Stricturing Crohn*s Disease assessment using advanced ultrasound and magnetic resonance imaging techniques for evaluation of inflammation and fibrosis

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The primary objectives of this study are to evaluate advanced MRI techniques (IVIM, T2*-mapping, motility) and advanced ultrasound techniques (CEUS, SWE and SICUS) to: 1. Identify advanced imaging techniques that correlate with stricture composition…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Gastrointestinal stenosis and obstruction
Study type	Observational invasive

Summary

ID

NL-OMON54948

Source
ToetsingOnline

Brief title
Ultrasound and magnetic resonance imaging in strictures in Crohn's Disease

Condition

- Gastrointestinal stenosis and obstruction
- Autoimmune disorders

Synonym
Crohn's disease, inflammatory bowel disease

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: geen financiering vereist

Intervention

Keyword: Crohn, MRI, stricture, ultrasound

Outcome measures

Primary outcome

MRI: - - IVIM fractional perfusion - T2*-value - Quantitated intestinal motility Ultrasound: - Speed of velocity of shear-wave (m/s) - Mean transit time of intravascular contrast (s) - Time to peak (s) - Blood volume per tissue (mL/100 mL tissue) - Blood flow (m/s) - Time between arrival of oral contrast at the stricture and passage through the stricture - Amount of bowel movements before oral contrast passes through the stricture Clinical: - Response to therapy after 26 weeks of treatment (defined by the continuation of medical therapy and the absence of the need for an intervention (balloon dilation or surgery)) Histopathology: - Inflammation grades - Fibrosis grades

Secondary outcome

- Conventional MRI parameters: length of the stricture, prestenotic dilatation, bowel wall thickness, bowel wall edema, bowel wall enhancement and stratification, fatty wrapping, fistulas and abscesses. - Conventional ultrasound parameters: length of the stricture, prestenotic dilation, bowel wall thickness, wall layer stratification, fatty wrapping, Doppler signal, motility, presence of lymph nodes, abscesses, fistulas. - Clinical information: medical history, sex, age, weight, height, current and previous medication -

Clinical activity scores: Harvey-Bradshaw Index (HBI) and Crohn*s Disease Obstructive Score (CDOS) - Blood: C-reactive protein, hemoglobin, platelet count, leukocyte count, erythrocyte count and albumin. - Faecal calprotectin

Study description

Background summary

Crohn*s disease is a chronic inflammatory disease characterised by episodes of relapse and periods of remission. Patients predominantly present with inflammatory disease, although approximately 11% of patients already exhibit strictures at diagnosis. Additionally, later during the disease course more than 30% of the patients develop intestinal strictures.1,6*8 As a consequence patients may present with symptoms of intestinal obstruction, such as bloating, abdominal pain, vomiting, inability to pass stool and restricted dietary intake.1,9 The treatment of strictures could be surgical or alternatively medical or endoscopic. In general, predominant-inflammatory strictures likely benefit from medical therapy whereas predominant-fibrotic strictures often require a surgical approach.1,3,6 Rarely is a stricture identified as merely inflammatory or fibrotic: a mixture of inflammation, muscular hypertrophy, collagen disposition and fibrosis has previously been identified in histological assessment of strictures.1,5,10 Consequently, the most optimal treatment has to be determined individually for each patient developing strictures. Furthermore, the development of antifibrotic medical therapies may offer an additional modality of treatment in the future.2 Therefore it is necessary to characterize predominant components of the stricture to guide clinical decision and identifying relevant parameters to use as endpoints for future clinical trials. Cross-sectional imaging techniques have high potential to satisfy this unmet need.2,3 Ultrasound and MRI can adequately characterize general features of a stricture, such as bowel wall thickening, luminal narrowing and the presence of a prestenotic dilation3. However, conventional imaging techniques are inconclusive in characterizing the stricture composition.3,5 However, advanced ultrasonography and MRI modalities may have the capability to adequately distinguish between fibrotic and inflammatory components.11*18 These modalities are well-tolerated, highly accessible and without radiation exposure, which makes them attractive for frequent use in patients with CD.3,19,20 Regarding advanced MRI-techniques, magnetization transfer, Intravoxel Incoherent Motion (IVIM) and T2*-mapping showed promising results when correlated with the resection specimen of stricturing CD patients. Magnetization transfer MRI can indirectly measure macromolecules, such as collagen, and it was shown to be accurate in grading different histopathological fibrosis classifications.12 IVIM is a sequence that measures

both diffusion and perfusion, influenced by changes in tissue composition due to inflammation and fibrosis. A recent study showed that IVIM was able to differentiate between four histopathological grades of fibrosis.11 T2*-mapping uses susceptibility differences and heterogeneities in the magnetic field that reflect the microstructure of the tissue. This sequence also showed promising results in measurement of fibrosis in the resection specimen of patients with stricturing CD.14 Both magnetization transfer, IVIM and T2*-mapping outperformed the more traditional contrast-enhanced (CE) imaging and diffusion-weighted imaging (DWI).11,12,14 Furthermore, quantified terminal ileal motility of Crohn*s disease patients has been shown to correlate with disease activity in the terminal ileum and was altered in stricturing segments.28,29 However, no data on correlation with histopathologic fibrosis is available. Advanced ultrasound modalities, such as contrast-enhanced ultrasound (CEUS), shear-wave elastography (SWE) and small intestinal contrast ultrasound (SICUS) recently became available and could improve the assessment of strictures.15*18,21*24 During CEUS intravascular contrast is injected and subsequently the vascularization of the bowel wall is analysed. 15,16,25 A recent study showed that blood volume and flow is lower in fibrotic resection specimens compared to non-fibrotic specimens16. SWE analyses stiffness of tissue, by measuring reverberation of sonographic waves on the tissue of interest. Consequently, it is possible to distinguish stiff from elastic tissue by measuring velocity of the shear waves. A few studies show promising value of SWE in stricturing disease and were found to correlate with muscular hypertrophy and fibrosis in surgical resection specimens. 15,18,26,27 Furthermore, CEUS peak flow enhancement was inversely correlated with SWE indicating less blood flow through stiffer tissue15. During SICUS, the small intestine is examined by using oral contrast, which improves detection of inflammatory lesions and strictures of the small bowel.21*24 The flow of contrast through the stenotic segment could indicate the severity of the stricture and improve further characterization of the stricture although no previous studies have investigated this. Histopathology of the resection specimen remains the ultimate reference standard for characterization of a stricture, however in studies this inherently creates a selection bias towards severe or predominant-fibrotic disease. Therefore, to evaluate predominant-inflammatory strictures, it is important to include patients that respond to anti-inflammatory treatment. To further establish the clinical impact, parameters that distinguish patients responding to anti-inflammatory treatment and patients requiring surgery need to be identified. This can identify novel biomarkers to guide clinical decision-making and to use in clinical trials regarding anti-fibrotic therapies. To date, no studies focused on cross-sectional imaging parameters in a broad spectrum of stricturing disease, both correlating findings to the composition of the resection specimen and the response to anti-inflammatory treatment. Therefore, it is important to conduct an all-encompassing study assessing imaging parameters according to a histopathological and a clinical reference standard. In conclusion, the aim of this study is to evaluate parameters of advanced ultrasound and MRI techniques to explore both the correlation with histology and to identify biomarkers that

distinguish patients responding to anti-inflammatory treatment and those requiring surgery.

Study objective

The primary objectives of this study are to evaluate advanced MRI techniques (IVIM, T2*-mapping, motility) and advanced ultrasound techniques (CEUS, SWE and SICUS) to: 1. Identify advanced imaging techniques that correlate with stricture composition as defined by the histopathologic degree of fibrosis and inflammation in the resection specimen 2. Identify parameters that distinguish patients responding to anti-inflammatory therapy and patients requiring surgery

Study design

Single-center, cross-sectional observational study Patients with proven Crohn*s disease that present with symptoms of obstruction (abdominal pain, nausea, vomiting, dietary restriction) and/or a small bowel stricture seen on endoscopy and/or cross-sectional imaging will be identified in the outpatient clinic or weekly multidisciplinary meeting. Patients will receive a conventional MRI, which is standard clinical care, with the addition of advanced sequences for the study (See *MR Imaging*). Then, all patients will receive advanced ultrasonography (See *Ultrasound*) prior to treatment. The multidisciplinary IBD team will be blind for the outcomes of all advanced imaging techniques for both MRI and ultrasound and treatment strategy will therefore not be influenced by these advanced imaging techniques. For optimal correlation with the resection specimen in patients undergoing surgery, the interval between imaging and surgery cannot exceed eight weeks. If this is the case, the MRI and ultrasound will be repeated. To address the objectives, MRI and ultrasound parameters are correlated with the histological outcome in those patients that will have surgical resection. The MRI and ultrasound parameters are compared between patients responding to anti-inflammatory treatment and patients having surgery to identify distinctive markers. Clinical data Clinical data from the medical records will be collected and will consist of medical history, gender, age, smoking status, weight, height, clinical disease activity scores (HBI, CDOS) and biochemical parameters in blood and stool. Clinical and biochemical activity parameters will be collected at inclusion and at 26 weeks. The clinical and biochemical assessment is part of the routine care and is not influenced by this study. Anti-inflammatory treatment assessment In the anti-inflammatory treatment group, patients will be divided in responders and non-responders. Response is defined as no surgery or endoscopic balloon dilatation, continuation of anti-inflammatory therapy and no clinical deterioration based on an increase in HBI and/or CDOS at 26 weeks. Non-responders can require surgery and may be transferred to the surgery group. When the initial imaging was performed more than eight weeks prior to surgery, imaging will be repeated for optimal correlation with histopathology. MR Imaging Patient preparation Patients will be prepared using the standard

clinical MR enterography procedure, encompassing 4 hours of fasting after which patients are requested to drink 1600 ml of a mannitol-solution as intraluminal contrast medium in 60 minutes prior to the MRI examination. MRI scanning MRI enterography will be performed on a 3.0 Tesla MRI (Ingenia, Philips, Best, The Netherlands) using a 16 channel body coil. Scanning will be performed according to the standard abdominal MRI protocol with antiperistaltic medication (Buscopan, Boehringer-Ingelheim, Germany) and a contrast-agent (Gadolinium, 0.1 mmol/kg) intravenously. The conventional protocol consists of a coronal dynamic motility sequence, coronal T2-weighted sequence, axial T2-weighted sequence with fat suppression, coronal T1-weighted pre- and post-contrast sequences, axial T1-weighted post contrast sequence. The additional research sequences consist of , IVIM and T2*-mapping which will add 15 minutes to the conventional protocol. Conventional parameters such as bowel wall thickness, bowel wall edema, prestenotic dilatation, bowel wall enhancement, bowel wall stratification, fatty wrapping, fistulas and abscesses will be reported. Intravoxel Incoherent Motion (IVIM) is a sequence that measures both perfusion and diffusion parameters, without the use of an intravenous contrast-agent, reflecting tissue characteristics that can be altered by inflammation and fibrosis. A recent study showed that IVIM fractional perfusion was able to differentiate between histopathological grades of fibrosis with a better accuracy than DWI and CE in stricturing Crohn*s disease patients.11 The sequence is safe and does not increase the burden for the patient. T2*-mapping reflects the microstructure of a tissue by using local susceptibility differences and inhomogeneities in the magnetic field. This sequence was able to accurately distinguish different grades of fibrosis and also outperformed more traditional sequences. Quantitated motility in the terminal ileum, has been shown to correlate with disease activity measured by endoscopy and histology from a biopsy in Crohn*s disease patients and is altered in stricturing disease. Changes might be different beween inflammation and fibrosis but It has not been evaluated in correlation with histopathology yet. Post-processing Post-processing of magnetization transfer, IVIM, T2*-mapping will be performed with in-house developed software to obtain quantitated data. Dynamic (motility) scans will be assessed with a previously validated algorithm (GIQuant, Motilent, London, UK) which is based on non-rigid image registration for automated motility analysis. Motility is quantified within a ROI delineating the affected bowel segment to produce a single, numerical motility score. Ultrasonography All ultrasonographic examinations will be executed using a Philips EPIQ 5G device. A convex probe (C5-1 MHz) will be used for an overview of the abdomen. Secondly, a linear probe (eL 18-4 MHz) will be used for detailed examinations and for all the measurements involving gastrointestinal ultrasound (GIUS), colour Doppler, CEUS, SWE and SICUS. Participants will be asked to fast for at least six hours prior to the examination. First, GIUS is performed to visualize colon, terminal ileum, ileum and jejunum successively and measure bowel wall thickness, Doppler signal according to the Limberg score, fatty wrapping, wall layer stratification, motility, presence of lymph nodes, abscesses, fistulas, prestenotic dilatation and narrowing of the lumen in all segments. The most narrowed part of the lumen

will be identified and considered the region of interest for ultrasound (ROI-US). Subsequently, intravascular contrast (Sonovue) for CEUS is injected and the ROI-US is visualized for 90 seconds. CEUS measurements will be performed, cine-loops will be recorded and analysed by software (VueBox®, Bracco, Italy) measuring flow through the bowel wall (mL/min per 100 mL tissue), peak volume, time to peak volume and wash out time. Then, SWE is performed where the velocity of shear waves (m/sec) will be measured. This will be measured ten times successively in the ROI-US and an average will be calculated. Then, SICUS will be performed. Participants ingest the oral contrast (17.4 gram of polyethylene glycol, PEG 4000 powder, dissolved in 500 mL tap water). Subsequently, progression of contrast through the small bowel is monitored. When contrast reaches the stricture, time between arrival of contrast and passage through the stricture will be recorded. Furthermore, the amount of bowel movements will be recorded before contrast passages the stricture. All measurements will be noted on an ultrasound assessment form. Regions of interest (ROI) for both MRI and ultrasound will be placed manually by two, independent observers (experienced radiologists and/or ultrasonographers) within the bowel wall of the strictured segment that is location-matched with the resection specimen. Histopathology In patients undergoing surgery, histological slides are retrieved in a predefined standardized way and location matched with MRI and ultrasound. Location matching of MRI and histopathology will be based on anatomical landmarks such as the most stictured part and the ileocecal valve, performed by the research coordinators, together with the radiologist and/or surgeon and/or pathologist. Histological evaluation of surgical specimens will be performed by two experienced gastrointestinal pathologists, independently, according to an adapted histological score by Chen et al.

Study burden and risks

Most of the MRI scans will be performed within routine clinical care with the addition of 15 minutes scanning time to the 30-45 minutes for the conventional protocol, resulting in a scanning protocol of maximally one hour. Routine clinical oral preparation (mannitol), intravenous antiperistaltic medication (buscopan) and contrast agent (gadolinium) are given. This requires one venepuncture which is not influenced by the study. The total time of the visit will be two hours due to the oral preparation, of which 15 minutes are added by the study. In patients scheduled for surgery with an MRI that is more than 8 weeks old, an extra MRI will be performed with the previous protocol.. The included patients will be subjected to an ultrasonographic exam: CEUS and elastography will take 10 minutes each, SICUS will take between 30 and 45 minutes resulting in a total examination time of 60 to 90 minutes. Ultrasonography itself is as safe procedure using sound waves to visualize abdominal organs. Administration of oral and intravascular contrast is a very safe procedure with hardly any side effects. In less than 1:10.000 patients an allergic reaction is reported with regards to intravascular contrast. For oral contrast no severe side effect have been reported. Regarding the contrast, oral

contrast is a dilution of macrogol in 500 mL of tap water. Intravascular contrast will form microbubbles when it is injected in the blood stream and will be breathed out within 15 minutes. No harmful effects to the lungs, kidneys or liver have been reported. The treatment strategy (medication or surgery) is decided within clinical care and is not influenced by the study. Blood samples and a stool sample will be collected at inclusion and are part of the standard clinical care.

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

* Endoscopical or histological confirmed Crohn*s Disease * Age * 18 year * Scheduled for surgical small bowel segment resection * One or more small bowel stricture(s) confirmed on endoscopy and/or cross-sectional imaging that is

scheduled for anti-inflammatory treatment

Exclusion criteria

* Isolated colonic stricture
* Endoscopic balloon dilation prior to baseline MRI or ultrasonography
* Pregnancy
* Age <18years
* Inability to give informed consent
* Ongoing gastroenteritis
* Specifically for MRI
o General contraindications for MRI (MRI-incompatible implants, pacemaker, claustrophobia, and pregnancy)
* Specifically for CEUS
o Chronic obstructive lung disease
o Acute coronary heart disease
o Clinically unstable heart disease
o Previous allergic reaction to Sonovue or to its components

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	17-12-2019
Enrollment:	42
Type:	Actual

Ethics review

Approved WMO Date:	12-09-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-03-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-07-2021
Application type:	Amendment
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
CCMO	NL71022.018.19
Other	NL9105