TITLE: Responsiveness of Magnetic Resonance Enterography Indices for Evaluation of Luminal Disease Activity in Crohn's Disease

SHORT TITLE: MRE Responsiveness in Crohn's Disease

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ABBREVIATIONS: CD, Crohn's disease; CDAI, Crohn's disease activity index; CDEIS, Crohn's disease endoscopic index of severity; HASTE, half-Fourier acquisition single-shot turbo spin-echo; MaRIA, magnetic resonance index of activity; MRE, magnetic resonance enterography; SES, standardized effect size; SES-CD, simple endoscopic score for Crohn's disease; VIBE, volumetric interpolated breath-hold examination.

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ABSTRACT (254/260 words)

Background and Aims: Magnetic resonance enterography (MRE) is having an increasing role in Crohn's disease; however, fully validated indices are needed. We evaluated the responsiveness of 4 MRE indices in luminal Crohn's disease.

Methods: Paired MRE images (pretreatment and posttreatment at week 12/14) from 41 patients were scored by 3 blinded radiologists. Disease activity was scored for 4 MRE indices (magnetic resonance index of activity [MaRIA], simplified MaRIA, London index, and London "extended" index) and a 100-mm VAS of overall disease activity. The criterion for change was an improvement by at least one-half of an SD in the VAS after treatment. Responsiveness was evaluated using the standardized effect size (SES). Longitudinal validity was evaluated using correlations between changes in MRE index scores and disease activity measures including endoscopy and the VAS.

Results: The SES was 1.17 (95% CI: 0.56, 1.77) for the simplified MaRIA, 0.98 (95% CI: 0.42, 1.55) for the MaRIA, 0.95 (95% CI: 0.38, 1.51) for the London "extended" index, and 0.85 (95% CI: 0.31, 1.39) for the London index. The simplified MaRIA was significantly more responsive than the London index (ΔSES=0.32 [95% CI: 0.05, 0.58]) but not the MaRIA (ΔSES=0.18 [95% CI: −0.01, 0.38]) or London "extended" index (ΔSES=0.22 [95% CI: −0.05, 0.50]). Correlations with endoscopy (simplified MaRIA: r=0.72) were not different from correlations with the VAS (London "extended" index: r=0.70).

Conclusions: Evaluated MRE indices showed moderate-to-large responsiveness and are suitable for use in clinical trials. The simplified MaRIA may be preferred due to its responsiveness and nonreliance on gadolinium administration.

Keywords: Imaging; inflammatory bowel disease; magnetic resonance index of activity; London index

INTRODUCTION

Crohn's disease (CD) can affect all layers of the bowel and any segment of the digestive tract from the mouth to the anus.[1] Recently, treatment targets have evolved from symptomatic improvement to endoscopic remission.[2] Ileocolonoscopy is the gold standard instrument for objective measurement of disease activity. However, it cannot detect extraluminal complications, incomplete examination can underestimate disease activity, and the full extent of small intestinal disease may not be accessible.[3]

Magnetic resonance enterography (MRE) is a noninvasive imaging modality, which is routinely used in clinical practice,[4] increasingly incorporated into multicenter clinical trials,[5] and may overcome some of the aforementioned limitations of ileocolonoscopy.[5] In clinical trials, using MRE during screening could assist in selecting a homogeneous patient population without penetrating complications or irreversible bowel damage that is unlikely to respond to medical intervention.[2] With evidence that transmural healing may be superior to endoscopic remission for predicting clinical outcomes[6] and with the development of drugs targeting intestinal fibrosis,[7] MRE will play an increasingly important role in defining eligibility and treatment response in clinical trials.

Validated scoring indices with demonstrated validity, reliability, and responsiveness are required to realize the benefit of MRE within clinical trials.[8] The magnetic resonance index of activity (MaRIA),[9] simplified MaRIA,[10,11] and the London index[12] have been formally derived and partially validated. The MaRIA assesses 4 items: wall thickness, relative contrast enhancement, edema, and ulcers. The simplified MaRIA uses dichotomized scoring of items (wall thickness >3 mm, presence of edema, fat stranding, and ulceration).[10,11] The London index assesses mural

thickness and mural T2 signal and was validated against histological assessment of resected specimens of the terminal ileum.[12] Mural enhancement and peri-mural T2 signal were proposed for inclusion in the London "extended" index.[3]

Importantly, responsiveness to change after therapeutic intervention has not yet been evaluated for these indices using quantitative statistical methods. The objective of this study was to assess and compare the responsiveness of the 4 MRE indices (MaRIA, simplified MaRIA, London, London "extended") in patients with active CD treated with a TNF antagonist or corticosteroid.

MATERIALS AND METHODS

Study population

Pretreatment and posttreatment ileocolonoscopic and MRE image data were acquired from 41 patients with active CD who participated in 2 prospective observational studies of pretreatment disease activity and response to therapy. These data comprised images from 24 patients who received 12 weeks of TNF antagonist (adalimumab) or corticosteroid treatment at one site in the multicenter FRAC study (Hospital Clinic of Barcelona; Barcelona, Spain) and 17 patients who received 14 weeks of TNF antagonist (n=16) or vedolizumab (n=1) treatment at the same site in a similar unpublished study. These studies defined *active CD* as a Crohn's disease activity index (CDAI) >150 and a Crohn's disease endoscopic index of severity (CDEIS) ≥7.[13]

Ethical approval was obtained from the Hospital Clinic of Barcelona (HCB/2017/0022). All patients provided written informed consent during their participation in the studies conducted at the institution, and appropriate waiver of consent was obtained for central assessment of images.

Study design

The primary objective of this study was to evaluate the responsiveness of overall measures of CD activity and component items for 4 luminal MRE indices. Three abdominal radiologists (JR, SAT, CS) scored disease activity indices in MRE image sequences after completing standardized onboarding and training. Images were read with an OsiriX MD DICOM viewer (Pixmeo SARL; Bernex, Switzerland), a Class II medical device approved by the US Food and Drug Administration.

The 41 pairs of images (pretreatment and posttreatment) were randomly divided amongst the central readers who were blinded to clinical information, treatment received, and study time point. Reads were limited to the terminal ileum and colonic segments. Each pair of images for a patient was read once by the same single central reader in random order. For a given set of images, the 4 indices were scored in fixed order: (i) (simplified) MaRIA component items; (ii) London ("extended") component items; (iii) VAS. The readers scored component items of the indices and were unaware of the total score for a given index.

Measures

The 4 indices and their calculations are outlined in Supplementary Appendix 1. The MaRIA assesses wall thickness and relative contrast enhancement as continuous variables and assesses edema and ulceration as binary categorical variables. The *ulceration* definition was modified from the original publication to clarify that "linear enhancing tracts within the bowel wall should be considered fissures (linear ulcers)." Definitions of remaining MaRIA items were unchanged.

The 2 additional weighted items of the London "extended" index maintained definitions from the original London index development process. Segmental scores were calculated using the predefined formula for each index. Total scores were calculated as the simple sum of individual bowel segment scores for each study assessment. Overall disease activity was evaluated using a 100-point VAS, where 0 indicates no disease and 100 indicates the most severe disease ever encountered. In addition to overall disease activity, disease activity in the terminal ileum was evaluated using a separate VAS. For a given set of images, a single reader provided the VAS. Readers also provided an assessment of luminal MRE technical quality.

MRE protocol and sequence acquisition

Patients from both studies underwent MRE before treatment and at week 12 or 14 of treatment (Supplementary Methods). After intravenous injection of 20-mg hyoscine butylbromide, precontrast fat-saturated T1-weighted volumetric interpolated breath-hold examination (VIBE) slices (1.6-2.4 mm thick) were acquired. Intravenous gadobutrol was then administered at 0.1 mL/kg body weight, and further fat-saturated T1-weighted VIBE slices were acquired in the coronal plane 70 seconds after injection and in the axial plane 180 seconds after injection.

Assessment of responsiveness and longitudinal validity

Responsiveness (ie, ability to detect change over time) was quantified using the *standardized effect size (SES)*, defined as the mean difference between improved and unimproved groups in change scores divided by the SD of change scores. The primary criterion for clinical improvement (change) was an improvement by at least one-half of an SD in the overall disease activity VAS.

This criterion has been commonly identified as a threshold for change discrimination across several chronic diseases.[14] Two secondary criteria for clinical improvement were ≥50% improvements in the CDEIS and CRP. The CDEIS was evaluated locally at the time of the examination by an expert endoscopist blinded to MRE results.[13] The primary analysis was responsiveness of the overall indices. In a sensitivity analysis of responsiveness in the terminal ileum, the criterion for *clinical improvement* was the change in ileal disease activity VAS rather than overall disease activity VAS. Longitudinal validity was assessed by evaluating correlations between changes in MRE index scores and changes in CDAI/CDEIS/CRP concentration/disease activity VAS.

Statistical analysis

Descriptive and summary statistics were used for patient baseline characteristics. To compute responsiveness, the sample was divided into clinically improved (changed) and not-improved groups using different definitions for change. Point estimates and 95% CIs for SES values were calculated as the average within-patient change from pretreatment to follow-up divided by the SD of the pretreatment scores within the clinically improved (changed) group.[15] The SES was interpreted according to the benchmarks suggested by Cohen: effect sizes of 0.2, 0.5, and 0.8 indicate small, moderate, and large degrees of responsiveness, respectively.[16] Differences in SES values among global MRE indices were determined along with the associated 95% CIs.[17]Longitudinal correlational analyses using the observed Pearson's correlation coefficients with 95% CIs were obtained using Fisher's z-transformation between the changes in MRE index scores and the changes in CDAI/CDEIS/CRP concentration/disease activity VAS. The magnitude

of correlation was interpreted according to Cohen, where 0.1, 0.3, and 0.5 indicate small, moderate, and large effects, respectively.[16]

Sample size considerations

For assessment of responsiveness of the global indices (sum of all segments), 41 paired MRE assessments were sufficient for the lower limit of the 2-sided 95% CI to have an 80% chance of being larger than zero if the true effect size is 0.62. All statistical calculations were performed using SAS version 9.4 (SAS Institute Inc.; Cary, NC, USA). The study was powered to assess the responsiveness of the overall indices rather than the subcomponents of these indices. Responsiveness assessments for individual bowel segments and individual index items should therefore be considered exploratory.

RESULTS

Study population

The cohort comprised 41 patients with CD, with a mean (SD) age of 35.6 (11.1) years and mean (SD) disease duration of 7.4 (8.0) years (Table 1).

Responsiveness of MRE indices

The number of patients determined as clinically improved varied according to the criterion that was applied. Among patients with complete paired MRE assessments, 44% (18/41) had at least one-half of an SD of improvement in overall VAS, 69% (27/39) had a ≥50% improvement in CDEIS, and 71% (29/41) had a ≥50% improvement in CRP concentration. Group means for each MRE index and each criterion for clinical improvement are shown in Supplementary Table 1.

All evaluated global MRE indices demonstrated large responsiveness when an improvement of at least one-half of an SD in overall disease activity VAS was used as the criterion for clinically meaningful change (Table 2). The simplified MaRIA was numerically most responsive and the London index was numerically least responsive. When the same primary criterion was used, responsiveness was similar between the MaRIA and the London "extended" index. Responsiveness was moderate for the ≥50% CDEIS improvement and ≥50% CRP improvement criteria.

Responsiveness of the simplified MaRIA was numerically lower in the terminal ileum and rectum than in the other segments (SES, 0.50-0.83) when the primary criterion for clinical improvement was applied (Table 2). Similar findings in the terminal ileum were observed across the other 3 MRE indices and when the other 2 criteria for clinical improvement were used. Responsiveness of individual index items across segments is shown in Supplementary Tables 2 and 3. In a sensitivity analysis of the terminal ileum, the responsiveness of all 4 MRE indices was higher when *clinical improvement* was defined by the ileal disease activity VAS than when the overall disease activity VAS definition was used (Supplementary Tables 4 and 5). In the terminal ileum, the London "extended" index was numerically most responsive and the MaRIA was numerically least responsive. For the individual index component items, responsiveness was similar in the terminal ileum and was numerically lower in the terminal ileum than in the other colonic bowel segments (Supplementary Table 6).

Differences in responsiveness and correlations between indices

Pairwise comparisons of responsiveness among the global MRE indices using an improvement of one-half of an SD in overall VAS as the criterion are shown in Table 3. In the sensitivity analysis of the terminal ileum, no statistically significant differences between the 4 MRE indices were observed (Supplementary Table 5).

Changes in MRE index scores from pretreatment to follow-up had large correlations with changes in the other MRE index scores in this study ($r>0.80$) (Supplementary Table 7).

Longitudinal validity of MRE indices

The strongest correlations with changes in MRE index scores were observed for changes in CDEIS and the disease activity VAS. The simplified MaRIA had the largest correlation with CDEIS and the London "extended" index had the largest correlation with the disease activity VAS (Table 4).

DISCUSSION

Several MRE indices for CD have been shown to be partially valid and reliable; however, their responsiveness has not yet been assessed. Responsiveness is a fundamental property of index evaluation because sensitive instruments improve the efficiency of clinical trials. We previously demonstrated the substantial interrater reliability of the MaRIA, London index, and London "extended" index.[3] The current study is the first to assess whether the MaRIA, simplified MaRIA, London index, and London "extended" index are responsive to change after routine clinical treatment. The simplified MaRIA was statistically more responsive than the London index, exhibited moderate-to-large effect sizes depending on the criterion of change applied, and had the

largest correlation with endoscopic disease activity. Responsiveness of the simplified MaRIA was not statistically significantly different from that of the MaRIA or London "extended" index.

Based upon multiple criteria for change (decrease of at least one-half of an SD in VAS, ≥50% decrease in CDEIS, ≥50% decrease in CRP), the MaRIA, simplified MaRIA and London "extended" indices consistently showed moderate-to-large effect sizes. The responsiveness of the simplified MaRIA (significantly more responsive than the London index), coupled with a lack of the need for gadolinium administration, suggests that the simplified MaRIA may be preferred as an evaluative index in drug development.[2] The London index was numerically least responsive, and responsiveness was similar between the MaRIA and London "extended" index. The MaRIA and London "extended" index may be considered interchangeable for measuring disease activity in response to treatments of known efficacy.

Although this study was not powered to assess responsiveness per individual bowel segment, all indices were numerically less responsive in the rectum and the terminal ileum than in the other segments. The rectum is often collapsed or poorly distended on MRE, which may have resulted in the lower reliability observed in this segment during a previous study.[3] This technical issue may have hampered measurement and affected the assessment of responsiveness within the rectum during the current study. Biological reasons such as the presence of deep ulcers may have also led to differential healing and lower responsiveness to change within the ileum and rectum compared to the rest of the colon.[18] Some evidence suggests that larger and/or deeper ulcers may heal less readily in the ileum and rectum than in the rest of the colon after TNF antagonist therapy.[18,19] These ulcers coupled with the heterogeneous treatments used in this study may have also led to

differential healing of bowel segments and the observed differences in segment-level responsiveness.[20] A sensitivity analysis showed higher responsiveness in the terminal ileum using the ileal disease activity VAS than when using the overall disease activity VAS in the primary analysis. This finding suggests methodological limitations in the primary analysis, as the overall disease activity VAS did not appear to adequately capture change in the terminal ileum. The sensitivity analysis also revealed that responsiveness in the terminal ileum was highest for the London "extended" index and lowest for the MaRIA, a notable finding given the role of MRE in small bowel assessment. This result may be related to the fact that the London indices were developed based on histopathology of resected specimens.

The MRE instruments in the terminal ileum were less responsive when using a ≥50% decrease in CDEIS as the criterion for change. This finding may relate to the established disagreement between endoscopy and MRE to assess inflammatory lesions and the typically low CDEIS scores, particularly in the ileum.[21] The lower ileal responsiveness of MRE indices using the CDEIS change criterion is also consistent with reports that patients with unequivocal MRE findings of ileal disease activity despite negative ileocolonoscopy are likely to have fibrosis causing persistent damage.[22] These discrepancies between endoscopy and MRE may be even more evident after medical therapeutic intervention with TNF antagonists or corticosteroids.[23] Ileocolonoscopy leads to incomplete assessment of the terminal ileum in its whole length, whereas MRE provides the full view of lesions in most patients. Although pretreatment disease severity is relatively uniform across sections, the intramural residual changes in the ileum for segments with endoscopic remission may be consistent with greater dispersion of responses after therapeutic intervention, emphasizing discrepancies between the 2 modalities.[22] In view of potential use in future clinical

trials, exploring options to optimize indices for ileal assessment is warranted, perhaps with the addition of the length of affected small bowel.

To date, the responsiveness of MRE indices has been studied only individually using different methodological approaches in heterogeneous patient cohorts, which limits direct comparisons between findings from these studies and our findings. Two previous studies demonstrated that changes in the simplified MaRIA were strongly correlated with changes in the CDEIS, with Spearman's correlation coefficients of approximately 0.7,[10,11] and the SES for the simplified MaRIA indicated large responsiveness.[11] Large responsiveness has also been reported for the MaRIA,[13] and changes in the MaRIA correlated significantly with changes in the SES-CD, although the strength of correlation was not reported.[24] These findings are broadly in line with our results. The London index was calculated for serial MRE evaluations in a retrospective cohort study without endoscopic assessment, but no measures of responsiveness were provided.[25]

The role of MRE in clinical trials is likely to further increase as antifibrotic drugs enter clinical development. Magnetic resonance enterography has been identified as optimal to assess response to therapy in predominantly stricturing disease, although indices for use in this indication require further validation as those currently available quantify inflammation.[26] Aside from the large responsiveness of the simplified MaRIA, practical and safety-related features of this index may further facilitate its uptake in clinical trials. Specifically, the simplified MaRIA does not require the application of contrast, which shortens the duration of the examination and potentially offers a safety advantage in view of the unknown effects of gadolinium deposition in the basal ganglia.[27] The removal of relative contrast enhancement also significantly shortens calculation time for the

radiologist.[11] Contrary to the score of normal segments in the original MaRIA (range, 4-6), the score of normal segments in the simplified MaRIA (0) precludes underestimation in patients with resected bowel segments. Reassuringly, the dichotomization of wall thickness in the simplified MaRIA did not decrease responsiveness to change. Finally, the time required to calculate the simplified MaRIA is only approximately 25% of the time required to calculate the original MaRIA.[11]

Limitations of the current study should be acknowledged. Although our findings are likely to be relevant when using the MRE indices for patients receiving drugs with mechanisms of actions different from those of the drugs used by patients in this study (ie, TNF antagonists, corticosteroids), this assumption remains to be tested. Estimates of index responsiveness are also contingent on cohort characteristics, which should be considered when designing clinical trials. Most patients in this study had an inflammatory disease phenotype; the responsiveness of the MRE indices in patients with a stricturing phenotype requires assessment, which is particularly relevant for future trials evaluating antifibrotic drugs. Neither diffusion-weighted images nor the small bowel proximal to the terminal ileum were assessed in this study. The study was powered to assess the responsiveness of the overall MRE indices; therefore, responsiveness values for individual bowel segments, in particular for the small bowel, should be regarded as exploratory only and deserve further analysis.

In conclusion, we demonstrated moderate-to-large responsiveness of all evaluated MRE indices using robust criteria for clinically meaningful change. The simplified MaRIA could be preferred

for use in clinical trials of new drugs for CD on the basis of its large responsiveness, previously observed reliability,[10,11] and practicality of calculation without the need for intravenous contrast.

REFERENCES

1. Roda G, Chien Ng S, Kotze PG, et al. Crohn's disease. Nat Rev Dis Primers 2020;6:22.
2. **Jairath V**, **Levesque BG**, Vande Casteele N, et al. Evolving concepts in phases I and II drug development for Crohn's disease. J Crohns Colitis 2017;11:246-255.
3. Jairath V, Ordas I, Zou G, et al. Reliability of measuring ileo-colonic disease activity in Crohn's disease by magnetic resonance enterography. Inflamm Bowel Dis 2018;24:440-449.
4. Maaser C, Sturm A, Vavricka SR, et al. ECCO-ESGAR guideline for diagnostic assessment in IBD Part 1: initial diagnosis, monitoring of known IBD, detection of complications. J Crohns Colitis 2019;13:144-164.
5. Danese S, Sandborn WJ, Colombel J-F, et al. Endoscopic, radiologic, and histologic healing with vedolizumab in patients with active Crohn’s disease. Gastroenterology 2019;157:1007-1018.
6. Castiglione F, Imperatore N, Testa A, et al. One-year clinical outcomes with biologics in Crohn's disease: transmural healing compared with mucosal or no healing. Aliment Pharmacol Ther 2019;49:1026-1039.
7. Henderson NC, Rieder F, Wynn TA. Fibrosis: from mechanisms to medicines. Nature 2020;587:555-566.
8. Mokkink LB, Terwee CB, Knol DL, et al. The COSMIN checklist for evaluating the methodological quality of studies on measurement properties: a clarification of its content. BMC Med Res Methodol 2010;10:22.
9. Rimola J, Rodriguez S, Garcia-Bosch O, et al. Magnetic resonance for assessment of disease activity and severity in ileocolonic Crohn's disease. Gut 2009;58:1113-1120.

10. Capozzi N, Ordas I, Fernandez-Clotet A, et al. Validation of the simplified magnetic resonance index of activity [sMARIA] without gadolinium-enhanced sequences for Crohn's disease. J Crohns Colitis 2020;14:1074-1081.
11. Ordas I, Rimola J, Alfaro I, et al. Development and validation of a simplified magnetic resonance index of activity for Crohn's disease. Gastroenterology 2019;157:432-439.
12. Steward MJ, Punwani S, Proctor I, et al. Non-perforating small bowel Crohn's disease assessed by MRI enterography: derivation and histopathological validation of an MR-based activity index. Eur J Radiol 2012;81:2080-2088.
13. Ordas I, Rimola J, Rodriguez S, et al. Accuracy of magnetic resonance enterography in assessing response to therapy and mucosal healing in patients with Crohn's disease. Gastroenterology 2014;146:374-382.
14. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. Med Care 2003;41:582-592.
15. Deyo RA, Diehr P, Patrick DL. Reproducibility and responsiveness of health status measures statistics and strategies for evaluation. Control Clin Trials 1991;12:S142-S158.
16. Cohen J. A power primer. Psychol Bull 1992;112:155-159.
17. Zou GY. Quantifying responsiveness of quality of life measures without an external criterion. Qual Life Res 2005;14:1545-1552.
18. Narula N, Wong ECL, Aruljothy A, et al. Ileal and rectal ulcer size affects the ability to achieve endoscopic remission: a post hoc analysis of the SONIC trial. Am J Gastroenterol 2020;115:1236-1245.

19. Reinisch W, Colombel JF, D'Haens G, et al. Characterisation of mucosal healing with adalimumab treatment in patients with moderately to severely active Crohn's disease: results from the EXTEND trial. J Crohns Colitis 2017;11:425-434.

20. Dulai PS, Singh S, Vande Casteele N, et al. Should we divide Crohn's disease into ileum-dominant and isolated colonic diseases? Clin Gastroenterol Hepatol 2019;17:2634-2643.

21. Nehra AK, Sheedy SP, Wells ML, et al. Imaging findings of ileal inflammation at computed tomography and magnetic resonance enterography: what do they mean when ileoscopy and biopsy are negative? J Crohns Colitis 2020;14:455-464.

22. Rimola J, Alfaro I, Fernández-Clotet A, et al. Persistent damage on magnetic resonance enterography in patients with Crohn's disease in endoscopic remission. Aliment Pharmacol Ther 2018;48:1232-1241.

23. Fernandes SR, Rodrigues RV, Bernardo S, et al. Transmural healing is associated with improved long-term outcomes of patients with Crohn's disease. Inflamm Bowel Dis 2017;23:1403-1409.

24. Stoppino LP, Della Valle N, Rizzi S, et al. Magnetic resonance enterography changes after antibody to tumor necrosis factor (anti-TNF) alpha therapy in Crohn's disease: correlation with SES-CD and clinical-biological markers. BMC Med Imaging 2016;16:37.

25. Tielbeek JA, Lowenberg M, Bipat S, et al. Serial magnetic resonance imaging for monitoring medical therapy effects in Crohn's disease. Inflamm Bowel Dis 2013;19:1943-1950.

26. Rieder F, Bettenworth D, Ma C, et al. An expert consensus to standardise definitions, diagnosis and treatment targets for anti-fibrotic stricture therapies in Crohn's disease. Aliment Pharmacol Ther 2018;48:347-357.

27. Gulani V, Calamante F, Shellock FG, et al. Gadolinium deposition in the brain: summary of evidence and recommendations. Lancet Neurol 2017;16:564-570.

Author names in bold designate shared co-first authorship.

TABLE LEGENDS

Table 1. Baseline demographics and patient characteristics in the overall cohort and stratified by criterion for clinical improvement. Abbreviations: CDAI, Crohn's disease activity index; CDEIS, Crohn's disease endoscopic index of severity. Values represent frequency (%) or mean ± SD. * 2 patients were missing one value for CDEIS.

Table 2. Standardized effect sizes for the responsiveness of global magnetic resonance enterography activity indices based on 3 criteria for change. Total scores were calculated as simple sums of observed segmental scores. Abbreviations: CDEIS, Crohn's disease endoscopic index of severity; MaRIA, magnetic resonance index of activity; SES, standardized effect size.

Table 3. Pairwise differences in responsiveness among magnetic resonance enterography indices based on the criterion of at least one-half of an SD improvement in the disease activity VAS (n=41). Abbreviations: MaRIA, magnetic resonance index of activity; SES, standardized effect size.

Table 4. Pearson's correlation coefficient (95% CIs) between changes (from pretreatment to follow-up) in global magnetic resonance enterography indices and changes in CDAI/CDEIS/CRP concentration/disease activity VAS. Abbreviations: CDAI, Crohn's disease activity index; CDEIS, Crohn's disease endoscopic index of severity; MaRIA, magnetic resonance index of activity.

TABLES

Table 1. Baseline demographics and patient characteristics in the overall cohort and stratified by criterion for clinical improvement.

		Criterion: Decrease of at least one-half of an SD in VAS		Criterion: ≥50% decrease in CRP		Criterion: ≥50% decrease in CDEIS*	
	Overall	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**
Baseline characteristic	n=41	n=23	n=18	n=12	n=29	n=12	n=27
Patient age (years)	35.6 ± 11.1	34.6 ± 10.4	36.8 ± 12.1	39.4 ± 13.6	34.0 ± 9.7	32.2 ± 9.2	36.9 ± 12.1
Disease duration (years)	7.4 ± 8.0	7.4 ± 8.2	7.4 ± 8.0	10.1 ± 10.2	6.3 ± 6.8	4.8 ± 4.4	7.9 ± 8.6
Female	23 (56)	14 (61)	9 (50)	9 (75)	14 (48)	8 (67)	14 (52)
Smoking status							
Nonsmoker	10 (24)	5 (22)	5 (28)	4 (33)	6 (21)	3 (25)	6 (22)
Former smoker	10 (24)	4 (17)	6 (33)	1 (8)	9 (31)	3 (25)	7 (26)
Smoker	17 (41)	13 (57)	4 (22)	6 (50)	11 (38)	5 (42)	11 (41)
Disease location							
Terminal ileum (L1)	18 (43.9)	13 (57)	5 (28)	6 (50)	12 (41)	6 (50)	11 (41)
Colonic (L2)	11 (26.8)	5 (22)	6 (33)	3 (25)	8 (28)	3 (25)	8 (30)
Ileocolonic (L3)	12 (29.3)	5 (22)	7 (39)	3 (25)	9 (31)	3 (25)	8 (30)
Disease behavior							
Inflammatory (B1)	25 (61)	15 (65)	10 (56)	7 (58)	18 (62)	8 (67)	16 (59)
Stricturing (B2)	5 (12)	3 (13)	2 (11)	2 (17)	3 (10)	0	5 (19)
Penetrating (B3)	8 (20)	4 (17)	4 (22)	3 (25)	5 (17)	4 (33)	3 (11)
Inflammatory + perianal (B1p)	2 (5)	1 (4)	1 (6)	0	2 (7)	0	2 (7)
Penetrating + perianal (B3p)	1 (2)	0	1 (6)	0	1 (3)	0	1 (4)
CDAI score	241.0 ± 110.8	241.6 ± 128.6	240.2 ± 86.6	220.4 ± 94.4	249.5 ± 117.4	222.5 ± 126.1	253.5 ± 106.6
CDEIS score*	12.0 ± 7.6	10.9 ± 8.0	13.3 ± 7.1	10.4 ± 4.6	12.6 ± 8.4	9.7 ± 5.3	13.5 ± 8.0
Treatment							
Adalimumab	27 (66)	15 (65)	12 (67)	7 (58)	20 (69)	6 (50)	20 (74)
Infliximab	7 (17)	3 (13)	4 (22)	3 (25)	4 (14)	1 (8)	5 (19)
Vedolizumab	1 (2)	1 (4)	0 (0)	0 (0)	1 (3)	1 (8)	0 (0)
Corticosteroids	6 (15)	4 (17)	2 (11)	2 (17)	4 (14)	4 (33)	2 (7)

Abbreviations: CDAI, Crohn's disease activity index; CDEIS, Crohn's disease endoscopic index of severity.
Values represent frequency (%) or mean ± SD.
* 2 patients were missing one value for CDEIS.

Table 2. Standardized effect sizes for the responsiveness of global magnetic resonance enterography activity indices based on 3 criteria for change.

	Improvement by at least one-half of an SD in overall VAS		≥50% improvement in CDEIS		≥50% improvement in CRP	
Index	**N improved/ N not improved**	**SES (95% CI)**	**N improved/ N not improved**	**SES (95% CI)**	**N improved/ N not improved**	**SES (95% CI)**
MaRIA						
Global (overall)	**18/23**	**0.98 (0.42, 1.55)**	**27/12**	**0.44 (0.05, 0.84)**	**29/12**	**0.57 (0.18, 0.97)**
Terminal ileum	17/19	0.21 (−0.27, 0.69)	23/11	0.09 (−0.32, 0.50)	26/10	0.20 (−0.19, 0.59)
Ascending colon	14/19	0.69 (0.10, 1.28)	22/9	0.42 (−0.02, 0.86)	24/9	0.41 (−0.00, 0.83)
Transverse colon	13/14	0.87 (0.22, 1.51)	18/7	0.66 (0.15, 1.18)	19/8	0.53 (0.05, 1.02)
Descending colon	17/17	0.74 (0.20, 1.28)	23/9	0.61 (0.16, 1.06)	24/10	0.62 (0.19, 1.06)
Sigmoid colon	17/16	0.50 (−0.00, 1.01)	22/9	0.51 (0.06, 0.95)	23/10	0.47 (0.04, 0.90)
Rectum	18/18	0.50 (0.01, 0.99)	23/11	0.26 (−0.16, 0.67)	25/11	0.27 (−0.13, 0.67)
Simplified MaRIA						
Global (overall)	**18/23**	**1.17 (0.56, 1.77)**	**27/12**	**0.62 (0.21, 1.04)**	**29/12**	**0.65 (0.25, 1.05)**
Terminal ileum	17/19	0.27 (−0.22, 0.75)	23/11	0.10 (−0.31, 0.51)	26/10	0.23 (−0.16, 0.62)
Ascending colon	14/19	0.68 (0.09, 1.27)	22/9	0.45 (0.01, 0.88)	24/9	0.40 (−0.02, 0.81)
Transverse colon	13/14	0.83 (0.19, 1.46)	18/7	0.68 (0.16, 1.19)	19/8	0.51 (0.03, 0.99)
Descending colon	17/17	0.75 (0.21, 1.29)	23/9	0.63 (0.18, 1.08)	24/10	0.60 (0.16, 1.04)
Sigmoid colon	17/16	0.50 (−0.01, 1.01)	22/9	0.53 (0.08, 0.98)	23/10	0.41 (−0.01, 0.84)
Rectum	18/18	0.32 (−0.15, 0.80)	23/11	0.29 (−0.13, 0.71)	25/11	0.33 (−0.07, 0.73)
London						
Global (overall)	**18/23**	**0.85 (0.31, 1.39)**	**27/12**	**0.36 (−0.03, 0.75)**	**29/12**	**0.42 (0.04, 0.80)**
Terminal ileum	17/19	0.23 (−0.25, 0.71)	23/11	0.15 (−0.26, 0.56)	26/10	0.17 (−0.22, 0.56)
Ascending colon	14/19	0.66 (0.08, 1.24)	22/9	0.44 (−0.00, 0.87)	24/9	0.41 (−0.01, 0.83)
Transverse colon	13/14	0.75 (0.13, 1.37)	18/7	0.59 (0.09, 1.10)	19/8	0.38 (−0.09, 0.84)
Descending colon	17/17	0.78 (0.24, 1.33)	23/9	0.60 (0.15, 1.04)	24/10	0.59 (0.15, 1.02)
Sigmoid colon	17/16	0.27 (−0.21, 0.76)	22/9	0.41 (−0.03, 0.84)	23/10	0.31 (−0.11, 0.73)
Rectum	18/18	0.22 (−0.24, 0.69)	23/11	0.33 (−0.09, 0.75)	25/11	0.27 (−0.13, 0.67)
London "extended"						
Global (overall)	**18/23**	**0.95 (0.38, 1.51)**	**27/12**	**0.50 (0.10, 0.90)**	**29/12**	**0.49 (0.11, 0.88)**
Terminal ileum	17/19	0.38 (−0.12, 0.87)	23/11	0.21 (−0.21, 0.62)	26/10	0.22 (−0.17, 0.60)
Ascending colon	14/19	0.49 (−0.07, 1.04)	22/9	0.41 (−0.03, 0.84)	24/9	0.28 (−0.12, 0.69)
Transverse colon	13/14	0.78 (0.16, 1.41)	18/7	0.62 (0.11, 1.13)	19/8	0.44 (−0.03, 0.91)
Descending colon	17/17	0.74 (0.20, 1.28)	23/9	0.65 (0.20, 1.11)	24/10	0.61 (0.17, 1.05)
Sigmoid colon	17/16	0.43 (−0.07, 0.93)	22/9	0.44 (0.00, 0.88)	23/10	0.33 (−0.09, 0.75)
Rectum	18/18	0.25 (−0.22, 0.72)	23/11	0.30 (−0.12, 0.72)	25/11	0.27 (−0.13, 0.67)

Total scores were calculated as simple sums of observed segmental scores.

Abbreviations: CDEIS, Crohn's disease endoscopic index of severity; MaRIA, magnetic resonance index of activity; SES, standardized effect size.

Table 3. Pairwise differences in responsiveness among magnetic resonance enterography indices based on the criterion of at least one-half of an SD improvement in the disease activity VAS (n=41).

Index #1		Index #2		
Name	**SES ± SE**	**Name**	**SES ± SE**	**Difference in SES (95% CI)**
MaRIA	0.98 ± 0.19	Simplified MaRIA	1.17 ± 0.20	−0.18 (−0.38, 0.01)
London	0.85 ± 0.18	London “extended”	0.95 ± 0.19	−0.10 (−0.30, 0.11)
MaRIA	0.98 ± 0.19	London	0.85 ± 0.18	0.13 (−0.04, 0.31)
MaRIA	0.98 ± 0.19	London “extended”	0.95 ± 0.19	0.04 (−0.21, 0.28)
Simplified MaRIA	1.17 ± 0.20	London	0.85 ± 0.18	0.32 (0.05, 0.58)
Simplified MaRIA	1.17 ± 0.20	London “extended”	0.95 ± 0.19	0.22 (−0.05, 0.50)

Abbreviations: MaRIA, magnetic resonance index of activity; SES, standardized effect size.

Table 4. Pearson's correlation coefficient (95% CIs) between changes (from pretreatment to follow-up) in global magnetic resonance enterography indices and changes in CDAI/CDEIS/CRP concentration/disease activity VAS.

Index	**CDAI** (n=40)	**CDEIS** (n=39)	**CRP** (n=41)	**VAS** **(n=41)**
MaRIA	0.17 (−0.15, 0.46)	0.61 (0.37, 0.78)	0.15 (−0.16, 0.44)	0.65 (0.43, 0.80)
Simplified MaRIA	0.22 (−0.10, 0.49)	0.72 (0.53, 0.85)	0.08 (−0.23, 0.38)	0.67 (0.46, 0.81)
London	0.15 (−0.17, 0.44)	0.51 (0.24, 0.71)	0.14 (−0.18, 0.43)	0.62 (0.38, 0.78)
London "extended"	0.20 (−0.12, 0.48)	0.56 (0.29, 0.74)	0.14 (−0.17, 0.43)	0.70 (0.50, 0.83)

Abbreviations: CDAI, Crohn's disease activity index; CDEIS, Crohn's disease endoscopic index of severity; MaRIA, magnetic resonance index of activity.