Prospective rAndomized controlled tRial of Crohn*s diseAse exclusion Diet vs corticosteroIds in patientS with activE Crohn*s disease

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Main objective: to assess whether CDED is superior to corticosteroids, in terms of endoscopic response, in patients with mildly to moderately active, luminal CD.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Gastrointestinal infections
Study type	Interventional

Summary

ID

NL-OMON53395

Source
ToetsingOnline

Brief title
PARADISE

Condition

- Gastrointestinal infections

Synonym
Crohn's disease, Inflamatory Bowel Disease

Research involving
Human

Sponsors and support

Primary sponsor: Assistance Publique-Hopitaux de Paris
Source(s) of monetary or material Support: • French Ministry of health : 779 529

¤ • Nestlé : 100 000 ¤ Gift from person in Israel of 300.000 ¤ (to be spend in Israel),Nestle

Intervention

Keyword: corticosteroïden, Crohn□s disease, Crohn□s disease exclusion diet, endoscopic response

Outcome measures

Primary outcome

Primary endpoint: endoscopic response at week 16, without corticosteroids or

further therapeutic intervention, assessed by a centralized, anonymous and

blinded, double lecture panel of panenteric PillCam Crohn*s Capsule (PCC).

Endoscopic response is defined by a decrease of at least 50% in the Lewis score

for patients with small bowel CD, decrease of SES-CD of at least 50% in

patients with colonic CD and both of these in patients with small bowel and

colonic CD, compared to baseline

Secondary outcome

Compare between the 2 arms of the trial:

- (Steroid-free) clinical remission (HBI <5) and response (a decrease of at

least 3 points in HBI)

- (Steroid-free) clinical remission (CDAI <150) and response (a decrease of at

least 70 points in CDAI)

- Need for further therapeutic intervention (i.e., steroids,

immunosuppressants, new biologic or surgery)

- Decrease of fecal calprotectin of at least 50%, off steroids.

- Fecal calprotectin of less than 250 µg/g, less than 100 µg/g and less than 50

µg/g

- CRP serum level

- Median HBI, calprotectin and CRP

- Endoscopic remission as defined as Lewis score <135 in the small bowel and/or SES-CD=0-2 in the colon, without further therapeutic intervention (surgery, biologics or dietary intervention)

- Endoscopic response and remission graded by Eliakim scores

- Segmental endoscopic response and remission

- Body weight, arterial pressure and fasting serum glucose

- Gut microbiota composition (PCR 16s, PCR 18S for fungi and protists, metabolomics and shotgun metagenomics) at baseline, week 6 and week 16

- Complianceto corticosteroid treatment: Medication Adherence Report Scale

- Compliance to CDED:

- o Dietary habits questionnaires

- o 72-H food diaries

- Safety will be assessed by the adverse events, either severe or not, and the SUSARQuality of life will be assessed by short IBDQ

- Work productivity and activity will be assessed by the WPAI questionnaire

Study description

Background summary

Current medical treatment of Crohn*s disease (CD) consists of immunosuppressive drug therapy (corticosteroids, azathioprine, methotrexate, anti-TNF monoclonal antibodies). These agents control symptoms of CD in most patients but their withdrawal leads to disease relapse. They are also associated with serious adverse events, such as infections and lymphoma (1, 2). Future CD drugs are small molecules or biologics that antagonize pro-inflammatory cytokines or gut

homing of lymphocytes. They have similar safety issues as the immunosuppressive agents currently in use.
Epidemiological and experimental studies have suggested that diet plays an important role in CD pathophysiology. The pathogenesis of CD appears to involve alteration of the microbiome as well as a breakdown in barrier function with defective bacterial clearance (3). Changes in dietary intake and industrialization may explain the rise in CD incidence over the past decades. These changes of food may induce alteration in the microbiome and impair the barrier function of the mucous layer and intestinal epithelium, which then allows adherence and immune triggering by the altered mucosal microbiome (3).
Exclusive enteral nutrition (EEN), consisting of a liquid formula diet while avoiding any other oral intake, has been used for decades to treat active CD in pediatric and adult patients. It improves symptoms and heals endoscopic lesions better than corticosteroids (4, 5, 6). EEN has no medical side effects, and is currently recommended as a first-line treatment in pediatric CD (7). However, long-term compliance of EEN is poor.
Crohn*s disease exclusion diet (CDED) is a new treatment of active CD. It is a whole-food diet coupled with partial enteral nutrition. It is aimed to restore intestinal barrier and improve microbiota composition by exclusion of dietary components that contribute to its dysfunction (3). A recent randomized, controlled trial has shown that CDED was equally effective and better tolerated than exclusive enteral nutrition in pediatric CD patients (8). Importantly it was also highly effective for reduction in inflammation and partially corrected dysbiosis. This is the first demonstration of the efficacy of an exclusion diet in CD. Yet, there are several questions remaining: does CDED have the same efficacy in adults, what is the effect on endoscopic lesions, and what is the relative efficacy of CDED as compared with current treatment (9). Crohn*s disease affects children but the majority of patients are adults. It is mandatory to ensure that CDED does not only relief symptoms, but also heals the mucosa.
In this randomized clinical trial, we aim to compare the tolerability and efficacy of CDED coupled with PEN with corticosteroids, in inducing endoscopic response.

Study objective

Main objective: to assess whether CDED is superior to corticosteroids, in terms of endoscopic response, in patients with mildly to moderately active, luminal CD.

Study design

This is a multicentre, open-label, comparative, randomized, 2:1, controlled, single-blind, superiority

Intervention

Groep 1 ontvangt het Crohns Disease Exclusie Dieet plus drinkvoeding
Groep 2 ontvangt corticosteroiden en kan daarna voor het Crohns Disease Exclusie Dieet kiezen.

Study burden and risks

So far, no risk associated with the exclusion diet, exclusive, partial enteral nutrition or CDED for Crohn's disease has been identified. Yet, CDED is burdensome because it consists in the avoidance of many food.
PCC carries the risk of intestinal obstruction or perforation if the capsule is blocked above an intestinal stricture. This risk can be avoided by the systematic use of the patency capsule prior to administration of the real capsule. Each of the two panenteric capsule endoscopies needs bowel preparation. However, patients whose endoscopic lesions are confined to the small bowel at the first PCC, will be prepared by only 1000 mL of PEG, 30 minutes after the second PCC. Moreover, PCC caries the risk of delayed or no excretion of the capsule and the risk of lesion or mucosal bleeding.
* The risk level of the study is B (= somewhat higher than the risk of standard medical care).
The potential benefit of the trial is that of an improvement of CD endoscopic lesions with dietary therapy that has no known side effects. Multiple studies have shown that healing of endoscopic lesions was associated with long-term beneficial outcomes.

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (16-17 years)
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Patients aged 16 to 70 years,
- With mild to moderate, luminal, active CD, defined by a HBI of 5 to 16, involving the small bowel, and/or the colon
- Not treated with corticosteroids at baseline
- Patients either naïve or previously exposed to a maximum of two classes of biologics or currently receiving a biologic therapy, and exposed to a maximum of two classes of biologic therapy, including the current one
- Patent small bowel as assessed by the patency capsule
- Active endoscopic lesions, as defined by Lewis score >= 225 in the small bowel and/or SES-CD>= 4 in the colon. The eligibility of the patient will be determined by the site investigator and a central reader.

Exclusion criteria

- Inability to follow the CDED during 16 weeks.
- Prior intolerance to corticosteroids.
- Ongoing infections, evolving virus diseases.
- Live vaccines.
- Arthritis or uveitis as main presenting symptoms.
- Patients with severe and/or predominant rectal or perianal disease.
- Heavy smokers (more than 10 cigarettes per day).
- Infliximab, adalimumab, methotrexate or azathioprine initiated less than 3 months before inclusion in this trial.
- Vedolizumab, ustekinumab initiated less than 6 months before inclusion in this trial.
- Change in methotrexate, azathioprine, infliximab, adalimumab, vedolizumab or ustekinumab dosage less than 3 months before inclusion.
- Pregnant or lactating women

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	09-04-2024
Enrollment:	50
Type:	Actual

Ethics review

Approved WMO Date:	18-09-2023
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-03-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-01-2025
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
ClinicalTrials.gov	NCT05284136
CCMO	NL82030.018.22