Assessment of Patient-reported Symptoms and Endoscopic, Histologic, and Biomarker Outcomes in Patients With Acute Pouchitis Treated with Antibiotics

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The primary objective of this study is to evaluate the reliability and responsiveness of patient reported symptoms and endoscopic and histologic items for assessing pouchitis disease activity in patients undergoing SOC antibiotic therapy.A secondary…

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

Summary

ID

NL-OMON54456

Source
ToetsingOnline

Brief title
POUCHITIS

Condition

- Gastrointestinal inflammatory conditions

Synonym
Acute Pouchitis, Inflammatory bowel disease

Research involving
Human

Sponsors and support

Primary sponsor: Alimentiv B.V.
Source(s) of monetary or material Support: Alimentiv Inc.

Intervention

Keyword: Endoscopic and Histologic disease activity assessment, Patient-reported symptoms, Pouchitis, SOC antibiotic

Outcome measures

Primary outcome

Participants will undergo a pouchoscopy with biopsies at Screening and Week 6 (EOS) for assessing the reliability and responsiveness of endoscopic and histologic items for assessing pouchitis disease activity. In addition, participants will complete a Patient eDiary daily for the duration of the study to evaluate the responsiveness of symptoms to change following treatment. Blood, mucosal biopsy, and stool samples will be collected to identify biomarkers of pouchitis disease activity, biomarkers associated with responsiveness to antibiotic therapy, and to evaluate changes to the microbiome following antibiotic therapy and therapy withdrawal.

Pouchitis Symptoms

Site investigators will rate the severity of pouchitis symptoms using the Clinical Global Impressions of Severity (CGI-S) at Screening and Week 6 (EOS) and change in pouchitis symptoms using the CGI of Change (CGI-C) scale at Week 6. Participants will rate their symptoms using the Patient*s Global Impression of Severity (PGI-S) and a 100-mm visual analog scale (VAS) at Screening and change in symptoms using the Patient*s Global Impression of Change (PGI-C) at

Week 6. In addition, participants will record stool frequency and rate rectal bleeding, fecal urgency, and abdominal cramps in the Patient eDiary at Screening and throughout the duration of the study. At Screening and Week 6, participants will also complete the St. Mark*s Fecal Incontinence Score (Vaizey Score) and a Symptoms and Impacts Questionnaire for Pouchitis.

Endoscopic Disease Activity

Trained central endoscopy readers will score pouchitis endoscopic disease activity in the worst affected area of the pouch body with the Endoscopic Pouch Activity Index, Mayo endoscopic subscore, and Simple Endoscopic Score for CD, endoscopic component items of the Pouchitis Disease Activity Index (PDAI), St. Mark*s Criteria, Heidelberg Pouchitis Activity Score (HPAS), Japanese Diagnostic Criteria for Pouchitis (JDCP), novel items identified by a modified Research and Development/University of California, Los Angeles (RAND/UCLA) methodology, and a 100-mm VAS of global endoscopic pouchitis disease activity (from 0 for *no disease,* to 100 for *worst ever seen*).

Histologic Disease Activity

Trained central histopathology readers will score pouchitis histologic disease activity with the Robarts Histopathology Index, Geboes Score, Nancy Index, the histologic disease severity score developed by Liszewski, a 100-mm VAS of global histologic pouchitis disease severity and histologic items from the PDAI, St. Mark*s Criteria, HPAS, JDCP, and novel items identified by modified

RAND/UCLA methodology.

Secondary outcome

not applicable

Study description

Background summary

Disease activity in patients with pouchitis can be assessed through any combination of clinical symptoms, endoscopy, or histopathology. Currently, 5 pouchitis disease activity indices exist: the Heidelberg Pouchitis Activity Score (HPAS) and Pouchitis Disease Activity Index (PDAI), which consist of clinical, endoscopic, and histologic items; the Japanese Diagnostic Criteria for Pouchitis (JDCP), consisting of clinical and endoscopic items; the St. Mark*s Criteria, consisting of endoscopic and histologic items; and the Endoscopic Pouch Activity Index (EPAI), which is an endoscopy-specific index. Two modifications of the PDAI also exist: the modified PDA (mPDAI), consisting of PDAI clinical and endoscopic items and the Objective Pouchitis Score (OPS), consisting of PDAI endoscopic and histologic items. Pouchitis indices were primarily developed as tools to aid clinicians in diagnosing pouchitis and were not intended for use as evaluative indices in clinical trials, although the PDAI and mPDAI have both been used for assessing the effectiveness of some therapies. Unfortunately, these indices were not developed using modern clinimetric methods and have never been fully validated and thus their value as robust evaluative indices for drug registration trials is unknown.

Using Research and Development/University of California, Los Angeles (RAND/UCLA) appropriateness methodology, experts deemed 2 endoscopic items in existing indices as *inappropriate* based on face validity. Most notably was *edema,* which is assessed in each index with an endoscopic disease activity component. In addition, several novel items for assessing pouchitis disease activity were identified. Together, these findings suggest that existing pouchitis indices are suboptimal. A post-RAND reliability study provided further support for the inadequacy of these indices by demonstrating suboptimal reliability for some items and substantial reliability and strong correlation with overall pouchitis disease activity for items not currently included in pouchitis disease activity indices. The responsiveness of these items to changes in disease activity has yet to be determined.

Most recently, we assessed the face validity of clinical, endoscopic, and histologic items in the current pouchitis indices with RAND/UCLA appropriateness methodology and found significant uncertainty among experts

regarding the appropriateness of many clinical, endoscopic, and histological items.22 Despite this uncertainty, experts agreed that stool frequency and fecal urgency were appropriate pouchitis symptoms to assess. In addition, experts deemed the assessment of endoscopic disease activity in the pouch body at least 10 cm above the pouch outlet as appropriate.

Experts agreed that erosions and ulcers, percentage of ulcerated area, and the percentage of the pouch affected area were appropriate endoscopic items to evaluate in pouchitis. For histopathology, the degree of lamina propria chronic inflammation (lymphocytes and plasma cells), epithelial neutrophils, and the presence of erosions and ulcerations were all considered appropriate existing histologic items for assessing pouchitis. In addition, experts recommended lamina propria neutrophils and epithelial damage (including surface epithelial injury and crypt destruction), which are assessed in the Geboes score and Robarts Histopathology Index (RHI) for UC, be assessed in pouchitis. The reliability and responsiveness of existing indices and items/descriptors for pouchitis, as well as indices commonly used in inflammatory bowel disease (IBD), will be evaluated in this study and a novel pouchitis disease activity index potentially developed.

Study objective

The primary objective of this study is to evaluate the reliability and responsiveness of patient reported symptoms and endoscopic and histologic items for assessing pouchitis disease activity in patients undergoing SOC antibiotic therapy.

A secondary objective of this study is to develop a novel index for assessing pouchitis disease activity.

Study design

This is a prospective, open-label, observational study of patients with acute pouchitis being treated with SOC antibiotic therapy (a known effective therapy in most patients), to evaluate the reliability and responsiveness of existing pouchitis indices and component items for assessing pouchitis disease activity. A total of 43 participants are planned to be enrolled at clinical sites in North America and Europe.

All participants with suspected acute pouchitis will undergo a SOC pouchoscopy at Screening with study-related biopsy sample collection. Participants will be prescribed antibiotic therapy as per current SOC guidelines for a 4-week (28 day) course of antibiotic treatment. For study sites in the Netherlands, appropriate antibiotic treatment for pouchitis will be defined according to local country guidelines, where participants failing to respond to 2 weeks of

the initially prescribed antibiotic will have the option to switch antibiotic treatment and can be treated with the other agent for 2 to 4 weeks.

Participants will collect stool samples, using study-provided at-home stool sample collection kits, for the purposes of fecal calprotectin (FC),microbiome, and metabolomics analyses at 3 time points in the study: Screening, End of Treatment (EOT), and Week 6 (End of Study [EOS]). Blood samples will be collected at Screening and Week 6 (EOS) for metabolomics, serology, proteomics, and RNA-Sequencing analyses.

Participants will rate their pouchitis symptoms in an electronic diary (*Patient eDiary*) at the Screening Visit, for symptoms experienced prior to the initiation of antibiotic treatment, and then once daily following the initiation of antibiotic therapy through to the Week 6 (EOS) Visit.

Participants will return to the clinic at Week 6 for a follow-up pouchoscopy with biopsies for endoscopic and histologic assessments of disease activity, respectively, as well as clinical assessment. The total anticipated duration of individual patient participation is approximately 6 weeks after initiating antibiotic therapy.

Endoscopic and Histologic Disease Activity Assessments
A total of 3 blinded expert endoscopists and histopathologists will serve as central readers for this study and score pouchoscopy videos and histologic slide images, respectively. Paired pouchoscopy videos and histologic slide images (Baseline [Screening] and Week 6) of adequate quality will be scored by central readers (see Outcome Measures). Each central reader will score all Week 6 pouchoscopy videos and histologic slide images twice, 2 weeks apart, for assessing reliability, and all Screening pouchoscopy videos/slide images will be scored once to be compared to post-treatment scores for assessing responsiveness.

Novel Pouchitis Disease Activity Index Development
A novel index will be developed using multiple linear regression with items that have moderate reliability and responsiveness. The index will be internally validated using the bootstrap method with 2000 replicates.

Study burden and risks

In this real-world observational study of patients with pouchitis prescribed SOC antibiotic therapy, the potential risks associated with study participation beyond their usual treatment are minimal. SOC assessments may differ according to local site and/or region-specific guidelines.

Study-specific assessments not considered SOC may include: biopsy during the pouchoscopy at Screening (the Screening pouchoscopy itself is SOC), an additional pouchoscopy with biopsy at Week 6 (End of Study [EOS]), stool sample

collection, blood sample collection, and completion of a daily Patient eDiary:
• Pouchoscopy and biopsies are generally well tolerated, although there is increased risk of bleeding and in rare cases, pouch perforation.
• Participants will collect stool samples using an at-home stool sample collection kit at Screening, End of Treatment (EOT), and Week 6 (EOS). The burden will be minimized by providing the stool collection kits in advance and allowing for samples to be mailed into the clinic or returned to the clinic in-person for the Screening and EOT samples.
• Blood sample collection at Screening and Week 6 (EOS) to allow for study-specific metabolomics, serology, proteomics, and RNA-Sequencing analyses. Risks associated with blood collection include pain, bruising, and a minimal risk of infection at the venipuncture site and dizziness.
• Lastly, participation in the current study will involve completion of a daily electronic diary of pouchitis symptoms (*Patient eDiary*). Although there is an increased burden associated with diary completion, the burden is minimized by participants being able to complete the diary electronically (i.e., on a personal mobile device or computer).

The potential benefit to participants includes closer monitoring of their pouchitis symptoms. Study results are expected to benefit future patients by potentially developing a fully validated index for assessing pouchitis disease activity that will stimulate the development of novel therapies for chronic pouchitis. In addition, this study may identify less invasive prognostic biomarkers of antibiotic responsiveness, which could help clinicians identify patients unlikely to respond to antibiotics and prevent prescribing a potentially ineffective first-line therapy and result in quicker delivery of an effective therapy.

Overall, the risk-to-benefit ratio is considered favorable, with the potential benefits to future patients outweighing the minimal risks to study participants.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

Participants must meet each of the following criteria for enrollment into the study:
1. Adults >=18 years of age.
2. Ileal pouch-anal anastomosis (IPAA) for ulcerative colitis (UC) (J-pouch only) >= 6 months prior to screening.
3. Diagnosis of acute pouchitis at screening by stool frequency (an absolute value of >= 6 stools / day ANDan increase of >= 3 stools / day above the post-IPAA baseline), and local endoscopy (presence of >= 1 erosion or ulceration of the pouch on endoscopy [not including ulceration occurring within 1 cm of the pouch staple or pouch suture line]).
4. Not currently taking antibiotics for pouchitis and no previous systemic antibiotic use for any reason within 4 weeks prior to the Screening pouchoscopy. Note: Initiation of antibiotics for treatment of acute pouchitis prior to the Screening pouchoscopy will be permitted only if the participant initiates treatment within 48 hours prior to the Screening pouchoscopy; use outside of the 48-hour window will not be permitted and these patients should not be included in the study.
5. Current treatment with 5-aminosalicylic acid drugs, immunosuppressants, antidiarrheals, antimotility agents, and probiotics is permitted, if patient has received a stable dose for >= 4 weeks prior to screening. Dose of concomitant therapy must remain stable during the study period.
6. Able to participate fully in all aspects of this clinical study.
7. Written informed consent must be obtained and documented.

Exclusion criteria

Participants who exhibit any of the following conditions are to be excluded from the study:
1. Pouch formations besides J-pouch (e.g., W-, S- and Kock pouches).
2. IPAA for familial adenomatous polyposis.
3. Pouchitis caused by other inflammatory etiologies (e.g., ischemia or infection).
4. Antibiotic-dependent pouchitis, defined by >= 3 months of cumulative antibiotic use over the 12 months prior to screening.
5. Isolated cuffitis, pouch-anal or pouch-ileal anastomotic stricture, perforating complications, or pelvic sepsis.
6. Known Crohn*s disease (CD) or suspected CD of the pouch, defined as complex perianal/pouch fistula and/or extensive length of prepouch ileitis with deep ulceration.
7. Anticipated changes in therapy during study period.
8. Use of oral corticosteroids. Participants must have discontinued oral corticosteroids within 1 month prior to screening.
9. Current use of any advanced oral small molecule drug (e.g., Janus kinase [JAK] inhibitors) for the treatment of pouchitis. Participants must have discontinued oral small molecule therapy within 2 weeks prior to screening.
10. Failed (i.e., inadequate response with, loss of response to, or intolerance to) 2 or more compounds or classes of advanced therapies such as biologics and/or small molecule drugs (i.e., 1 biologic and 1 JAK inhibitor, 2 biologics in the same class, or 2 biologics from different classes) for the treatment of pouchitis.
11. Participants who are pregnant or breastfeeding.
12. Known history of allergy, intolerance, or are refractory to ciprofloxacin AND metronidazole AND any component of amoxicillin/potassium clavulanate combination.
13. Unable to undergo endoscopic evaluation.
14. Serious underlying disease other than acute pouchitis and UC that in the opinion of the investigator may interfere with the participant*s ability to participate fully in the study.
15. History of alcohol or drug abuse that in the opinion of the investigator may interfere with the participant*s ability to comply with the study procedures.
16. Prior enrollment in the current study.

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-08-2022
Enrollment:	5
Type:	Actual

Ethics review

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

Approved WMO Date:	07-03-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl

Approved WMO Date:	15-11-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam)

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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
CCMO	NL78787.018.21