Prediction of Maintained Mucosal Healing in Patients with Crohn's Disease under Treatment with Infliximab Using Diffusion-Weighted Magnetic Resonance Imaging

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Key Words

Magnetic resonance imaging · Infliximab · Crohn's disease · Diffusion-weighted imaging

Abstract

Background: Maintenance of mucosal healing may lead to a better outcome in patients with Crohn's disease (CD). Magnetic resonance diffusion-weighted imaging (MR-DWI) scans 1 year after infliximab (IFX) induction therapy were assessed as predictors of maintained response, or remission, through 3 years of treatment in patients with CD. **Summary:** MR-DWI and endoscopy data were prospectively collected throughout IFX treatment. Altogether, 86 lesions from 13 patients given IFX as induction (weeks 0, 2 and 6) and maintenance (5 mg/kg every 8 weeks beginning at week 14) therapy were analyzed with MR-DWI for 0.5–1.5 years from the starting point. Mucosal findings were confirmed by endoscopy at 1 and 3 years (gold standard). Of the 86 lesions, 65 were graded '0' and 21 were graded '1' based on their hyperintensity (HI; or lack thereof) on MR-DWI. Two years after the first evaluation, 7 of 15 false-negative lesions had turned positive based on colonoscopy findings, and 60 of 62 true-negative lesions had not. Thus, 0.03% of those predicted to remain in remission had relapsed (negative predictive value 0.9677,

$p < 0.0001$). MR-DWI-HI at 1 year coincided with the presence of endoscopic inflammation, with sensitivity of 66.67%, specificity of 80.52%, and an area under the curve (AUC) value of 0.7359 (0.5479–0.9240, $p = 0.0211$). The AUC value of MR-DWI-HI at 3 years was 0.8402 (0.7460–0.9343, $p = 0.001$) with sensitivity of 94.12% and specificity of 73.91%. **Key Message:** A definition of the response on the basis of MR-DWI-HI might be helpful for optimizing treatment for patients with CD under treatment with IFX.

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Introduction

Intestinal complications of Crohn's disease (CD) are progressive in the presence of chronic persistent inflammation. Consequently, the operative rate is estimated to be 80% at 20 years after onset of the disease [1–3]. After surgery, 40% of patients are symptomatic within 4 years [4], and many patients ($\approx 30\%$) experience disease recurrence and require a second operation within 10 years [5]. In an attempt to avoid multiple operations, several trials

H.S. and Y.I. contributed equally to this work.

Table 1. Patient characteristics

Case No.	Age, years	Sex	Disease duration, years	Disease location	Disease behavior	Medication before inclusion	Surgery before inclusion	CDAI from the start point			CRP from the start point, mg/dl		
								before	1 year	3 years	before	1 year	3 years
1	44	F	20.4	Ileocolonic	Inflammatory	5ASA, GC, MNZ	Seton drainage	236	124	86	0.1	0.1	0.01
2	34	M	16.8	Ileocolonic	Stenotic	5ASA, AZA, GC, ED	Ileocecal resection, seton drainage	314	335	139	0.1	1.0	1.1
3	38	M	15.3	Ileocolonic	Inflammatory	5ASA, 6MP, GC	–	119	51	51	3.4	0.29	0.44
4	37	M	14.2	Colonic	Stenotic	5ASA	Seton drainage	290	80	59	1.3	0.6	0.02
5	26	F	8.9	Ileocolonic	Stenotic	5ASA, 6MP, GC, ED	Seton drainage	231	296	166	7.1	2.5	0.14
6	26	F	4.2	Ileocolonic	Inflammatory	5ASA	–	176	62	164	0.9	0.1	0.32
7	26	M	7.8	Ileocolonic	Inflammatory	5ASA, GC	–	149	70	73	3.5	0.03	0.02
8	25	M	7.7	Ileocolonic	Inflammatory	5ASA, GC, MNZ	–	287	25	11	2.1	0.05	0.95
9	23	M	6.9	Ileocolonic	Stenotic	5ASA, 6MP, ED	–	98	83	56	0.4	0.06	0.411
10	34	M	7.6	Ileocolonic	Penetrating	5ASA, ED	Ileocecal resection	158	100	134	0.4	0.11	0.79
11	12	F	4.8	Ileocolonic	Inflammatory	5ASA, ED	–	138	90	67	0.1	0.1	0.1
12	36	M	10.3	Ileocolonic	Stenotic	5ASA, GC	Left hemicolectomy, partial resection of the ileum	499	184	243	1.9	0.8	1.0
13	26	M	12.9	Colonic	Inflammatory	5ASA, MNZ	Left hemicolectomy	235	169	185	0.7	1.6	4.96

CDAI = CD activity index; 5ASA = 5-aminosalicylate; GC = glucocorticoids; MNZ = metronidazole; 6MP = 6-mercaptopurine; AZA = azathioprine; ED = elemental diet.

of nonsurgical treatment for stenosis have been performed. Immunosuppressant [6] and biological [7, 8] therapies might reduce the need for surgery but must be given early in disease progression, before the development of irreversible anatomical lesions [9]. Infliximab (IFX) treatment seems to be effective for preventing the development of new anastomotic lesions defined by endoscopic findings at 1 year [10]. These recent experiences and clinical trials have substantiated that the decreased disease activity achieved by the induction of biological agents is likely to achieve a better outcome.

Despite recent developments in diagnostic imaging, the issue of defining minimal activity in CD patients remains confusing. Hence, there is some concern that the disease is underreported, especially during its early course, which might result in missing critical windows within which to identify ways to better treat the individual patient. Because CD lesions are progressive and are characterized as transmural inflammation, anticipation of the lesion before it becomes irreversible and detecting it in areas not limited to changes in the mucosal surface might shed light on the therapeutic strategy.

In this respect, magnetic resonance diffusion-weighted imaging (MR-DWI) well characterizes the presence of active CD lesions. Its sensitivity is 58.33%, and its specificity is 84.48% [11].

We evaluated whether prospective use of MR-DWI and endoscopy would predict mucosal healing. For this

purpose, we addressed each segment of the colon and (neo) terminal ileum, assessing them with both MR-DWI and endoscopy. We showed that radiologically the lack of MR-DWI hyperintensity (HI) after treatment would predict the maintenance of (continued) mucosal healing for the next 2 years.

Patients and Methods

This study was performed during the period 2009–2012 at Hiroaki University Hospital. Institutional review board approval was obtained, and informed consent was waived.

CD was diagnosed according to the criteria provided by the Investigation and Research Committee for Intractable Inflammatory Bowel Disease organized by the Japanese Ministry of Public Welfare, as described previously [12, 13]. The patients' medical histories, including abdominal and extra-abdominal complaints, associated disease, CD behavior and the CD activity index, location of CD lesions, duration of the disease, past surgery, endoscopic dilatation, and current and previous medical treatment, were obtained.

Inclusion Criteria

A total of 13 CD patients were included in the study. Their baseline demographic and clinical characteristics are shown in table 1.

Exclusion Criteria

Exclusion criteria included pregnancy and general contraindications to IFX or radiology-based examinations. Patients with abscesses, ileoileal fistulas or ileocolonic fistulas were also excluded.

Table 2. Sensitivity, specificity, positive and negative predictive values of MR-DWI-HI for endoscopic activity after 1 year of IFX treatment

Data analyzed	Endoscopic activity positive	Endoscopic activity negative	Total
MR-DWI-HI positive	6	15	21
MR-DWI-HI negative	3	62	65
Total	9	77	86
Sensitivity (95% CI)	0.6667 (0.2993–0.9251)		
Specificity (95% CI)	0.8052 (0.6991–0.8867)		
PPV (95% CI)	0.2857 (0.1128–0.5218)		
NPV (95% CI)	0.9538 (0.8710–0.9904)		
Likelihood ratio	3.422		

Fisher's exact test was used to evaluate the contingency analysis for MR-DWI-HI and the endoscopic findings. PPV = Positive predictive value; NPV = negative predictive value.

Treatment

Patients were scheduled to receive infusions of IFX (5 mg/kg) at 0, 2 and 6 weeks (induction phase), followed by 5 mg/kg every 8 weeks thereafter (maintenance phase). Continued use of drugs already being taken, such as salicylates and/or immunomodulators, was permitted during the intervals between evaluations.

Evaluation

The MRI examinations were performed as described previously [11]. Briefly, MRI scans were obtained using a 1.5-T GE Signa HDXt scanner (GE Healthcare, Waukesha, Wis., USA) with phased-array body coils. The protocol comprised a 2-dimensional single-shot fast spin echo short echo time sequence in the axial and coronal planes, a 2-dimensional steady-state free precession with fat saturation in the coronal plane, and a diffusion-weighted sequence in the axial plane. The diffusion-weighted sequence employed a diffusion factor b fixed at 800 s/mm² and provided 2 sets of images, 1 for the expected b value and another for $b = 0$. The acquisition was performed in the axial plane using a field of view ranging from 35 to 40 cm and a 7-mm slice thickness with a 1.4-mm gap in respiratory triggering. Two stations were needed to cover the abdomen and the pelvis. The duration of the entire examination was less than 20 min.

Seven segments were identified for MR-DWI colonography analysis: rectum, sigmoid, left colon, transverse colon, ascending colon, cecum and ileum. Partially resected segments were not included in the study. During the maintenance phase, the presence and absence of radiological signs of MR-DWI-HI in a given segment were rated '1' and '0', respectively. The mucosal lesions in a given segment were confirmed on endoscopy (CF-SV-L; Olympus Medical Systems, Tokyo, Japan) as the diagnostic gold standard.

A total of 86 lesions from 13 patients were assessed by MR-DWI and endoscopy before each scheduled IFX infusion. These examinations were performed 1 and 3 years after the starting point of the IFX therapy. The median interval between MR-DWI and endoscopy was 3 months (95% confidence interval, CI, 2–6) at 1

Table 3. Negative predictive value of MR-DWI-HI at 1 year for endoscopic remission over the next 2 years

Data analyzed	Endoscopic relapse (3 years)	Endoscopic remission (3 years)	Total
MR-DWI-HI positive (1 year)	7	8	15
MR-DWI-HI negative (1 year)	2	60	62
Total	9	68	77
Sensitivity (95% CI)	0.7778 (0.3999–0.9719)		
Specificity (95% CI)	0.8824 (0.7813–0.9478)		
PPV (95% CI)	0.4667 (0.2127–0.7341)		
NPV (95% CI)	0.9677 (0.8883–0.9961)		
Likelihood ratio	6.611		

Fisher's exact test was used to evaluate the contingency analysis for MR-DWI-HI and the endoscopic findings. PPV = Positive predictive value; NPV = negative predictive value.

year, and 3 months (95% CI 2–4) at 3 years. The C-reactive protein (CRP) level was evaluated just before each IFX infusion. The data were collected prospectively.

Statistical Analysis

A p value <0.05 was considered statistically significant in all analyses. Probability values and confidence intervals were calculated at the 95% level. Fisher's exact test was used to evaluate the contingency analysis for MR-DWI-HI and the endoscopic findings.

Receiver operating characteristic (ROC) analysis was performed to compare the diagnostic performance of the parameters. The area under the ROC curve (AUC) was used to choose a threshold value for each test parameter by maximizing the combination of sensitivity and specificity.

Results

Lesion Detection, Negative Predictive Value, ROC Analysis

Of the 86 lesions evaluated in this study, 65 were graded '0' and 21 were graded '1' based on MR-DWI-HI. Among those lesions, 6 of 21 positive lesions were also positive on colonoscopy (true positive), but 15 lesions were not (false positive; table 2). Of the 65 MR-DWI-HI-negative lesions, 3 were positive on colonoscopy (false negative; table 2). Thus, MR-DWI-HI predicted the presence of synergistic mucosal changes on colonoscopy with a sensitivity of 80.52% and specificity of 66.67% ($p = 0.0018$; table 2).

Fig. 1. Effect of IFX on maintaining mucosal healing as evaluated with MR-DWI and endoscopy. MR-DWI shows hyperintensity in the bowel wall before IFX therapy (a) and its virtual disappearance after 1 (b) and 3 (c) years of treatment. Coexistence of longitudinal ulcers on the transverse colon (d) indicates active inflammation before IFX therapy. Coincident with MR-DWI, endoscopic findings at 1 (e) and 3 (f) years of treatment show no active lesions, suggesting the usefulness of MR-DWI hyperintensity as a marker for prognosticating outcome.

Two years after the first evaluation, 7 of the 15 false-positive lesions had turned true positive on colonoscopy, and 60 of the 62 true-negative lesions had not (i.e. case 7; fig. 1; table 3). Thus, 0.03% of those predicted to remain in remission had relapsed (negative predictive value 0.9677, $p < 0.0001$), and 46.7% of those predicted to relapse did so (table 3).

MR-DWI-HI at 1 year was able to predict the presence of endoscopic inflammation with a sensitivity of 66.67%, specificity of 80.52% and AUC value of 0.7359 (95% CI 0.5479–0.9240, $p = 0.0211$; fig. 2). Also, MR-DWI-HI at 3 years suggested endoscopic inflammation with sensitivity of 94.12%, specificity of 73.91%, and AUC value of 0.8402 (95% CI 0.7460–0.9343, $p = 0.001$; fig. 2).

Discussion

Using endoscopy as the reference standard, we evaluated the accuracy of MR-DWI for assessing disease extent and severity in 86 CD lesions under IFX treatment. The study demonstrated that MR-DWI-HI negatively predicted the development of endoscopic remission over the following 2 years. MR-DWI is sensitive to molecular diffusion based on the Brownian motion of the spins in biological tissue. It derives its image contrast from differences in the motion of water molecules between tissues [14]. The feasibility of using MR-DWI in CD patients has been assessed, and it is now being explored for evaluating

Fig. 2. ROC analysis for the coexistence of inflammation as defined by MRI and endoscopy. The ROC curve analysis of MR-DWI-HI prediction for the presence of endoscopic inflammation was evaluated 1 and 3 years from the starting point of IFX treatment.

the disease. In addition to being able to estimate the accuracy of MR-DWI for detecting mucosal lesions, we hypothesized that MR-DWI-HI negativity might be associated with continuing response to treatment.

Our major concern was the underreporting of disease activity, especially during the early course of CD. It might lead to missing critical windows wherein we could identify site-specific markers, rather than general biomarkers,

that would contribute to tailoring treatment strategies for the individual patient. In this respect, our study revealed that 0.03% of those predicted to remain in remission do, in fact, relapse. Also, 46.7% of those predicted to relapse become truly positive for CD over the following 2 years (table 3). As a result, MR-DWI at 3 years reflected endoscopic findings with more accuracy using the AUC value (fig. 2). Thus, our study demonstrated the usefulness of MR-DWI for identifying treatment markers.

Aside from imaging, many laboratory data are available regarding predictors of response for short- and long-term clinical benefit during therapy with biological agents [15–17]. Survival analysis demonstrated that patients in whom CRP levels normalized early (after 4 weeks of a 10-week period) had better long-term outcomes. The CRP level at the time of endoscopy significantly correlated with the degree of mucosal healing [16, 17]. The positive predictive value of 51.8% for continuing remission at 54 weeks means that a clinician could predict a 1-year response in a patient. It is notable that the positive predictive values for the 3-month CRP level for predicting a response at 1 year are similar to those found previously [18]. Therefore, a negative CRP test was identified as a predictor for sustained clinical benefit for 1 year, but 25% of those predicted to remain in remission did relapse, and only 22% of those predicted to relapse did so [19]. The present study defined that, at 1 year, negative MR-DWI-HI might correlate with continuing remission during 3 years of IFX treatment (i.e. case 7; fig. 1). This potential for anticipating endoscopic recurrence was equivalent to that of CRP, even in our study. The additional beneficial potential of MR-DWI was the identification of inflamma-

tory lesions noninvasively. Taken together, MR-DWI-HI would be useful in CRP-positive cases to define the site of inflammation and recurrence before the patient undergoes colonoscopy.

Our study included only a small number of patients from a single center, but the data were collected prospectively with 3-year follow-up periods. Further long-term study is needed to clarify the potential of MRI for identifying treatment markers on a large scale. Concomitant with recent advances in new biologic therapy [2], such a study might define true indications of modification under treatment with biological agents for CD.

Conclusion

A definition of the response to treatment based on MR-DWI findings might be helpful for optimizing the indications for endoscopy and further treatment of CD patients.

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Disclosure Statement

The study was not supported by any pharmaceutical company. The authors have no conflicts of interests to declare.

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