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Evaluation of ileal Crohn's disease response to TNF antagonists: Validation of MR enterography for assessing response. Initial results

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ABSTRACT

Purpose: To assess the value of MRI obtained before and after treatment in detecting mucosal healing in patients with ileal Crohn's disease (CD) treated with anti-TNF drugs.

Methods: In this IRB approved retrospective study, 24 patients (M/F 11/13, age 34.0 ± 12.5 years, age range 19–55 years) with ileal CD who underwent anti-TNF treatment, with pre- and post-treatment MRI (mean delay between MRIs 92 ± 57 weeks) were included. All patients underwent routine MR enterography (MRE), which included diffusion-weighted imaging (DWI). Two readers evaluated qualitative features (wall thickness, presence of edema and length of involvement) in consensus and one reader measured the following quantitative variables: relative contrast enhancement (RCE) and apparent diffusion coefficient (ADC) to derive the MaRIA and Clermont scores at baseline, post-treatment and their changes (ΔMaRIA, ΔClermont). Ileocolonoscopy results were used as the reference standard. Data was evaluated using Mann-Whitney *U* test and receiver operating characteristics analysis to assess the utility of the measures for the detection of mucosal healing.

Results: Twenty-four ileal segments were assessed in 24 patients. Nine patients showed mucosal healing while 15 had no mucosal healing on post-treatment endoscopy. Pre-treatment Clermont score and wall thickness and post-treatment MaRIA and Clermont scores, wall thickness, edema, length of involvement as well as ΔMaRIA and ΔClermont were all significantly different in patients with and without mucosal healing (p-range: 0.001-0.041) while MaRIA pre-treatment and ADC pre- and post-treatment were not. Pre-treatment Clermont score as well as post-treatment MaRIA and Clermont scores, wall thickness and ΔMaRIA were all significantly predictive of detection of mucosal healing (AUC 0.813-0.912; p = 0.003-0.024) after anti-TNF treatment.

Conclusion: Pre-treatment Clermont score as well as post-treatment MaRIA and Clermont scores, wall thickness and ΔMaRIA are significantly predictive of response to anti-TNF drugs in ileal Crohn's disease. These results need to be verified in a larger study.

1. Introduction

Crohn's disease (CD) is a chronic relapsing and remitting disorder that can involve the entire length of the digestive tract [1]. To date, anti-tumor necrosis factor (TNF) biologic therapy has been administered in Crohn's disease patients alone or in combination with other treatments. Up to one third of the patients treated with anti-TNF therapy experience primary failure [2–5]. Given the potential side effects and the costs of biologics, the key point in clinical practice remains to determine predictors of anti-TNF efficacy.

The gold standard for assessing ileal and colonic disease activity is colonoscopy with distal ileoscopy. Mucosal healing, as assessed by ileocolonoscopy, has been associated with better outcomes in CD in terms of reduction of relapse rates, decreasing hospitalization

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requirements, and reducing the need for surgery [6–9]. As clinical assessment of disease activity is a poor predictor of the presence of lesions [2,10,11] and the need to repeat colonoscopy during CD monitoring is cumbersome and costly, magnetic resonance imaging (MRI) has been increasingly used for the diagnosis and monitoring of CD patients [12–19]. The Magnetic Resonance Index of Activity (MaRIA) score obtained with MRI has been shown to be effective in assessing ileal and colonic inflammation [17,19] and therapeutic response in patients treated with corticosteroids or anti-TNF drugs [15]. The Clermont index, a new index similar to the MaRIA but including functional imaging, namely diffusion-weighted imaging (DWI), has been described more recently, obtaining promising results in ileal CD in assessing response to anti-TNF therapy using clinical and laboratory parameters as the reference standard [20,21]. The introduction of this measure in clinical trials would have the advantage of avoiding the use of intravenous gadolinium chelate, thus improving its acceptance.

To date, however, there are little data investigating changes in MaRIA and Clermont scores as well as apparent diffusion coefficient (ADC) measured with DWI for predicting remission of ileal CD after anti-TNF drugs especially using mucosal healing as assessed by endoscopy as the reference standard.

The aim of this study was to evaluate the potential value of MRI-based metrics such as the MaRIA/ Clermont scores and ADC at baseline and post-treatment, as well as changes in MRI parameters in predicting mucosal healing in patients with ileal CD treated with anti-TNF drugs.

2. Materials and methods

2.1. Patients

This retrospective study was IRB-approved and the requirement for informed consent was waived. Our institutional database was queried between January 2010 and December 2016 to identify patients with ileal or ileocolonic CD who began treatment with a TNF-antagonist and had MRE examinations before and after treatment. A total of 40 patients with ileal/ileocolonic CD who had multiple MRE examinations were identified (Fig. 1). Sixteen patients were excluded because of no post-treatment ileocolonoscopy (n = 8) and resection of terminal ileum in between 1st and 2nd MRE (n = 8). Finally, 24 patients (M/F 11/13, age 34.0 ± 12.5 years, age range 19–55 years) were included (Fig. 1, Table 1). The mean delay between 1st and 2nd MRE was 92 ± 57 weeks

Table 1

Patients' characteristics. Qualitative values are shown in numbers and percentages of patients. Quantitative values are shown as mean ± standard deviation (minimum, maximum).

Parameter	
Sex (M/F)	11/13
Age at baseline (y)	34.0 ± 12.5 (19,55)
BMI at baseline (kg/m^2)	23.9 ± 6.9 (16.3, 39.5)
Duration of disease at baseline (y)	10.3 ± 9.0 (1,39)
Disease location	
Ileal, n (%)	16 (67 %)
Ileocolic, n (%)	8 (33 %)
Anti-TNF type	
Adalimumab (Humira), n (%)	11 (46)
Infliximab (Remicade), n (%)	11 (46)
Golimumab (Simponi), n (%)	1 (4)
Certolizumab (Cimzia), n (%)	1 (4)
Concomitant treatments	
5-Aminosalcylate, n (%)	0 (0)
Steroids, n (%)	1 (4)
Immunosuppressants (6-Mercaptopurine, Methotrexate, Azathioprine)	14 (54)
CRP baseline (mg/l)	33.6 ± 42.1 (0.5,155.3)
CRP follow-up (mg/l)	27.1 ± 48.6 (0.6, 164.7)
Smoking status at baseline (Y/N)	2/22

(range 27–222 weeks), and the treatment duration before 2nd MRE was 75 ± 51 weeks (range 19–187 weeks). All patients were anti-TNF therapy naïve before the baseline MRI. C-reactive protein (CRP) values within 3 months of the 1st and 2nd MRE were obtained from the patients' medical records (Table 1).

2.2. MRI acquisition

Different state-of-the-art systems were used: 3 T GE 750® (n = 4; GE Healthcare, Waukesha, WI, US), 3 T Magnetom Skyra ® (n = 2; Siemens Healthineers, Erlangen, Germany), 1.5 T GE Signa ® (n = 30) or 1.5 T Magnetom Aera/Avanto® (n = 12; Siemens Healthineers). Routine abdomen and pelvis MRE protocol (Table 2) included non-fat suppressed axial and coronal single-shot fast spin-echo T2-weighted imaging (WI) (HASTE/SSFSE), axial fat suppressed fast spin echo (FSE)
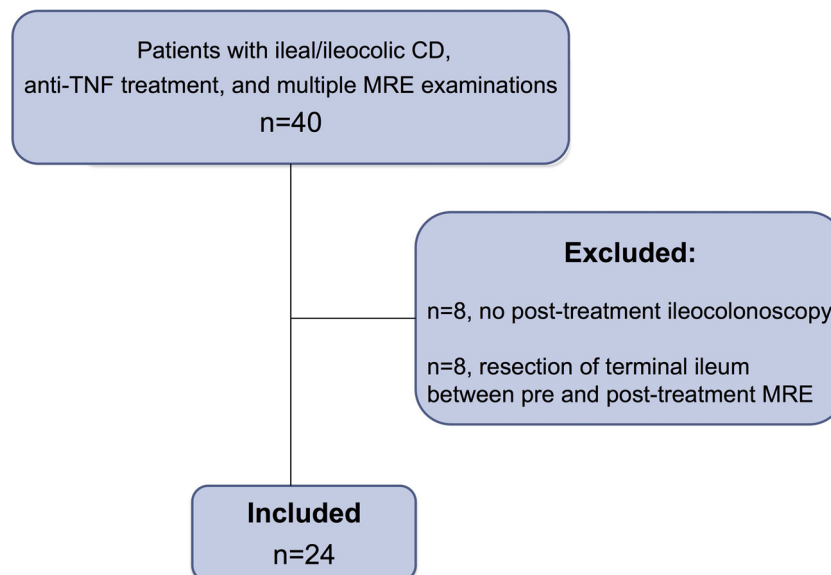

Fig. 1. Flow chart showing inclusion and exclusion of patients from the retrospective study. CD = Crohn's disease; MRE = magnetic resonance enterography; TNF = tumor necrosis factor.

Table 2
Protocol parameters of the MRE sequences used for evaluation of the bowel in the abdomen and pelvis.

	T2-weighted HASTE	T2-weighted FSE	CE-T1-weighted	DWI
Orientation	Axial and coronal	Axial	Axial	Axial
Sequence type	HASTE/SSFSE	FSE	3D SPGR	2D EPI
TR (ms)	550 or 900	3200 or 4200	2.7-3.9	4000-6000
TE (ms)	90 or 200	100	1.2	60-70
FA (deg)	90	90	10 or 15	90
b-values (s/mm^2)	–	–	–	0, 500 OR 0/50, 400, 800 OR 0, 50, 500,1000
Diffusion directions	–	–	–	3
FOV (mm)	380 × 300	380 × 300	380 × 300	380 × 300
Slices	60-80	50	120	50
ST (mm)	4-6	6	5	6
Matrix	256 × 192	256 × 150	224 × 160 or 256 × 150	128 × 128
Acceleration factor	2	2	2	2
Fat suppression	no	yes	yes	yes

HASTE: HAlf fourier Single- shot Turbo spin-Echo; FSE: fast spin-echo; CE-T$_1$w: gadolinium contrast-enhanced T$_1$-weighted; DWI: diffusion-weighted imaging; TR: repetition time; TE: echo time; FA: flip angle; FOV: field of view; ST: slice thickness;
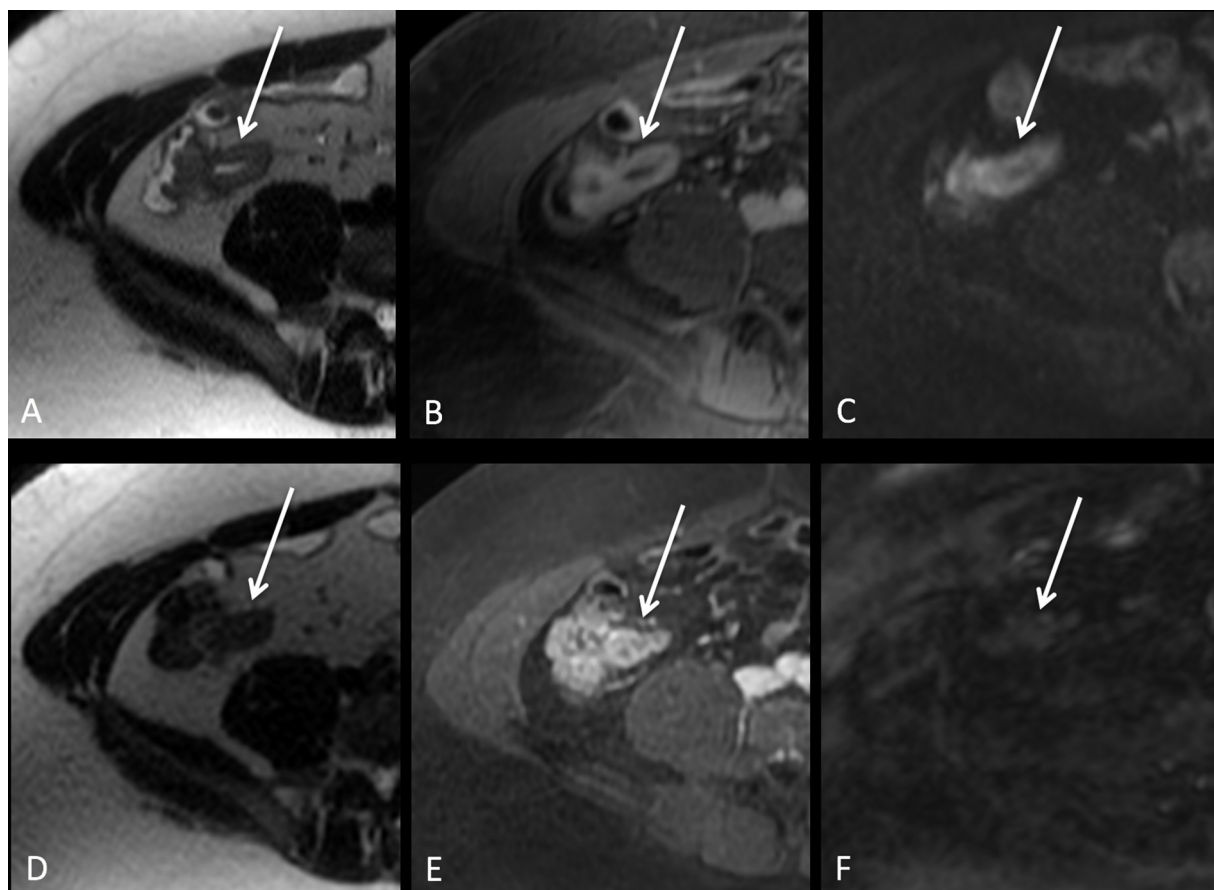

Fig. 2. 20-year old man with ileal Crohn's Disease (CD). A) T2WI (TR/TE: 550/90 ms) shows thickened (12 mm) and edematous terminal ileum. B) T1WI post-contrast (TR/TE: 2.7/1.2 ms) shows avid enhancement (relative contrast enhancement, RCE 553.9) in the terminal ileum. C) DWI image (TR/TE: 4000/70 ms, b = 500 s^2/mm) shows diffusion restriction with low ADC (1.47×10^{-3}mm/s^2, not shown). After anti-TNF treatment: T2WI (D) shows normal TI thickness, T1WI post-contrast (E) shows normal enhancement (RCE 0.4). On DWI (F) there is no residual signal intensity with increased ADC (2.34×10^{-3}mm/s^2), with concomitant mucosal healing on endoscopy. MaRIA pre was 34.1, MaRIA post 4.5, ΔMaRIA -86.8; Clermont pre was 28.5, Clermont post 6.9 and ΔClermont -75.8.

T2WI, T1WI in- and out-of-phase, DWI and 3D dynamic contrast-enhanced (CE)-T1WI including subtracted images (Figs. 2 and 3).

For dynamic CE-T1WI, unenhanced, early arterial phase (25 s), late arterial phase (60 s) and late venous phase (180 s) were obtained using a 3D T1WI breath-hold fat-suppressed spoiled gradient-recall echo sequence before and after administration of gadoterate meglumine (Dotarem ®, Guerbet LLC, Princeton, NJ, USA) injected at a rate of 2 ml/s followed by a 20 ml saline flush using a bolus tracking method. DWI was performed in the axial plane with tri-directional diffusion gradients using 2 b-values (n = 4) (0 and 500 s/mm^2), 3 b-values (n = 35) (0 or 50, 400 and 800) or 4 b-values (n = 9) (0, 50, 500, and 1000s/mm^2). The combinations of b-values used in our clinical practice consist of a very low and a high b-value (for eliminating the microperfusion effect) and an intermediate b-value (b = $400-500$ s/mm^2) on which subtle
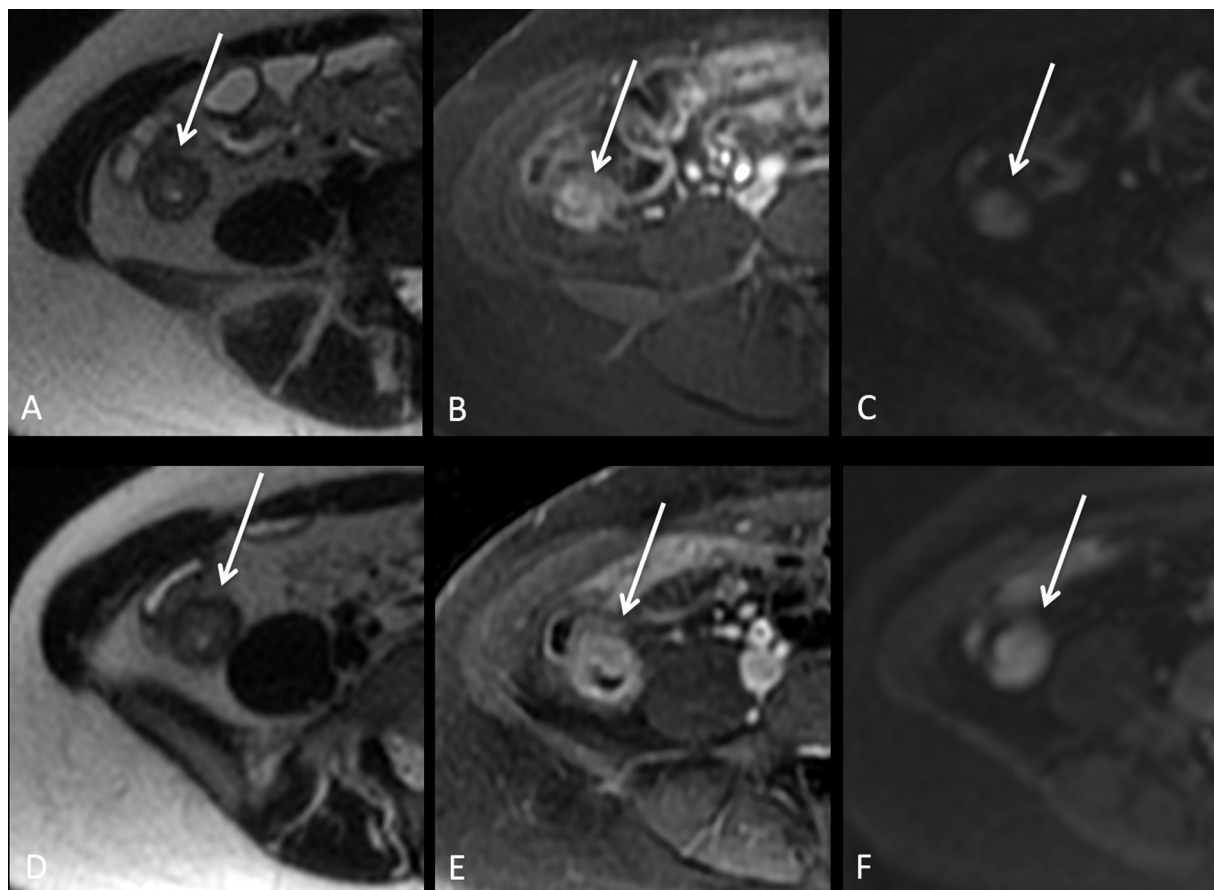
Fig. 3. 21-year old woman with ileal Crohn's Disease (CD). A) T2WI (TR/TE: 606/90 ms) shows thickened (11 mm) and edematous terminal ileum. B) T1WI post-contrast (TR/TE: 3.9/1.2 ms) shows avid enhancement (relative contrast enhancement, RCE 241.6). C) DWI image (TR/TE: 6300/60, b = 400 s^2/mm) shows diffusion restriction with a low ADC (0.61 × 10^{-3} mm/s^2, not shown). After anti-TNF treatment: T2WI (D) shows continuous thickening (11 mm), T1WI post-contrast (E) shows avid enhancement (RCE 242.9). On DWI (F) the signal intensity is continuously high indicating diffusion restriction with a low ADC (1.18 × 10^{-3} mm/s^2, not shown), with no mucosal healing on endoscopy. MaRIA pre was 26.3, MaRIA post 26.4, ΔMaRIA 0.10; Clermont pre was 28.0, Clermont post 27.2 and ΔClermont -2.8.

signal changes are more apparent than on high b-values [22]. To reach an adequate distention of the whole small intestine, 45 min before the MRI each patient was required to drink approximately 1500 ml of a barium sulfate suspension (VoLumen ®, Bracco Diagnostics Inc., Monroe Township, NJ, USA). To increase image quality and reduce bowel peristalsis, 1 mg glucagon was administered intramuscularly 5 − 10 min before the examination, except in diabetic patients.

2.3. Image analysis

2.3.1. Qualitative image analysis

Two observers (observer 1, – and observer 2, –, both with 2 years of experience in abdominal MRI), who were blinded to the ileocolonoscopy results, reviewed the images in consensus on a PACS workstation. They identified index CD lesions in the terminal ileum and evaluated wall thickness in well-distended ileal loops (in mm), presence/absence of mural edema, ulcers, stenosis, fistulas, abscesses and target sign in consensus. Furthermore, the length of involvement in the terminal ileum was noted. Edema was defined as hyperintensity of the terminal ileum wall relative to the signal of psoas muscle on T$_2$-weighted images [17]. Ulcers were defined as deep depressions in the mucosal surface of the thickened segment [17]. Stenosis was defined as focal stricturing disease in T$_2$-weighted and all T$_1$-weighted (before and after contrast enhancement) images [18,23]. Fistulas were defined as tracts between different bowel segments or bowel segments and muscle on both T$_2$ and T$_1$-weighted imaging [18,23]. Abscesses were defined as rim-enhancing

fluid accumulations on post-contrast T$_1$-weighted imaging, in proximity to fistulas or their tracts [23]. The target sign was defined as layered enhancement pattern of the bowel wall on T$_1$-weighted images [18,23].

2.3.2. Quantitative image analysis

Observer 1 (–) marked the index lesions in the terminal ileum to perform the quantitative analysis.

2.3.2.1. MaRIA score.
Pre- and post-contrast wall signal intensity (WSI) at 60 s measured on T1WI was quantitatively analyzed for wall contrast enhancement. Quantitative measurements of WSI were obtained selecting an oval or circular region of interest (ROI) with largest thickening (ROI size: 61 ± 34.7 mm^2, range 2 − 113 mm^2) in the same lesion where the qualitative measurements were performed. WSI corresponded to the average of three WSI measurements. Each ROI was placed before and after contrast administration in the same location by copying the ROI. In case of stratification of the enhancement pattern, ROIs were placed in the enhancing layer. Relative contrast enhancement (RCE) was calculated according to the following formula: RCE = [(WSI post-gadolinium-WSI pre-gadolinium)/WSI pre-gadolinium] x 100 x (SD noise pre-gadolinium/SD noise post-gadolinium), where SD noise pre-contrast corresponds to the average of three SD of the SI measured outside of the body before gadolinium contrast injection, and SD noise post-gadolinium corresponds to the SD of the same noise after gadolinium contrast administration [24].

Table 3
Qualitative and quantitative MRI findings before and after anti-TNF treatment in 24 ileal segments of 24 CD patients. Qualitative values are shown in numbers and percentages of patients. Quantitative values are shown as mean ± standard deviation (minimum, maximum).

	Pre-treatment MRI			Post-treatment MRI		
	Mucosal healing (n = 9)	No mucosal healing (n = 15)	p	Mucosal healing (n = 9)	No mucosal healing (n = 15)	p
Wall thickness (mm)	7.3 ± 3.0 (2,12)	9.7 ± 1.9 (6,13)	0.041	3.7 ± 1.2 (2,6)	7.8 ± 2.1 (4,11)	0.00005
Mural edema, n (%)	7 (78)	15 (100)	0.558	2 (22)	13 (87)	0.008
Ulcers, n (%)	0 (0)	2 (13)	0.599	0 (0)	2 (13)	0.599
Stenosis, n (%)	0 (0)	2 (13)	0.599	0 (0)	2 (13)	0.599
Fistula, n (%)	3 (33)	4 (27)	0.815	0 (0)	2 (13)	0.599
Abscess, n (%)	1 (11)	3 (20)	0.726	0 (0)	2 (13)	0.599
Target sign, n (%)	1 (11)	4 (27)	0.558	0 (0)	3 (20)	0.403
Length of involvement (cm)	8.5 ± 8.8 (0,27)	13.9 ± 8.9 (3,37)	0.096	3.8 ± 7.7 (0, 24)	9.0 ± 7.5 (0,31)	0.007
RCE (%,)	343.7 ± 404.6 (-57.8,1243)	329.8 ± 370.2 (74.9,562)	0.972	168.5 ± 219.7(-34.1,656.3)	452.5 ± 639.5(55.2,922.8)	0.374
MaRIA score	23.3 ± 10.4 (8.1,40.4)	27.5 ± 8.5 (14.9,36)	0.301	10.4 ± 5.1 (3.8,17.6)	26.6 ± 12.9 (8.3,33.1)	0.001
Clermont score	18.0 ± 6.0 (7.7, 24)	25.0 ± 5.9 (15.2,38.6)	0.011	9.5 ± 5.4 (2.0,18.6)	21.1 ± 6.6 (-52.2, 19.2)	0.0003
ADC (x10^{-3})	1.81 ± 1.01 (0.50, 3.84)	1.71 ± 0.71 (0.60, 2.56)	0.875	2.33 ± 1.29 (0.50,4.77)	2.07 ± 1.00 (1.15,5.21)	0.548

ADC: apparent diffusion coefficient; MaRIA: Magnetic Resonance Index of Activity; RCE: relative contrast enhancement;

MaRIA was calculated using the following formula:

MaRIA = (1.5*wall thickness + 0.02*RCE + 5*edema + 10*ulceration).

2.3.2.2. ADC/Clermont. To perform quantitative ADC measurements, we selected cases that were imaged with b-values of 0 or 50 and 400 or 500, due to minimal discrepancies between protocols over time. These b-values were selected because they were the most common combinations among the different DWI protocols used. However, the b-values used in the MRE examinations before and after treatment for each patient were always the same. Observer 1 manually placed oval or circular ROIs on DWI in the bowel wall with the maximum wall thickening and matched as closely as possible to the ROIs drawn on the native and CE-T1WI. The SI were recorded, and ADC values were calculated by computing the following formula: ADC = log [(SI (b1)/SI (b2)]/(b2−b1), where b1 was 0 or 50 and b2 was 400 or 500 (depending on patients), respectively, and SI (b1) and SI (b2) are the lesion signal intensities on DWI with b = 0 or 50 and 400 or 500, respectively.

Clermont score was calculated using following formula [25]:

Clermont = (1.646 x wall thickness – 1.321 x ADC + 5.613 x edema + 8.306 x ulceration + 5.039).

ΔMaRIA, ΔClermont and ΔADC were measured as: ΔMaRIA/Clermont/ADC (%) = [(MaRIA/ Clermont/ ADC post-treatment – MaRIA/ Clermont/ ADC pre-treatment)/ (MaRIA/ Clermont/ ADC pre-treatment)] x 100.

2.4. Reference standard

The reference standard for assessment of CD lesions in the terminal ileum was based on ileocolonoscopy reports, as assessed by the study coordinator (–). Ileocolonoscopy was performed as close as possible to the 2nd MRI (mean interval between 7 ± 52 weeks). Mucosal healing was confirmed when the report stated: "ileal mucosa within normal limits", "terminal ileum appeared normal", "normal ileum" and "ileum appeared to be normal and was without evidence of erosions or erythema."

2.5. Statistical analysis

Quantitative variables were expressed as mean ± standard deviation and categorical variables as frequencies or percentages. A Mann-Whitney *U* test was used to test for significant differences in wall thickness pre- and post-treatment, RCE pre- and post-treatment, MaRIA pre, post-treatment and ΔMaRIA, Clermont pre-, post-treatment and ΔClermont, ADC pre-, post-treatment and ΔADC between patients with and without mucosal healing. Receiver operating characteristics analysis was performed for all above parameters to assess the utility of the measures for the detection of mucosal healing. All statistical analyses were conducted using SPSS software (release 21.0; SPSS, Chicago, Il). A two-tailed p-value less than 0.05 was considered to indicate a significant difference.

3. Results

24 ileal segments of 24 patients (M/F 11/13, mean age 34 y) were evaluated. Nine patients showed mucosal healing, while 15 patients showed no mucosal healing. The population's characteristics are described in Table 1. Of note, CRP at baseline (33.6 ± 42.1 mg/ml) and follow-up (27.1 ± 48.6 mg/ml) was not significantly different (p = 0.694).

3.1. Qualitative image analysis

A significant difference between patients with and without mucosal healing was found for wall thickness pre- (p = 0.041) and post-treatment (p = 0.00005), for edema (p = 0.008) post-treatment and for length of involvement post-treatment (p = 0.007). No significant differences were found for ulcers, stenosis, fistula, abscess and target sign pre- and post-treatment (Table 3).

3.2. Quantitative image analysis

MaRIA post-treatment (p = 0.001), ΔMaRIA (p = 0.010), Clermont pre- (p = 0.011) and post-treatment (p = 0.0003) and ΔClermont (p = 0.028) were significantly different in patients with and without mucosal healing, while RCE pre- and post-treatment, MaRIA pre-treatment and ADC pre- and post-treatment and ΔADC were not different. Both, MaRIA as well as Clermont scores decreased after treatment (Tables 3 and 4).

Wall thickness post-treatment, MaRIA post-treatment, ΔMaRIA and Clermont pre- and post-treatment were all significantly predictive (p < 0.05) of mucosal healing, with wall thickness, MaRIA and Clermont post-treatment performing best (p < 0.01). The area under the receiver operating curve (AUROC) ranged from 0.813 for ΔMaRIA to 0.938 for wall thickness post-treatment. The AUROC of Clermont pre-treatment was 0.835, of MaRIA post- 0.901 and of Clermont post-treatment 0.912 (Table 5). Accuracy (Table 5) ranged from 50 % for ΔMaRIA to 93.% for Clermont post-treatment 91.2 %, with high

Table 4
Changes in MRI parameters before and after anti-TNF treatment in 24 ileal segments of 24 patients with Crohn's disease (CD). Quantitative values are shown as mean ± standard deviation (minimum, maximum).

	Mucosal healing (n = 9)	No mucosal healing (n = 15)	p
ΔMaRIA (%, mean ± SD)	−47.97 ± 30.40 (-86.7,1.2)	−4.01 ± 35.64 (-55.9,27.4)	**0.01**
ΔClermont (%, mean ± SD)	−45.60 ± 29.74 (-74.7,-6.2)	−14.82 ± 21.54 (-52.2, 19.2)	**0.028**
ΔADC (%, mean ± SD)	123.1 ± 306.0 (-73.4,857.9)	54.7 ± 129.1 (-58.1,452.9)	0.925

ΔMaRIA, Clermont and ADC were measured as: ΔMaRIA/Clermont/ADC (%) = [(MaRIA/ Clermont/ ADC post-treatment – MaRIA/ Clermont/ ADC pre-treatment)/ (MaRIA/ Clermont/ ADC pre-treatment)] x 100.

accuracy observed for MaRIA post-treatment (85.7 %) and wall thickness post-treatment (83.3 %).

4. Discussion

In this initial study, we observed that pre-treatment Clermont score and wall thickness and post-treatment MaRIA and Clermont scores, wall thickness, edema, length of involvement as well as ΔMaRIA and ΔClermont were all significantly different in patients with and without mucosal healing while MaRIA pre-treatment and ADC pre- and post-treatment were not. Pre-treatment Clermont score as well as post-treatment MaRIA and Clermont scores, wall thickness and ΔMaRIA detected mucosal healing after anti-TNF treatment. These results suggest a potential role of baseline MRI in stratifying patients who could profit from a therapy with TNF antagonists or not.

Rimola et al. [17,19] prospectively evaluated the ability of MRI to accurately assess inflammation in CD using ileocolonoscopy as the reference standard. They demonstrated that the MaRIA score was significantly correlated with the Crohn's Disease Endoscopic Index of Severity (CDEIS) [26] and could represent an alternative in the evaluation of ileocolonic CD [16]. Wagner et al. [27] furthermore showed that MRI is able to predict the histopathological tissue composition of ileal CD, including inflammation and predominant muscular hypertrophy versus predominant fibrosis. Ordas et al. [15] demonstrated that MRI is an accurate and reliable tool for the assessment of treatment response and mucosal healing in CD. In their study, 48 patients were prospectively evaluated by endoscopy and MRE before and 12 weeks after completing treatment with corticosteroids or anti-TNF drugs. MaRIA was used to quantify treatment-induced changes using the CDEIS as the reference standard. MaRIA decreased significantly ($p < 0.001$) from baseline to week 12 in segments achieving mucosal healing (CDEIS < 3.5). By contrast, MaRIA did not change significantly in segments not achieving mucosal healing. A MaRIA score post-treatment < 11 had a sensitivity of 94 % and a specificity of 69 % of mucosal healing.

In line with these results, we observed a significant decrease of MaRIA score in patients with mucosal healing (p = 0.001) whereby patients with no mucosal healing showed no significant change in MaRIA. However, in our study a MaRIA score < 17.99 had a sensitivity of 77 % and a specificity of 100 % of mucosal healing. One of the

reasons for these different results might be the inclusion criteria. While Ordas et al. evaluated lesions in ileum and colon, we only assessed lesions in the terminal ileum. Also, in their study patients were treated with either corticosteroids or anti-TNF drugs, while in our study all patients were treated with anti TNF drugs. Furthermore, they performed the MRE 12 weeks after completing treatment, while in our study the mean time from induction of the therapy to 2nd MRE was more delayed (75 ± 51 weeks). Longer follow-up times in our study may have caused us to capture patients for whom efficacy of anti-TNF treatment was lost with new flare-ups, which is why we may have observed limited value of the pre-treatment scores for detecting future response. The restrospective design of our study, in which patients underwent a 2nd MRE for clinical reasons that vary from patient to patient, may have also introduced confounders to detecting response to treatment.

More recently, the Clermont index, a new index similar to the MaRIA score but including ADC has been described, with promising results [25,28]. Parallel to the development of the Clermont index, the same group reported the potential benefit of using ADC for detecting segments with activity. The introduction of this parameter in clinical trials could have the advantage of avoiding the use of gadolinium based contrast agents.

In a recent study, Buisson et al. [21] assessed the value of ADC as predictor of remission of ileocolonic CD after anti-TNF induction therapy (n = 40). Clinical response was defined as a ΔCrohn's disease activity index (CDAI) ≥100 while remission was defined as CDAI < 150 and a C-reactive protein < 5 mg/L at week 12. In their study, a high ileal MaRIA (25.4 ± 8.4 vs 20.6 ± 9.5, p = 0.05) and a high Clermont score (27.2 ± 8.4 vs 21.4 ± 9.4, p = 0.05) were predictive of clinical response at week 12, while neither ileal MaRIA nor ileal Clermont were predictive of remission at 12 weeks.

In contrast, in our study, we observed that patients with mucosal healing compared to those without mucosal healing showed lower ileal MaRIA at baseline MRI (23.25 ± 10.41 vs 27.52 ± 8.52) without reaching significance (p = 0.301). A low Clermont score at baseline MRI was predictive of mucosal healing (17.97 ± 6.01 vs 25.03 ± 5.93, p = 0.011). In contrast to our study, Buisson et al. used clinical and laboratory parameters for the definition of remission or response while we used endoscopy, which may explain discrepancy in results.

Table 5
Diagnostic performance expressed as areas under the ROC curve [AUROC, 95 % confidence intervals (CI)], and threshold observed to maximize the sensitivity and specificity determined by ROC analysis to assess the utility of each measure for the detection of mucosal healing. Only significant parameters are listed.

	AUROC	CI	p	Threshold	Sensitivity (%)	Specificity (%)	TP	TN	FP	FN	Accuracy (%)
Wall thickness post-treatment (mean ± SD, mm)	0.938	0.840-1.000	0.001	< 6.5	73.3	100.0	9/24 (37.5)	11/24 (45.8)	4/24 (16.7)	0/24 (0)	83.3
MaRIA post-treatment (mean ± SD)	0.901	0.766-1.000	0.004	< 17.99	77	100	8/21 (38.1)	10/21 (47.6)	3/21 (14.3)	0/21 (0)	85.7
Δ MaRIA (%, mean ± SD)	0.813	0.602-1.000	0.024	< -24.78	77	71.4	7/21 (33.3)	3/21 (14.3)	10/21 (47.6)	1/21 (4.8)	50
Clermont pre-treatment (mean ± SD)	0.835	0.659-1.000	0.016	< 24.02	69.2	100	8/23 (34.8)	9/23 (39.1)	6/23 (26.1)	0 (0)	73.9
Clermont post-treatment (mean ± SD)	0.912	0.773-1.000	0.003	< 9.41	100	71.4	6/23 (26.1)	15/23 (65.2)	0/23 (0)	2/23 (8.7)	91.3

TP: true positive rate; TN: true negative rate; FP: false positive rate; FN: false negative rate, expressed as proportion of patients (percentage).

Bhatnagar et al. [20] measured bowel wall ADC in 17 CD patients before and after initiation of anti-TNF drugs. A clinical global assessment of disease activity at the time of MRI was assigned, and the cohort was divided into responders and non-responders. In their study, ADC changed significantly in clinical responders but not in non-responders (1.56 vs 2.41, p = 0.01 and 1.41 vs 1.74, p = 0.15), as opposed to our study. An explanation for these conflicting results might be the difference in the reference standard. Furthermore, in their study small and large bowel were assessed while we only focused on the terminal ileum. Also, the used b-values are slightly different (0, 50, 100, 300, 600 s/mm^2 in their study).

Although TNF antagonists are recommended to treat adults with severe active CD refractory to conventional therapy, up to one third of the patients, and up to 50 % of patients with terminal ileum involvement, do not respond [2–5]. This is problematic as TNF antagonists are costly and have side effects. Our data, in combination with existing literature, suggest that MRI is a useful tool to assess whether patients could profit from a therapy with TNF antagonists or not.

There were several limitations in our study. First, our preliminary study was retrospective, with heterogeneity of follow-up period, of clinical motivation for the post-treatment MRE, and MR platforms, despite our strict inclusion/exclusion criteria. Second, mucosal healing was evaluated in a binary fashion, using the endoscopic reports available in the patient's medical record, which is not suitable for patients with intermediate disease severity. Third, we did not perform inter-observer assessment of the qualitative and quantitative MRE parameters. Fourth, imaging was performed with slightly different MRE protocols on multiple platforms and quantitative inter-patient DWI analysis was performed using slightly different b-value combinations. However, the intra-patient b-values were always the same. This was unavoidable as our imaging protocols were modified over the years.

Despite the limitations of this retrospective preliminary study, the results are encouraging. As future work, our group will perform a prospective study, enrolling bio-naïve patients with ileal/ilecolonic Crohn's disease treated with anti-TNF therapy, who will be assessed by MRE at baseline and after two standard follow-up periods (as early as 12 weeks and as long as 6 months). We will use ileocolonoscopy performed at our center, and scored by the Simplified Endoscopic Score in Crohn's Disease (SES-CD), as the reference standard to assess severity of disease before treatment and mucosal healing after treatment. The MRE protocol will include qualitative evaluation of mural and extramural involvement, the Clermont and MaRIA scores, as well as quantitative MRE evaluations of diffusion and perfusion that have shown potential for differentiation of abnormal bowel segments [29].

In conclusion, pre-treatment Clermont score as well as post-treatment MaRIA and Clermont scores, wall thickness and ΔMaRIA detect response to anti-TNF drugs in ileal Crohn's disease. These results need to be verified in a larger prospective study.

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Declaration of Competing Interest

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