Diffusion-weighted Magnetic Resonance Imaging in Crohn Disease: Current Status and Recommendations

ABSTRACT

Over the past years, technological improvements and refinements in magnetic resonance imaging hardware have made high quality diffusion-weighted imaging (DWI) routinely possible for the bowel. DWI is promising for the detection and characterization of lesions in Crohn disease (CD) and has been advocated as an alternative to intravenous gadolinium-based contrast agents. Furthermore, quantification using the apparent diffusion coefficient may have value as a biomarker of CD activity and has shown promise. In this article, we critically review the literature pertaining to the value of DWI in CD for detection, characterization and quantification of disease activity and complications. Although the body of supportive evidence is growing, it is clear that well-designed, multicenter studies are required before the role of DWI in clinical practice can be fully established.

Index terms: Diffusion weighted imaging; Crohn Disease; MR-enterography; MR imaging; Imaging techniques; Inflammatory bowel disease

Core tips: Recent technical refinements have facilitated application of diffusion-weighted MR imaging (DWI) to evaluate the bowel and an increasing number of studies have investigated the utility in Crohn Disease (CD). The objectives of this narrative review were threefold. First, to detail the current role of DWI in the investigation of CD patients. Second, to discuss the diagnostic accuracy for specific clinical scenarii in CD patients, and third, to provide some guidance to the radiologist as to how and when to perform DWI in the context of CD.

INTRODUCTION

Crohn disease (CD) is a relatively frequent condition in the young, affecting approximately 0.4% of the general population in developed countries (1). Current treatments consist mainly of immunosuppressive and immunomodulatory agents. However for patients with major complications, surgery that may result in substantial morbidity is required (2,3). A comprehensive evaluation of patients with CD, including an accurate initial diagnosis, evaluation of disease extent, assessment of inflammatory activity and detection of potential complications, remains challenging. While video-endoscopy allows visual and histological assessment of the upper (esophagus to proximal jejunum) and lower (colorectum and terminal ileum) digestive tract, the video-endoscopic workup of the small bowel is often limited. Indeed, enteroscopy is a long and cumbersome procedure that requires general anesthesia, and small bowel videocapsule endoscopy is only conceivable once a small bowel stenosis has been ruled out by imaging. Several imaging techniques are now available for the evaluation of patients with small bowel CD, including ultrasonography (4), computed tomography (CT), CT-enterography (CTE) and magnetic resonance enterography (MRE) (5,6). At the same time, the small bowel follow-through in the assessment of CD has been uniformly abandoned (7-9). While endoscopy optimally evaluates the appearance of the mucosal surface, cross-sectional imaging also allows investigating the wall of the small bowel and surrounding tissues

Since CD affects mainly young patients who will require repeated examinations during their lifetime, an accurate imaging technique without ionizing radiation is critical for this subgroup of patients (10). Consequently, MRE has become the first line imaging technique for the evaluation of CD. MRE allows evaluation of the entire digestive tract including small bowel, colon, rectum, anus and perineum. MRE offers excellent patient acceptance, lack of ionizing radiation, high degrees of accuracy and good reproducibility (11-13). Traditional limitations of MRI cited in the past are a relatively high cost, low spatial resolution, susceptibility to artifacts and lack of wide-spread availability. However, the advent of major improvements in hardware and software in recent years, have largely overcome these technical limitations (6).

Current MR protocols include rapid MR sequences that allow data acquisition during a single breath-hold, thereby keeping motion artifacts to a minimum. MR protocols typically include rapid morphological sequences along with gadolinium-chelate enhanced sequences

that provide functional information (14). DWI is a relatively recent technique that provides information regarding the presence of inflammation, necrosis and tumor cellularity (15). Imaging of the bowel with DWI remains challenging, however, because of its relatively long acquisition times, sensitivity to bowel motion and the presence of T2 shine through effects, that are frequently encountered in the bowel lumen (14). However, recent technical refinements have improved the feasibility of using DWI to evaluate the bowel, and several recent studies have evaluated its accuracy and performances in CD patients (16-30).

The objective of this systematic review was threefold: 1) To highlight the current role of DWI in the investigation of CD patients; 2) To evaluate its performance in specific clinical scenarii 3) To provide recommendations and guidance to radiologists as to when and how to perform DWI in a context of CD.

LITERATURE REVIEW

A computer-assisted literature search was performed by two radiologists to identify scientific articles evaluating the use of DWI for MRE in patients with CD. The MEDLINE, EMBASE and Cochrane databases were searched for relevant articles with MeSH terms (Crohn disease/diagnosis; Diffusion Magnetic Resonance Imaging/methods; Diffusion/Crohn disease; Diagnostic Imaging/Diffusion/Crohn disease; Diagnostic Imaging/Diffusion Magnetic Resonance Imaging/Crohn disease). The search included the time period from February 1994, when DWI of the abdomen was first described by Muller et al. (31) to December 2015. Review articles, letters, editorials, comments, and case reports were not selected. Only studies dealing with adult CD patients were included. The list of articles was supplemented by cross-checking of the reference lists of all potentially relevant articles and by a manual search of references of all available reviews. We identified fifteen articles which focused on adult CD, and evaluated the performances or added value of DWI in MRE protocols (16-30). An additional search was made in February 2016 to identify pertinent studies published after the initial time frame search (32,33).

TECHNICAL REVIEW

Basic principles of DWI

Initially DWI was used primarily for studying disease processes of the brain, but more recently, this technique has been applied to the study of abdominal organs (34-39). DWI reflects the changes in water motility caused by interactions with cell membranes, macromolecules, and alterations of the tissues which modify the Brownian motions and distribution of fluids (40). The use of DWI helps quantify this restriction of motion. DWI is performed by using a T2-weighted fat-suppressed MR sequence with the addition of a diffusion gradient, which is quantified by a diffusion coefficient called "b-value" (41). By increasing the diffusion coefficient, the signal in areas of free diffusion decreases more rapidly, while in regions where diffusion is restricted the signal decreases more slowly.

The decay of the signal can be modeled using a mono-exponential equation, a bi-exponential, or using more complex models (42). The acquired images must be post-processed to extract parametric maps representing the different factors of the fitted equation. The most commonly used technique, available on all commercially available MR scanners, is the mono-exponential fitting method, which provides a single parametric map called the apparent diffusion coefficient (ADC) map (38,43,44). This map provides numerical values in order to facilitate the quantification of diffusion restriction. This technique is sufficient for most routine applications, but neglects other important parameters such as microcirculation related diffusion, and perfusion fraction, which influence the images obtained with very low b-values. The value of the ADC map as a biomarker has been widely investigated in brain tumors and more recently in other organs such as the liver (45-48). ADC measurements require high quality images with an adequate signal-to-noise ratio because artifacts, in particular motion artifacts, can alter the measurements. These technical limitations have largely been overcome with the combination of high magnetic fields MR scanners (1.5 and 3 Tesla), the decrease in acquisition time, multichannel coils and parallel imaging techniques. New pulse sequences such as echo-planar imaging have contributed to a dramatic decrease in acquisition time, resulting in images that are now less sensitive to bowel peristalsis and respiratory movements.

Diffusion tensor imaging (DTI) is a sequence that uses additional directional gradients and allows differentiating the relative degree of diffusion of protons according to several directions. It requires a dedicated acquisition with several directions of the diffusion gradients and is used to visualize fiber tracks in the brain in which diffusion is preferentially restricted in one direction. However, despite some publications in the liver and in the abdomen, the application of DTI in the abdomen, and more specifically in the bowel is really challenging

because of bowel peristaltism and respiratory motions (49,50). Moreover, besides the technical challenge of obtaining relevant images in the abdomen, there is no clear application of DTI in the abdomen yet. Most studies have focused on the depiction liver fibrosis or evaluation of kidneys but found no added value to conventional DWI (51).

Technical considerations of DWI for MRE

While routine MR imaging protocols have become relatively well standardized, the parameters used for DWI vary among centers as shown in Table 1. Optimal distension of the small bowel is a prerequisite for any enterography technique. Most authors recommend that patients fast before DW-MRE, with a delay varying from 2 to 6 hours (16-27). It is assumed that fasting helps limit peristaltic movements of the bowel and maximizes the contrast between the lumen and the bowel wall. In our clinical practice, 6 hours fasting is a minimum and we recommend performing MRE in the morning. Although there is no clear and definite evidence that antiperistaltic agents are helpful, they are generally used by many centers and therefore may be considered as recommended. Enteral contrast agents used consist of a hyperosmolar agent such as polyethylene glycol solution (25), diluted mannitol (16) or barium sulfate suspension (Volumen®, E-Z-EM Canada Inc., Anjou-Quebec, Canada) (22) There is not any strong evidence in the literature supporting the superiority of one particular oral contrast agent. The agents that are being used usually have hyperosmolar properties and are ingested from 45 to 60 minutes before the examination.". Only one study reported not administering oral contrast for DW-MRE (23). Optimal small bowel distension requires that the patient drinks at least 1 liter of oral contrast agent before the examination. To improve small bowel distension, some researchers have advocated the use of MR enteroclysis. This technique consists of placing a nasojejunal tube beyond the ligament of Treitz under fluoroscopic guidance, and filling the bowel with 1 to 1.5 liter of water before image acquisition (52-55). However, none of these authors have evaluated DWI in association with enteroclysis. Moreover, there is no demonstrated benefit in terms of sensitivity or specificity for depicting active lesions in CD, and enteroclysis is often poorly tolerated by patients (56,57). That is why we do not recommend it in everyday practice and it conveys additional radiation burden.

A number of authors recommended placing the patients in a prone position to improve bowel distension and limit peristalsis and motion artifacts (58-61). However, improvement in accuracy when comparing the prone and supine positions in patients with CD has not been demonstrated (58). Moreover, the prone position increases the risks of vomiting (58). We would recommend the prone position although some patients may sometimes feel uncomfortable.

In all but one study (27), DW images were acquired in the transverse plane. This is because DW images obtained in the transverse plane are less prone to motion artifacts than those acquired in the coronal plane. Some authors have used a navigator-triggered technique for image acquisition, especially in the upper abdomen (62-64). Advantages include decreased motion artifact and increased signal-to-noise ratios. When using a navigator-triggered technique, DW images are acquired only during the expiratory phase. The major disadvantage of this technique is that it results in increased acquisition times. The mean acquisition time is rarely reported in studies using this technique, because it depends on the respiratory frequency (one respiratory cycle corresponds to the repetition time) and thus varies among patients. For example, the acquisition of navigator-triggered DW images of the upper abdomen requires 3 to 4 minutes with both 1.5 and 3 Tesla MR units. Other researchers prefer the use of a signal averaging technique so that the resulting DW images are obtained from several acquisitions while the patient breathes freely (23). These reducing motion artifact as well as increases the signal-to-noise ratio of the image. Finally, other authors propose that the images be acquired during several breath holds (26). The advantage of the latter two techniques is that images are acquired more rapidly. However, the images are often reported to contain less detail, which may result in altered ADC measurements (65,66). If only one plane is performed, the transverse plane plane should be favored. Considering motion artifacts, we prefer the triggering technique. Although the acquisition time is increased, the triggering technique provides better image quality

Current implementation of DWI on commercially available MR scanners, does not allow the acquisition of 3D DW images and very thin contiguous slices of the abdomen in routine. Slice thickness typically varies between 5 and 8 mm with an inter slice gap of 0 to 3 mm (16,18-27). The longitudinal coverage of the acquisition depends on the number of channels of the body coil. State of the art MR scanners allow a single data acquisition of the whole abdomen within an acceptable amount of time. However, with older models, two or even three separate acquisitions are needed to fully cover the entire abdomen.

Rationale for using DWI for evaluation of the bowel

The rationale for using DWI in CD is threefold: First, it may improve the accuracy of MRI for disease detection. Second, it may improve MRI accuracy for disease activity evaluation and treatment monitoring. Finally, DWI may obviate the need for administration of intravenous contrast (67).. Some researchers have postulated that DWI might be equivalent or at least non inferior to gadolinium-chelate enhanced dynamic MR sequences in the detection of inflammatory lesions of CD (28). These authors propose a subjective evaluation of high b-values images assessing for the presence of restriction (i.e. high signal intensity in association with corresponding low ADC values) of the bowel wall. However, there is no robust evidence to date to support this hypothesis (16,28). Several artifacts are commonly encountered when performing DWI of the bowel. The T2-shine-through effect is related to the spontaneous high signal intensity of bowel contents on T2-weighted images (Fig. 1). DWI is based on T2-weighted images with the addition of specific diffusion gradients. DW images, may thus, show high signal intensity not related to restricted diffusion but to spontaneous high signal intensity on T2-weighted images (68). In these cases, ADC calculation as depicted on the ADC map allows distinction between true restricted diffusion and T2- shine -through effect (69). Restricted diffusion will result in low values on the ADC map, while T2-shine through will maintain high ADC values. T2- shine-through effects may be reduced with the use of high b values and short echo times. Motion artifacts are a significant challenge with DWI, and are most marked with long acquisition times. This is especially true for DWI of the bowel. These motion artifacts may be reduced with the use of appropriate gating techniques, fast image acquisition techniques (i.e., echo planar imaging or parallel imaging) and the use of intravenous antiperistaltic agents before image acquisition (i.e., N-butylscopolamine or glucagon, which may be repeated during the MR examination) (70). In addition, a number of motion compensation software algorithms have also been developed recently (71).

Reported b-values used for DWI of the bowel are similar in all studies (16-27). Both a very low b value ranging from 0 to 50 s/mm² and a high b-value is recommended. In most studies, a b value of 800 s/mm² is used to obtain a high contrast-to-noise ratio (17-19,23,25-27). Only Qi et al. have evaluated different b-values and compared the sensitivities for depicting CD-related lesions with four b-values (800, 1500, 2000 and 2500 s/mm²) at 3 Tesla (72). They have reported a poor sensitivity for very high b values (2000 and 2500 s/mm²) and

similar sensitivities for b=800 and b= 1500 s/mm², with a better specificity with b=1500 s/mm² [48]. Although Qi et al. enrolled only 36 patients in their study, their standard of reference consisted of endoscopic findings in all patients. However, in a more recent study, the same authors found a better sensitivity for b=800 s/mm², along with better contrast-to-noise and signal-to-noise ratios. The authors do not provide any explanation for the difference they found in their two studies, therefore, the optimal b values to be used for DWI of the bowel is not yet clearly defined (19). In our clinical practice, we use 3 b values (b=50, b=500, and b=1000 s/mm²). This allows the calculation of ADC value and the signal to noise ratio is very satisfying on our MR-scanners. Sometimes, the b=500 value is helpful when the increase in signal intensity is subtle on the b=1000 images. The use of at least two b values is required, including a low value (b=50 rather than b=0) for the calculation of ADC to get rid of the microperfusion fraction, and a high b value (800 or 1000 s/mm²) depending on the MR system.

New T1-weighted rapid MR sequences including LAVA-Flex® (Liver acquisition with volume acceleration flex, General Electric Healthcare, Milwaukee, USA) or CAIPIRINHA-VIBE® (Controlled Aliasing in Parallel Imaging Results in Higher Acceleration - gradient recall echo volumetric interpolated breath-hold examination, Siemens Healthcare, Erlangen, Germany) or e-THRIVE (T1-weighted high resolution isotropic volume excitation, Philips Healthcare, Best, The Netherlands) have been developed and allow the acquisition of thin slices with high spatial and contrast resolution, potentially increasing conspicuity of lesions (Fig. 2) (73,74). Finally, the most acknowledged useful application of DWI is the use of ADC value as a quantitative biomarker of disease activity (17). ADC has the potential to become a powerful tool for assessing and monitoring the response to immunosuppressive treatments. Today, several MRI scores of disease's activity exist and are based on a number of morphological criteria including wall thickness, and semi-quantitative evaluation of contrast enhancement (27,75). Post-processing of DW images is fully automatized, whereas other functional imaging techniques such as quantification of dynamic contrast-enhanced imaging, require a very specific acquisition, precise registration and dedicated software for post-processing at the penalty of added costs (76,77). Limitations of ADC measurements include, lack of reproducibility between MRI vendors, non-standardized sequence parameters (b-values) and varying magnetic fields strengths (78). However, the greatest challenge for ADC measurements of the bowel wall is the small size of the region of interest to be measured. The measurement of ADC of such a small structure is hardly reproducible, and this remains the

major limitation of using ADC in everyday practice. Among the studies that have evaluated the quantitative value for ADC for depicting active lesions, none has evaluated the reproducibility of this measure and rarely described precisely how ROI were selected and placed. It is clear that the ROIs used to contour the bowel wall are always small and subject to inter- and intra-observer variabilities, which remain today the main limitation of this approach. It is assumed that further development of automatized segmentation software will increase the reliability of these measures in the future and allow an accurate histogram analysis of ADC map (79).

It is currently standard of practice that gadolinium-based contrast agents should not be administered to patients with chronic renal impairment, because of the potential risk of nephrogenic systemic fibrosis (80). One main advantage of DWI is to avoid the use of intravenous gadolinium based contrast agents, and to rely on the spontaneous contrast of DWI instead. As inflammatory tissue restricts diffusion of water, its signal intensity is high on DWI using high b value while normal tissues signal is suppressed. Thus, DWI images with high b-values have a spontaneous contrast that may highlight disease activity in the same way as contrast enhanced images do.

CLINICAL APPLICATIONS

Efficacy of DWI in detecting active CD in small bowel

To date, several studies have evaluated the efficacy of DWI in detecting active small bowel CD (16-27). All of these studies, however, have included only a limited number of patients. The majority of studies included less than 47 patients (16,17,19,21-24,26,27,30) with the exception of one study that enrolled 130 patients (25). In all these studies, DWI had a high sensitivity for the detection of inflammatory lesions of CD (Table 2).

In a prospective study that involved 44 patients with CD, Kim et al. emphasized the quality of their standard of reference, which was ileocolonoscopy (24). They reported a sensitivity of 94% and a specificity of 71% for DWI in detecting active CD similar to other studies (17,19,21-27). In another study from the same cohort, the authors found a sensitivity of 93% and a specificity of 67% for DWI used in combination with T2-weighted images, which was equivalent to T1-weighted images obtained after intravenous administration of gadolinium chelate combined with T2-weighted images using a subjective grading of active

lesions on high b-value DWI (28). These authors found a clear added-value of DWI compared to conventional MRE for the depiction of bowel inflammation resulting from aphtous lesions, erythema or edema (sensitivity=62% vs. 18%; $P<0.001$). Their study suggests that DWI may help detect patients with severe active lesions that would require optimized therapy (24).

Oto et al. conducted two studies in 11 and 18 patients, and found sensitivities of 94.7 and 94% and specificities of 82.4 and 88 % for detecting active CD with DWI, respectively (21,22). In these two studies, the standard of reference was endoscopy and/or surgery with pathological examination performed less than 4 weeks after the MRI. Kiryu et al. reported a sensitivity, specificity, and accuracy for the detection of active CD in the small bowel with DWI of 86.0, 81.4, and 82.4%, respectively in 31 patients (23). However, this study was performed at 1 Tesla without bowel distention and used the small bowel follow-through as the standard of reference.

Buisson et al. reported a sensitivity of 100% of DWI for the detection of small bowel inflammation in a series of 31 patients (27). The most recent study by Qi et al. confirmed the high sensitivity (93.5%) and specificity (89.47%) of DWI for the diagnosis of active CD in 36 patients (19). Of interest, Qi et al. evaluated 100 small bowel segments individually and used videoenteroscopy, performed in all patients less than 7 days after MRI, as a standard of reference (19).

In our clinical practice, when the administration of intravenous contrast agent is contra-indicated (i. e., glomerular filtration rate < 30 mL/min), we use DWI to assess visually the presence of active lesion.

Evaluation of colonic inflammation:

Several studies have evaluated the performances of DWI for depicting inflammation due to CD in the colon (Table 4). Since endoscopic and histologic assessment is considerably easier in the colon than in the small bowel, the standard of reference is often stronger for colonic evaluation than for evaluation of the small bowel (17,24). However, performances of DWI vary greatly among studies. Kim et al. reported a sensitivity of 76% and a specificity of 57%, in a prospective study evaluating the presence of inflammatory colonic lesions on a per-segment analysis (27 segments in 44 patients) (24). The lower sensitivity was obtained by Oussalah et al. who reported a sensitivity of 58.3% and a specificity of 84.5% in a prospective study with 61 patients using a per-segment analysis (n=211 segments) (20). However, their

specificity was higher, indicating stricter reading rules. Other authors, however, have reported higher performances of DWI in detecting active CD of the colon. Kiryu et al. retrospectively analyzed 128 large bowel segments in 31 patients and found a sensitivity of 85.7% and a specificity of 75.7% at 1 Tesla (23). Hordonneau et al. prospectively analyzed 486 colonic segments in 130 patients and found a sensitivity of 96.9% and a specificity of 99.1% (25). These variations in diagnostic performance can be explained by different standards of reference; indeed, Hordonneau et al. used an MRI score whereas Oussalah et al. used colonoscopy (20,25).

Despite variations reported in the diagnostic performances of DWI for assessing colonic CD, the performances achieved are lower in the colon than in the small bowel, especially for specificity. This discrepancy may be explained by the artifacts generated by air in the colon . Moreover, no water enema was used in most studies (23-25). Diagnostic performance of DWI in the colon and rectum might be improved with adequate preparation and the administration of a water enema. In addition, image analysis in several studies was undertaken on a single small bowel segment (terminal ileum) and in the colon and the results were not presented using a segment by segment basis (17,21,81). Nevertheless, false positive and false negative findings were more often reported in the colon than in the terminal ileum.
In our experience, DWI in the colon remains difficult, and despite we clearly see the inflammatory lesions of the colon on DWI, we are not convinced that the performances are sufficient to replace colonoscopy.

Characterization of CD lesions and monitoring of disease activity:

Another important goal of MRI in CD is to assess the active inflammatory and/or fibrotic pattern of bowel stenosis. To date, repeated endoscopic mucosal assessment remains, in combination with clinical and biological parameters, the standard of reference for monitoring CD activity (82). However, the small bowel, except for the terminal ileum, remains difficult to reach using conventional endoscopic techniques.

Inflammation and fibrosis both may result in bowel wall thickening on morphological T2-weighted MR images, and show enhancement after intravenous administration of a gadolinium chelate. The best criterion to discriminate between these two lesions is the overall decreased enhancement of fibrotic lesions that enhance progressively and transmurally (i. e., “en bloc” enhancement), as compared to the stratified pattern of enhancement seen with

inflammatory lesions. Another criterion is hypomotility of fibrotic lesions as seen on dynamic cine steady-state images (83). However, it remains challenging to differentiate these two entities on MR imaging at times, especially because the pathologies can co-exist and MR features may overlap. The differentiation of fibrotic versus inflammatory lesions has important therapeutic implications. Fibrotic lesions improve little with medical therapy and, when responsible for bowel obstruction, require surgical resection or endoscopic dilation. Conversely, inflammatory lesions are managed conservatively with medical therapy (steroids, immunosuppressive or immunomodulatory agents) (5,12).

In inflammatory bowel disease, the wall of the bowel shows diffusion restriction with a low ADC value and high signal intensity on DWI using low and high b-values. Conversely, the wall of normal bowel shows no diffusion restriction and has decreased signal at high b values. Similarly, fibrotic tissue does not restrict diffusion, and shows higher ADC values and a signal that decreases at high b-values. In all studies except one, active inflammatory CD was considered present on DWI when restricted diffusion (i. e., low ADC value on ADC map and high signal intensity on high b-value images) was observed (Table 3). In five studies, an ADC threshold value was calculated to discriminate between active and non-active CD lesions (21,22,25,27,30).

In an initial study, Oto et al. reported a threshold value of $2.0x10^{-3}$ mm^2/s yielding a sensitivity of 84% and a specificity of 91% for distinguishing active from inactive lesions (21). In a later publication, the same group reported a threshold value of $2.4x10^{-3}$ mm^2/s yielding a sensitivity of 94% and a specificity of 80% (22). In both studies, the accuracy of DWI was excellent with areas under the ROC curves of 0.938 [95%CI: 0.873-1] and 0.92 [95%CI%:0.87-0.97], respectively. Several studies have emphasized the ability of DWI to discriminate between active and inactive CD lesions, but only two focused on the characterization of fibrotic lesions (16,29). Tielbeek et al. found significantly lower ADC values and high signal intensity on high b-value images in fibrotic lesions compared to non-fibrotic lesions, thus suggesting that DWI may not be useful for this indication.. These authors have hypothesized that fibrotic tissue reduces the extracellular space and therefore leads to restricted diffusion (16). Catalano et al. also found that ADC values were lower in fibrotic tissue (29). However, this study focused on PET/MRI rather than DWI, and the results of this preliminary study were observed only in 19 patients.

Recently, several groups of researchers have developed CD activity scores based on MRI findings, given the critical role of MRE in monitoring CD patients, (83-89). The MaRIA

score is the only MRI based score that has been evaluated in a large series of patients and is based on findings using standard MRI sequences (25). The MaRIA score is calculated as follows: 1.5 x wall thickening (mm) + 0.02 x relative contrast enhancement (RCE) + 5 x edema + 10 x ulcers (90,91). This score has recently been evaluated in prospective single center studies (27,90,91). In a series of 31 patients, Buisson et al. reported a threshold value of $1.6x10^{-3}$ mm^2/s yielding a sensitivity of 82.4% and a specificity of 100% for differentiating active from non-active disease (27). Hordonneau et al. conducted a large study in 130 CD patients with a total of 352 bowel segments and found a sensitivity of 85.9% and a specificity of 81.6% for discriminating between active and non-active CD lesions with the MaRIA score as a standard of reference (25). However, in a prospective study, Sato et al. found a low correlation (r=0.6) between the MaRIA score and the CD Endoscopic Index of Severity (CDEIS) (17,81). This discrepancy may be partly explained by the differences in standard of reference. Pathological evaluation of active vs. non active disease is limited to the extent of the sampling while studies which use MRI itself as a standard of reference analyze the small-bowel in the whole length. However the limitations of using MRI as a standard of reference for evaluating MRI score remain a considerable limit of any study on MRE. Nevertheless, the MaRIA score remains the score with the strongest validation studies to date.

In addition, Hordonneau et al. constructed a new score replacing gadolinium administration by DWI (DWI-MaRIA score or Clermont score) [25]. These authors found a good correlation between the MaRIA and the Clermont score, but this score has not yet been validated prospectively (27). The DWI-MaRIA or Clermont score is calculated with the following equation :-1.321 x ADC (mm^2/s) + 1.646 x wall thickening (mm) + 8.306 x ulcers + 5.613 x edema + 5.039. Hordonneau et al. found also an excellent correlation between the MaRIA and the Clermont Score (r=0.99) (25). This activity score is emerging as a promising biomarker of bowel inflammation in CD, but confirmatory studies are currently lacking. This is because most studies have compared DWI findings to other MRI-based scores such as the MaRIA score (25).

Qi et al. have evaluated a MRI score, which includes the classical criteria of other scores and two DWI findings, including hyperintensity and stratification (19). However, this composite MRI score did not show good correlation with CDAI (r=0.53).

In our experience, quantitative evaluation of ADC value is barely reproducible although ADC value is decreased in inflammatory lesions. Moreover, calculation of the different published scores is cumbersome and difficult to use when confronted to clinical practice outside studies.

Disease severity at MRI and prediction of outcome

Severe endoscopic lesions at colonoscopy have been identified as predictors of a more aggressive clinical course in CD, with higher risk of penetrating complications and higher rates of colectomy (92). Buisson et al. prospectively evaluated 44 CD patients with DWI-MRE and evaluation of the Clermont Score (33). They reported a negative correlation between ADC-value and CD Endoscopic Severity Index in 194 bowel segments analyzed. They also reported a lower ADC in segments with deep ulcers or superficial ulcerations. A cut-off value of 1.42 x 10^{-3} mm²/s yielded a sensitivity of 0.91% and a specificity of 0.83% for detecting deep ulcerations. Jauregui-Amezaga et al. prospectively assessed the outcome of 112 CD patients with colonoscopy and MRI at baseline (93). Predictors of disease severity at MRI were determined by magnetic resonance index of activity (MaRIA) score and its individual components including wall thickness, relative contrast enhancement, mural edema and mucosal ulceration. Disease severity as measured by endoscopy (CDEIS) or MRI (MaRIA) did not differ between patients who required and those that did not require surgical resection during follow-up. MRI demonstrated ulcers in 79/112 (71%) patients while colonoscopy showed ulcers in 94/112 (84%). In this cohort treated with current strategies (70% of patients received anti-TNF agents), surgical resection was not associated with the presence of severe endoscopic lesions at baseline colonoscopy or with the identification of ulcerations at MRI. Multivariate logistic regression analysis identified the following independent predictors for surgical resection: presence of perianal disease at baseline, fibrotic stenosis at MRI, and intra-abdominal fistulae at MRI. These data suggest that the need for surgical resection in patients with CD is best established by a combined clinical and MRI assessment.

Recently, Buisson et al. reported the results of a prospective study including 40 consecutive patients (32). These researchers found that patients who experienced remission 12 weeks after anti-TNF therapy had lower baseline ADC values and higher MaRIA scores (32). They reported a cut-off ADC value of 1.96 x 10^{-3} mm²/s yielding a sensitivity of 70.0%

and a specificity of 65.0% to predict remission at the 12th week, with an area under the ROC curve equal to 0.703[95%CI: 0.535-0.872].

Complications of IBD

Recent studies suggested that the performance of MRI and DWI might surpass those of CT for the diagnosis of acute complications due to CD (94,95). Seastedt et al. reported a sensitivity of 75% and 68% for diagnosis of stenosis with CTE and MRE respectively and a sensitivity of 50% for CTE and 60% for MRE for the diagnosis of fistula. MRE sensitivity was 68% for stenosis and 60% for fistula. Several complications may occur in patients with CD during their lifetime such as strictures, fistulas, abscesses and gastrointestinal tract obstruction (Fig. 4) (96). The performance of standard MRE without DWI in depiction these complications have already been investigated and are at least as good as CT, however, further studies are needed to evaluate the role of DWI in this clinical setting (97,98).

Abscess. No study has prospectively evaluated the performances of DWI for depicting complications of CD such as fistulas, stenosis and abscesses (Fig. 3). The accuracy of DWI for depicting abscesses in the abdomen or pelvis is good with a sensitivity reaching 92% and a specificity reaching 100% (99). However, no study has evaluated DWI in the context of MRE in CD patients for this indication (100-104). The high density and viscosity of pus in abscesses restricts the diffusion of water, and ADC values are low in abscesses (101). The detection of abscesses in CD patients is a critical issue because their presence warrants major changes in patient management, including discontinuation of immunosuppressive therapy, starting antibiotic therapy, performing percutaneous drainage or surgical treatment in case of failed conservative therapy (105,106).

Enteric fistulas. Enteric fistulas are well depicted with DWI (Fig. 5). On DW images obtained with high b values, they present as hyperintense tubular or serpiginous structures that connect separate bowel segments or communicate with the skin surface or other organs (107). Sinus tracts are also well visualized, presenting as hyperintense blind-ended, tubular structures (Fig. 6) (107). Several studies have evaluated the performance of DWI for depicting peri-anal fistulas (108-110) but only one has evaluated DWI in enteric fistulas (111). Schmid-Tannwald et al. evaluated 14 patients with 19 internal fistulas and 6 sinus tracts and found

similar added value for DWI compared with contrast-enhanced T1-weighted images using two independent readers (111). Although this study included several types of fistulas, the results suggest that DWI may be helpful particularly in patient with impaired renal function, where gadolinium administration should be avoided. However, these promising results require confirmation with larger prospective studies.

Neoplasms. Gastrointestinal neoplasms represent a well-known complication of CD (Fig. 7) (112-114). Their detection remains challenging and may occur too late to allow curative treatment (115,116). CD related intestinal neoplasms have been described using CT (7-9,100,117-120). However, as MR imaging is increasingly performed in CD patients, it is not rare to discover neoplasms with this technique (100,116). Several recent studies have shown a high degree of accuracy for DWI in depicting small bowel tumors (61,121). Amzallag-Bellenger et al. conducted a prospective study in 75 patients and achieved a sensitivity, specificity, PPV, NPV and accuracy for the detection of small bowel tumors of 96%, 96%, 93%, 98% and 96% respectively (61). Others have also found that DWI helps depict rectal cancers (122,123). Barral et al. reported in a retrospective analysis with a limited number of patients, that all six rectal tumors for which DW-MR imaging was part of the MR imaging protocol, showed restricted diffusion (100).
In our experience, DWI is very accurate for the diagnosis of complications of CD.

Fistula-in-ano

Fistula-in-ano occurs in 20-50% of patients with CD during their lifetime. MRI is already a well validated technique for depicting fistula tracts and abscesses(124). To date, only three retrospective studies have evaluated DWI for the diagnosis of fistula-in-ano, including depiction of fistula tracks, diagnosing abscesses, differentiating abscesses and inflammatory masses, and for monitoring disease activity (108-110).

Dohan et al. have showed that DWI is very accurate at differentiating perianal abscesses which require surgery, from inflammatory masses, which require immunosuppressive therapy (108). In their study, the optimal ADC cut-off value was 1.186×10^{-3} mm^2/s for the diagnosis of abscesses, yielding a sensitivity of 100 % [95% CI: 77 %-100 %], a specificity of 90 % [95% CI: 66%-100%], a positive predictive value of 93 %

[95% CI: 82.8%-100%] and a negative predictive value of 90% [95 % CI: 78 %-100%] [71]. The area under the ROC curve was 0.971 indicating that DWI is extremely powerful for this indication. This study suggests that DWI may replace dynamic MR sequences that require the intra-venous administration of a gadolinium chelate. In regards to monitoring CD activity, Yoshizako et al. found a good correlation between ADC values and disease activity in 24 patients (109) whereas Dohan et al. did not (108,109). For Yoshizako et al., an optimal cut-off ADC value of 1.109 10^{-3} mm^2/s in the fistula track yields a sensitivity of 95.7%, a specificity of 50%, a positive predictive value of 71%, and a negative predictive value of 90% for differentiating patients with active CD from patients with non-active CD (109). The main difference between these two studies is the standard of reference used for determining the degree of inflammatory activity. Yoshizako et al. used a composite index, including the need for surgery and surgical findings, and assigned patients to only two groups (109). In contradistinction, Dohan et al. used the Van Assche classification, which is a prospectively validated score based solely on imaging criteria, with continuous variables ranging from 0 to 24 (125). The difference between these two retrospective studies highlights the challenge of retrospectively evaluating the inflammatory status in CD. There is lack of standardized ways to quantify CD activity currently and that even in prospective studies. Clinical indexes such as the CDAI or composite criteria such as the Lémann score assess the patient's general condition, while DWI only evaluates local inflammation (126).

All studies found that fistulous tracks are easier to depict with DWI in comparison to other sequences and achieved sensitivities of approximately 100% (108-110). These high sensitivities are largely obtained because of the effective suppression of the surrounding normal tissue signal that DW images provide. We think that further studies are needed but DWI is really promising in the pelvis and in the assessment of fistula-in-ano.

CONCLUSION AND RECOMMENDATIONS

Most published studies suggest that DWI achieve a high degree of accuracy in the field of CD and should be routinely included in MR imaging protocols. However, further studies are required to assess more precisely the added value of DWI for specific clinical indications. DWI examinations should be performed with a low b-value (0 - 50 mm^2/s) and a high b value (800 to 1000 mm^2/s) depending on the MR equipment. The transverse plane for DW image acquisition is less sensitive to motion artifacts and should be preferred imaging plane. Bowel

distention and the administration of anti-peristaltic agents are recommended by all authors in recent studies and help improve image quality. There is no evidence that respiratory triggering surpasses breath-hold or free-breathing acquisition, but most recent studies recommend that respiratory triggering be applied despite an increased acquisition time and that is the technique we currently use in our daily practice. However, in the clinical routine, most sites prefer to use free-breathing acquisition due to the shorter imaging times.

There is currently no accepted optimal cut-off ADC value to discriminate between active and non-active CD, but DWI using high b-value images can be used to help depict inflammatory bowel segments and complications such as fistulas and abscesses. To date, ADC measurements do not seem helpful to differentiate between fibrotic and inflammatory segments because both result in restricted diffusion. In fistula-in-ano, DWI is very helpful especially when intravenous administration of a gadolinium chelate is not possible and may probably replace it in the future.

Administration of a gadolinium chelate remains the standard of care to date, however, DWI can be used as a valuable sequence for the depiction of lesions in everyday clinical practice. Further technical improvements with thinners slices and multicenter validations are required before DWI can replace gadolinium enhanced sequences or be used as a reliable quantitative biomarker for monitoring disease activity.

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Figure Legends

Figure 1. 25-year-old woman with active Crohn disease.

A. Diffusion-weighted MR image (b value=1000) in the transverse plane shows high signal intensity of the proximal jejunum (arrows).

B. ADC map do not show ADC restriction.

C. T1-weighted MR enterography after intravenous administration of a gadolinium chelate in the transverse plane shows only collapsed small-bowel in this area and no inflammatory enhancement (arrow).

Figure 2. 22-year-old man with active Crohn disease.

A. Diffusion-weighted MR image (b value=1000) in the transverse plane shows high signal intensity involving a long segment of terminal ileum with dilatation of the small bowel (arrowheads).

B. ADC map shows ADC restriction (ADC value = 1.243×10^{-3} mm^2/s).

C. T1-weighted MRE after administration of a gadolinium chelate in the transverse plane confirms the marked inflammatory enhancement of the dilated segment (arrowheads).

D. In the same patient, DWI depicts the inflammatory stenosis (arrow) and the post-stenotic dilatation (arrowheads).

E. ADC map shows restricted diffusion (ADC value = 1.453×10^{-3} mm^2/s).

F. T1-weighted MR-images after intravenous administration of gadolinium chelate in the coronal plane shows marked enhancement of the stenosis (arrow).

Figure 3. 26-year-old woman with a story of multiple bowel resections for active CD resistant to immunosuppressive therapy who had incomplete colonoscopy.

A. Diffusion-weighted MR image (b value=1000) in the transverse plane shows high signal intensity of the transverse colon with a reduced lumen (arrow).

B. ADC map shows ADC restriction in the thickened colonic wall (ADC value = 1.460 x 10^{-3} mm^2/s).

C. T1-weighted MRE after intravenous administration of a gadolinium chelate in the transverse plane confirmed the colonic inflammatory stenosis with an intense enhancement of a long inflammatory colon (arrowhead). Notice the blurring artifacts related to peristaltic movements of the bowel, which impair the quality of the images (arrow).

Figure 4. 51-year-old woman with a story of ileo-cecal resection for active Crohn disease.

A. Diffusion-weighted MR image (b value=1000) in the transverse plane shows high signal intensity of the ileo-colonic anastomosis suggesting anastomotic recurrence (arrow).

B. ADC map shows ADC restriction in the anastomosis (ADC value = 1.289 x 10^{-3} mm^2/s).

C. T1-weighted MRE after administration of a gadolinium chelate in the coronal plane confirmed the anastomotic recurrence of Crohn disease with a long inflammatory segment of the ileum side of the anastomosis (arrow).

Figure 5. 32-year-old man with active Crohn disease.

A. Diffusion-weighted MR image (b value=1000) in the transverse plane shows high signal intensity between several bowel segments (arrow).

B. ADC map shows ADC restriction in the whole area (ADC value ranging from = 1.085 to 1.562 x 10^{-3} mm^2/s).

C. T1-weighted MRE after intravenous administration of a gadolinium chelate in the transverse plane shows the complex enteric fistula (arrow), which was confirmed by surgical resection.

Figure 6. 34-year-old man with active Crohn disease.

A. Diffusion-weighted MR image (b value=1000) in the transverse plane shows high signal intensity areas besides an ileal inflammatory segment (arrow) and another high signal intensity mass containing signal void suggesting gas (arrowhead).

B. ADC map shows an ADC restriction in both areas, but an even lower ADC value in the area containing gas (ADC value = 1.100 versus 1.544 x 10^{-3} mm^2/s).

C. Abdominal CT after intravenous administration of iodinated contrast material confirms the presence of an inflammatory ileoduodenal fistula (arrow) and the presence of an abscess in the right flank where ADC value was the lower (arrowhead).

Figure 7. 53-year-old woman with treated Crohn disease since thirty years.

A. T2-weighted HASTE (half-Fourier acquisition single-shot turbo spin-echo) MR image shows hypointense mass into the lumen of right colonic angle (arrow).

B. Diffusion-weighted MR image (b value=1000) in the transverse plane shows high signal intensity of the mass (arrow).

C. ADC map shows ADC restriction in the mass (ADC value = 0.762×10^{-3} mm^2/s), which is suggestive of tumor lesion.