...

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

Summary

ID

NL-OMON55227

Source
ToetsingOnline

Brief title
PAZAZ

Condition

- Gastrointestinal inflammatory conditions

Synonym
chronic bowel inflammation, Inflammatory bowel disease

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Crohn's and Colitis foundation of America;Wetenschappelijke Adviesraad van Stichting Steun Emma Kinderziekenhuis

Intervention

Keyword: (sustained) remission, antibiotics, Crohn□s disease, microbiome

Outcome measures

Primary outcome

Primary Outcome variable: Sustained remission defined as no need of re-induction for clinical flare (new course of nutritional therapy, need to start steroids), steroid dependence, biologic (anti-TNF) use, and/or intestinal surgery by 12 months.

Secondary outcome

Secondary Outcome variables: Longitudinal (clustered and with respect to baseline) changes in disease activity indices (PCDAI: 0-100) components and inflammatory markers in stool and blood at each study visit up to 12 months. Longitudinal (clustered and with respect to baseline) changes in patient-reported outcomes (PRO) by 12 months.
Exploratory Outcome variable: Longitudinal (clustered and with respect to baseline) changes in fecal microbiome taxonomic composition or in total gene (metagenome) content. The changes will be analyzed for association with changes in disease activity (e.g. relapse or sustained remission) over time up

to 12 months.

Study description

Background summary

Crohn*s disease (CD) is a major phenotype of inflammatory bowel disease (IBD) characterized by transmural (often granulomatous and patchy) inflammation throughout the gastrointestinal (GI) tract, most often involving the ileum and colon. Chronic inflammation within the GI tract can cause progressive tissue damage leading to serious complications requiring surgery, including intra-abdominal abscesses, fistulas, and intestinal strictures. CD is highly heterogeneous with respect to age of onset, disease location (i.e. anatomical extent) and behavior (i.e. inflammatory or stricturing/penetrating disease). Disease course is also highly variable among patients with some experiencing chronically active severe disease while other have intermittent periods of clinical remission and disease exacerbation (i.e. *flares*). Patient responses to therapy are also highly variable, but the reasons for this are not fully understood.

Current treatments for CD aim to not only control symptoms but to maintain clinical remission and mucosal healing (deep remission). Recently, the Crohn*s Disease Exclusion diet was shown to be associated with comparable efficacy but superior tolerance and maintenance of remission than exclusive enteral nutrition in a randomized controlled trial.Corticosteroids, enteral nutrition, thiopurines, methotrexate and biologics (such as monoclonal antibodies against tumour necrosis factor-α: *anti-TNF*) are effective to modulate inflammatory activity, but surgery is still frequently required.

The exact cause of CD is unclear, but current thinking holds that disease results from a defective or inappropriate activation of the mucosal immune system response to commensal gut microbiota, collectively termed the gut microbiome. Certain bacteria can adhere to and invade epithelial cells of the inflamed mucosa and granulomas to replicate inside macrophage phagolysosomes. Numerous CD susceptibility genes are involved in pathways that govern innate immunity, recognition of bacterial pathogens, and handling of intracellular bacteria. Diversion of the fecal stream can lead to clinical improvement in medically refractory Crohn*s colitis.

The field of microbiome research has grown exponentially over the past several years. Studies using next-generation sequencing and new bioinformatics approaches have begun to characterize fundamental differences in the gut microbiome in children (and adults) with CD versus healthy controls. The ileum and colon is densely populated with a variety of metabolically active bacteria

that interact with the host immune system. The collective genomic content of the microbiome*the metagenome*has been estimated to contain at least 100-times more genes than the human genome. The influence of the microbiome on disease pathogenesis and progression in CD is a significant area of research interest, since a breakdown in the balance between protective and harmful bacteria (termed *dysbiosis*) is the current prevailing hypothesis for the development of CD. Animal studies have shown that bacterial load and the composition of bacterial communities can influence both the site and degree of inflammation in the GI tract. Several studies applying microbial profiling and in-depth sequencing techniques to the collective DNA content of gut microbiota (i.e. microbiome) of CD patients have shown distinct microbiome profiles associated with different clinical outcomes or responses to treatment.

The probable role for bacteria in triggering disease activity implies that antibiotics could have a role in CD therapy. However, while several meta-analyses support the use of antibiotics in controlling luminal inflammation, results of individual trials are heterogeneous. Recently, a combination of azithromycin/metronidazole has been found to be superior to metronidazole alone for induction of remission and improvement in fecal calprotectin. However, individual responses to this antibiotic treatment were variable, showing the percentage of clinical response to equal that of remission. This *all or nothing* phenomenon suggests that the effect of antibiotics may depend on the type of microbiota involved and their susceptibility to antibiotics.

The purpose for the proposed pilot trial is to determine whether personalized, microbiome-informed administration of an azithromycin/metronidazole antibiotic can improve clinical response to nutritional induction therapy and prolong remission compared to induction therapy alone.

Study objective

The primary objective is to evaluate the potential efficacy of personalized adjunctive antibiotic therapy in maintaining clinical remission in pediatric subjects undergoing SOC induction therapy for mild to moderate Crohn*s disease who have a relapse-associated microbiome profile

The secondary objectives are to evaluate the potential efficacy of personalized adjunctive antibiotic therapy in improving PRO, components of established disease activity measures in remission, as well as *biochemical* remission in pediatric subjects undergoing SOC induction therapy for mild to moderate Crohn*s disease who have a relapse-associated microbiome profile.

The exploratory objective is to investigate relationship between changes in subject microbiome composition and changes in disease activity over time.

Study design

This is a multi-center, randomized, controlled open-label add-on design trial pilot study to evaluate the efficacy of personalized adjunctive antibiotic (azithromycin + metronidazole) therapy in pediatric subjects with mild to moderate Crohn*s disease (CD) who have a relapse-associated microbiome profile. The study hypothesis is that adjunctive antibiotic therapy will improve clinical response to standard of care (SOC) induction therapy in a subgroup of CD patients with a relapse-associated microbiome profile. This is an add-on design trial for subjects already receiving SOC induction therapy; there will be no placebos.

Prior to starting SOC induction therapy at week 0, subjects will provide a baseline stool sample that will be screened for microbiome profiles associated with risk of relapse according to an established statistical model.
At week 4, subjects with a relapse-associated microbiome will be randomized into either a control arm that will continue to receive SOC induction therapy for an additional 8 weeks, or a treatment arm that will receive adjunctive antibiotic therapy in addition to continuing to receive SOC induction therapy for an additional 8 weeks. Subjects who do not have a relapse-associated microbiome will enter a separate control arm that will continue to receive SOC induction therapy and will have data collected for exploratory objectives. Subjects who are not in clinical remission by week 4 will receive antibiotic therapy regardless of microbiome signature at baseline. Subjects will be monitored for an additional 40 weeks after the treatment period (52 weeks total).

Intervention

Antibiotics will be administered orally for an 8-week period. Azithromycin will be administered at a dose of 7.5mg/kg to a maximum of 500mg/day for 5 consecutive days per week for the first 4 weeks and then 3 consecutive days/week for 4 weeks. Metronidazole will be administered 10mg/kg twice daily to a maximum of 1000mg/day for 8 weeks.

Study burden and risks

The available information suggests that the present clinical study has an acceptable risk-benefit ratio.

Approximately 50% of pediatric patients with CD will relapse within a year of starting induction therapy and require repeated courses of induction therapy and/or treatment escalation.41,42 Subjects in the antibiotic treatment arm of this trial will continue to receive standard therapy and are at comparable risk of relapse as subjects in the control arms. In group C of subjects not achieving remission with nutritional induction therapy alone, there will be no

randomization and antibiotics will be given as additional induction treatment.

The risk of rare, but serious, heart-related side effects from the antibiotic drug azithromycin are minimized by screening patients for heart rhythm irregularities prior to administering antibiotics. Metronidazole presents minimal risk to the subjects and is routinely used in this pediatric population. The safety monitoring practices employed by this protocol are adequate to protect the subjects* safety and detect all anticipated adverse events.

Subjects in the antibiotic intervention arm may experience direct health benefit through the study treatment by reducing their risk of disease flare thus avoiding additional intestinal damage as well as additional immune suppression or surgery. There will be no additional direct benefit for subjects in the reference arms because they will be receiving standard care. The knowledge gained from this trial could lead to improved treatment approaches for a subgroup of patients who have a relapse-associated microbiome profile.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

1. Provision of signed and dated informed consent form (and assent form, as applicable)
2. Stated willingness to comply with all study procedures and availability for the duration of the study
3. Male or female, aged 3 to 17 years
4. Diagnosed with CD according to standard clinical and histological criteria, within 36 months of week 0
5. Exhibiting mild to moderate symptoms of active disease, as determined by a PCDAI score >10 (or >7.5 excluding the height item) and <=37.5
6. Evidence of active inflammation based on either: fecal calprotectin level >=250 microgram/g (local laboratory or pre-arranged sponsor testing) within 30 days prior to week 0 visit; or according to accepted endoscopic and histologic evidence obtained during an endoscopy procedure completed within 30 days prior to Week 0 Visit.

Exclusion criteria

1.Current or previous use of anti-TNF or other biologic therapy
2.Presence of stricturing, penetrating (intestinal or perianal) and/or fistulizing CD.
3.Pregnancy or lactation
4.Have undergone intestinal resection
5.Laboratory diagnosis of Clostridium Difficile Infection (CDI), if performed for clinical indication
6.Treatment with another investigational drug or other intervention within 30 days before week 0
7.Risk factors for arrhythmia including history of prolonged QTc, hypokalemia or hypomagnesemia, resting bradycardia, or concurrent treatment with other drugs with potential for QT prolongation.
8.History of Cockayne syndrome
9.Prior diagnosis of any hematologic condition/blood dyscrasia which may result in leukopenia (even if leukocyte count is normal at screening)
10.Known allergy or intolerance to azithromycin or metronidazole
11.Subjects who received IV anti-infective within 35 days prior to week 0 visit or oral anti-infectives within 14 days prior to the week 0 visit.

12.Subject on oral aminosalicylates who has not been on stable doses for greater than, or discontinued within, at least 14 days prior to week 0.
13.Subject on cyclosporine, tacrolimus or mycophenolate mofetil. Stable doses (no change within 14 days prior to week 0) of Azathioprine, 6-mercaptopurine or MTX are not a reason for exclusion.
14.Subject who received fecal microbial transplantation within 35 days prior to week 0 visit.
15.Screening laboratory and other analyses show any of the following abnormal results:
o AST, ALT > 2 X upper limit of the reference range (as determined locally at each site)
o Urea, Creatinine > 1.5X upper limit of the reference range (as determined locally at each site)
o White blood cell (WBC) count < 3.0 X 109/L
o Total bilirubin >= 20 micromol/liter (1.17mg/dl); except for subjects with isolated elevation of indirect bilirubin relating to Gilbert syndrome
o Hemoglobin < 80 gram/liter
o Platelets < 100,000/µL

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	13-08-2021
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Flagyl
Generic name:	Metronidazole
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Zitrhomax of Zmax
Generic name:	Azithromycin
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	04-02-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-01-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-05-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-06-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-11-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-11-2021
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	EUCTR2019-004219-29-NL
CCMO	NL71847.018.19