Understanding mechanisms of interventions and opportunities for personalized treatment in perianal fistulizing Crohn*s disease

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Ethical review	Approved WMO
Status	Recruitment started
Health condition type	Gastrointestinal inflammatory conditions
Study type	Observational invasive

Summary

ID

NL-OMON50884

Source
ToetsingOnline

Brief title
AMFIBIO - Amsterdam Fistula Biology

Condition

- Gastrointestinal inflammatory conditions

Synonym
perianal fistulzing Crohn's disease / perianal fistulas in Crohn's disease

Research involving
Human

Sponsors and support

Primary sponsor: Amsterdam UMC

Source(s) of monetary or material Support: The Leona M. and Harry B. Helmsley Charitable Trust, New York USA

Intervention

- No intervention

Keyword: Crohn, Fistula, Perianal

Explanation

N.a.

Outcome measures

Primary outcome

Presence and amount of inflammatory cell subtypes, stromal cells and
 identification of mucosal microbiome in rectal biopsies and fistula scrapings
 that relate to prediction of response to treatment for complex perianal Crohn*s
 fistulas. Response and remission will be measured by a combination of clinical
 and MRI endpoints.

Secondary outcome

- The proportion of patients with a combination of clinical and radiological
 remission (defined as fistula drainage assessment (FDA)-100% and remission
 according to the MAGNIFI-CD index *) and response (defined as FDA-50% or
 remission according to the MAGNIFI-CD index *, or FDA-50% and response
 according to the MAGNIFI-CD index*. All other combinations will be scored as
 non-responder.
*Cut-off values for response and remission according to the MAGNIFI-CD index
 are currently under investigation.
- The proportion of patients with radiological remission defined as a
 completely fibrotic tract on MRI at week 26
- The proportion of patients with clinical fistula response and remission
 measured by the perianal disease activity index (PDAI; defined as PDAI<=4 for
 response and PDAI-50% for remission) at week 26 compared to baseline
- Proportion of patients with symptomatic response and remission measured at
 week 26 compared to baseline by resp. a 25% and 50% reduction on a 10 cm
 patient scored visual analogue scale of global disease severity
- Proportion of patients with symptomatic response and remission measured by
 the IBDQ-32 questionnaire (defined as IBDQ-32 <168 for remission and delta
 IBDQ-32 >27 for response) at week 26 compared to baseline
- Proportion of patients with response and remission of quality-of-life
 measured by the CAF-QoL questionnaire (Crohn*s Anal Fistula - Quality of Life
 score) at week 26 compared to baseline

- Proportion of patients in clinical remission and response for Crohn*s disease
activity at week 0, 9 and 26 measured by the Harvey-Bradshaw Index (HBI;
defined as HBI < or = 4 for remission and HBI - 3 for response)
- Proportion of patients achieving biochemical remission at week 9 and 26
(defined as serum C-reactive protein <5.0 mg/L and fecal calprotectin < 250
mg/g)
- Time to biochemical remission (defined as serum C-reactive protein <5.0 mg/L
and fecal calprotectin < 250 mg/g)
- Proportion of patients with extraintestinal manifestations at week 26 as
compared to baseline
- Adverse events</p>

Study description

Background summary

Complex perianal fistulizing Crohn*s disease (pCD) is a frequent and debilitating complication of Crohn*s disease (CD) with major impact on quality of life and morbidity. Crohn*s perianal fistulas are challenging to treat as they are often refractory to conventional medical treatment strategies such as antibiotics, immunomodulators and biologic drugs, such as anti-tumor necrosis factor agents (anti-TNF). Furthermore, current fistula treatment algorithms - in the absence of data - do not include a personalized approach of care. Here we aim to investigate a novel biomarker assay by a multi-omics approach that predicts treatment response for patients with complex perianal Crohn*s disease during different treatment modalities of known efficacy (anti-TNF and mesenchymal stem cells) and experimental strategies (hyperbaric oxygen treatment, HBO).

Study objective

The primary objective of this study is to establish molecular profiles in lower rectal biopsies as close to the internal fistula orifice tissue and fistula scrapings based on single cell RNA sequencing, cellular protein expression by CyTOF and microbiome in pCD patients which can predict response to treatment. Identification of these profiles in peripheral blood should lead to a biomarker panel that could allow stratification to a more personalized treatment approach in perianal Crohn*s disease.

Study design

Prospective, monocenter observational cohort study for biomarker research with a 26-week follow-up will be intensively followed with pelvic MRI, sigmoidoscopy

with biopsies, clinical assessment and fecal and blood sampling.

Intervention

n/a

Study burden and risks

Burden: all subjects need to undergo three moments of clinical evaluation and investigations, most of these will be scheduled during clinical necessary hospital visits. Although additional blood and fecal sampling, and an additional MRI and sigmoidoscopy with biopsies is an extra burden in this study.
Benefits: patients do not directly benefit from the study procedures, but could do indirectly if a successful biomarker panel is created in this study.

Contacts

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Trial sites

Trial sites in the Netherlands

Amsterdam UMC
Target size: 114

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

All patients in treatment groups:
1. Confirmed diagnosis of CD with previously or currently documented luminal inflammation (endoscopy and histopathology)
2. Complex perianal fistula, defined as either involving the upper two-third of the sphincter complex (i.e., high intersphincteric, high transsphincteric, suprasphincteric or extrasphincteric course of the fistula tract), having multiple external openings, are associated with pain or fluctuation suggesting a perianal abscess or are associated with a rectovaginal fistula or anorectal stricture or active rectal ulcers, with active drainage (fluid loss on gentle compression; perianal fistulas that were previously close but that reopened can be included).
3. Age 16 or older
4. Signed informed consent

Mesenchymal stem cell patients:
5. Failure of conventional fistula treatment (anti-TNF and at least one surgical closure)

Hyperbaric oxygen patients:
6. Failure of conventional fistula treatment (anti-TNF)

In this observational study we will monitor three control groups at one study point. The following inclusion criteria will be used.

Patients with cryptoglandular fistulas without CD:
• Active cryptoglandular fistula, either superficial or complex
• No previous documentation of CD activity and a fecal calprotectin <250
• Age 16 y/o or older

Patients with CD with active proctitis and without perianal CD
• Confirmed diagnosis of CD with previously documented luminal inflammation and

rectal ulcerations >5mm (endoscopy and histopathology)
• Age 16 y/o or older
• CD treatment naive patients (i.e., immunomodulators, anti-TNF, other biologicals)

Patients with CD without proctitis and without perianal CD:
• Confirmed diagnosis of CD with previously documented luminal inflammation (endoscopy and histopathology), no earlier documentation of rectal ulcerations >5mm
• Age 16 y/o or older
• CD treatment naive patients (i.e., immunomodulators, anti-TNF, other biologicals)

Exclusion criteria

1. Patients with Ulcerative Colitis or IBD-U
2. Presence of impassible anal stricture
3. Superficial fistula only
4. Rectovaginal fistulas
5. Patients with ongoing abdominal or undrained perianal abscesses after repeated examination-under-anesthesia with drainage by incision or seton placement
6. Patients with a seton in situ >12 months
7. Patients with an stony
8. Enteric pathogens (such as Salmonella, Shigella, Yersinia, Campylobacter and C. difficile) etected by stool analysis within 2 weeks prior to enrollment or at screening
9. Active or planned pregnancy
10. Absolute contra-indications to perform MRI (e.g., claustrophobia), for relative contra-indications (e.g., metal implants) the MRI protocol could be adjusted upon decision with the treating physicians and patient
11. Contra-indication for endoscopy
12. Active participation in another interventional trial
13. Patients who received any investigational drug in the past 30 days or 5 half-lives, whichever is longer
14. Pregnancy and lactation
15. Patients with a history of colon cancer or colonic dysplasia, unless sporadic adenoma, which has been removed
16. A history of alcohol or illicit drug use that in the opinion of the principal investigator (PI) would interfere with study procedures
17. Patients with psychiatric problems that in the opinion of the PI would interfere with study procedures
18. Patients unable to attend all study visits
19. Patients with a history of non-compliance with clinical study protocols

Anti-TNF patients
20. Patients previously exposed to anti-TNF
21. Previously unacceptable side effects or intolerance to all immunosuppressants (both thiopurines and methotrexate)
22. Treatment with vedolizumab or ustekinumab within 30 days
23. Active or latent tuberculosis (screening according to national guidelines)
24. Cardiac failure in NYHA stage III-IV
25. History of demyelinating disease
26. Recent live vaccination (<= 4 weeks)
27. 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
28. History of cancer in the last 5 years with the exception of non-melanoma skin cancer
29. Male patients with negative EBV serology

Mesenchymal stem cell patients:
30. Presence of rectal ulcerations according current indication registration
31. Hypersensitivity to the product, bovine serum or any of the excipients (Dulbecco*s Modified Eagle*s Medium, containing amino acids, vitamins, salts and carbohydrates, and human albumin)

Hyperbaric oxygen patients:
32. Unfit for hyperbaric oxygen therapy as assessed by the hyperbaric physician
33. Contraindication for hyperbaric oxygen therapy: sensitivity to barotrauma, claustrophobia per assessment of hyperbaric oxygen specialists.

Study design

Design

Study phase:	N/A
Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	No intervention
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment started
Start date (anticipated):	10-09-2021
Enrollment:	113
Duration:	6 months (per patient)
Type:	Actual

Medical products/devices used

Product type:	N.a.

IPD sharing statement

Plan to share IPD: Yes

Plan description
N.a.

Ethics review

Approved WMO Date:	19-08-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-09-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-01-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Not approved Date:	23-12-2022
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214

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Approved WMO Date:	08-05-2025
Application type:	Amendment
Review commission:	METC Amsterdam

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
OMON	NL-00768
CCMO	NL76851.018.21
Research portal	NL-007687