Efficacy of AlbenDazole to inDuce mUcosal healing in Patients with Crohn's disease on anti-TNF monotherapy: ADD UP

No registrations found.

Ethical review	Positive opinion
Status	Recruiting
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON29213

Source
NTR

Brief title
ADD UP

Health condition

Crohn's disease

Sponsors and support

Primary sponsor: Amsterdam University Medical Center (location meibergdreef)
Source(s) of monetary or material Support: ZonMW

Intervention

Outcome measures

Primary outcome

• Proportion of patients with absence of ulcers on centrally read endoscopies after 12 weeks

of albendazole and anti-TNF combination treatment compared to placebo

Secondary outcome

Key secondary endpoints

• Proportion of patients with endoscopic response on centrally read endoscopies defined as a reduction in the Simple Endoscopic Severity index (SES-CD) score by ≥ 50% compared to baseline

• Proportion of patients with endoscopic remission on centrally read endoscopies defined as a SES-CD score < 3 in general or < 2 in case of L1 (ileal) disease

• Clinical endpoints:

o Change in CDAI from baseline to W12

 Clinical remission: CDAI < 150

 Clinical (partial) response: decrease in CDAI ≥ 70 points [CR-70])

o General and change in quality of life, as measured by the IBDQ, SF-12 and EQ-5D-5L at baseline, week 12 and 36

o Patient Reported Outcome Measure (PROM): assessment of the general and change in functional status and well-being measured from the patients' perspective by the IBD-CONTROL questionnaire [25], at baseline, week 12 and 36

Other secondary endpoints

• Change in Anti-TNF serum concentration and anti-drug-antibodies from baseline to W12

• Proportion of patients with hs-CRP < 5mg/L at W12

• Proportion of patients with fecal calprotectin < 250 µg/g at W12

• Proportion of patients with fecal calprotectin <100 µg/g at W12

• Change in Anti-TNF serum concentration and anti-drug-antibodies from baseline to W12

• Histological changes from baseline to W12 based on centrally read scanned biopsies using the colonic and ileal global histologic disease activity scoring system (CGHAS/IGHAS, appendix 14.2) and the Robarts histology index (RHI, appendix 14.3).

• Presence of type 2 regulatory wound-healing macrophages (CD14+CD68+CD206+) by immunohistochemical staining and fluorescence-activated cell sorting on intestinal biopsies

• Occurrence of (serious) adverse events

• Quality Adjusted Life Years (QALYs)

• Costs

• Identification of baseline predictive genetic marker for therapy response to albendazole

Study description

Background summary

Rationale: Crohn’s disease (CD) is a chronic inflammatory bowel disorder (IBD) with a major impact on quality of life. Mucosal healing is an important treatment outcome to prevent long term complications of the disease. Regulatory M2 type macrophages play a key role in wound healing and were shown to be induced by anti-TNF treatment in vitro and in vivo. Moreover, thiopurines promote anti-TNF induced mucosal healing and enhance the generation of anti-TNF induced M2 macrophages, which might be a key underlying mechanism of action. The use of thiopurines however, is accompanied by evident downsides. In up to 25% thiopurines need to be discontinued due to intolerance or side effects. We aimed to find an alternative and initiated a drug screen in collaboration with the target Discovery Institute at the University of Oxford.

A library of 1600 FDA approved compounds was screened for the capacity to potentiate anti-TNF medicated induction of M2 macrophages in vitro using a human mixed lymphocyte reaction. During this screen, several benzimidazoles, including albendazole and mebendazole, were identified. Our preclinical work at the Tytgat Institute at the AMC confirmed that albendazole potentiates the efficacy of anti-TNFα therapy both in vitro and in an IBD mouse model. Albendazole is an antihelminthic agent with a well described safety profile. Potentially it could be a novel therapeutic agent for anti-TNF-α combination therapy in patients with Crohn’s disease.

Objective: To evaluate the safety and efficacy of 12 weeks albendazole treatment added to anti-TNF monotherapy in adult patients with Crohn’s disease with incomplete mucosal healing.

Study design: Multicentre randomised double-blind, placebo-controlled trial with 2 parallel groups (albendazole and placebo)
Study population: Adult Crohn’s disease patients with incomplete mucosal healing (SES-CD > 6 or ≥4 for isolated ileal disease) on anti-TNF monotherapy (either infliximab or adalimumab) for ≥4 months. Only patients with therapeutic drug levels and no measurable anti-drug antibodies are eligible. Concomittant use of an immunomodulator (methotrexate, azathioprine, 6-mercaptopurine, 6-thioguanine) within three months before enrollment is an exclusion criterion. Patients who previously failed on combination therapy (anti-TNF +

immunomodulator) – defined as discontinuation on this combination therapy due to refractory disease activity – are also not eligible for enrollment. A detailed overview of in- and exclusion criteria can be found at et section 4.1 and 4.1 (page 15 & 16).

Intervention: 110 subjects are randomly assigned to receive either albendazole or placebo (1:1) in combination with continued anti-TNF treatment at unchanged dose. Patients will receive oral albendazole treatment for 12 weeks in a weight adjusted dosage or placebo.

Main study endpoints: Proportion of patients with absence of ulcers on centrally read endoscopies after 12 weeks of albendazole and anti-TNF combination treatment compared to placebo
Nature and extent of the burden and risks associated with participation, benefit and group relatedness: It seems plausible that patients have benefit from the addition of albendazole to anti-TNF monotherapy. According to the extensive experience with albendazole (in similar dosage and duration) for other indications, the drug is known with a positive safety profile. In order to remain vigilant concerning possible side effects, several safety measures are in place. Firstly, an interim analysis will be performed after 15 patients in each arm have finished the intervention phase (week 12). Stopping rules, with emphasis primarily on patient safety and secondarily on efficacy, are in place which will guide the choice whether or not to continue. The interim analysis will be evaluated by a DSMB. Secondly, repeated blood samples are taken to monitor complete blood count and liver enzymes. Predefined criteria are in place concerning dose adjustments following liver enzyme elevation.

Peripheral blood is sampled 5 times on top of standard clinical care with a negligible risk and low burden. Subjects will be subjected to one additional (end of study) ileocolonoscopy on top of standard clinical care. This ileocolonoscopy is performed in order to assess endoscopic disease activity and evaluate the intervention’s efficacy. Patients have established increased risk of persistent intestinal inflammation as determined by a repeated elevated faecal calprotectin. As part of standard clinical care patients will receive a screening colonoscopy to objectify refractory mucosal inflammation. During endoscopy biopsies are taken to determine histological disease activity. The procedure itself in combination with biopsy procurement include a minimal risk of complications, mainly bleeding or perforation (<1:10.000)[1]. In case a complication occurs, endoscopic treatment (clip placement to achieve hemostasis) is effective in most cases. Rarely, hospital admission with/without surgical intervention, antibiotic therapy and/or blood transfusion is required. Patients need to fill in 3 quality of life questionnaires and 1 ‘Patient Reported Outcome’ questionnaire at three different timepoints. Moreover, 1 cost questionnaire required for the economic evaluation will be administered at week 12 and week 36.

Study objective

Albendazole could be a novel therapeutic agent for anti-TNF alpha combination therapy in patients with Crohn's disease

Study design

The study design will comprise three phases (figure 1):

1) Screening phase (up to 14 days) to determine patients' eligibility for the study

2) Intervention phase (12 weeks)

3) Follow up phase (24 weeks)

Intervention

110 subjects are randomly assigned to receive either albendazole or placebo (1:1) in combination with continued anti-TNF treatment at unchanged dose. Patients will receive oral albendazole treatment for 12 weeks in a weight adjusted dosage or placebo

Contacts

Public
Academic Medical Center Amsterdam, Department of gastroenterology and hepatology, C2-231

Toer W. Stevens
Meibergdreef 9

Amsterdam 1105 AZ
The Netherlands
(020-56)65584
Scientific
Academic Medical Center Amsterdam, Department of gastroenterology and hepatology, C2-231

Toer W. Stevens
Meibergdreef 9

Amsterdam 1105 AZ
The Netherlands
(020-56)65584

Eligibility criteria

Inclusion criteria

• Patients ≥18 years and ≤65 years

• Diagnosis of CD, based on endoscopy and histopathologic examination of mucosal biopsies

• Written informed consent

• Active mucosal disease as defined by a repeated faecal calprotectine ≥ 250 µg/g at 2 consecutive occasions (≥2 weeks and ≤3 months interval) AND presence of mucosal lesions as defined by a SES-CD > 6 (≥ 4 for L1 (ileal) disease) on screening ileocolonoscopy

• On anti-TNF therapy (ADM at a dose of 40mg Subcutaneous (SC) every week (QW) or every other week (Q2W) and IFX at a dose of 5-10 mg/kg every 4-8 weeks) for a period of at least 4 months at stable dose.

• Therapeutic trough serum concentrations of anti-TNF at screening (for IFX ≥ 3 µg/ml and for adalimumab (ADM) ≥ 5 µg/ml) and undetectable levels of anti-drug antibodies (ADA's) at baseline.

Exclusion criteria

• Ulcerative colitis or indeterminate colitis

• Current malignancy

• Women: current pregnancy wish, pregnancy or lactation. Men: active child wish

• Ongoing use of an immunomodulator (including azathioprine, methotrexate, 6-thioguanine, 6 mercaptopurine or mycophenolic acid).

• Prior failure on anti-TNF and immunomodulator combination therapy due to refractory disease per treating physicians opinion.

o NOTE: Patients with prior use of co-therapy who stopped the IMM due to stable disease (with continued anti-TNF treatment), prior IMM monotherapy and prior intolerance to IMM's are considered eligible for enrolment

• Elevated liver enzymes (ALAT, ASAT, LDH, γ-GT, AF) >1.5 times the upper limit of normal (ULN)

• Current use of any CYP3A4 inducing or inhibiting agents (outlined in table 1, section 5.3, page 18)

• Patients on prednisone >10mg/day or budesonide >6mg/day

• Patients who require rescue therapy with corticosteroids during the screening phase

• Leukopenia (leukocyte count < 4x10^9/L) and/or thrombopenia <50 x 10^9/L

• Other conditions which in the opinion of the investigator may interfere with the subject’s ability to comply with the study procedure

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	19-07-2018
Enrollment:	110
Type:	Anticipated

Ethics review

Positive opinion

Date:	19-07-2018
Application type:	First submission

Study registrations

Followed up by the following (possibly more current) registration

ID: 48703
Bron: ToetsingOnline
Titel:

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
NTR-new	NL7184
NTR-old	NTR7375
CCMO	NL63032.018.17
OMON	NL-OMON48703

Study results