Best Practice & Research Clinical Gastroenterology 38-39 (2019) 101621

Contents lists available at ScienceDirect

Best Practice & Research Clinical Gastroenterology

journal homepage: https://ees.elsevier.com/ybega/default.asp

"Can Magnetic Resonance Enterography (MRE) replace ileo-colonoscopy for evaluating disease activity in Crohn's disease?"

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ARTICLE INFO

Article history:
Received 1 March 2019
Accepted 23 May 2019

Keywords:
Crohn's disease
MRI
MRE
Magnetic resonance enterography

ABSTRACT

Crohn's disease is a form of chronic inflammatory bowel disease that can lead to structural bowel damage due to transmural inflammation. Ileo-colonosocopy is currently essential for initial diagnosis. Reassessment of disease burden is frequently needed during episodes of active disease and when evaluating treatment efficacy. This review compares the role of Magnetic Resonance Enterography (MRE) and ileocolonoscopy in Crohn's disease management and whether cross-sectional imaging can replace invasive endoscopic tests. MRE can give information on the small bowel not visible at ileo-colonoscopy, and on extra-luminal complications. Evaluation of the bowel by MRE allows assessment of the sub-mucosa and serosa, and thus transmural healing. MRE offers a well tolerated investigation and additional information on disease activity to better manage patients with Crohn's disease.

Increasingly, there are a range of newer techniques such as diffusion weighted imaging, magnetisation transfer and motility MRI which provide greater information on fibrosis and predictors to treatment response which has been lacking despite the use of ileo-colonoscopy for several decades.

Introduction

Crohn's disease (CD) is a form of chronic inflammatory bowel disease (IBD) that can lead to structural bowel damage due to scarring and carries significant disability. IBD is now a global disease, with rapidly increasing incidence in the developing countries, and continues to have a significant burden in the western societies with prevalence exceeding 0.3% [1]. In addition to complications related to the disease process like abscess formation, strictures and fistulae, CD results in an increase in all-cause mortality both in adults and children [2,3]. Historical therapeutic strategies have failed to alter the disease progression in CD and this has led to newer treatment targets including early intervention with effective treatment, treat to target, tight disease control and monitoring which can improve patients' outcomes. These targets require regular and timely patient assessments to measure clinical (Patient Reported Outcomes, PRO), endoscopic (mucosal healing) and radiological outcomes in order optimise management proactively. The STRIDE program made recommendations on the targets in the treatment of CD - resolution of abdominal pain and normalisation of bowel habit along with absence of ulceration on ileocolonoscopy [4]. The clinical outcomes were to be measured every 3 months while endoscopic ones every 6–9 months during active phase of the disease [4]. Biomarkers are only adjunctive measures of inflammation which if raised should trigger a colonoscopy or cross-section imaging before treatment optimisation.

Potent immunosuppressive treatments including biologics (anti-tumour necrosis alpha; anti-integrin etc) have revolutionised the treatment of CD but requires optimisation in order to maintain patient benefit. Biologics in particular suffer from primary or secondary loss of response affecting durability and drug intolerances. At one year, up to 40% of patients lose responsiveness to these medications [5] and hence repeated re-assessments with biomarkers, endoscopic and radiological modalities may be required to ensure targets are met with these drugs. Timely escalation of treatment in the CALM study based on a combination of patient symptoms (Crohn's Disease Activity Index, CDAI), faecal calprotectin < 250 and CRP < 5 led to improved outcomes (mucosal healing) after 48 weeks of treatment [6].

With increasing availability and experience of MRI (Magnetic Resonance Imaging) techniques, there are now more diagnostic modalities available for the treating physician for monitoring patients with CD. We review the current roles of ileocolonoscopy and MRI in the management of CD and evolving concepts where cross-

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https://doi.org/10.1016/j.bpg.2019.05.008
1521-6918/

sectional imaging like MR enterography may in fact be more beneficial and even replace endoscopy.

Ileocolonoscopy in CD

The current gold standard for diagnosis of CD is a combination of clinical assessment, inflammatory markers, cross-sectional imaging and ileocolonoscopy [7]. At initial diagnosis, ileocolonoscopy is the standard of care since this allows direct mucosal visualisation and the ability to acquire tissue samples for histological assessment and confirmation.

Ileocolonoscopy is one of the most extensively evaluated investigative modality in the management of Crohn's disease. There is a wealth of data providing useful information both in assessing and monitoring CD. In addition, it helps in disease prognostication where the presence of deep and extensive ulceration (covering more than 10% of the mucosal area of at least one segment of the colon) predicted an aggressive clinical course with increased risk of penetrating complications and surgery [8]. The risk of colectomy in patients with and without severe endoscopic lesions were 31% and 6% at 1 year and 42% and 8% at 3 years, respectively [8]. The importance of endoscopy has increased further with mucosal healing (MH), being proposed as a treatment target. Healing of mucosal ulcerations has been well studied with ileocolonoscopy and has shown to predict better outcomes in CD patients with improved short- and long-term clinical remission (CR) [9] and has been proposed as a therapeutic target [4]. Two meta-analyses published in 2016 by Shah et al. and Reinink et al. reported long-term clinical remission (defined as achievement of CR at a minimum of 50 weeks from study onset) with MH and a decrease in CD-related hospitalisations and surgery [9,10]. A similar trend has also been reported in population-based studies on MH in CD where there was a decrease in inflammatory relapses and requirement for steroids [11,12].

Ileocolonoscopy has allowed the development of several validated CD scoring tools in classifying the severity of the disease. The disease activity measuring scores include the Crohn's Disease Endoscopic Index of Severity score (CDEIS) [13] and the Simplified Endoscopic Activity Score for Crohn's Disease (SES-CD) [14] and the post-operative Rutgeert's endoscopic grading score [15]. SES-CD is a simpler score to calculate than the CDEIS and thresholds for endoscopic disease severity has been defined in the literature [16]. Though these scores are not used routinely in clinical practice, they are utilised extensively in clinical trials of new drugs in CD. Decreases in these endoscopic scores have shown to translate into clinical benefit - a post hoc analysis of the SONIC trial data reported a minimal clinically important improvement in endoscopic disease activity of 50% based on SES-CD and CDEIS scores for sustained clinical benefit at week 50 [17]. Endoscopic assessment is probably also important before therapy de-escalation. In the study of infliximab discontinuation in CD patients in stable remission on combined therapy with immunosuppressors (STORI trial), full endoscopic healing was associated with lower risk of relapse after infliximab withdrawal at 1 year while lack of MH was associated with a disease relapse of over 60% in 1 year [18].

Are there drawbacks with ileocolonoscopy?

The endoscopic scoring systems are based on qualitative and subjective elements which can raise issues with reproducibility. In the EXTEND trial (Extend the Safety and Efficacy of Adalimumab through Endoscopic Healing), the agreement between central reader and site reader for CDEIS and SES-CD was overall moderate to high but the scoring of different segments of the colon varied significantly with scores for the right colon demonstrating only weak agreement [19]. Similar concerns over the post-operative Rutgeert's scoring was noted which demonstrated agreement to be fair at best among a group IBD specialist [$k = 0.57$ (0.51–0.65)] and general gastroenterologists [$k = 0.67$ (0.60–0.72)] [20].

Targeting MH in CD is challenging (in comparison to ulcerative colitis) since CD can affect any part of the gastrointestinal tract and hence may not be endoscopically accessible. A study from Mayo clinic reported normal ileocolonoscopy in 53.7% of patients with active small bowel CD due to skipping of the terminal ileum or the inflammation was restricted to the intramural part of the ileum [21]. In addition, the repeated use of ileocolonoscopy is hampered by its costs, procedural risks like perforation, bleeding and sedation related cardiovascular complications, endoscopy unit resources and patient acceptance. Surrogate markers for mucosal healing in the form of faecal calprotectin is associated with a sensitivity of 0.80 and specificity of 0.82 for a cut-off of 250ug/g for active IBD [22] but are inferior to direct mucosal visualisation. In addition, the degree of endoscopic healing required to make a meaningful change in long term outcomes is still debated. CD being a transmural disease from a pathophysiological stand-point, achieving MH may not reflect the ongoing inflammation and intestinal damage occurring beneath the surface of an endoscopically healed lumen.

Therefore mucosal healing may be a less accurate predictor of very-long-term outcomes in CD. Improvements in cross sectional imaging and newer techniques in particular with MR may provide information not available via endoscopy. It is quite possible that in order to achieve long-term modification of the natural history of CD, full thickness bowel wall healing (transmural) may be required.

In order to monitor mucosal or transmural healing, repeated reassessments need to occur. Ileocolonoscopy is mandatory for initial diagnosis and histological assessment. However, for the ongoing assessment of disease, MRI is much more acceptable and has a shorter recovery time than ileocolonoscopy [23]. In the METRIC trial, participants were asked if they were willing to undergo a repeat MRI or colonoscopy: 91% of patients were willing to have a repeat MRI, whereas only 75% were willing to undergo a colonoscopy. 10% would not undergo a repeat colonoscopy [23] (Table 1).

Magnetic Resonance Enterography (MRE) in CD

The ability of modern imaging has rapidly improved to the extent that it is able to detect mucosal injury approaching a performance that is comparable to ileocolonoscopy. The historical methods of assessing small bowel utilizing barium small bowel series were initially replaced with computed tomography enterography (CTE) using low density, non-absorbable oral contrast along with multi-detector scan technology to provide reliable small bowel resolution [24]. Despite excellent spatial resolution and wide availability, radiation exposure has limited its widespread use and the development of non-ionising imaging methods. MRI is a sophisticated imaging technique which detects energy emissions from protons in a magnetic field. MRE is a special MRI technique utilising high speed MR technology and a biphasic oral non-absorbable contrast to provide a radiation-free modality to evaluate the small bowel and is equivalent to CTE in assessing the small bowel [25]. It lends itself to frequent re-evaluation and surveillance of CD activity when compared to CTE which risks cumulative exposure to ionising radiation [26] particularly in the management of young patients with IBD [27]. Similar to CTE, it is shown to detect features of disease activity in the small bowel with sensitivities and specificities of 85% and 91% respectively [28,29]. When evaluated for SB ulcerations detected on double balloon enteroscopy, MRE demonstrated a diagnostic accuracy of 90.9% (95% CI: 87.9–93.2%)

Table 1
Advantages and disadvantages of ileocolonoscopy.

Advantages of ileocolonoscopy	Disadvantages of ileocolonoscopy
Mandatory for initial histological diagnosis	May miss isolated small bowel CD that skips the terminal ileum
Allows direct visualisation of mucosa	No information on bowel function and fibrosis
Changes occur more rapidly on ileocolonoscopy than MRI with treatment.	Will not pick up extraluminal disease e.g. fistulas, abscesses
	Patient acceptability is lower than with MRI

for endoscopic healing and was shown to have predictive potential for prognosis [30].

MRE findings during active CD include mural hyperenhancement and bowel wall thickening. Mural hyper-enhancement refers to increased signal in diseased segments compared with adjacent healthy segments. Pathological mural thickness is defined as a thickness of greater than 3 mm in a bowel loop that has fluid [31]. It is thought that inflammation in CD spreads to serosal surface of the bowel and causes fat deposition in the mesentery. The "comb sign" describes an engorged vasa recta [32]. As well as mural disease, MRE can demonstrate extraluminal disease that may not be visible on endoscopic assessment such as fistulae, sinus tracts, phlegmons and abscesses. A conventional MRE sequence consists of T1 images which are obtained with IV contrast, and T2 weighted sequences which are better able to measure wall thickness, enhancement after contrast and oedema [33]. Positive contrast or "bright lumen" MR techniques utilise enteral gadolinium and produces hypersignal on T1 and T2 weighted sequences that do not have any enhancement. These demonstrate wall thickening on T1 weighted images. "Dark lumen" MR using water rectal enema achieves high contrast after IV contrast administration e.g gadolinium. Initial evaluation suggests these techniques are superior in detecting active disease, such as mucosal hyper-enhancement and mesenteric fat stranding [27].

1) MR Scores in CD

In an effort to standardise the MRE readings, several MR scores have been validated of which MaRIA (Magnetic Resonance Index of Activity) score has been the most studied. The MaRIA score was developed to exploit the evolving MRI techniques [34,35]. Fifty patients underwent ileocolonoscopy as the gold standard investigation and the severity of disease was determined by using the CDEIS score, alongside MR, on the same day. A weighted sum score of wall thickness, relative contrast enhancement (RCE), oedema and mucosal ulceration were regressed against CDEIS to yield the final MaRIA score:

MaRIA (segment) = 1.5 x wall thickness (mm) + 0.02 x RCE + 5 x oedema + 10 x ulceration

The global MaRIA score is the sum of the MaRIA in ileum, ascending colon, transverse colon, descending colon, sigmoid and rectum. The area under the curve (AUC) for detection of active disease was 0.891. Using a cut off score $\geq$7.3 for active disease in any segment, the sensitivity for this score was 0.81 and specificity 0.89 [34]. This was validated in another cohort of 50 patients who were undergoing ileocolonoscopy either for dysplasia or assessment of active disease. This study confirmed wall thickness, relative contrast enhancement, oedema and ulcers on MRI were independent predictors of disease severity [35]. In this cohort, the total segment value correlated well with CDEIS score ($r = 0.83$).

The MaRIA score predicts responsiveness to treatment with biologics. In this study, a segmental MaRIA score <7 was defined as mucosal healing and <11 as ulcer healing. MRE successfully determined ulcer healing and endoscopic remission with 90% and 83% accuracy. MaRIA score predicted endoscopic remission (CDEIS <3.5) with a sensitivity of 83% and a specificity of 84% (AUC 0.864). In areas with mucosal ulceration, the MaRIA score was as effective as the CDEIS score to predict ulceration and the change in MaRIA and CDEIS score correlated well [36].

2) Newer MRI techniques under development

MRI appears to be as effective as endoscopic assessment at predicting ulcer healing, and MRI techniques are evolving rapidly-providing previously unavailable information. Data on fibrosis (Magnetisation transfer or MT) and bowel wall function (Motility MRIs or mMRI) can rapidly stratify people to those who will gain little benefit from biologics and are probably best treated by surgical excision. Some of the newer MRI techniques are discussed below:

Diffusion Weighted Imaging (DWI): Current MRI techniques use T1 and T2-weighted images with IV contrast to assess the bowel. Recent FDA notification on gadolinium based contrast agents (GBCA) raised concern on its long term health effects (https://www.fda.gov/Drugs/DrugSafety/ucm589213.htm) and hence there is an increased focus on non-contrast methods of disease assessment. Diffusion Weighted Imaging (DWI) uses the motion of water at the cellular and subcellular level to provide image contrast, allowing the enhanced detection of diseased bowel and assess response to treatment. DWI demonstrates higher signal in inflamed bowel segments, and apparent diffusion coefficients can be compared [37]. The obvious advantage of DWI is that it can be done without contrast. An MRI-DWI-colonography score has also been developed, demonstrating that MRI techniques can also predicts colonic ulceration. The DWI-MRI based Nancy Score has shown to predict mucosal healing - Nancy Score of five or less had a sensitivity of 70% and a specificity of 80% for predicting mucosal healing by endoscopy [38].

Magnetisation Transfer (MT): Fibrosis is an important pathophysiological process in CD that leads to strictures unresponsive to biologic agents. Transmural fibrosis cannot be evaluated by mucosal biopsy and fibrotic lesions can appear similar to inflammatory lesions on MRE e.g. thickened bowel wall. Current techniques do not allow us to evaluate fibrosis effectively. In the future, magnetisation transfer based MRI (MT) can be used to measures tissue fibrosis. In animal models, MT ratios in animals injected with a fibrosing agent correlated well with tissue collagen ($R = 0.74$) [39]. In humans, MT was assessed in patients prior to elective surgery for CD. Normalised MT ratios correlate strongly with fibrosis ($r = 0.769$; $p = 0.000$) and outperformed diffusion coefficient and contrast enhanced imaging [40].

Motility MRI (mMRI): A limitation of MRI is that the changes often lag behind ileocolonoscopy when assessing treatment responses. However, mMRI protocols are much more responsive to treatment. This involves imaging sequences rapidly capturing the same section of the bowel through time: this creates a moving image of the bowel and allows the measurement of gut function. In healthy volunteers, mMRI was found to be repeatable and sensitive in detection of drug-induced motility changes [41]. An initial study in 13 patients examining mMRI in CD demonstrated contraction frequency correlated well with CRP ($r = -0.701$) and calprotectin

Table 2
Advantages and disadvantages of MRE.

Advantages of MRE	Disadvantages of MRE
Picks up small bowel CD that skips the terminal ileum	Changes may lag behind ileocolonoscopy.
Better patient acceptability	No single protocol that evaluates both small bowel and colon
Detects extraluminal disease not directly visualised in the lumen.	Theoretical risk of gadolinium induced nephropathy.
Newer techniques offer information on fibrosis, motility	Subject unable to enter scanner due to metallic implants or claustrophobia
	MR environmental risk

($r = -0.85$) [42]. In another cohort of 82 patients, terminal ileal motility was assessed against CDEIS, endoscopic acute histologic inflammatory score (EAIS) and MaRIA scores. The AUROC was 0.86 and 0.87 with CDEIS and EAIS as standard respectively [43]. There is currently a multi-centre MOTILITY trial underway, assessing response to anti-TNF agents (UCL MOTILITY trial ISRCTN14481560, unpublished data). Motility MRI was associated with therapeutic response to treatment- anti-TNF responders had a greater improvement in motility than non-responders [44] (Table 2, Figs. 1 and 2).

Will endoscopic tests like ileocolonoscopy be replaced by MRE?

Ileocolonoscopy will continue to be used for the initial diagnosis of CD and its ability to sample abnormal intestinal mucosa under direct visualisation and to exclude other diagnosis in the form of infection, TB and tumours is currently unsurpassed. It currently remains the standard of care for assessment of colonic involvement in CD and in the surveillance of bowel cancer in patients with long standing Crohn's colitis. There is sufficient evidence in support of endoscopic MH as a treatment endpoint along with surrogate stool biomarkers and is widely used in clinical practice. However with the above limitations of ileocolonoscopy, it is likely to be less utilised for regular disease monitoring and its staging. Given the skipping nature of CD in adults and children, ileocolonoscopy is unable to assess the full burden of CD in order to guide management decisions for individual patients. Cross sectional imaging like MRE is able to identify complications like stenosis, fistulae and intra-abdominal abscesses which helps to stratify the behaviour of CD appropriately before initiation of medical or surgical treatment [36]. Increasing evidence suggests that MRE compared favourably with endoscopy in assessing mucosal ulceration [30,45] and being less invasive than ileocolonoscopy makes it ideal for regular reassessments.

The drawbacks with MRI are lack of optimal sequences for colonic assessments where colonoscopy may be a better assessment tool currently. In the colon, some areas are not optimally distended with contrast and therefore mural changes may not be observed, debris in the bowel may be mistaken for polyps and changes following surgical intervention may look like tumours [46]. In addition, MRE may be unsuitable for some patients who may not be able to drink 2 litres of contrast relatively quickly, or those who suffer claustrophobia.

Despite these, MRE informs management changes more frequently than repeated ileocolonosocpy. Garcia-Bosch reviewed

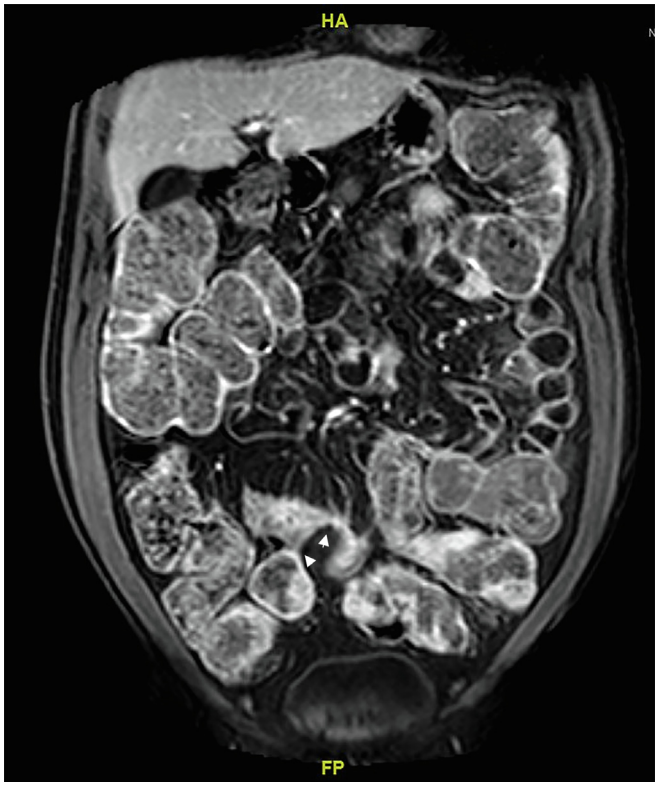

Fig. 1. MRE demonstrating entero-enteric fistulae of small bowel (arrow heads) in a patient with CD.

Fig. 2. MRE demonstrating comb's sign or engorgement of vasa rectae as a result of CD.

100 cases of CD which had both MRI and ileocolonoscopies performed. MRI as first examination was considered sufficient for management in 80% of cases, while this was only the case in 34% of cases where colonoscopy was the first examination [47]. MRI findings such as perianal disease, stenosis and/or intra-abdominal fistulae were independently found to predict abdominal surgical resection for CD [48]. MRI is thus rapidly becoming an important tool in the management of CD.

Transmural healing, a new target of therapy

Whilst mucosal healing has been the target of treatment in CD, longer-term population studies have not shown change in hospitalisations, surgery or patient reported outcomes [12]. This may be because CD results in full thickness inflammation and transmural healing is necessary to alter the natural history of disease. Transmural inflammation can persist despite mucosal healing: in a paediatric cohort of patients, 6% of children were found to have mucosal healing with ongoing transmural inflammation [49].

The exact definition of transmural healing (TH) is not yet established: Castigone *et al* [50,51] defined TH as a bowel wall thickness of <3 mm assessed by bowel ultrasonography; Eder *et al* defined it as a reduction in a simplified MRI score [52]. Others defined TH as active or inactive disease defined by the radiologist [53,54].

Despite the heterogeneity in the definition, studies generally report favourable outcomes for TH [55]. For instance, bowel wall healing assessed by MaRIA score predicted clinical corticosteroid-free remission (CFREM) (OR 4.42) and CD-related surgery (HR 0.16) [56]. Fernandes et al. [54] found patients with transmural healing had the lowest rates of hospital admission, therapy escalation and surgery. In the paediatric population, MRE remission was associated with fewer medication changes or surgery [53]. The studies of TH are limited by heterogeneity, small numbers and little data on changes to imaging with time [55]. Further clinical trials and population-based studies are necessary to assess the natural history of transmural healing. If indeed transmural healing alters the natural history, MRE will become an increasingly important STRIDE treatment target with ileocolonoscopy required only for initial diagnosis of small bowel CD.

Conclusions

Whilst colonoscopy plays a primary role in initial diagnosis, MRE provides many benefits, both in initial disease staging and repeated reassessment of disease. Its use should be integrated into treatment protocols, especially as newer MR techniques will be able to provide further information on bowel function and fibrosis. These techniques will allow us to better stratify those who may need surgery as the initial management of their CD.

Practice points:

1) Ileo-colonoscopy still has a role and allows for initial histological diagnosis
2) MRE is needed to completely stage CD before starting potentially disease modifying treatment like biologicals
3) MRE is more acceptable to patients and hence repeatable
4) Increasingly MRE is able to provide as much information as ileocolonoscopy

Research Points:

1) Development of newer techniques like MT and motility MR that will enable better characterisation of CD and thereby better treatment
2) Validate transmural healing in larger cohorts of patients and longitudinal studies to evaluate changes in outcomes in comparison to mucosal healing
3) Development of MRI tools to predict early post-operative Crohn's disease

Conflicts of interest

Abbvie and Takeda have sponsored educational activity for Dr Fumi Varyani. Dr Fumi Varyani has previously received funding from the Wellcome Trust (Grant number 107490/Z/15/A0 and an NIHR Academic Clinical Fellowship. Dr Samuel has received educational grants from Abbvie, Takeda, MSD, Ferring and Pharmacosmos. He has served on the advisory board for Takeda and Falk and received speaker fees from MSD, Takeda, Abbvie and Pharmacosmos.

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