Persisting signs of disease activity at Magnetic Resonance Enterocolonography predict clinical relapse and disease progression in quiescent Crohn's disease

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Abstract

Introduction : **Deep remission including clinical remission and tissue healing has been advocated as the therapeutic target in Crohn's disease. Yet, the definition of deep remission remains unclear.**

The aim of this study was to assess the persisting lesions at magnetic resonance enterocolonography (MREC) in clinically quiescent Crohn's disease as well as their relapse predictive value.

Methods : **we performed a prospective monocentre cohort study. We included patients with clinical remission. At baseline, these patients had blood tests, the measurement of fecal calprotectin and underwent a MREC. They were then followed up clinically for a minimum of 1 year. A relapse was defined by a HBI > 4 with an increase of at least 3 points. Correlations between clinical, demographic, biological parameters and MREC signs were assessed as well as the time-to-relapse predictive value of the studied variables.**

Results : **Twenty seven patients were recruited. Fourteen out of 27 had persisting disease activity at MREC. MREC signs only partly correlated with biomarkers. Ten out of 27 patients relapsed over a median follow up of 25 months. In univariate analysis, relative contrast enhancement of the most affected segment (HR : 2.56 ; P = 0.046), ulcers (HR : 12.5 ; P = 0.039), fistulas (HR : 14.1 ; P = 0.009) and target sign (HR : 3.63 ; P = 0.049) were associated with relapse. In multivariate analysis, fistula was the only one.**

Conclusions : **Half of the patients with clinically quiescent Crohn's disease had persisting signs of disease activity at MREC. These signs predicted time-to-relapse.** (Acta gastroenterol. belg., **2015**, 78, **274-281**).

Key words : Crohn, Magnetic resonance enterocolonography, relapse, remission, calprotectin.

Introduction

Crohn's disease is a progressive disease in a subset of patients, with tissue damage accumulating over time (1). Therefore a treat to target approach has been advocated, aiming at tissue healing beyond the control of the symptoms (2,3). The aim of this treat-to-target approach is to prevent the progression of the disease. The degree of tissue healing to be reached to achieve this aim is still unclear. In patients in clinical remission, the persistence of blood or stool markers of active inflammation is associated with an increased risk of relapse (4-6). Likewise, the absence of mucosal healing has been associated with the risk of relapse, the risk of hospitalization, and the risk of surgical resection (7-9). Hence a full mucosal healing has been advocated as the ultimate therapeutic objective and the guarantee that the disease would not progress. However, several data have come to qualify this assumption. First, in a large monocentre experience from Belgium, partial mucosal healing had a similar effect on the risk of subsequent abdominal surgery as a full healing suggesting that this kind of partial healing would be sufficient (9). Second, in the specific situation of treatment de-escalation and more specifically infliximab withdrawal, full mucosal healing did not guarantee the absence of clinical relapse, which occurred in about one third of patients with mucosal healing (10). Finally, the transmural nature of Crohn's disease has been re-emphasized, suggesting that an isolated mucosal healing with potentially remaining transmural inflammatory process not assessed by endoscopy may not mean full tissue healing (11). From this point of view, magnetic resonance assessment of the bowel has become a standard to evaluate both activity of Crohn's disease (12,13) and tissue damage (14). Specific scores have been proposed to assess disease activity (12,13), response to treatment (15) and tissue damage (14). More specifically, for disease activity, the Magnetic Resonance Index of Activity (MaRIA) score has been shown to correlate well with endoscopic scores of severity (12,13). However, the assessment of tissue healing by magnetic resonance, being transmural and even extraenteric, goes beyond the exclusive mucosal assessment of endoscopy.

The first aim of our study was to assess the degree of tissue healing observed at magnetic resonance enterocolonography (MREC) in patients with clinically quiescent Crohn's disease and to correlate potential MREC signs and scores of persisting disease activity with blood and stool biomarkers. The second aim was to prospectively assess the time-to-relapse predictive value of these MREC signs and scores, in clinically quiescent Crohn's disease.

Patients and methods

We prospectively recruited patients with Crohn's disease seen as outpatient in our IBD clinic. The patients had to be in clinical remission, defined by a Harvey

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Bradshaw index ≤ 4, have a history of small bowel involvement by Crohn's disease, and give an informed consent for the study. Those patients underwent a MREC exploration, standard blood tests including blood cells counts, albumin and C-reactive protein measurement. The patients were also requested to bring a stool sample for fecal calprotectin measurement. Blood tests were performed using routine techniques. Fecal calprotectin was routinely measured using the Bühlmann ELISA (quantitative ELISA, range 30-1800 μg/g).

MREC was performed within one month of the bioclinical assessment.

All examinations were performed using a 1.5 T MR Unit (Symphony ; Siemens Medical Solutions, Erlangen, Germany). On the MRI table, patients were placed in the supine position for comfort reason (and subsequently better cooperation). Abdominal phased-array body coil was used to cover the entire field of the abdomino-pelvic region. A suitable repletion of the whole small intestine and colon was obtained by giving per os a mixture of Sorbitol and Methyl-Cellulose (about 1.4 L, as far as the patient can reasonably tolerate) and by administration of a lukewarm water enema about 1 L (according to patients' tolerance). Hypotonia was induced by administration of a peppermint oil capsule (Will Pharma) at the beginning of the oral intake and by IV injection of hyoscine butylbromide (Boehringer Ingelheim) (40 mg in two steps : the first one at the beginning of the examination, before the enema, and the second one just before the acquisition of the contrast-enhanced sequences).

The MR protocol included the following sequences : coronal True Fast Imaging with steady Precession (TRUE FISP) with Fat Saturation (FatSat), (slice thickness 5 mm, TR/TE 5.17/2.59 ms, field of view (FOV) 500 × 500 mm, flip angle 78°) ; coronal Volumetric Interpolated Breathold Examinations (VIBE) with FatSat before and after contrast injection (at the arterial (30 seconds) and portal (70 seconds) phases, (slice thickness 3 mm, TR/TE 4.30/1.44 ms, field of view 450 × 450 mm, flip angle 12°) ; coronal T2 Half-Fourier Single-shot Turbo spin-echo (HASTE) with and without FatSat, (slice thickness 5 mm, TR/TE 1310/90 ms, field of view 450 × 360 mm, flip angle 142°) ; axial T2 Half-Fourier Single-shot Turbo spin-echo (HASTE) without FatSat, (slice thickness 4 mm, TR/TE 1310/88 ms, field of view 340 × 272 mm, flip angle 142°) ; axial T1 VIBE "late" (about 5 minutes), (slice thickness 4 mm, TR/TE 5.22/2.42 ms, field of view 360 × 360 mm, flip angle 12°).

The enhancement was obtained by intra-venous injection of 0.2 ml/kg body weight of a gadolinium chelate (Gadobenate dimeglumine-Bracco) at a rate of 2 ml/sec.

All examinations were reviewed on a PACS (Agfa Healthcare) workstation by a single radiologist (PM) experienced in MREC. The MaRIA score was calculated (12). A segmental MaRIA score was calculated too with focus on the most severely affected segment. The following parameters were evaluated in each segment : relative contrast enhancement (RCE) calculated according the following formula taking into account wall signal intensity (WSI) and standard noise (SD) (12) : RCE = ((WSI postgadolinium– WSI pregadolinium)/(WSI pregadolinium))X100X(SD noise pregadolinium/SD noise postgadolinium) ; maximal bowel wall thickness ; mural edema in T2 (hyperintensity of the bowel wall relative to the signal of the psoas muscle) ; presence of ulcer(s) ; presence of pseudo-polyps ; presence of lymph nodes/adenomegalies (≥ 1 cm in the small diameter) ; presence of a bowel lumen dilatation (diameter > 4 cm proximal to visible bowel wall lesions). The following parameters were assessed in the most affected segment : the target sign (layered enhancement of the bowel wall) ; the comb sign ; presence of fistula(e) ; presence of a late "diffuse and homogeneous" parietal enhancement ; presence of mesenteric infiltration ; presence of abscess(es).

The patients were also classified depending on the MREC semiology in four categories : no persisting abnormality, parietal inflammation (presence of a submucosal edema on T2w sequences and a target sign), parietal and extraenteric signs of disease activity (presence of a submucosal edema on T2w sequences, a target sign and a comb sign), isolated extraenteric inflammation (comb sign).

The patients were then prospectively followed up for at least one year. A relapse was defined by a Harvey Bradshaw index > 4 with an increase of at least 3 points as compared to baseline and the necessity to change the type or dosage of the medical treatment or the need for a surgical intervention. There was no further planned MREC in the follow-up.

No specific sample size calculation was made for this exploratory study. We planned to recruit around 30 patients within 6 months. Results are presented as medians and interquartile ranges for continuous variables and frequency tables for discrete variables. Some variables were logarithmically transformed to normalize distribution. Correlations between continuous variables were assessed by Spearman correlation test. Comparisons of means were made by the Student t test and the comparisons between discrete variables were made by Fisher's exact test. Time-to-clinical relapse predictive value of clinical, biological and MREC variables has been studied by univariate and multivariate Cox regression using stepwise selection. Results were considered as significant at the 5% level ($p < 0.05$). Calculations were made with the SAS software version 9.3 (SAS Institute, Cary, NC, USA) and graphs with the S-Plus software version 8.1 (TIBCO Spotfire).

The protocol was reviewed and accepted by the ethics committee of Liège University Hospital on January the 24th of 2012.

Results

Twenty-seven patients were recruited between March and September 2012. Baseline clinical, demographic and

Table 1. — **Patients characteristics**

Male gender, n (%)		16 (59.3)
Age (yrs)	median (IQR)	31 (26-40)
Disease duration (yrs)	median (IQR)	7 (2-12)
Duration of remission (months)	Median (IQR)	15 (4-72)
Active smokers, n (%)		7 (25.9)
BMI (kg/m^2)	median (IQR)	21.4 (19.8-23.2)
Age at diagnosis (Montreal), n (%)	A1	5 (18.5)
	A2	19 (70.4)
	A3	3 (11.1)
Location (Montreal), n (%)	L1	11 (40.7)
	L2	0 (0)
	L3	12 (44.4)
	L1+L4	2 (7.4)
	L3+L4	2 (7.4)
Behaviour (Montreal), n (%)	B1	13 (48.1)
	B2	9 (33.3)
	B3	5 (18.5)
Perianal lesions, n (%)		3 (11.1)
Harvey Bradshaw Index, n (%)	0	5 (18.5)
	1	7 (25.9)
	2	1 (3.7)
	3	7 (25.9)
	4	7 (25.9)
CRP (mg/L)	median (IQR)	2.1 (0.9-4.6)
Fecal calprotectin (µg/g)*	median (IQR)	300 (92-470)
Albumin (g/dl)**	median (IQR)	45 (41.5-47.0)
Platelet count (10^9/L)	median (IQR)	288 (260-328)
Hemoglobin (g/L)	median (IQR)	14 (13.3-14.8)
Treatment, n (%)	mesalazine	5 (18.5)
	steroids	0 (0)
	immunosuppressant	7 (25.9)
	anti-TNF	15 (55.6)
	none	5 (18.5)

* n = 13 ; ** n = 24.

Montreal classification : L1 = ileal, L2 = colonic, L3 = ileocolonic, L4 = upperGI tract ; B1 = non structuring/non penetrating, B2 = stricturing, B3 = penetrating; A1 = < 17 years, A2 = 18-40 years, A3 = > 40 years.

biological characteristics of the patients are presented in Table 1.

MREC signs and scores are presented in Table 2 ; 13/27 (48.1%) had no remaining sign of disease activity at MREC ; 5/27 (18.5%) had only mural signs of disease activity ; 8/27 (29.6%) had mural and extraenteric signs of disease activity ; 1/27 (3.7%) had only extraenteric signs of disease activity.

Correlation between clinical and biological variables and the MREC signs and scores is shown in table 3a and 3b. Most significant correlations were found between MREC signs and platelet counts or fecal calprotectin, particularly for the MaRIA score and the segmental MaRIA score in the most severely affected segment (Fig. 1).

All the patients were followed up till the study end in September 2014. Median follow-up was 25.1 months (IQR : 22.1-27.1). Ten out 27 patients relapsed with a median time to relapse of 8.9 months (IQR : 5.7-19.3).

Parameters associated with the time-to-relapse in univariate analysis are shown in table 4. In multivariate analysis, only the presence of a fistula at MREC was significantly associated with the time-to-relapse (HR = 14.1 ; 95%CI = 1.9-101.9 ; p = 0.009) (Fig. 2).

Only two patients had to undergo surgical resection. The only factor associated with a shorter time-to-relapse

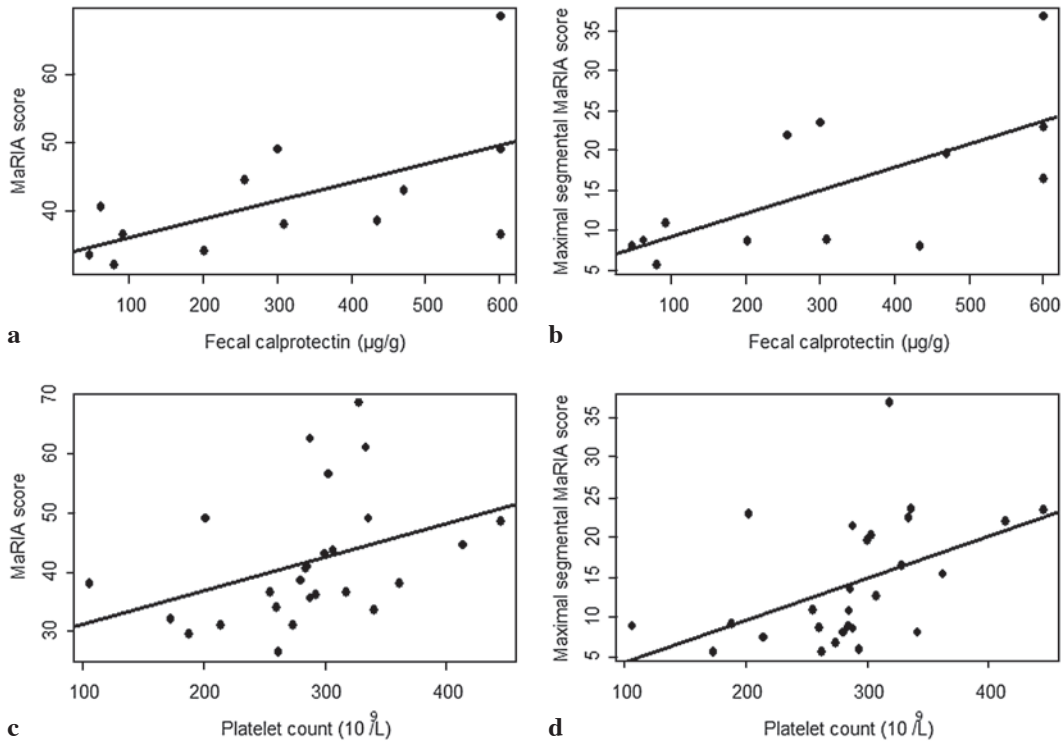

Fig. 1. — (a) Correlation between fecal calprotectin and MaRIA score (r = 0.59 ; p = 0.03) ; (b) fecal calprotectin and segmental MaRIA in the most affected segment (r = 0.66 ; p = 0.01) ; (c) platelet count and MaRIA score (r = 0.51 ; p = 0.006) ; (d) platelet count and segmental MaRIA in the most affected segment (r = 0.55 ; p = 0.003).

Table 2. — **MREC signs and measurements**

Bowel wall edema in T2, n (%)	10 (37)
Target sign, n (%)	10 (37)
Ulcer, n (%)	1 (3.7)
Late contrast enhancement, n (%)	21 (77.8)
Bowel lumen dilatation, n (%)*	1 (3.7)
Fistula, n (%)	2 (7.4)
Abcess, n (%)	0 (0)
Comb sign, n (%)	9 (33.3)
Mesenteric infiltration, n (%)	4 (14.8)
Mesenteric adenomegalies, n (%)**	5 (18.5)
Relative contrast enhancement, median (IQR)***	106 (76.5-144)
Bowel wall thickness (mm), median (IQR)	6 (4-9)
MaRIA score, median (IQR)	38.5 (34-48.5)
Modified MaRIA score, median (IQR)****	52.6 (45.7-60.7)
Maximal segmental MaRIA score, median (IQR)*****	10.8 (8.1-21.4)

* presence of a bowel lumen diameter > 4 cm upstream to the lesions.

** presence of lymph nodes > 1 cm.

*** RCE was calculated according the following formula: RCE = ((WSI postgadolinium–WSI pregadolinium)/(WSI pregadolinium))X100X(SD noise pregadolinium/SD noise postgadolinium).

**** calculated as the MaRIA score but also including a proximal and mid-ileal segment and a jejunal segment.

***** Segmental MaRIA score in the most affected segment.

Table 3a. — **Clinical and biological variables according to MREC signs (expressed as discrete variables)**

		HBI	BMI	dis. dur. (yrs)	CRP (mg/l)	Fec. calpro (µg/g)	Album. (g/L)	Hemogl. (g/L)	Platelets (10^9/L)
Bowel wall edema in T2	Yes (n = 10)	1 (1-3)	22.9 (21.8-25.3)	8 (5-12)	2.4 (1-4.6)	600 (300-600)	43.5 (39.5-47.5)	14 (11.8-14.8)	323 (288-336)
	No (n = 17)	3 (1-4)	20.5 (19.8-21.9)	7 (2-15)	2 (0.9-3.4)	147 (71-372)	45.5 (43-47)	14 (13.3-14.6)	280 (255-293)
	p value	*0.093*	*0.13*	*0.81*	*0.91*	*0.024*	*0.42*	*0.85*	*0.023*
Target sign	Yes (n = 10)	3 (1-3)	22.5 (19.8-29.9)	10.5 (7-12)	2.6 (1.5-5.2)	385 (256-600)	41 (32-47)	13.7 (11.8-15)	311 (285-336)
	No (n = 17)	1 (0-4)	20.6 (19.9-22.5)	6 (2-11)	2 (0.7-2.7)	92 (62-434)	45 (44-47)	14.1 (13.3-14.6)	284 (255-293)
	p value	*0.37*	*0.071*	*0.74*	*0.64*	*0.15*	***0.037***	*0.66*	*0.055*
Ulcer	Yes (n = 1)	1 (1-1)	18.3 (18.3-18.3)	12 (12-12)	2.5 (2.5-2.5)	600 (600-600)	32 (32-32)	11.8 (11.8-11.8)	318 (318-318)
	No (n = 26)	3 (1-4)	21.6 (19.9-23.2)	7 (2-12)	2.1 (0.9-4.6)	278 (86-452)	45 (42-47)	14.1 (13.3-14.8)	287 (260-328)
	p value	*0.46*	*0.31*	*0.57*	*0.8*	*0.17*	*0.008*	*0.19*	*0.65*
Late contrast enhancement	Yes (n = 21)	3 (1-4)	21.9 (20.1-23.8)	7 (4-13)	2.1 (0.9-4.6)	256 (92-309)	45 (43-48)	14.1 (13.5-15.5)	285 (255-328)
	No (n = 6)	1 (1-3)	20.2 (18.3-20.6)	8.5 (1-12)	2 (1.5-2.5)	452 (240-535)	42 (40-46)	12.6 (11-13.5)	302 (293-318)
	p value	*0.39*	*0.095*	*0.56*	*0.43*	*0.41*	*0.18*	*0.007*	*0.45*
Bowel lumen dilatation*	Yes (n = 1)	3 (3-3)	29.9 (29.9-29.9)	7 (7-7)	0.2 (0.2-0.2)	NA	NA	15.3 (15.3-15.3)	334 (334-334)
	No (n = 26)	2.5 (1-4)	21.1 (19.8-23.2)	7 (2-12)	2.1 (1-4.6)	300 (92-470)	45 (41.5-47)	13.9 (13.3-14.6)	287 (260-318)
	p value	*0.58*	*0.046*	*0.81*	*0.69*	*NA*	*NA*	*0.25*	*0.5*
Fistula	Yes (n = 2)	2 (1-3)	19 (18.3-19.7)	12.5 (12-13)	3.6 (2.5-4.6)	428 (256-600)	41 (32-50)	13.4 (11.8-15)	366 (318-414)
	No (n = 25)	3 (1-4)	21.8 (20.1-23.2)	7 (2-12)	2 (0.9-3.4)	300 (80-470)	45 (42-47)	14 (13.3-14.6)	286 (260-307)
	p value	*0.89*	*0.23*	*0.34*	*0.79*	*0.42*	*0.37*	*0.79*	*0.095*
Comb sign	Yes (n = 9)	2 (1-3)	22.6 (19.7-23.2)	9 (7-12)	2.5 (2-4.6)	600 (470-600)	43 (38-46)	14 (11.8-14.5)	318 (300-334)
	No (n = 18)	3 (1-4)	21.1 (20.1-22.5)	6.5 (2-12)	1.8 (0.7-3.4)	147 (71-304)	46 (44-47)	14 (13.3-14.8)	282 (255-293)
	p value	*0.55*	*0.58*	*0.76*	*0.95*	***0.003***	*0.19*	*0.5*	*0.035*
Mesenteric infiltration	Yes (n = 4)	2 (1-4)	19.9 (18.7-22)	12 (11.5-13.5)	2.3 (1.8-3.9)	331 (62-600)	39 (32-47.5)	14 (12.7-14.8)	294 (285-311)
	No (n = 23)	3 (1-4)	21.8 (19.9-23.8)	7 (2-12)	2 (0.7-4.6)	300 (92-470)	45 (42.5-47)	14 (13.3-14.7)	288 (255-334)
	p value	*0.89*	*0.29*	*0.16*	*0.62*	*0.89*	*0.051*	*0.97*	*0.73*
Mesenteric adenomegalies**	Yes (n = 5)	3 (2-3)	22.5 (19.7-23.2)	7 (2-9)	2.7 (2.3-4.6)	256 (80-600)	41 (41-44)	13.4 (11.8-14.6)	286 (202-414)
	No (n = 22)	2 (1-4)	21.1 (19.9-23.2)	7 (4-12)	2 (0.7-3.4)	305 (92-470)	46 (43-47)	14.1 (13.3-14.8)	288 (262-318)
	p value	*0.69*	*0.63*	*0.41*	*0.97*	*1.0*	*0.53*	*0.49*	*0.54*

* presence of a bowel lumen diameter > 4 cm upstream to the lesions.
** presence of lymph nodes > 1 cm.

Table 3b. — **Clinical and biological variables according to MREC measurements (continuous variables)**

	HBI	BMI	disease duration (yrs)	CRP (mg/l)	Fecal calpro. (μg/g)*	Albumin (g/L)**	Hemoglobin (g/L)	Platelet count (10^9/L)
MaRIA score	-0.35 *(p = 0.07)*	0.35 *(p = 0.07)*	-0.14 *(p = 0.50)*	0.11 *(p = 0.59)*	0.59 *(p = 0.03)*	-0.16 *(p = 0.46)*	-0.02 *(p = 0.92)*	0.51 *(p = 0.006)*
Modified MaRIA score	-0.44 *(p = 0.02)*	0.32 (p = 0.10)	-0.04 (p = 0.84)	0.08 (p = 0.69)	0.66 *(p = 0.01)*	-0.26 (p = 0.21)	-0.12 *(p = 0.56)*	0.53 *(p = 0.005)*
Maximal Segmental MaRIA score	-0.28 *(p = 0.16)*	0.29 *(p = 0.15)*	0.09 *(p = 0.65)*	0.11 *(p = 0.58)*	0.66 *(p = 0.01)*	-0.14 *(p = 0.53)*	-0.15 *(p = 0.46)*	0.55 *(p = 0.003)*
Maximal relative contrast enhancement	-0.24 *(p = 0.23)*	0.23 *(p = 0.24)*	0.01 *(p = 0.96)*	0.08 *(p = 0.68)*	0.52 *(p = 0.07)*	-0.24 *(p = 0.25)*	-0.27 *(p = 0.17)*	0.39 *(p = 0.04)*
Bowel wall thickeness	-0.16 *(p = 0.43)*	0.16 *(p = 0.42)*	0.09 *(p = 0.64)*	0.14 *(p = 0.48)*	0.64 *(p = 0.02)*	-0.20 *(p = 0.35)*	-0.24 *(p = 0.23)*	0.56 *(p = 0.002)*

* n = 13 ; ** n = 24.

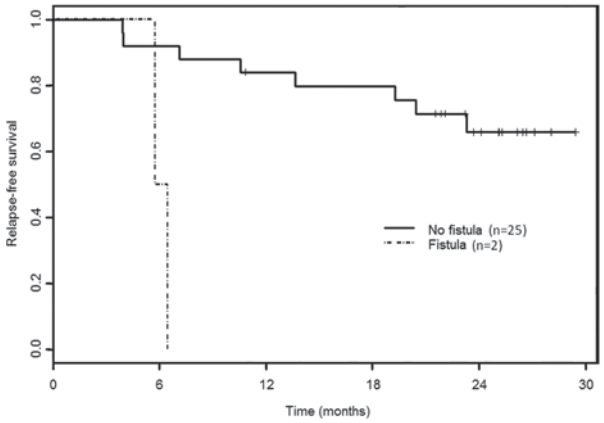

Fig. 2. — Time-to relapse according to the presence of an intra-abdominal fistula at MR entero-colonography (HR = 14.1 ; 95%CI = 1.9-101.9 ; p = 0.009).

in univariate analysis was the existence of MREC signs of fistula (HR = 17.7 ; 95%CI = 1.1-294.7 P = 0.045), while a lower blood hemoglobin (P = 0.054) and a higher relative contrast enhancement in the most affected intestinal segment (P = 0.053) were borderline for significance. The first operated patient had a fistula and a stricture in the terminal ileum at MREC ; he was operated 10 months later and surgical resection specimen confirmed these lesions. The second operated patient had an ileal stricturing disease at MREC ; she was operated 6 months later in a context of occlusion and surgical resection specimen confirmed the occlusive stricture of the terminal ileum.

Discussion

Our study shows that half of the patients with clinically quiescent Crohn's disease have persisting signs of inflammation at MREC. These signs correlate only moderately to main biological signs of inflammation. It also shows the ability of MREC signs to predict time-to-relapse in those quiescent Crohn's disease patients. It finally suggests the superiority of these signs over classical stool and blood biomarkers for this prediction.

The first objective of the present study was to better characterize the nature of the persisting inflammatory process which may be disclosed by MREC in clinically quiescent Crohn's disease. Our study population includes patients with different types of treatment and disease history and represents thus a range of what can be observed in routine practice. Half of the patients had remaining signs of disease activity at MREC. This discrepancy between clinical activity mainly based on subjective symptoms evaluation and more objective signs of inflammation has already been shown for blood and stool biomarkers (4-6) as well as endoscopy (16,17). A good correlation between endoscopic and MRI assessment of disease activity has already been shown (12,13). The main advantage of MRI is to enable full gastro-intestinal tract assessment in only one single procedure. In the present study 5/27 patients presented lesions in segments which are out of reach of classical ileocolonoscopy. Biomarkers are less invasive and cheaper than endoscopy or MRI but their correlation with mucosal healing at endoscopy has been shown to be variable (18,19). The same is shown in the present study : there was no significant correlation between the most broadly used biomarker, CRP, and most of the MREC signs of disease activity. The absence of correlation with signs of inflammation in the bowel wall had already been shown with CT scanner (20). However, a significant correlation was found with extraenteric signs of inflammation including the comb sign and creeping fat. In the present study, only a minority (9/27) of the patients had extraenteric signs of disease activity, which may have led to a lack of power to show this association. Among biomarkers, only platelet count and fecal calprotectin significantly correlated with MREC signs of disease activity. These markers have already been shown to be reliable markers of tissue healing at endoscopy (21,22) and this is therefore not surprising to find a good correlation with the MaRIA score, which was consistently showed to correlate with endoscopic score of activity (12,13). In the present study, fecal

Table 4. — **Time-to-relapse predictive value of the studied parameters in univariate analysis. Only parameters with a p value < 0.1 are showed. Fecal calprotectin and MaRIA score are also showed although their p value is > 0.1**

	Hazard Ratio	95%CI	*p Value*
CRP (logarithm)	1.61	0.97-2.67	*0.064*
Platelet count	1.01	0.99-1.02	*0.085*
Fecal calprotectin	1.001	0.99-1.004	*0.74*
Parietal and extraenteric signs*	3.6	0.89-14.5	*0.072*
MaRIA (logarithm)	0.85	0.07-11.20	*0.90*
segmental maximal MaRIA** (logarithm)	3.04	0.81-11.45	*0.10*
Maximal relative contrast enhancement	2.56	1.02-6.45	*0.046*
Ulcer	12.5	1.13-138	*0.039*
Target sign	3.63	1.01-13.1	*0.049*
Comb sign	3.13	0.88-11.2	*0.078*
Fistula	14.1	1.95-102	*0.009*

* defined as mucosal enhancement, submucosal edema and a comb sign.
** MaRIA in the most affected segment.

calprotectin and platelet count correlated both with bowel wall and extraenteric signs of disease activity. This is not surprising either since almost all the patients (8/9) with remaining extraenteric signs of disease activity (comb sign and/or mesenteric infiltration) at MREC had also signs of activity in the bowel wall (T2 edema and/or target sign).

The second objective of our study was to assess the relapse predictive value of MREC signs in clinically quiescent Crohn's disease. A relapse predictive value has already been shown for several blood markers, including CRP, but also erythrocytes sedimentation rate, cytokines such as interleukin-6 or the soluble receptor of interleukin-2 (4-6). An increased intestinal permeability has also been associated with this increased risk of relapse (23). More recently, attention has been focusing on stool markers, particularly fecal calprotectin. Fecal calprotectin appeared superior to classical blood markers to predict relapse (6). At the same time, fecal calprotectin also correlated better with endoscopic scores of severity (19). Overall, these elevated biomarkers, and particularly fecal calprotectin, have thus been interpreted as being surrogate markers of incomplete disease control, leading to a risk of disease relapse and beyond that, disease progression. Meanwhile treatment strategies have evolved towards a treat-to-target approach, the treatment being optimized according to the results of the monitoring of disease activity using objective markers (2,3). In this setting, MREC presents many theoretical advantages in the assessment of Crohn's disease patients. It allows, in one single procedure, the assessment of the whole intestine and the assessment of both the bowel wall and extraenteric inflammatory process. In a retrospective study, we suggested that among patients in clinical remission, the subgroup who had endoscopic mucosal healing or a normalization of magnetic resonance imaging of the intestine had a lower risk of relapse and a lower risk of abdominal surgery (24). In the present prospective study we confirm that MREC is able to predict time-to-relapse in clinically quiescent Crohn's disease. Although only few surgical events were observed, our results suggest that MREC can also predict the risk of surgical resection and thus the tissue damage progression. Isolated specific signs were better predictors than more global assessment like differentiating between normal and abnormal, or the global and modified MaRIA. The MaRIA score, best associated with endoscopic scores of severity, and assessing the activity of the disease at the mucosal level was not a predictor of the time-to-relapse. This may be linked to the fact that it is not the global mean severity of the disease which is important here but rather the severity of focal lesions, and even more specifically specific signs associated with this severity, i.e. intensity of contrast enhancement, the presence of a target sign, a mucosal ulcer or a fistula, which was in multivariate analysis the only element selected. Although this has to be interpreted with caution due to the fact that only two patients had fistula, this kind of lesion has already recently been shown to predict the risk of surgery in active Crohn's disease patients (25). The signs that best predicted the time-to-relapse were not only mucosal signs, which could also be assessed by endoscopy, but also transmural signs, including bowel wall edema and fistula, which are more difficult to assess by endoscopy. Importantly, in the present study, these MR signs were better predictors of time-to-relapse than biomarkers. CRP and platelets count were only borderline significant for relapse prediction and fecal calprotectin was not. This may be linked to a lack of power, particularly for fecal calprotectin (significant proportion of missing values), since these markers have previously clearly been shown to be associated with the risk of relapse. On the other hand, it emphasizes the strength of MR signs in this prediction, already statistically significant in a relatively small set of patients.

Our study has strengths and weaknesses. The main strengths are its originality, its prospective nature and the careful assessment of the MR images by a single experienced radiologist. The main weaknesses are the relatively small sample size, but which was sufficient to demonstrate the value of MREC in the assessment of clinically quiescent Crohn's disease, and the fact that half of the patients did not bring back a stool sample for fecal calprotectin assessment. This particularly small sample size for fecal calprotectin may also explain why the median value is a bit higher than previously reported in the literature for Crohn's disease patients in remission. However, this assessment was not a main aim of our study. Another weakness is the fact that the baseline MREC could have influenced the management of the patients and thus influenced the outcome. However, this was not the case as no change in treatment was performed within three months after this exploration. Finally, the confirmation of the clinical relapse with objective markers of activity including a new MREC would have helped to strengthen the potential predictive value of this exploration.

In conclusion, in patients with clinically quiescent Crohn's disease, MR signs of disease activity (both extraenteric and in the bowel wall) may persist in a subset of patients and usually coexist. These signs such as the presence of a target sign and the relative contrast enhancement in the bowel wall as well as the presence of mucosal ulcers and the presence of enteric fistula are associated with shorter time to relapse in patients with clinically quiescent Crohn's disease. This association was stronger than for classically used blood or stool biomarkers. These predictors should be validated in a larger independent cohort and an intervention study should be performed to evaluate if a treatment optimization is able to decrease the risk of relapse and disease progression in this situation.

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