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Article

Magnetic resonance imaging-quantified small bowel motility is a sensitive marker of response to medical therapy in Crohn's disease

Dr Andrew A Plumb¹; Dr Alex Menys¹; Dr Evangelos Russo²; Dr Davide Prezzi^{1,4}; Dr Gauraang Bhatnagar¹; Dr Roser Vega³; Professor Steve Halligan¹; Professor Tim R Orchard²; Professor Stuart A Taylor¹

¹*Centre for Medical Imaging, University College London*

²*Department of Gastroenterology, Imperial College London*

³*Department of Gastroenterology, University College London Hospitals NHS Trust*

⁴*Department of Cancer Imaging, King's College London*

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Summary

Background:

Magnetic resonance enterography (MRE) can measure small bowel (SB) motility, reduction in which reflects inflammatory burden in Crohn's Disease (CD). However, it is unknown if motility improves with successful treatment.

Aims:

To determine if changes in segmental SB motility reflect response to anti-TNF α therapy after induction and longer term.

Methods:

46 patients (median 29 years, 19 females) underwent MRE before anti-TNF α treatment; 35 identified retrospectively underwent repeat MRE after median 55 weeks of treatment and 11 recruited prospectively after median 12 weeks. Therapeutic response was defined by physician global assessment (retrospective group) or a ≥ 3 point drop in the Harvey-Bradshaw Index (prospective group), C-reactive protein (CRP) and the MaRIA score. Two independent radiologists measured motility using an MRE image-registration algorithm. We compared motility changes in responders and non-responders using the Mann-Whitney test.

Results:

Anti-TNF α responders had significantly greater improvements in motility (median=73.4% increase from baseline) than non-responders (median=25% reduction, $p<0.001$). Improved MRI-measured motility was 93.1% sensitive (95%CI 78.0-98.1%) and 76.5% specific (95%CI 52.7-90.4%) for anti-TNF α response. Patients with CRP normalization (<5mg/L) had significantly greater improvements in motility (median=73.4% increase) than those with persistently elevated CRP (median=5.1%, $p=0.035$). Individuals with post-treatment MaRIA scores of <11 had greater motility improvements (median=94.7% increase) than those with post-treatment MaRIA score >11 (median 15.2% increase, $p=0.017$).

Conclusions:

Improved MRI-measured SB motility accurately detects response to anti-TNF α therapy for CD, even as early as 12 weeks. Motility MRI may permit early identification of non-response to anti-TNF α agents, allowing personalized treatment.

Introduction

Crohn's disease (CD) treatment has advanced significantly with the availability of monoclonal antibodies (mAbs) directed against tumor necrosis factor alpha (TNF α), since they reduce symptoms, improve quality of life and increase mucosal healing in patients with severe disease[1]. Approximately 15-30% of patients with CD will require anti-TNF α mAbs[1] but only a proportion achieve a clinically meaningful response[2]; approximately 10-30% fail induction and a further 20-50% will have lost response by one year[3]. Monitoring therapeutic response is problematic because no single test is perfect. Clinical indices such as the Crohn's disease activity index (CDAI) have been criticized as subjective, non-specific, cumbersome and poorly-reproducible[4]. Biochemical measures are often non-specific for CD and endoscopy is both invasive and cannot assess transmural disease. A non-invasive technique that reliably detects therapeutic response at an early stage would be a major clinical advance, as it would allow timely triage of non-responders to an alternative therapeutic strategy; whether by dose escalation, switching to an alternate drug class, or via surgical intervention.

Magnetic resonance enterography (MRE) is widely disseminated and is recommended by consensus guidelines as a first-line test for the diagnosis and monitoring of CD[5]. Conventional MRI markers of activity such as wall thickness, contrast enhancement and T2 mural signal are useful in staging disease, but morphological changes lag behind clinical response to anti-TNF α therapy, limiting utility for early response assessment. For example, Van Asshe et al reported significant reductions in a morphological MRI activity score only by week 26 after infliximab induction and long-term persistence of transmural abnormality on MRE despite good clinical response[7].

Alternatively, software quantification of segmental bowel motility using MRE is emerging as a valuable marker of inflammatory activity in CD. MRE-measured motility has a consistent negative correlation with endoscopic and histopathologic measures of inflammation [8,9] – the greater the inflammatory burden, the larger the reduction in segmental motility. Return of motile function in response to therapy could conceivably occur more rapidly than standard morphological changes, since motility is determined by both gut structure and its neuronal control; the latter potentially responding rapidly. This could aid therapeutic decision-making earlier in the patient trajectory. To date there are no published data documenting whether or not MRE-derived motility changes improve following successful treatment, and, if so, whether this occurs soon after treatment initiation.

We hypothesized that 1) patients responding to anti-TNF α mAbs would have greater improvements in MRE-measured segmental small bowel (SB) motility than non-responders and 2) motility changes in diseased segments occurs rapidly after initiation of anti-TNF α treatment, allowing MRE to distinguish responders from non-responders at an early stage. To investigate these hypotheses, we analysed MRE-measured segmental SB motility in patients pre- and post-treatment with anti-TNF α mAbs.

Materials and Methods

To address our two related hypotheses, we analysed two separate groups of patients: 1) A retrospective cohort of individuals who had undergone MRE with

motility assessment as part of routine clinical care pre- and then again during or post medium- and long-term treatment with anti-TNF α mAbs (i.e. late follow-up imaging), and (2) A prospective cohort of patients undergoing MRE before and 12 weeks after induction with anti-TNF α mAbs (i.e. early follow-up imaging) as part of a wider research study.

Ethical considerations

Both the prospective and retrospective studies were approved by the relevant local Research Ethics Committees (prospective: NRES Committee South East Coast Surrey; 12/LO/1018; retrospective: NRES Committee North West London;10/H0720/91) and site Research & Development departments. All participants for the prospective study gave informed written consent.

Inclusion and exclusion criteria

Patients were identified for inclusion in the retrospective cohort using a single centre's departmental Inflammatory Bowel Disease (IBD) Biologics audit data, a more detailed version of the UK Royal College of Physicians/British Society of Gastroenterology National Biologics Audit[10]. All adult (≥ 18 years) or adolescent (≥ 14 years) patients commenced on either infliximab (IFX; Remicade, Schering-Plough) or adalimumab (ADA; Humira, AbbVie) for active small bowel or ileocolonic CD (Montreal L1, L3 +/- L4 disease[11]) between March 2009 and June 2014 were cross-referenced against the hospital Radiology Information System. Patients were eligible for inclusion if they had completed both (a) a MRE examination with SB motility assessment within 1 month of starting anti-TNF α mAbs and (b) a follow-up MRE examination with SB motility assessment after initiation of anti-TNF α therapy. Those who had not completed SB motility assessment at MRE or who had incomplete follow-up data to determine their response to therapy (e.g. failed to attend follow-up appointments) were excluded.

For the prospective study, consecutive consenting adult (>18 years) patients who were scheduled to commence IFX or ADA for active ileal or ileocolonic (Montreal L1, L3 +/- L4 disease) CD on the recommendation of their treating gastroenterologist were recruited from a tertiary IBD centre. Patients were excluded if they were unable to undergo MRI or were known to have co-existent malignancy, colorectal polyps, active infection, celiac disease, an estimated glomerular filtration rate of $<60\text{ml/min/1.73m}^2$ or pregnancy. Since these patients were also scheduled to undergo 18-fluorodeoxyglucose positron emission tomography with computed tomography (FDG-PET/CT) as part of a separate study, we also excluded patients with a history of cancer or a family history of cancer (defined as malignancy in a first degree relative diagnosed at <55 years) and those who had participated in research involving ionizing radiation in the preceding 3 years.

For both groups, we recorded (a) disease distribution according the Montreal classification (b) disease duration and age at diagnosis (c) history of surgery and (d) plasma CRP level at the time of baseline and follow-up MRE.

Imaging protocol, analysis and viewing conditions

All patients were scanned on one of 6 MRI units: three of 1.5Tesla field strength (Siemens Avanto or Symphony, Siemens Healthcare, Erlangen, Germany) and three of 3Tesla field strength (Philips Achieva or Ingenia, Philips Healthcare, Best, The Netherlands; or Siemens Verio, Siemens Healthcare, Erlangen, Germany). Patients were scanned using the manufacturer's body coils after ingesting 1.2-2.0L of 2.5% mannitol solution. Imaging protocols are available in the Appendix. In brief, the motility sequences are acquired during a series of 20 second breath-holds, during which multiple coronal MRI images are captured at 1 second intervals in the same anatomical position. This thereby generates a series of images depicting motion at a frame-rate of 1 image/second ("cine loops"). These 20 second blocks are then repeated at multiple positions until the entire small bowel volume has been imaged (7-15 blocks according to body habitus). Subsequently, imaging data were anonymized with a study code and copied to a secure central research office for processing and analysis.

Motility data were processed and quantified according to a previously published and validated method[12]. This uses an optic flow registration algorithm to estimate deformation of each frame of a given cine loop from an initial target frame, thereby serving as a measure of motility (since we expect deformation of images acquired in the same anatomical position to be primarily due to motion). Such motion can be quantified by taking the standard deviation of the Jacobian determinant of this deformation (quantified in arbitrary units, AU), which has previously been shown to correlate with histological inflammation[9]. Motility measurements mainly reflect local bowel motion rather than bulk bowel transit times; a typical range for a healthy adult is 0.15-0.55 AU in the fasting state[13]. To facilitate analysis, we used a graphical user interface (GUI) developed using Matlab (The MathWorks, Inc., Natick, MA; Figure 1) which both displays the cine loops and permits the user to define which areas of small bowel should be subjected to motility analysis by encompassing them in a freehand region of interest (ROI). For each patient, two experienced radiologists (BLINDED, 10 years experience of MRE or BLINDED, 7 years experience), aided by the designer of the GUI (BLINDED) independently and in separate reading sessions drew a polygonal ROI on a single segment of small bowel demonstrating the most severe mural thickening on the motility images. The ROI was drawn to include the bowel wall and lumen but extra-enteric tissues were excluded (Figure 1). Radiologists were blinded to all clinical, demographic and follow-up information throughout to avoid bias when defining their ROIs. This process was repeated for the post-treatment MRE scans. Care was taken to match the position of the ROI to that placed on the pre-treatment images. When placing ROIs, radiologists were blinded to all other MRI sequences other than the cine motility block to avoid morphological MRI changes biasing their placement (in six cases (two for reader 1, four for reader 2), limited anatomical correlation was permitted to confirm that the ROI was placed on small bowel rather than colon).

A third radiologist (BLINDED, 6 years of experience of MRE) applied a validated MRE-based score of CD activity[14] and response to treatment[6], the Magnetic Resonance Index of Activity (MaRIA) score, to the segment of bowel selected by the two observers by using the formula:

$$\text{MaRIA} = [1.5 \times \text{wall thickness(mm)}] + [0.02 \times \text{relative contrast enhancement}] \\ + [5 \times \text{oedema}] + [10 \times \text{ulceration}].$$

Definitions of response to therapy

Independent of the MRE analysis, each patient was classified as either a “responder” or a “non-responder” to anti-TNF α therapy. For the retrospective cohort, a physician global assessment (PGA) was used[15]. Specifically, an experienced gastroenterologist (BLINDED, 20 years experience in gastroenterology) used the electronic patient record to review all available clinical data (including outpatient clinic letters, biochemistry results including C-reactive protein (CRP), imaging, endoscopy and histopathology reports) to define a composite global assessment of response to treatment. This judgment was made using information available at the time of the follow-up MRE examination, ignoring subsequent data. Patients who had required dose escalation, a switch to an alternative biologic agent or colorectal or intestinal surgery were considered to be non-responders. For the prospective cohort, response was defined as a reduction in Harvey Bradshaw Index of 3 or more points between baseline and 3 months after initiation of anti-TNF α therapy, and no requirement for dose escalation, a switch to an alternative agent or surgery. Since HBI and the PGA are to a degree subjective, we also analysed whether motility improvements were seen in patients with normalization of CRP (defined as a reduction from >5mg/L at baseline to \leq 5mg/L at follow-up, mirroring a post-hoc analysis of the ACCENT-1 trial[16]) or with improvements in the independently-applied MaRIA score. Specifically, based on recent work investigating the MaRIA score as a proxy for ulcer healing after medical treatment[6], patients with a follow-up segmental score of <11 were deemed responders. Finally, we also assessed patients with either endoscopic or surgical proof of their eventual response to therapy (judged subjectively by BLINDED); to be included in this analysis, patients had to have undergone ileocolonoscopy within 3 months of the baseline MRE and either ileocolonoscopy or surgery within 3 months of the post-treatment MRE.

Statistical analysis

Data were collated using Microsoft Excel 2011 for Mac (Microsoft Corp, Redmond, WA, USA) and analysed using R version 3.0.1 (R Foundation for Statistical Computing, Vienna, Austria). Motility data were not normally distributed and therefore between-group comparisons for each reader were made by the Mann-Whitney-Wilcoxon test. Reproducibility of motility scores between readers was assessed using the intraclass correlation coefficient and Bland-Altman limits of agreement[17]. To determine the optimal cut-point at which a change in motility was associated with response to therapy, empirical and smoothed receiver-operating characteristic (ROC) curves were constructed using the pROC package for R{Robin, 2011 #646}. 95% confidence intervals were computed using the DeLong method for empirical curves and using 10,000 bootstrap replicates with the percentile method for smoothed curves. ROC curves were constructed for each radiologist and compared using the bootstrap method. Summary sensitivity and specificity for response were estimated using mean motility scores for both radiologists. To account for possible covariates that might confound the association between motility changes and response, we performed multilevel logistic regression with response as the outcome variable, mean segmental motility as the predictor variable (averaged between radiologists) and age, disease duration (in years), distribution (according to the Montreal classification) and history of surgery as covariates. Study group (i.e. retrospective or prospective) was included as a random intercept term to account for possible clustering effects. For all analyses, $p < 0.05$ was taken to represent statistical significance.

Results

Baseline clinical data

40 patients were recruited to the retrospective study (March 2009-June 2014) and 17 to the prospective study (November 2012-March 2014). Six patients in the prospective study and 5 in the retrospective study did not complete motility MRE at both timepoints, and hence were excluded from further analysis, leaving 11 patients (6 males) and 35 patients (21 males) respectively. No adverse events were recorded. Demographics are summarized in Table 1. The prospective group was, on average, older than the retrospective group (median age 40 years vs 23 years, $p=0.015$) and more likely to have isolated ileal (L1) disease (prospective: 6/11, 54.5%; retrospective: 5/35, 14.3%, $p=0.02$). Approximately half of the patients in both groups had required previous surgery (prospective: 6/11, 54.5%; retrospective: 16/35, 45.7%, $p=0.87$). There was no significant difference in baseline or post-treatment CRP between the two groups (Table 1). The median time between initiation of anti-TNF α therapy and follow-up was 55 weeks (range 11.5 to 123 weeks) in the retrospective group and 11.6 weeks (range 9.6 to 17.7 weeks) in the prospective group. A single patient in the retrospective group underwent follow-up imaging earlier than 90 days after initiating anti-TNF α therapy, and a single patient in the prospective group underwent follow-up MRE later than 90 days.

Reproducibility of motility measurements

Motility measurement was possible in all patients for both readers. Overall, there was a good association between the two readers' motility scores at baseline (ICC=0.65, $p<0.001$) and after treatment (ICC=0.71, $p<0.001$). The mean difference in motility scores between readers was 0.0043AU at baseline (Bland-Altman 95% limits of agreement=0.22AU) and -0.0062AU after treatment (Bland-Altman 95% limits of agreement=0.23AU).

Disease response: Retrospective group

Overall, based on the PGA, 22/35 (62.9%) patients responded to anti-TNF α treatment and 13/35 (37.1%) patients did not. Baseline motility (averaged between readers) was not significantly different between the two groups (responders: median=0.15AU; non-responders: median=0.21AU, $p=0.086$, Table 2). Conversely, following treatment, motility was significantly greater in responders (median=0.33AU) than in non-responders (median=0.23AU, $p=0.0086$). Accordingly, the change in motility between baseline and follow-up examination was significantly greater in responders (median absolute change=0.142AU; median percentage change = 105.8% increase) than non-responders (median absolute change = -0.081AU, median percentage change = 25.0% reduction, $p=0.0001$, Figure 2). Overall, any increase in motility between baseline and follow-up was 95.5% sensitive (95%CI 78.2-99.8%) and 84.6% specific (95%CI 57.8-95.7%) for distinguishing response from non-response. ROC AUC was 93.0% (95%CI 83.4-100%) for the empirical curve and 89.5% (95%CI 80.2-96.6%) for the smoothed curve. The optimal operating point for the smoothed curve corresponded to a sensitivity of 84.2% and a specificity of 79.1%.

Disease response: Prospective group

A similar proportion of patients responded to therapy as in the retrospective group: 7/11 (63.6%) patients were responders and 4/11 (36.4%) were non-responders. There was no significant difference in baseline motility between responders (median=0.12AU) and non-responders (median=0.17AU, $p=0.97$, Table 2). Changes in motility between baseline and follow-up MRE examinations were significantly greater for responders (median absolute change=0.026AU, median percentage change=31.1% increase) than non-responders (median absolute change = -0.026AU, median percentage change =21.0% reduction, $p=0.04$, Figure 2). Any increase in motility between baseline and follow-up was 85.7% sensitive (95%CI 48.7-99.3%) and 75% specific (95%CI 30.1-98.7%) for the distinction between responders and non-responders, with ROC AUC of 78.6% (95%CI 42.9-100%) for the empirical curve and 82.9% (95%CI 67.8-98.4%) for the smoothed curve. The optimal operating point for the smoothed curve corresponded to a sensitivity of 72.8% and a specificity of 78.5%.

When both groups were combined, the same trends were observed (Table 2), with no significant difference in baseline motility between responders and non-responders ($p=0.07$) but significantly greater motility in responders after therapy ($p=0.005$). Pre- and post-treatment values of motility, split by reader and clinical outcome, are shown in Figure 3. Any increase in motility between baseline and follow-up MRE was 93.1% sensitive (95%CI 78.0-98.1%) and 76.5% specific (95%CI 52.7-90.4%) for response. Overall, the ROC AUC for an increase in motility between baseline and follow-up MRE was 91.5% (95%CI 82.3-100.0%) for the empirical curve and 87.7% (95%CI 78.5-94.6%) for the smoothed curve, with no significant difference between readers (reader 1: ROC AUC_{smooth}=85.0%, 95%CI 74.7-93.3%, ROC AUC_{empirical}=87.9%, 95%CI 77.2-98.6%; reader 2: ROC AUC_{smooth}=84.6%, 95%CI 73.5-92.2%, ROC AUC_{empirical}=87.0%, 95%CI 76.1-98.0%, $p=0.86$, Figure 4).

Comparison to changes in CRP

Five patients (all from the retrospective group) had no CRP measurement at the time of follow-up imaging, leaving 41 patients for further analysis. Normalization of CRP on treatment (i.e. reduction from >5mg/L pre-therapy to ≤5mg/L at follow-up) occurred in 17/41=41.5% of patients. Patients with normalized CRP had a median increase in motility of 0.10AU (median percentage change of 73.4%) between baseline and follow-up imaging. The 24 of 41 (58.5%) patients without normalization of CRP had significantly smaller changes in motility (absolute change of 0.005AU, median percentage change of 5.1%, $p=0.0035$). This remained statistically significant after excluding 15 patients with a normal CRP at baseline – the 9 patients with a persistently raised CRP at both baseline and follow-up had a median motility change of 0.04AU (0.0%), a statistically significant difference from patients with normalized CRP on treatment ($p=0.005$, Figures 5 and 6).

Comparison to changes in MaRIA score

39 patients had MRE acquisitions with correct intravenous contrast enhancement timing, permitting measurement of the ileal MaRIA score. There was a statistically significant negative correlation between motility and MaRIA scores (i.e. improved motility was associated with reduced MaRIA score, $r=-0.38$, $p=0.016$, Figure 5). Patients with a post-treatment segmental MaRIA score of <11 had significantly greater improvements in motility than patients with persistently raised MaRIA scores (post-treatment MaRIA<11: median change in motility=0.021AU, a 15.2% increase; post-treatment MaRIA≥11: median change in motility=0.17AU, a 94.7% increase,

p=0.017, Figure 6). When judged against clinical outcomes of HBI (prospective cohort) or PGA (retrospective cohort), responders had greater improvements in segmental MaRIA score (median change=8.5 point reduction) than non-responders (median change=2.6 point reduction) although the difference was not statistically significant (p=0.07).

Comparison to endoscopic / histological outcomes

9 patients had pre-treatment ileocolonoscopy and post-treatment ileocolonoscopy (n=7) or surgery (n=2), all in the retrospective study cohort. Within this subset, changes in motility were significantly greater in patients who had responded to therapy than in non-responders (responders: median motility change=0.14AU, a 60.3% increase; non-responders: median motility change= -0.13AU, a 25.0% decrease, p=0.032, Figure 6).

Adjustment for covariates

Logistic regression confirmed that a greater motility at follow-up MRE was significantly associated with response when adjusting for all covariates (OR=1.10, 95%CI 1.02-1.20, p=0.017). Improved motility between baseline and follow-up was even more strongly associated with response (OR=1.24, 95%CI 1.08-1.43, p=0.0027) i.e. for each 0.01 AU increase in motility between baseline and follow-up, the odds of that patient being a responder increased by 1.24 (Table 3).

Discussion

In this study, we measured MRE-quantified small bowel motility pre- and post treatment with anti-TNF α mAbs and found that motility improvements are strongly associated with clinical response to therapy, both in the short-term (3 months) and longer-term. Overall, an improvement in motility was 93.1% sensitive and 76.5% specific for response to treatment. Furthermore, patients with normalization of CRP on treatment (a documented predictor of long-term response to anti-TNF α treatment[16]), post-treatment MaRIA scores of <11 (a non-invasive marker of ulcer healing[6,14]) or endoscopic/surgical proof of response also had improved motility, whereas those with persistently abnormal results on these reference standards did not.

Motility disturbance in active IBD is well documented for both ulcerative colitis (UC)[18,19] and CD[20]. Previous work using MRE has shown not only that motility is reduced in active CD, but also that the degree of such reduction is a quantitative marker of the severity of enteric inflammation, whether judged by endoscopic, histologic or morphological MRE criteria[9,21]. The mechanisms by which reduced motility occurs are not well understood. However, active CD is accompanied by inflammatory involvement of the submucosal or myenteric plexuses (i.e. plexitis)[22] which likely disrupts the normal neuronal control of gut motion. The degree to which this dysmotility improves following treatment or remission of CD has been studied less, partly because of the relative difficulty and inconvenience of manometric measurements. Although the available literature suggests that there are detectable small bowel[23] and gastric[24] motility disturbances even in inactive CD, these studies compared motility in CD patients with healthy controls rather than within the same individual after treatment. We are not aware of any intra-individual comparisons of motility pre- and post-treatment in CD. However, unlike manometry-

based techniques, MRE is both well-tolerated and commonly acquired as part of routine clinical practice. Since we have shown here that improvements in MRE-measured motility have considerable potential as a marker of response to therapy, this could be incorporated into current care pathways with relatively little inconvenience for patients.

The timecourse of symptomatic improvement, mucosal healing and resolution of transmural lesions after commencing anti-TNF α therapy have been investigated by several prior studies. Clinical improvement (as measured by CDAI) is frequently apparent by 2 weeks[25,26]. Mucosal healing can be detected at 10-12 weeks[27,28]. MRE parameters have been relatively less studied. Recently, when using a validated activity index (the MaRIA score) one prospective study found good agreement with endoscopic mucosal healing at 12 weeks[6] although the MaRIA score itself includes a measure of mucosal ulceration. Previous data evaluating transmural disease using MRE suggests a more prolonged time course for changes in response to treatment, with complete normalization being rare even at 26 weeks[7]. In the present study, we found that motility changes occur rapidly after treatment initiation; improvements in motility were apparent by 12 weeks, raising the possibility that MRE motility assessments may be valuable as an objective marker of early disease response.

The main limitations of our study relate to the definitions of disease response. We used a ≥ 3 -point change in the common clinical scoring system, the HBI, to define response to therapy in the prospective study, which correlates well with a 100-point change in the Crohn's Disease Activity Index[29]. However, such changes do not capture all elements of response to anti-TNF α therapy and may not necessarily directly reflect inflammatory activity. Similarly, in the retrospective study we used a physician global assessment definition of response to therapy based on a retrospective case review. While this arguably reflects the situation in routine practice, has been used previously in the literature[15] and acknowledges that no single test or clinical index can define response to therapy in isolation, there is the possibility of bias in such a retrospective assessment, although motility measurements and response categorisation were made independently of each other to mitigate this. Furthermore, our results were consistent across both response definitions, and were supported by changes to the inflammatory marker CRP and the validated MRE measure of disease activity, the MaRIA score. Additionally, the subset of patients with endoscopic or surgical proof of their response status showed the same results as the overall cohort, adding weight to the validity of our findings.

The fact that motility MRE showed imperfect agreement with CRP is likely due to the limitations of CRP as a marker of response to therapy, particularly since MRE showed greater concordance with response as defined by the HBI or the physician global assessment. We observed imperfect agreement between response status as judged by motility changes and by the MaRIA score. This could be due to our use of a segmental rather than global MaRIA score (since we were unable to evaluate the colon in the manner described by Rimola et al, which requires a colonic water enema). In our study, segmental MaRIA was less sensitive and specific for clinically-defined response than segmental motility measurements; whether this is due to use of segmental rather than global MaRIA, limitations with our composite reference standard or a true superiority of motility measurement over MaRIA is speculative. Some non-responders may have had fibrostenotic disease, explaining their non-response to anti-TNF α therapy; such patients may be optimally evaluated by a MRE study including delayed contrast-enhanced sequences[30].

A further limitation of our study relates to the choice of motility metrics. Although mean segmental motility provides an excellent, repeatable and reproducible measure of overall bowel motion[31], it does not separately quantify individual measures of contractile activity (e.g. contraction frequency and amplitude) or estimate transit times. We anticipate that technical developments of motility MRE analysis[21] will make such improvements possible in the short term. Finally, the number of patients included in this study (particularly the prospective arm) was relatively small; our data require confirmation in a larger prospective cohort.

In summary, improvements in MRE-quantified segmental small bowel motility are significantly greater in patients who respond to anti-TNF α mAbs than in non-responders. These improvements can be demonstrated as early as 12 weeks after commencing anti-TNF α therapy, suggesting that motility improvements may be valuable as an early marker of response to treatment.

Figure legends

Figure 1.

Example of the graphical user interface used by the radiologist when defining diseased small bowel. (A) demonstrates a single frame from a 20-second breath-hold cine imaging block over the terminal ileum (arrow), performed prior to anti-TNF α treatment. The software computes a parametric map of motility, colour-coded in (B), with red denoting greater motion and blue denoting less motion. The radiologist-drawn ROI in (B) corresponds to an area of low motion, quantified as 0.07 arbitrary units (AU). (C) depicts follow-up imaging, with the same part of the small bowel (terminal ileum) shown by the arrow. The radiologist-drawn ROI in (D) now corresponds to an area of increased motility, measuring 0.34AU.

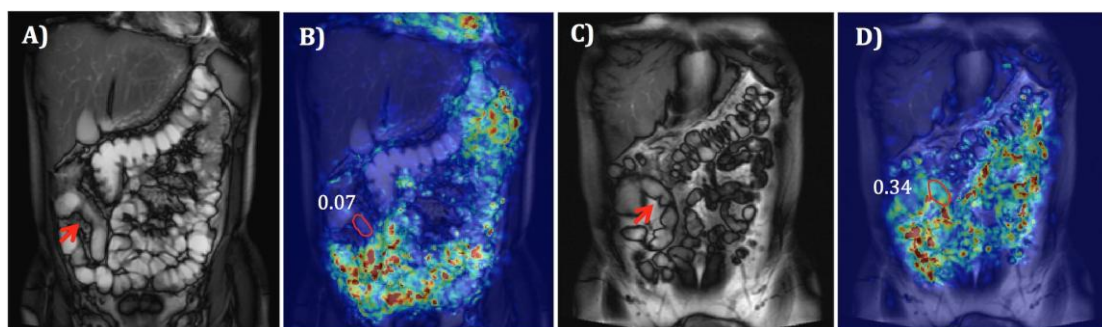


Figure 2.

Boxplots showing absolute change in motility between baseline and follow-up for non-responders (N) and responders (R), for the retrospective group, the prospective group and both groups combined. All p values are for Mann-Whitney U-test comparisons between the two groups. Whiskers show the range.

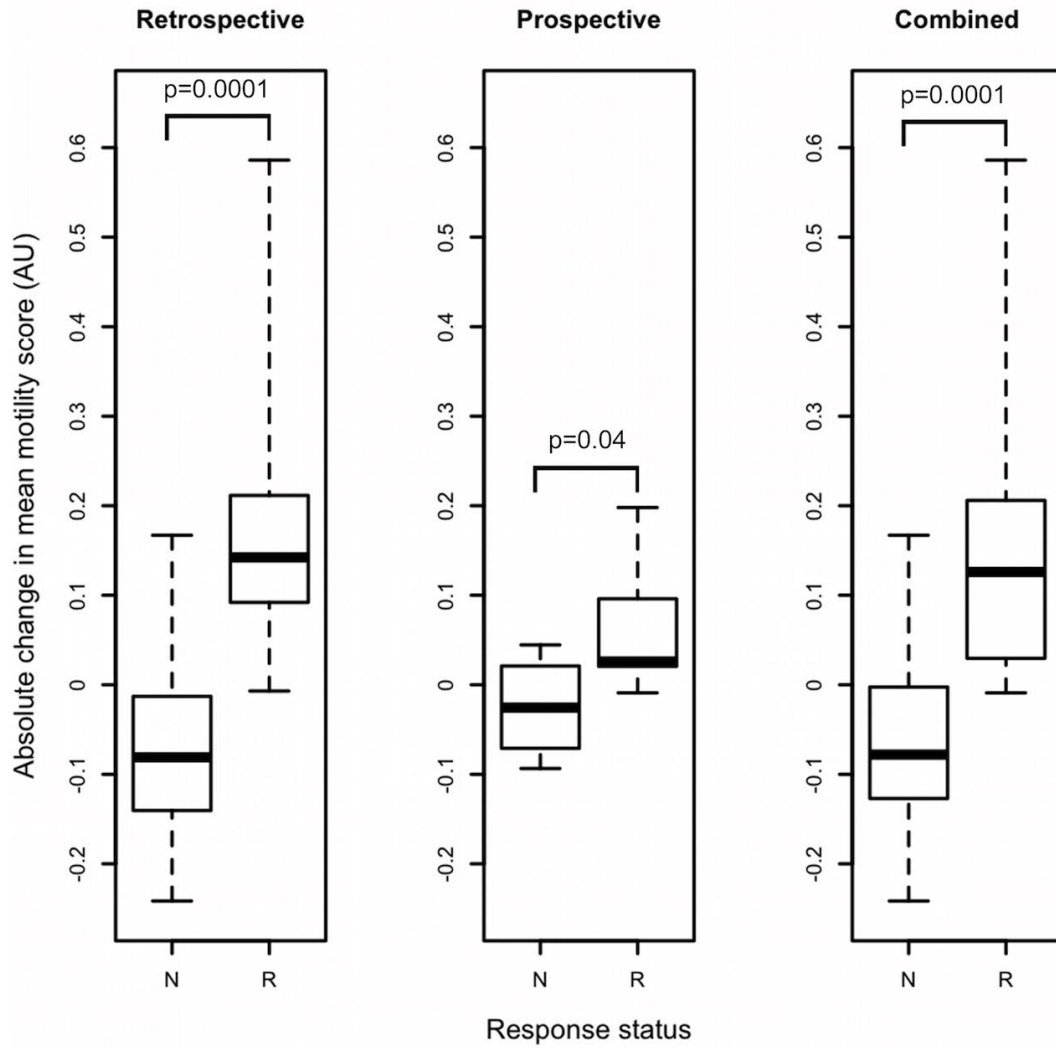


Figure 3.

Stripcharts showing motility data at baseline (Scan 1) and after treatment (Scan 2), for both radiologists. The left hand panels depict results for patients who were deemed responders to therapy, with non-responders shown in the right hand panels. Green dashed lines show patients with motility increase between the two timepoints, red dashed lines show patients with motility decrease.

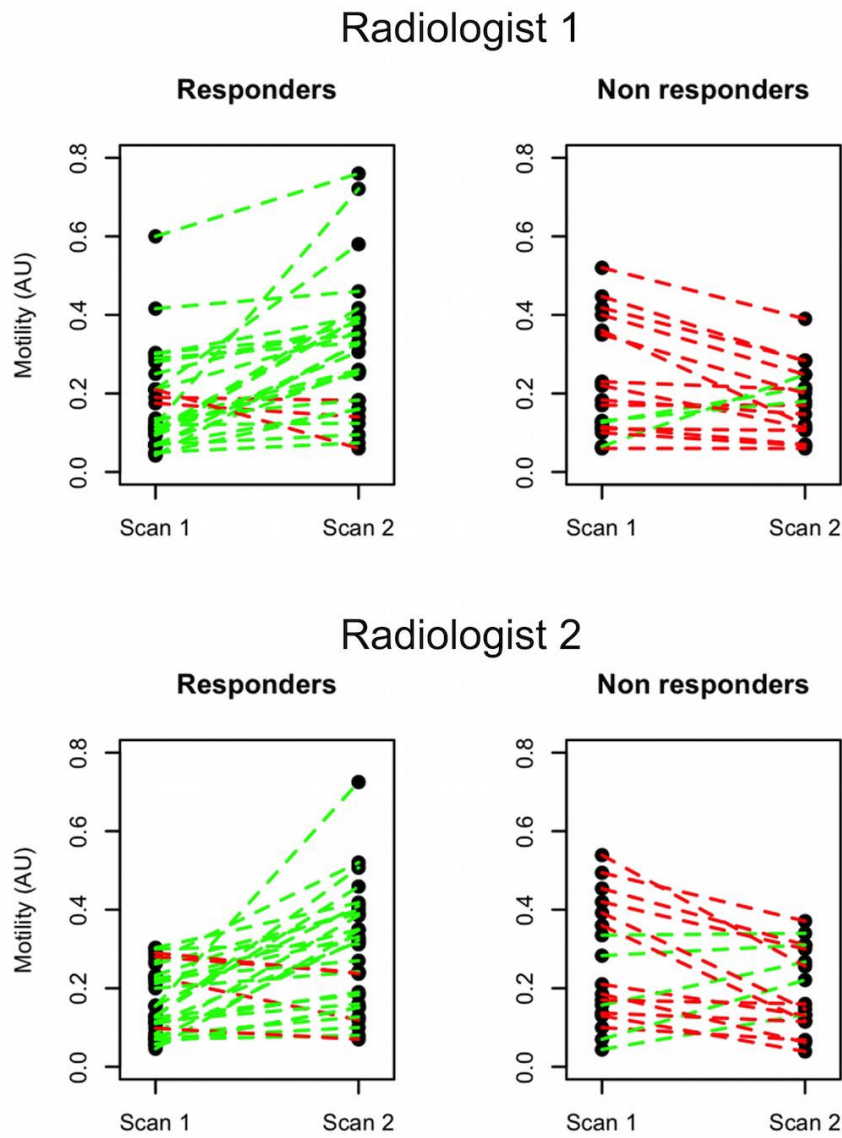


Figure 4.

Receiver operating characteristic curves for changes in motility between baseline and follow-up to discriminate responders from non-responders for (a) radiologist 1 and (b) radiologist 2. The optimal operating point is shown as a triangle for the empirical curve and a circle for the smoothed curve. Grey shaded region indicates 95% confidence intervals derived from 10000 bootstrap replicates.

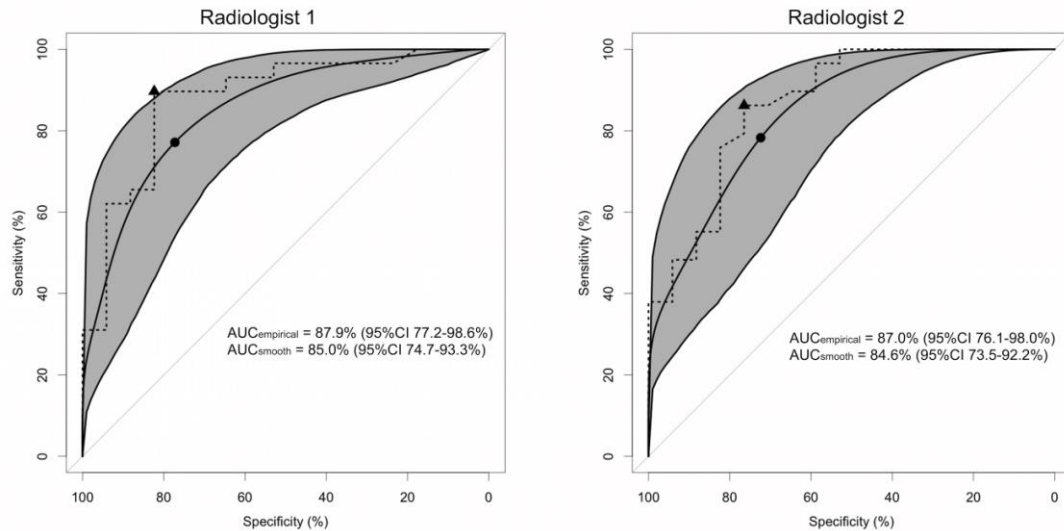


Figure 5.

Scatterplots depicting relationships between pre- and post-treatment motility change and (a) change in C-reactive protein (CRP) and (b) change in MaRIA score. Solid line = linear regression model, with Pearson correlation coefficient (r) and probability (p). Green markers = responders to anti-TNF therapy, red markers = non-responders, judged using Harvey-Bradshaw Index (prospective cohort) or a Physician's Global Assessment (retrospective cohort).

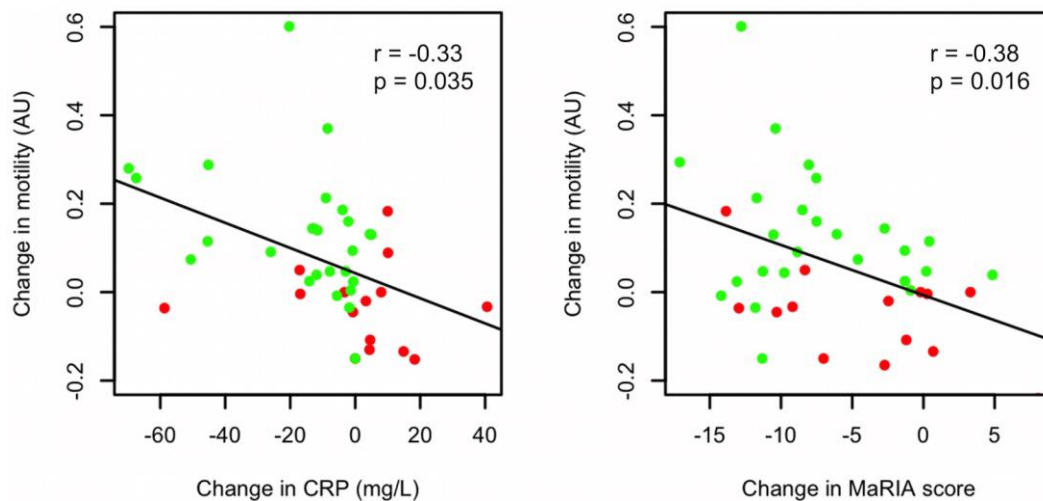
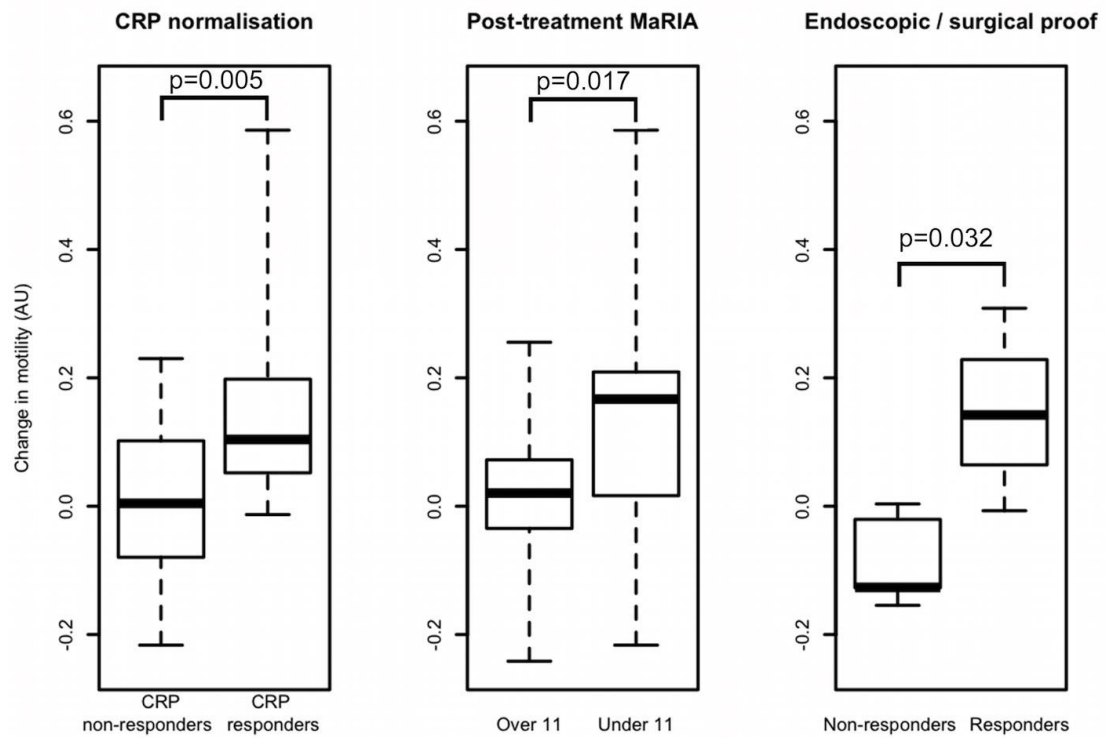


Figure 6.

Boxplots showing percentage change in motility between baseline and follow-up for non-responders and responders, as judged by normalized C-reactive protein (CRP, left-hand panel), post-treatment MaRIA (middle panel) and endoscopic / surgical outcome (right-hand panel). All p values are for Mann-Whitney U-test comparisons between the two groups. Whiskers show the range.



Tables

Table 1.
Baseline patient demographics

	Prospective group (n=11)	Retrospective group (n=35)	p value
Males (%)	6 (54.5%)	21 (60%)	1.0
Median age (range)	40 years (22-57 years)	23 years (15-65 years)	0.015
Median age at diagnosis (range)	31 years (6-44 years)	16 years (6-53 years)	0.060
Median disease duration (range)	4 years (1-30 years)	5 years (1-31 years)	0.22
Disease location			
L1 (%)	6 (54.5%)	8 (22.9%)	0.11
L3 (%)	5 (45.5%)	27 (77.1%)	-
Number of previous surgical procedures			
0 (%)	6 (54.5%)	16 (45.7%)	0.87
1 (%)	4 (36.4%)	8 (22.9%)	-
2 (%)	1 (9.1%)	8 (22.9%)	-
3+ (%)	0 (0.0%)	3 (8.6%)	-
Anti-TNF agent			
Infliximab (%)	5 (45.5%)	22 (62.9%)	0.48
Adalimumab (%)	6 (54.5%)	13 (37.1%)	-
Median C-reactive protein (mg/L)			
Pre treatment (range)	22 (2-32)	15 (1-38)	0.72
Post treatment (range)	9 (1-23)	13 (4-30)	0.09

Table 2.

Comparison between baseline, pre- and post-therapy motility for responders and non-responders, split by study group. All motility measurements are mean scores for both radiologists.

Retrospective group			
	Responders (n=22)	Non-responders (n=13)	p value
Median baseline motility, AU (range)	0.15 (0.044-0.38)	0.21 (0.068-0.51)	0.08
Median follow-up motility, AU (range)	0.33 (0.13-0.72)	0.23 (0.065-0.38)	0.009
Median change in motility, AU (range)	0.14 (-0.007-0.59)	-0.081 (-0.24-0.17)	0.0001
Prospective group			
	Responders (n=7)	Non-responders (n=4)	p value
Median baseline motility, AU (range)	0.12 (0.060-0.30)	0.17 (0.075-0.26)	0.97
Median follow-up motility, AU (range)	0.20 (0.077-0.44)	0.11 (0.07-0.26)	0.16
Median change in motility, AU (range)	0.026 (-0.009-0.20)	-0.026 (-0.09-0.045)	0.04
Both groups combined			
	Responders	Non-responders	p value
Median baseline motility, AU (range)	0.14 (0.044-0.38)	0.26 (0.068-0.51)	0.07
Median follow-up motility, AU (range)	0.29 (0.08-0.72)	0.20 (0.065-0.38)	0.005
Median change in motility, AU (range)	0.13 (-0.09-0.59)	-0.078 (-0.24-0.17)	0.0001

Table 3.

Patient factors associated with response to anti-TNF therapy, derived by multilevel logistic regression and expressed as odds ratios.

	Odds ratio (95% CI)	p value
Age (per year)	0.97 (0.90-1.05)	0.44
Disease duration (per year)	0.96 (0.84-1.10)	0.56
Previous surgery (vs no previous surgery)	0.64 (0.20-2.06)	0.46
Isolated ileal disease (vs ileocolonic disease)	0.48 (0.05-4.37)	0.52
Change in motility (per 0.01 unit change)	1.24 (1.08-1.43)	0.0027

Statement of Interests

Authors' declaration of personal interests:

(i) SAT undertakes paid MRI reporting for Robarts. AAP has received payment for educational lectures organised by Warner Chilcott (now Actavis) and by Acelyt. TRO has spoken at meetings sponsored by Abbvie, Falk, Ferring, Merck and Warner Chilcott and has sat on advisory boards for Abbvie, Falk, Ferring, Merck, Napp, Takeda, Vifor Pharma and Warner Chilcott (now Actavis).

(ii) AM is CEO of Motilent, an image analysis company.

(iii) Motilent has a patent filed for systematic measurement of morphological changes of a tubular structure, although this technology was not used in the present study. Motilent had no control over data analysis.

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Author contributions

AP: data acquisition, data analysis, manuscript drafting, manuscript approval
AM: data acquisition, data processing, data analysis, manuscript editing, manuscript approval
ER: study design, design, ethical permissions, data acquisition, manuscript editing, manuscript approval
DP: study design, data acquisition, manuscript editing, manuscript approval
GB: study design, data acquisition, manuscript editing, manuscript approval
RV: data acquisition, manuscript editing, manuscript approval
SH: study design, manuscript editing, manuscript approval
TRO: study concept, study design, manuscript editing, manuscript approval
SAT: study concept, study design, data analysis, manuscript editing, manuscript approval

All authors approved the final version of the manuscript.
SAT is guarantor.

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