A Prospective Multicenter Randomized Controlled, Open-label Study to Compare the Efficacy of Subcutaneous Infliximab Monotherapy with Subcutaneous Infliximab and Concomitant Immunosuppression in the Treatment of Moderate to Severe Crohn's Disease.

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The aim of this study is to investigate the efficacy of subcutaneous IFX in the treatment of moderate to severe Crohn*s disease with and without concomitant immunosuppression, as measured by the proportion of patients in corticosteroid-free clinical...

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

Summary

ID

NL-OMON54347

Source
ToetsingOnline

Brief title
DIRECT-CD

Condition

- Gastrointestinal inflammatory conditions
- Autoimmune disorders

Synonym

Crohns disease, Inflammatory bowel disease

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Celtrion,Farmaceutisch bedrijf;Celltrion en medicatie

Intervention

Keyword: Combination therapy, Crohns Disease, Infliximab, Subcutaneous

Outcome measures

Primary outcome

Proportion of patients in corticosteroid-free clinical remission (as defined by

CDAI<150) AND endoscopic response (a drop of at least 50% in SES-CD compared

to baseline) at week 26.

Secondary outcome

The proportion of patients in endoscopic remission at week 26 (defined as the

absence of ulcerations larger then 5mm)

Proportion of patients with endoscopic remission at week 26 (as measured by

SES-CD<=2)

Proportion of patients with endoscopic response at week 26 (as measured by at

least 50% reduction in the SES-CD as compared to baseline)

Proportion of patients in corticosteroid-free clinical remission at week 26

(defined as a CDAI>150)

The proportion of patients in CSF deep remission at week 26, as defined by corticosteroid-free clinical (CDAI<150) AND endoscopic remission (defined as the absence of ulcerations larger then 5mm)

Proportion of patients in clinical remission at week 2, 4, 8, 14 and 26 (defined as a CDAI <150)

Proportion of patients achieving clinical response at week 2, 4, 8, 14 and 26 (defined as a CDAI-70)

Proportion of patients achieving clinical response at week 26 (defined as a CDAI-100)

Proportion of patients in symptomatic remission at week 2, 4, 8, 14 and 26 (defined as a PRO-2, stool frequency and abdominal pain, <8)

Proportion of patients achieving symptomatic response at week 2, 4, 8, 14 and 26 (defined as a PRO-2 -8)

Time to symptomatic remission (defined as a PRO-2, stool frequency and abdominal pain, <8)

Proportion of patients in biochemical remission at week 8, 14 and 26 (CRP <= 5.0 mg/L and fecal calprotectin < 250 mg/g)

Time to biochemical remission (CRP <= 5.0 mg/L and fecal calprotectin < 250 mg/g)

Proportion of patients achieving minimally clinically important difference in quality of life at week 2, 4, 8, 14 and week 26 compared to baseline as assessed by the IBDQ and EQ-5D-5L questionnaire

Proportion of patients developing anti-drug antibodies (ADA) against IFX at week 2, 4, 8, 14 and 26 as measured by a drug-tolerant assay

IFX trough levels at week 2, 4, 8, 14 and 26

HLA haplotyping and genotyping for correlation with efficacy and ADA development

DNA methylation association IFX therapy response

Thiopurine metabolites at baseline, week 14 and week 26 (for patients randomized for the combination therapy group, only at baseline for those in the monotherapy group and with previous IS use)

Proportion of patients having IFX trough levels of > 5ug/ml at week 26

Proportion of patients achieving histological healing at week 26

Proportion of patients (of those with active perianal disease at baseline) in

clinical remission and response of their perianal disease, as defined by the

fistula drainage assessment (FDA) at week 26

Proportion of patients with extraintestinal manifestations at week 26 as

compared to baseline

Adverse events

Study description

Background summary

Crohn's disease (CD) is a chronic inflammatory bowel disease (IBD) that results in progressive bowel damage and disability. Since curative therapy is not yet available, CD is a lifelong disease and the aim of the therapy is to induce remission in the short term and to maintain remission in the long term. The recognition that chronic and untreated inflammation, even when asymptomatic, ultimately leads to poor outcomes leads to treatment goals evolving towards a combination of clinical and endoscopic remission.

A recent 1-year study showed that the efficacy and safety of the SC and IV formulations are comparable and unaffected by switching patients from IV to SC administration. Interestingly, the SC formulation of IFX has been associated with lower immunogenicity (i.e., slower rate of anti-drug antibody formation) compared to continuous IV treatment in both the RA (69 vs 33% in IV 3 mg / kg vs SC 120 mg EOW through w30) as in the IBD population (54 vs 38% IV 5 mg / kg vs SC 120/240 mg EOW through w30). In these studies, to our knowledge, patients were not systematically assigned concomitant immunosuppressive therapy. Long-term use of combination immunosuppressive therapy has been associated with increased risk of infection and malignancy.

Administration of IFX in combination with immunosuppressant combination therapy in CD leads to improved outcomes, and the benefit of combination therapy appears to be primarily determined by the effect of thiopurines on the pharmacokinetics and immunogenicity of infliximab in patients on combination therapy. However, the literature data is conflicting on the long-term risk of infection and malignancy in patients on combination treatment compared to anti-TNF monotherapy, so monotherapy would be preferable in terms of long-term

safety.

Study objective

The aim of this study is to investigate the efficacy of subcutaneous IFX in the treatment of moderate to severe Crohn*s disease with and without concomitant immunosuppression, as measured by the proportion of patients in corticosteroid-free clinical remisison (as defined by a CDAI<150) and endoscopic response (as defined by a SES-CD drop of at least 50%) at week 26. We hypothesize that subcutaneous IFX monotherapy is non-inferior to subcutaneous IFX with concomitant immunosuppression in inducing this combined primary endpoint of CSF clinical remission and endoscopic response by week 26.

Study design

This is a randomized controlled multicentre trial to investigate the efficacy of subcutaneous infliximab monotherapy compared to subcutaneous infliximab in combination with concomitant immunosuppression in inducing CSF clinical remission and endoscopic response after 26 weeks of treatment.

158 test subjects will participate in this study at approximately 13-20 locations in the Netherlands (peripheral and university hospitals). The estimated enrollment is 0.5 patient / center / month, leading to an inclusion duration of 16 months once all centers are open. First enrollment is expected in Q1 2021.

Treatment Arms:
Group 1: Subcutaneous IFX monotherapy 240mg at week 0 and week 2 and then 120mg EOW
Group 2: Subcutaneous IFX 240mg at week 0 and week 2 and then 120mg EOW in combination with immunosuppressive

Randomly assigned to either of these groups in a 1:1 ratio. Randomization will be stratified according to immunosuppressive use at screening.

Intervention

After consent, the patient is centrally randomized (1: 1) to either infliximab mono- or combination treatment. Following the screening procedure, patients randomized to the monotherapy group will begin subcutaneous IFX monotherapy at 240 mg at weeks 0 and 2 and then 120 mg EOW thereafter.

Patients randomized to combination IFX therapy will also start on subcutaneous IFX 240 mg at weeks 0 and 2 and then 120 mg EOW and will also receive 6-mercaptopurine 1-1.5 mg / kg (or if they are already on azathioprine or thioguanine , they will receive a continuous dose of 2-2.5 mg / kg or 20 mg

once daily unless shunter status, metabolite levels or previous adverse events suggest differently) or in case of adverse events or investigators individual consideration, instead of thiopurine, methotrexate 15 mg/week s.c. in combination with folic acid 5mg/week is to be started as soon as possible.

According to local protocols, if the dose of concomitant immunosuppression is gradually built up, the target dose of concomitant immunosuppression should be reached by week 2 of study product administration. Patients randomized to IFX monotherapy will not receive concomitant immunosuppression, or if they are already receiving concomitant immunosuppression, immunosuppressive treatment will be discontinued on screening.

The aim of this study is to investigate the efficacy of subcutaneous IFX in the treatment of moderate to severe Crohn's disease with and without concomitant immunosuppression, as measured by the proportion of patients with corticosteroid-free clinical remission (as defined by a CDAI <150). and endoscopic response (as defined by an SES-CD decrease of at least 50%) at week 26.

Biopsies are collected during colonoscopy (five segment 2 biopsies) screening and week 26. Additional blood samples from Infliximab serum concentrate and ADA weeks 2, 4, 8, 14, 26. Thiopurine metabolites blood collection baseline, weeks 14, 26, (epi) genetic analysis baseline and week 26.

Study burden and risks

Risk:
Remsima subcutaneous injection and its combination with immunosuppressants can reduce diarrhea and abdominal discomfort, but this is not certain. At any time during this exam, your disease or your symptoms may return or get worse.

Complications can arise with a viewing examination of the bowel. During the viewing examination, a tear or hole may develop in the intestinal wall. Or a bleeding. This is uncommon and affects less than 1 in 1,000 people. Then we try to treat you immediately. Sometimes you have to stay in hospital. And sometimes we have to repair the complication with surgery.

Burden:
The administration of Inflectra by means of an abdominal injection at home replaces the administration via the blood vessels in the hospital and reduces the risk of inflammation from infusion.

Participating in this study may have disadvantages, you may experience adverse effects of the drug. You may also be bothered by the measurements during the examination, for example from a blood sample. Filling in the questionnaires can be confronting. Participation in the study takes extra time and you must adhere to agreements that are part of the study.

Benefit:
Literature data is conflicting on the long-term risk of infection and malignancy in patients on combination treatment compared to anti-TNF monotherapy, so monotherapy would be preferable in terms of long-term safety.

In the pivotal studies of subcutaneous IFX, the new formulation has been associated with a lower immunogenicity compared to intravenous IFX, indicating a potential for monotherapy alone. If subcutaneous IFX monotherapy proves to be non-inferior in efficacy to combination therapy, this could provide a safer treatment for patients with IBD with more flexibility, eliminating the infusion unit capacity.

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 or older diagnosed with Crohn*s disease

Patients with moderate to severely active Crohn*s disease with a Crohn*s Disease Activity Index (CDAI) of 220 to 450 and presence of endoscopic ulceration in the terminal ileum, colon or both. Minimal SES-CD is >= 6 or >= 4 for isolated ileal disease.

Patients who had no response or loss of response to or have had intolerable side effects to one or more to the following: glucocorticoids, thiopurines (azathioprine/6-mercaptopurin/6-thioguanin), methotrexate , adalimumab, vedolizumab or ustekinumab OR patients in need of immediate top-down treatment with IFX at the discretion of the treating physician.

In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements.

The subject signs and dates a written, informed consent form and any required privacy authorization prior to the initiation of any study procedure.

Male or non-pregnant, non-lactating females. No wish to become pregnant in the coming 26 weeks.

Exclusion criteria

Main Criteria for Exclusion

Patients at imminent need of surgery as judged by the treating clinician

Patients with the short bowel syndrome, an ostomy or a symptomatic non-inflammatory stricture

Patients previously exposed to IFX (intravenous or subcutaneous)

Previously unacceptable side effects or intolerance to all immunosuppressants (both thiopurines and methotrexate)

Treatment with adalimumab within 15 days and vedolizumab and ustekinumab within 30 days

Patients who have had a primary non-response to adalimumab or had intolerable class-related side effects (as evaluated at the discretion of the treating physician)

Enteric pathogens (such as Salmonella, Shigella, Yersinia, Campylobacter and C. difficile) detected by stool analysis within 2 weeks prior to enrollment or at screening

Ongoing participation in another interventional trial

Patients with Ulcerative Colitis or IBD-U

Patients with ongoing abdominal or undrained perianal abscess

Patients with a history of colon cancer or colonic dysplasia, unless sporadic adenoma, which has been removed

Active or latent tuberculosis (screening according to national guidelines)

Cardiac failure in NYHA stage III-IV

History of demyelinating disease

Recent live vaccination (<= 4 weeks)

Patients with ongoing acute/chronic infection (including but not limited to HIV, hepatitis B and C) with the exception of chronic herpes labialis or cervical HPV

History of cancer in the last 5 years with the exception of non-melanoma skin cancer

A history of alcohol or illicit drug use that in the opinion of the principal investigator (PI) would interfere with study procedures

Patients with psychiatric problems that in the opinion of the PI would interfere with study procedures

Patients unable to attend all study visits

Patients with a history of non-compliance with clinical study protocols

Contraindication for endoscopy

Patients who received any investigational drug in the past 30 days or 5 half-lives, whichever is longer

Pregnancy or lactation or wish to become pregnant in the coming 26 weeks

Study design

Design

Study phase:	4
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	25-11-2021
Enrollment:	158
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Imuran
Generic name:	Azathiopurine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Methotrexate Ebetrex
Generic name:	Methotrexate
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Puri nethol
Generic name:	6-Mercaptopurine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Remsima
Generic name:	Infliximab
Registration:	Yes - NL intended use

Product type:	Medicine
Brand name:	Thiosix
Generic name:	Tioguanine
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	25-03-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-10-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-10-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-09-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-11-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-07-2023
Application type:	Amendment
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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	EUCTR2021-000469-33-NL
CCMO	NL76663.018.21