Amsterdam Fistula Biology

No registrations found.

Ethical review	Positive opinion
Status	Recruiting
Health condition type	-
Study type	Observational non invasive

Summary

ID

NL-OMON26943

Source
NTR

Brief title
AMFIBIO

Health condition

Complex perianal Crohn's disease

Sponsors and support

Primary sponsor: Amsterdam UMC loc AMC
Source(s) of monetary or material Support: Helmsley Foundation, New York USA

Intervention

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
- Changes in 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 luminal 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)
- Adverse events

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 novel strategies (hyperbaric oxygen treatment, HBO).
Because pCD involves many different pathological pathways (inflammatory, microbial and

tissue remodeling mechanisms), we aim to investigate the mechanism of action of the different treatment modalities and biomarkers that will allow stratification to a more targeted approach. By doing so, we will also create a research platform to be used for rapid evaluation of novel potential treatments. Response to the different treatments will be assessed by clinical and imaging criteria (magnetic resonance imaging, MRI).
Virtually no appropriate molecular biomarkers are available to date to predict the course of pCD and response to any intervention. To chart the pathological mechanisms involved and their complex interplay, a single cell profiling approach is the most “state of the art” allowing deep understanding of disease processes and predictive biomarker discovery. This approach enables the detection of typical cell populations involved in pathology and healing and may lead to possible stratification for treatment options upfront based on pre-existing molecular modules.
Our workflow aims for an in-depth analysis of cells and gene signatures in pCD tissue (biopsies taken close to the fistula orifices) before and during treatment. We will combine RNA sequencing at the individual cell level with protein discovery and microbial sequencing. All data will be analyzed with advanced integrated biostatistics.
This experiment will be done in combination with advanced PET-CT imaging for activated fibroblasts (FAPI) in a subset of patients, since it is believed that fibroblast activation is critical for definitive fistula closure.
After a discovery set of pCD patients and non-IBD controls, a comparable patient cohort will be recruited for validation using targeted biomarker analysis with a Cytof (protein) panel derived from the results of the tissue discovery experiment. In parallel, we will explore if the protein profile can also be found in the peripheral blood. Both techniques can eventually be used in clinical practice. Our high volume multidisciplinary fistula clinic and the translational research facilities at Amsterdam UMC are capable to deliver this research in a timely fashion. This whole research package should make personalized and more effective management of fCD a true possibility in the foreseeable future. Physicians will collect a biopsy or a blood sample from their patients for protein analysis and based on the outcome offer the most beneficial treatment upfront.

Study objective

With this approach we aim to find inflammatory cell types that contribute to the pathophysiology of perianal Crohn’s fistulas.

Study design

sep/2021-apr/2022: Start inclusion discovery cohort and first review of scRNA-seq and CyTOF data
apr/2022-okt/2022: Complete inclusion discovery cohort and full analysis of scRNA-seq, CyTOF and microbiome data. Development of CyTOF panel for validation cohorts. Start inclusion validation cohort
okt/2022-aug/2023: Complete inclusion validation cohort, finalize all technical and sequence analysis, full integration of data, publication

Contacts

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Eligibility criteria

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)

Patients with cryptoglandular fistulas without CD:
• Active cryptoglandular fistula, either superficial or complex
• No previous documentation of CD activity and a fecal calprotectin <250 (19)
• 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
• No previous use of immunomodulators or 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
• No previous use of immunomodulators or 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 ostomy
8. Enteric pathogens (such as Salmonella, Shigella, Yersinia, Campylobacter and C. difficile) detected 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 both anti-TNFs
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)
32. Age < 18 years old

Hyperbaric oxygen patients:
33. Unfit for hyperbaric oxygen therapy as assessed by the hyperbaric physician
34. Contraindication for hyperbaric oxygen therapy: sensitivity to barotrauma, claustrophobia per assessment of hyperbaric oxygen specialists.
35. Age < 18 years old

Study design

Design

Study type:	Observational non invasive
Intervention model:	Parallel
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	N/A , unknown

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-09-2021
Enrollment:	104
Type:	Anticipated

IPD sharing statement

Plan to share IPD: Yes

Ethics review

Positive opinion

Date:	10-02-2021
Application type:	First submission

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
NTR-new	NL9709
Other	MEC AMC : METC2021_094

Study results