Efficacy of AlbenDazole to inDuce mUcosal healing in Patients on anti-TNF monotherapy: ADD UP trial

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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.

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

Summary

ID

NL-OMON48703

Source
ToetsingOnline

Brief title
ADD UP

Condition

- Gastrointestinal inflammatory conditions
- Autoimmune disorders

Synonym
Crohn's disease, Inflammatory bowel disease

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: ZonMW

Intervention

Keyword: Albendazole, anti-TNF, Crohn's disease, Mucosal healing

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

1.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

2.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

3.Costs per Quality Adjusted Life year (QALY)

4.Clinical endpoints:

4.1Change in CDAI from baseline to W12

4.1.1Clinical remission: CDAI < 150

4..1.2 Clinical (partial) response: decrease in CDAI >= 70 points [CR-70])

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

4.3 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

4.4 Occurrence of (serious) adverse events (SAE)

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

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

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

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

9. 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).

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

Study description

Background summary

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 ant-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.

Study 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

Double-blind placebo-controlled randomized clinical trial. This trial will comprise two phases. In phase 1 30 patients will be included. After 15 patients in each treatment arm have completed the intervention phase (12 weeks albendazole/placebo treatment) and thereby have reached the primary outcome assessment, an interim analysis will be conducted. The results of the interim analysis will be interpreted by a DSMB. The members of the DSMB will draw up recommendations based on predefined stopping rules and dose reduction rules. Depending on the recommendations of the DSMB the second phase of the trial will be initiated in which the remaining 80 patients will be included.

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 matched placebo

Study burden and risks

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 several 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, (Yao, M.D., 2009, Gastrointest Endosc)). In case a complication occurs, endoscopic treatment (hemostasis/clipping) is effective in most cases. Rarely, hospital admission with/without surgical intervention, antibiotic therapy and/or blood transfusion can be required. Patients need to fill in 3 quality of life questionnaires and 1 *Patient Reported Outcome* questionnaire at three different timepoints. Moreover, 2 questionnaires concerning the economic evaluation need to filled in at week 12 and week 36.

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

1. Patients >= 18 years and <=65 years
2. Diagnosis of CD, based on endoscopy and histopathologic examination of mucosal biopsies
3. Written informed consent
4. Active disease as defined by a repeated faecal calprotectine >= 250 µg/g at 2 consecutive occasions (>=2 weeks and <=3 months interval) AND absence of mucosal healing as defined by and SES-CD > 6 (>= 4 for L1 (ileal) disease) on consecutive ileocolonoscopy
5. On anti-TNF monotherapy (ADM at a dose of 40mg Subcutaneous (SC) every week (QW) or every other week (Q2W) and IFX at a dose of approximately 5mg/kg every eight weeks) for a period of at least 6 months
6. No active combination therapy: anti-TNF + an immunomodulator (IMM). Prior use of co-therapy where IMM stopped due to stable disease, prior IMM monotherapy and prior intolerance to IMM*s are eligible
7. Therapeutic serum concentrations of anti-TNF at baseline (for IFX >= 3 µg/ml and for adalimumab (ADM) >= 5 µg/ml and undetectable levels of anti-drug antibodies (ADA*s)

Exclusion criteria

1. Patients < 18 years or >65 years old
2. Ulcerative colitis or indeterminate colitis
3. Currently ongoing malignancy
4. Women: current pregnancy wish, pregnancy or lactation. Men: active child wish
5. Use of an immunomodulator (including azathioprine, methotrexate, 6-thioguanine or 6 mercaptopurine)
6. Prior failure on anti-TNF and immunomodulatory combination therapy due to refractory disease per treating physicians opinion
7. Presence of measurable anti-drug antibodies and absence of therapeutic anti-TNF drug levels
8. Elevated liver enzymes (ALAT, ASAT, LDH, γ-GT, AF) >1.5 times the upper limit of normal (ULN)
9. Current use of any CYP3A4 inducing or inhibiting agents
10. Leukopenia (neutrophil count < 1.8x10^9/L) and/or thrombopenia <50 x 10^9/L
11. 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
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	08-10-2018
Enrollment:	110
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Eskazole
Generic name:	Albendazole
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	03-04-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-07-2018

Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-06-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-07-2019
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

ID: 29213
Source: NTR
Title:

In other registers

Register	ID
EudraCT	EUCTR2017-001737-85-NL
CCMO	NL63032.018.17
OMON	NL-OMON29213