A Prospective, Open-label Pilot Study to Evaluate Effector mechanisms of Hyperbaric Oxygen Therapy in Patients with Moderate-to-Severe Ulcerative Colitis: The PARADOX study

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This study has been transitioned to CTIS with ID 2024-515278-28-00 check the CTIS register for the current data. To analyze the molecular effects and dose-response relationship of HBOT in patients with moderate-to-severe UC refractory to medical...

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

Summary

ID

NL-OMON52110

Source
ToetsingOnline

Brief title
PARADOX study

Condition

- Gastrointestinal inflammatory conditions

Synonym
IBD, ulcerative colitis

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: European Crohn's and Colitis Organization (ECCO)

Intervention

Keyword: Hyperbaric oxygen therapy, Multi-omics, Ulcerative colitis

Outcome measures

Primary outcome

Co-primary outcomes will be assessed within 3 days after the last HBOT session and at week 12 post-treatment in the cohort that reaches predefined response. Changes between baseline and last day of HBOT will be analyzed to assess the mechanistic effects of HBOT. The co-primary outcomes include mucosal immune cell populations, RNA transcription profiles regarding pro- and anti-inflammatory, HIF-dependent and mucosal barrier function cascades, cytokine profiles, changes in microbiome and blood flow assessed by ultrasonography.

Secondary outcome

- Response after completion of HBOT and at week 12 post-treatment defined as a reduction in complete MAYO score of 3 points AND at least 1 point reduction in the MAYO ES WITHOUT escalating therapy such as dose escalations, switching to another drug, adding corticosteroids or colectomy,
- Clinical disease activity assessed by the PRO-2 score during treatment at day 2, 4, 6 and the last day of treatment, for the group with 20 and 30 sessions: day 10 and 14 and the group with 30 sessions: day 20, and after treatment at week 2, 4, 6, 9, 12 and 26

- Endoscopic disease activity assessed by Mayo endoscopic score within 3 days of last HBOT session and at week 12 post-treatment,

- Histologic disease activity assessed by Robarts* histopathology index within 3 days of last HBOT session and at week 12 post-treatment,

- Biochemical disease activity assessed by CRP, albumin and fecal calprotectin at day 0 and 6, for the group with 20 and 30 sessions: day 10 and for the group with 30 sessions: day 20, and for all groups: within 3 days of last HBOT session, week 6, 12 and 26.

- Ultrasonographic disease activity assessed by intestinal ultrasound parameters (Bowel wall thickness (mm), color Doppler Signal, presence of inflammatory fat, loss of haustrations, loss of stratification, presence of lymph nodes) at baseline, after HBOT and at week 12.

- Quality of life assessed by EQ-5D-5L during treatment at day 0, 6 and the last day of treatment, for the group with 20 and 30 sessions: day 10 and the group with 30 sessions: day 20, and after treatment at week 2, 6, 12 and 26

- Dose-response relationships for 10, 15 or 20 days of HBOT on the co-primary and secondary outcomes above.

- Adverse events. All adverse events related or not to study procedures or hyperbaric oxygen therapy will be registered. Side-effects and complications of HBO will be scored by a hyperbaric physician, for the example of barotrauma by the modified TEED score.

Study description

Background summary

Ulcerative colitis (UC) is characterized by relapsing and remitting symptoms of urgency, diarrhoea, fatigue and abdominal pain, which significantly impact patient*s quality of life. Despite the increase in treatment options, a group of patients remain refractory to sequential drug treatment, ultimately requiring proctocolectomy. Recently, hyperbaric oxygen therapy (HBOT) was shown effective in a difficult to treat population of patients with acute severe ulcerative colitis (ASUC) as an add-on treatment, showing benefit already after a few days of treatment. However, the molecular effects and dose-response relationships remain unclear.

Study objective

This study has been transitioned to CTIS with ID 2024-515278-28-00 check the CTIS register for the current data.

To analyze the molecular effects and dose-response relationship of HBOT in patients with moderate-to-severe UC refractory to medical therapy, more specifically to evaluate:
- Clinical, endoscopic, histological and ultrasonographic disease activity
- Mucosal blood flow, oedema and oxygen delivery
- Mucosal immune cell populations
- Mucosal transcriptional profiles, mainly hypoxia inducible factor (HIF) dependent cascades
- Mucosal cytokine profiles
- Drug penetration
- Mucosal stem cell populations important to mucosal healing
- Dose-response relationship of HBOT
- Feasibility of HBOT in treatment-refractory UC

Study design

This study is a prospective, open-label, single-center pilot study. Patients older than 16 y/o, visiting the IBD clinic at the Amsterdam UMC, with moderate-to-severe UC refractory to (anti-TNF and vedolizumab) therapy and on a stable dose of ustekinumab or tofacitinib will undergo daily sessions of HBOT. Initially 8 patients undergoing 10 sessions will be recruited. If predefined criteria (Total MAYO score -3 and endoscopic MAYO score -1 without therapy escalation in at least 50% of the patients) for response are not met, a second cohort of 8 patients undergoing 20 sessions will be recruited. If this cohort still does not meet response, a third cohort undergoing 30 sessions will be recruited. Molecular effects will be analyzed in the first cohort fulfilling the response criteria on colonic mucosal biopsies obtained during sigmoidoscopy. Responders will be compared to non-responders. Total follow-up

will be 26 weeks or until colectomy.

Intervention

Patients take place in a hyperbaric chamber pressurized to 2.4-2.5 atmosphere absolute (243-253 kPA), while breathing 100% oxygen through a mask for 80 minutes. Including 5-minute air breaks, the total procedure lasts 110 minutes. Subjects will initially undergo 10 sessions of hyperbaric oxygen, one session per day. If the predefined proportion of clinical responding patients is not reached within the first patient cohort, a second cohort will be recruited for 20 sessions. A third cohort receiving 30 sessions will be recruited if the clinical response outcome is not reached within the second cohort. There will be an intention to treat for the predefined number of sessions.

Study burden and risks

Burden: hyperbaric oxygen requires daily visits to the hyperbaric oxygen facility; possible side-effects are barotrauma of the ears and temporary myopia. Severe side-effects are rare. Besides hyperbaric treatment, all subjects need to undergo 7 moments of clinical evaluation and investigations including 3 sigmoidoscopies. In addition to these visits, patients will undergo 10 times of blood sampling and stool collection within 26 weeks, bringing a total of 14 blood sampling and stool collection moments. Most of these will be scheduled during clinical necessary hospital visits. The additional blood and fecal sampling and sigmoidoscopies with biopsies are an extra burden in this study.
Benefits: patients could benefit of a novel treatment with previous successful results and thereby reducing the need for proctocolectomy; besides the direct effect they could benefit from unraveling working mechanisms of hyperbaric oxygen and its value for the treatment of ulcerative colitis in the long term.

Contacts

Public
Academisch Medisch Centrum

Meibergdreef 9
Amsterdam 1105AZ
NL
Scientific
Academisch Medisch Centrum

Meibergdreef 9
Amsterdam 1105AZ

NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

In order to be eligible to participate in this study, a subject enrolled in the treatment groups must meet all of the following criteria: All patients in treatment groups: 1. Documented diagnosis of UC >= 4 months prior to entry into the study, confirmed with endoscopy and pathology results available in the source documents 2. Moderately to severely active UC as defined by a total MAYO score of >= 5 and a MAYO ES of >= 2 determined within 7 days of starting HBOT treatment 3. Subjects must have failed or be intolerant (discontinued the medication due to an adverse event as determined by the investigator) of the following treatments: a. Oral corticosteroids b. Azathioprine or 6-mercaptopurine c. Anti-TNF therapy: infliximab, adalimumab or golimumab d. vedolizumab e. Current treatment with ustekinumab (or another p19 inhibitor in a clinical trial) or small-molecule therapy (e.g., tofacitinib) 4. Current treatment with a stable dose of ustekinumab or tofacitinib (>12 weeks of stable dose and interval of ustekinumab and >6 weeks of tofacitinib) 5. Age 16 or older 6. Approved for compassionate use of hyperbaric oxygen therapy by the treating physician and the health insurance company 7. In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements. 8. The subject signs and dates a written, informed consent form and any required privacy authorization prior to the initiation of any study procedures. 9. Male or non-pregnant, non-lactating females. Females of child bearing potential must have a negative serum pregnancy test prior to randomization, and must use a hormonal (oral, implantable or injectable) or barrier method of birth control throughout week 26. Females unable to bear children must have documentation of such in the source records (i.e., tubal ligation, hysterectomy, or post-menopausal [defined as a minimum of one year

since the last menstrual period]).

Exclusion criteria

A subject will not be eligible for participation in this study if any of the following criteria apply:
1. Presence of indeterminate colitis, microscopic colitis, ischemic colitis, infectious colitis or clinical findings suggestive of Crohn*s disease
2. Subjects without previous treatment for UC (i.e., treatment-naïve)
3. Subjects at imminent need of surgery as judged by the treating clinician
4. Subjects with evidence of colonic adenomas or dysplasia. However, subjects with prior history of adenomatous polyps will be eligible if the polyps have been completely removed and the subjects are free of polyps at baseline
5. Subjects who have positive stool examinations for enteric pathogens (including Salmonella, Shigella, Yersinia, Campylobacter, C. difficile) detected by stool analysis within 2 weeks prior to enrollment pathogenic ova or parasites, at baseline
6. Patients with an ostomy
7. Unfit for hyperbaric oxygen therapy as assessed by the hyperbaric physician.
8. Contra-indication for endoscopy
9. Patients who received any investigational drug in the past 30 days or 5 half-lives, whichever is longer
10. A history of alcohol or illicit drug use that in the opinion of the principal investigator (PI) would interfere with study procedures
11. Patients with psychiatric problems that in the opinion of the PI would interfere with study procedures
12. Patients unable to attend all study visits
13. Patients with a history of non-compliance with clinical study protocols

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	03-01-2023
Enrollment:	24
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Oxygen Medicinal Gas SOL 100% v/v medicinal gas, compressed
Generic name:	Compressed Medicinal Oxygen Gas 100%
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	11-05-2022
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-07-2022
Application type:	First submission
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

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2024-515278-28-00
EudraCT	EUCTR2021-003913-21-NL
CCMO	NL78575.018.22