illumination intensity in the blue light range mainly absorbed by hemoglobin. In the near future, CE might be installed in diagnostic and therapeutic functions, such as in magnifying endoscopy systems, targeted biopsy forceps, and drug delivery systems.

## CONFLICT OF INTERESTS

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EXPERT REVIEWS

# Magnetic resonance enterography of Crohn's disease

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Magnetic resonance enterography (MRE) has been reported to be a useful modality for the evaluation of luminal inflammation and extraintestinal complications in Crohn's disease (CD). A recent study indicated that the diagnostic ability of MRE was comparable to the diagnostic ability of other devices, such as ileocolonoscopy. MRE can be performed repeatedly because there is no radiation exposure. Therefore, MRE is useful as a method of follow-up for younger patients with established CD. It is useful for evaluating the efficacy of medical treatments, such as biologics. MRE can detect small intestinal lesions even if the endoscope does not pass through the stenosis. The concerns of availability of expertise and the costs associated with MRE should be addressed so MRE can be widely used for CD patients in the near future.

**KEYWORDS:** Crohn's disease • diagnostic accuracy • endoscopic remission • enteroscopy • magnetic resonance enterography

Crohn's disease (CD) is an immune-mediated disease with abdominal symptoms that include diarrhea, abdominal pain and perianal fistulas. Inflammation in CD involves the entire gastrointestinal tract, especially the small intestine. Ileocolonoscopy is useful for detecting inflammation in the colon and the terminal ileum; however, this technique is unable to assess the mid-small intestine. More recently, novel technologies to enable inflammatory bowel disease diagnosis have been developed, such as capsule endoscopy (CE) and balloon-assisted enteroscopy (BAE). These technologies have been established as useful modalities for the diagnosis and assessment of disease extent and severity. However, CD lesions are typically transmural and lead to progressive damage and complications, such as fistulas and abscesses. Thus, cross-sectional imaging is critical for the assessment of CD lesions. Computed tomographic and magnetic resonance enterography (CTE and MRE) have been reported to be useful modalities for the evaluation of luminal inflammation and extraintestinal complications in CD. MRE can be performed without radiation exposure, making it the preferred imaging technique for the evaluation of CD in children and adolescents. In this article, we have reviewed recent trends and topics regarding MRE for patients with CD.

## MRE protocol

In reviewing the diagnostic accuracy of MRE, we should note the heterogeneity of MR imaging protocols, such as the use of different MRI magnets (1.5 Tesla [1.5T] or 3 Tesla [3T]), enteral contrasts and preparations for bowel distention. The diagnostic accuracy might differ according to the protocol of MRE. The 3T magnet increases the signal-to-noise ratio and reduces the time of image acquisition compared with the 1.5T magnet [1]. The 3T MRI is superior to 1.5T for detecting ulcers, whereas 3T is as accurate as 1.5T in detecting bowel wall thickness, enhancement and fistulas.

MRE requires the administration of a large amount of contrast medium orally. Typically, transit to the right colon has been observed within at least 40–60 min [2]. A recent review stated that MRE performed 40 min after the ingestion of oral contrast material is practical for patients' compliance and for providing effective MRE imaging [3,4]. In the authors' institution, patients are typically ordered to ingest 1500 ml of polyethylene glycol within 60 min prior to scanning.

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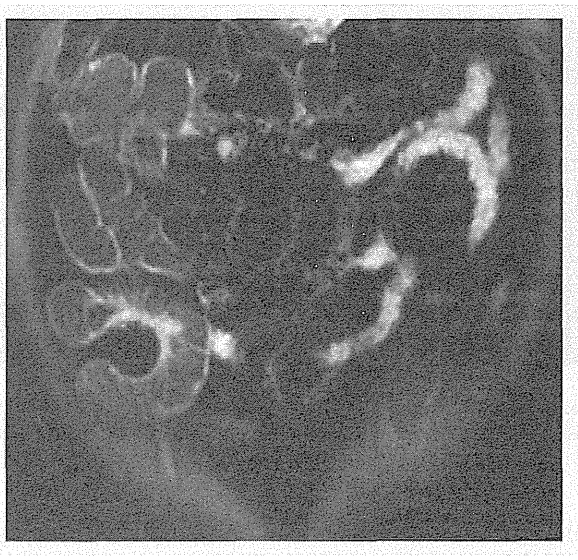

**Figure 1. Coronal true imaging with T1-weighted images revealed that mural enhancement is observed in the proximal ileum after injection of gadolinium.**

Bowel distention with MR enteroclysis is superior to distention with MRE in most studies [5–8]. However, the use of MRE is associated with reduced abdominal discomfort and nausea compared with MR enteroclysis. Patients are exposed to radiation during the placement of the naso-jejunal catheter when MR enteroclysis is performed [9]. Furthermore, a prospective randomized study showed that the diagnostic accuracy of MR enterography was comparable to the accuracy of MR enteroclysis [6,10]. Thus, MRE could be used to follow-up patients without proximal small intestinal lesions of CD [3].

Rectal contrast might increase the diagnostic accuracy in detecting lesions in the rectum and distal colon; however, rectal contrast causes more patient discomfort than MRE procedures done without using rectal contrast. For patients undergoing colonoscopy, the requirement for colonic distention during MRE is reduced [11]. Intravenous gadolinium chelate contrast agent is used to differentiate between active and inactive disease. Gadolinium chelate given to patients (approximately 60 s) prior to 3D T1-weighted image with fat suppression was acquired in the authors' institution.

The main limitation of MRE is bowel motion, which could potentially obscure relevant findings. Thus, anti-peristaltic agents such as scopolamine butylbromide or glucagon are used to minimize bowel motion just before MRE is performed. A recent study indicated that the quality of the MRE without anti-peristaltic agents was judged to be inferior to CTE, although the diagnostic results were equivalent [12]. The authors typically used anti-peristaltic agents for MRE to obtain high-quality imaging except in patients with contraindications for these agents.

## Findings of MRE

The MRE findings for CD include wall thickness, wall hypersignal, extravascularity, swelling of lymph nodes, ulcerations, fistulas, edema, strictures and extraintestinal complications. In patients with active intestinal inflammation, mural enhancement is observed after the injection of gadolinium (Figure 1). Mural hyperenhancement is related to active inflammation and is the most sensitive finding of active CD lesions [3,13,14]. Wall thickness is also frequently observed; however, wall thickness without high intensity remains in responders after medical treatment in some cases (Figure 2).

Intestinal strictures can be detected on MRE. MRE enables the assessment of proximal small intestinal lesions beyond severe strictures even if the endoscope does not pass through the stenosis (Figure 3). This is the advantage of MRE for the assessment of intestinal lesions in patients with CD, compared with ileocolonoscopy and BAE. Moreover, while BAE has been available for evaluating small intestinal lesions of CD, it is hard to observe the mucosa along the entire length of the small intestine using either the oral or anal approach in one session of BAE. Intestinal strictures with marked intestinal distension suggest moderate-to-severe strictures, resulting in indications for surgery if the patients have any abdominal symptoms. Strictures with hypoenhancement are typically observed in fibrotic strictures, whereas inflammatory strictures have wall thickness with mural hyperenhancement and edema [15]. However, it is not easy to distinguish fibrotic strictures from inflammatory strictures on MRE in some cases, because the strictures are usually constructed of both fibrotic and inflammatory lesions.

Fistulas could be detected on MRE (Figure 4), although early fistulas might be difficult to detect because of the lower spatial resolution of MRE.

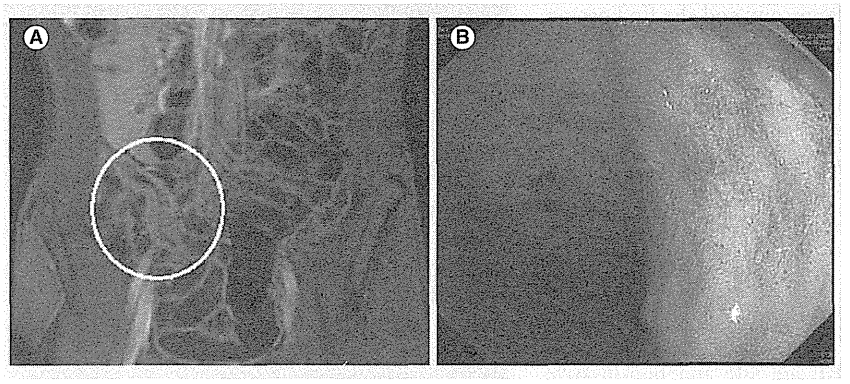


**Figure 2. Comparison between ileal lesion on MRE and endoscopic finding.**
**(A)** Increased wall thickness was observed at the terminal ileum. However, mural and transmural enhancement is minimal. **(B)** The endoscopic findings revealed no inflammation at same area.

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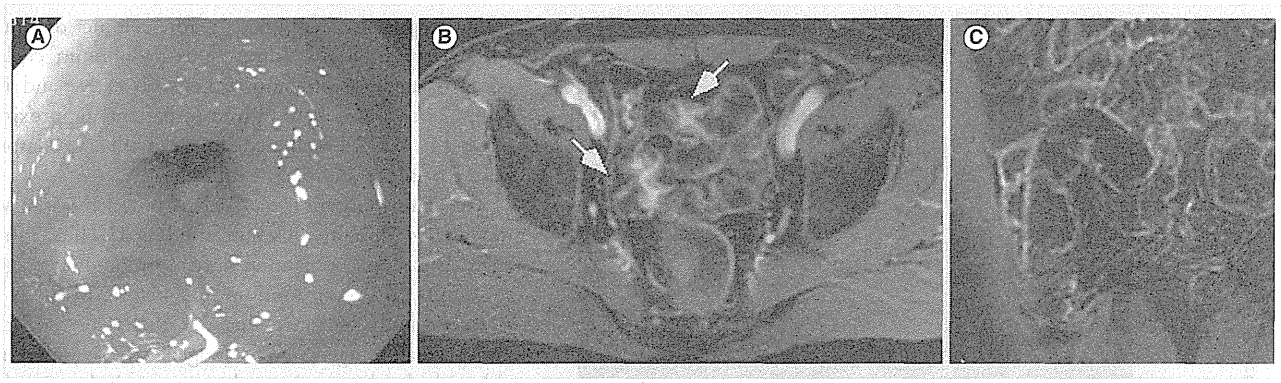


**Figure 3. Ileal stricture in patients with Crohn's disease. (A)** A moderate stricture was found at the proximal ileum, and balloon-assisted enteroscopy did not pass through the stenosis. **(B)** Ileal lesions with mural enhancement and **(C)** severe strictures with bowel distention were observed on the T1-weighted image.

Extraintestinal complications, such as abscesses, could also be detected on MRE. It is important to assess fistulas and abscesses because these lesions are frequently associated with medical treatment failure, including secondary loss of responsiveness for anti-TNF-α agents [16].

MRE could be used as an observer-independent diagnostic device for the evaluation of CD lesions, although there have been few studies to assess the interobserver agreement in MRE for diagnostic assessments in patients with CD. A recent study indicated that high interobserver agreements for mural inflammation and lymphadenopathy were found in patients with active CD lesions [17]. Another study indicated that wall thickness, the presence of edema, enhancement patterns and length of the disease in each segment showed good interobserver variability between all investigators [18].

## The diagnostic accuracy of MRE

Previous reports regarding the diagnostic accuracy of MRE are summarized in Table 1 [12,14,19–28]. MRE has been shown to have excellent sensitivity and specificity for CD lesions. In most studies, the diagnostic accuracies of MRE were assessed by comparing the findings on ileocolonoscopy and the findings on MRE. A recent systematic review showed that the sensitivity and specificity of MRE for the diagnosis of suspected CD was 78 and 85%, respectively [29]. For the extension of CD lesions, the sensitivity and specificity of MRE for small bowel lesions were 74 and 91%, respectively [29]. The diagnostic accuracy for the extension and disease severity of MRE was comparable to the accuracy of CTE [20–23,25,27,28]. No significant differences were observed between MRE and CTE in detecting fistulas [30]. MRE might be preferred to CTE to assess the location and severity of the disease because of the reduced radiation exposure for young patients.

Ultrasonography (US) and MRE are safe and non-invasive devices; however, US is less expensive compared with MRE and could be performed at the bedside. Recently, a diagnostic study for patients with suspected CD was performed to compare the accuracy of MRE and US [25]. For the detection of small intestinal lesions of CD, the sensitivity, specificity, positive predictive value and negative predictive value for MRE and US were high (94–97%). However, US was less accurate than MRE in defining CD extension. A recent systematic review indicated that US, computed tomography and MRE have high accuracy for detecting fistulas, abscesses and strictures, whereas US has high false positives for abscesses [29]; MRE is preferred to US for deep-seated fistulas [31].

The advantages of CE and BAE are that they can directly observe mucosal inflammation, whereas MRE is particularly useful for detecting transmural inflammation, stenosis and extraintestinal lesions, including abscesses and fistulas [32]. MRE is useful when evaluating small and large intestinal lesions even in cases with severe strictures, where full evaluation of the small

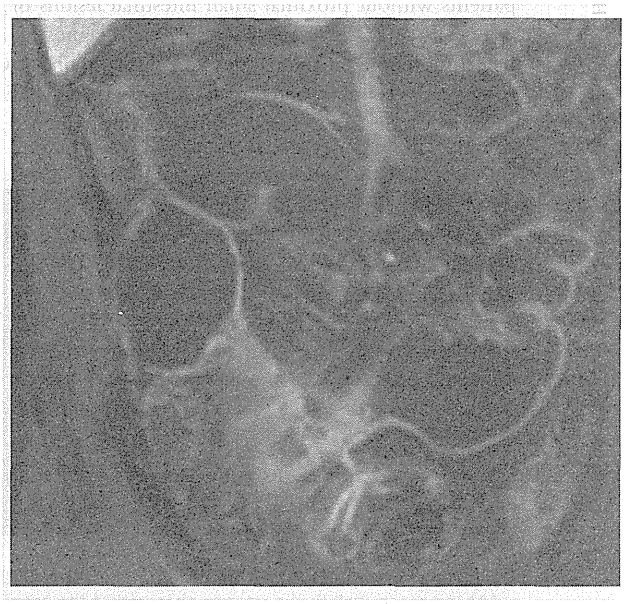

**Figure 4. Coronal true imaging with T1-weighted images revealed an ileoileal fistula with inflammation.**




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**Table 1. Summary of the accuracy of magnetic resonance enterography for Crohn's disease lesions by comparing the findings of conventional diagnostic devices.**

| Study (year) | Diagnostic devices as gold standard | Number of cases | Location of assessment on MRE | Accuracy of MRE for CD lesions (%) | Ref. |
|---|---|---|---|---|---|
| Schreyer *et al.* (2005) | Ileocolonoscopy | 30 | Colon, TI | Sen 55, Spe 98 | [19] |
| Lee *et al.* (2009) | Ileocolonoscopy | 30 | TI | Sen 83, Spe 100 | [20] |
| Rimola *et al.* (2009) | Ileocolonoscopy | 50 | Colon, TI | Sen 81, Spe 89 | [14] |
| Siddiki *et al.* (2009) | Ileocolonoscopy | 44 | TI | Sen 91, Spe 67 | [21] |
| Fiorino *et al.* (2011) | Ileocolonoscopy | 44 | TI, colon | For TI<br>Sen 81, Spe 93 (MRE)<br>Sen 81Spe 91 (CTE) | [22] |
| Grand *et al.* (2012) | Ileocolonoscopy | 310 | TI, colon | Sen 85, Spe 80 | [12] |
| Grand *et al.* (2012) | Histological findings | 310 | TI | Sen 87, Spe 88 | [12] |
| Jensen *et al.* (2011) | Ileocolonoscopy/surgery | 50 | SI | Sen 74, Spe 80 (MRE)<br>Sen 83, Spe 70 (CTE) | [23] |
| Hyun *et al.* (2011) | Ileocolonoscopy/BAE | 30 | SI, colon | For SI lesions<br>Sen 62, Spe 93<br>For colonic lesions<br>Sen 86, Spe 95 | [24] |
| Castiglione *et al.* (2013) | Ileocolonoscopy | 249 | SI | Sen 96, Spe 94 (MRE)<br>Sen 94, Spe 97<br>(bowel sonography) | [25] |
| Takenaka *et al.* (2014) | BAE | 100 | SI | Ulcerative lesions:<br>Sen 82, Spe 88<br>Major stricture<br>Sen 59, Spe 90 | [26] |
| Quencer *et al.* (2013) | Histological findings | 23 | SI | Sen 88, Spe 79 (MRE)<br>Sen 100, Spe 62 (CTE) | [27] |
| Dillman *et al.* (2011) | Histological findings | 22 | SI, colon | Sen 66, Spe 90 | [28] |

BAE: Balloon-assisted enteroscopy; CTE: Computed tomographic enterography; MRE: Magnetic resonance enterography; SI: Small intestine; Sen: Sensitivity; Spe: Specificity; TI: Terminal ileum.

bowel would be virtually impossible to achieve using CE or even BAE. Thus, these technologies appear to complement each other. The diagnostic accuracy of CE and MRE has been compared in the recent studies [33–38]. Recent meta-analysis demonstrated that the diagnostic yield for CE and MRE were comparable [33]. Albert *et al.* investigated the detection rate of small intestinal lesions on CE, MRI and double-contrast fluoroscopy in patients with suspected CD [34]. CE was not accomplished in approximately one-third of patients (14/41) due to bowel strictures in this study. CE was slightly more sensitive than MRI, whereas MRE detected inflammatory conglomerates and enteric fistulae in five cases [34]. In another study, CE was found to be superior to MRE in detecting mucosal lesions in patients with CD; however, MRE could detect severe inflammatory lesions within the bowel wall [33]. These results suggested that CE is capable of detecting mucosal lesions that may be missed by MRE, while MRE is helpful in identifying transmural CD and extraluminal lesions.

Takenaka *et al.* recently compared the diagnostic accuracy of MRE with BAE [26]. In this prospective study, MRE and single BAE were performed in 100 patients. Ulcerative lesions, mucosal lesions and intestinal damage were evaluated. MRE detected ulcerative lesions in the small intestine with a sensitivity of 82%. The specificity for ulcerative lesions and mucosal lesions were 88 and 95%, respectively. MRE detected major stenosis (stricture that the scope could not pass) with a sensitivity of 59% and a specificity of 90%, and strictures were detected with a sensitivity of 41% and a specificity of 94%. MRE is useful for detecting active lesions in the small intestine. However, MR imaging is less sensitive for detecting strictures, which single BAE is able to detect. BAE is preferred for identifying intestinal damage.

When the lesions identified by MRE were compared with the surgical findings in patients with CD, MRE could identify small bowel CD lesions, such as fistulas and abscesses; the results showed that 27 of 30 ileoenteric or ileocolonic fistulas

and 8 of 9 abscesses were detected using MRE in patients who required surgery [39]. Discrete proximal small intestinal lesions might not be detected in all cases because of insufficient bowel distension at the proximal small bowel. Another study using surgical pathological inflammatory grading was significantly associated with MRI findings such as the wall thickness, degree of wall enhancement on delayed phase, pattern of enhancement on both parenchymatous, T2 relative hypersignal wall, blurred wall enhancement, comb sign, fistula, and abscess [40]. The contrast enhancement ratio of abnormal distal ileal segments with inflammation was higher than that with fibrosis only [39], suggesting that strictures with inflammation could be distinguished from fibrotic strictures. However, these studies were not confirmed by another study, which indicated that fibrosis was not associated with wall thickness or with T2 hypersignal [41]. Another study showed that fibrotic lesions alone were also associated with wall thickness, T2 wall hypersignal, comb sign, fistula and abscess [40]. Inflammation with fibrotic changes is frequently observed at the strictures and it is not easy to distinguish inflammatory strictures from fibrotic strictures; recent consensus guidelines from the European Crohn's and Colitis Organisation stated that no validated criteria have been established to determine the fibrotic lesions on MRE [31].

For pediatric CD, MRE is more useful in detecting small intestinal lesions than it is in adolescents because MRE is less complicated than colonoscopy and could be performed without radiation exposure. In some cases of CD, frequent assessment of disease severity and extension of the disease is necessary; therefore, examinations without radiation exposure are important especially for children. A recent systematic review indicated that the pooled sensitivity and specificity for MRE detection at the terminal ileum of CD were 84 and 97%, respectively, in pediatric CD patients [42]. In all studies, ileocolonoscopy was used as the reference test. The diagnostic accuracy for barium enteroclysis was assessed and compared with that of colonoscopy in 3 of the 11 studies in this systematic review. The sensitivity and specificity (72 and 73%) for barium enteroclysis was lower than that for MRE in pediatric CD patients [43–45]. Even if a patient is younger than 10 years old, MRE could be performed without sedation [46]. For children, it is important to perform the MRE procedure in a short time. To reduce the number of MRE sequences, the performance of contrast-enhanced T1-weighted MR alone in the evaluation of CD lesions was compared with the performance of all MRE imaging sequences [47]. This study indicated that the sensitivity, specificity and diagnostic accuracy for detecting active inflammation using contrast-enhanced T1-weighted MR alone were 83, 87 and 85%, which were inferior compared with using all MRE sequences. A higher false-positive rate of abscesses was observed from contrast-enhanced imaging alone, and the absence of abscesses were confirmed when non-fat-suppressed Half fourier Acquision Single shot Turbo spin Echo (HASTE) was conducted in addition to the contrast-enhanced imaging. It is important to reduce the time of the MRE procedure (reduce the number of MR sequences), especially for pediatric patients. However, non-fat-suppressed HASTE imaging might be needed to maintain diagnostic accuracy of MRE in patients with CD.

## Comparison of MRE findings with biomarkers

It is important to assess the disease activity of CD for appropriate management of the disease. Clinical symptoms and clinical activity indexes such as the Crohn's disease activity index and Harvey–Bradshaw index are important markers for evaluating the severity of CD. However, these indexes are subjective and are affected by psychological factors. It is necessary to assess biological markers, such as C-reactive protein, white blood cell counts and fecal calprotectin; these biological markers might be elevated in infectious diseases and other chronic inflammatory diseases. MRE enables the simultaneous assessment of the extension and severity of CD. The findings on MRE are closely correlated to clinical severity and serological markers with the previously described reference standards. The wall thickness, T2 signal intensity, T1 enhancement and presence of lymph nodes on MRE are related to Crohn's disease activity index, endoscopic severity (Crohn's disease endoscopic index of severity [CDEIS], simple endoscopic score for Crohn's disease) and histological examinations from biopsy or surgical specimens [48] and to Inflammatory Bowel Disease Questionnaire. MRE could also assess the Montreal classification-based disease behavior in patients with CD [49]. However, assessments using imaging such as endoscopy and CT/MR enterography in addition to clinical symptoms and biological markers are necessary for the management of CD to guide therapeutic decisions.

## Assessment of disease severity using scores on MRE

Many investigators have scored disease severity on MRE in patients with CD. More recently, the magnetic resonance index of activity score (MaRIA) was developed by comparing the MRE findings with the CDEIS [14]. After assessment with logistic regression, MRE findings, such as the wall thickness, relative contrast enhancement, edema and ulceration, were selected as independent factors for the prediction of endoscopic severity. The MaRIA score was constructed using these four factors. The MaRIA score had a significant correlation with the CDEIS, C-reactive protein and clinical activity score [14,50]. Macarini *et al.* developed the MRE score by assessing disease severity in 100 patients with CD [51]. The MRE score is composed of multiple MRE parameters, such as wall thickness, wall enhancement, enhancement pattern (transmural, layer), fibrofatty proliferation and local complications [45]. The MRE score was correlated to the Crohn's disease activity index and Inflammatory Bowel Disease Questionnaire. Steward *et al.* developed the Crohn's Disease Activity score, which was derived with reference standards of histological scores in surgical specimens [52]. They demonstrated that the mural thickness and T2 signal were the best predictive factors for histological severity.

Using the scoring system on MRE, disease severity and responsiveness for medical treatments could be objectively assessed (Table 2). Ordás *et al.* demonstrated a significant decrease in the mean MaRIA score at 12 weeks after treatment with anti-TNF-α


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**Table 2. Responsiveness of MRI lesions or indexes to medical treatment.**

| Study (year) | Medical treatment | Assessment of activity index for MRE | Change of MRE parameter over time during medical treatment | Ref. |
|---|---|---|---|---|
| Ordás *et al.* (2014) | Corticosteroids (n = 14) Adalimumab (n = 34) | MaRIA score (wall thickness, RCE, edema, ulcers) | Mean MaRIA score (baseline → at 12 weeks) Endoscopic healed 18.9 → 8.7 Non-healed 22.1 → 20.8 | [53] |
| Assche *et al.* (2013) | Infliximab (n = 20) | MICD (transmural inflammation, extramural lesion, sign of obstruction) | Median MICD (baseline → 2 weeks → 26 weeks) 7.0 → 6.5 → 5.0 | [54] |
| Tielbeek *et al.* (2013) | Adalimumab (n = 30) Infliximab (n = 20) | Inflammatory score (mural thickness, mural T2 signal, perimural T2 signal T1 contrast) | Mean inflammatory score (first MRE → second MRE) Clinical responder 5.19 → 3.12 Non-responder 5.55 → 5.92 | [55] |

MICD: MRE score of severity in ileal Crohn's disease; MRE: Magnetic resonance enterography.

agents or steroids compared with the score at baseline if endoscopic healing was obtained; the mean score was not significantly changed among patients without endoscopic healing [53]. The magnitude of change in the CDEIS scores correlated to those in the MaRIA scores. Another study indicated that the clinical effects of infliximab (IFX) could be assessed by MRE in patients with ileal CD. In this study, the MRE index improved in 44% at 2 weeks and in 80% at 26 weeks after treatment with IFX, and the improvement of ileal lesions on MRE correlated to clinical responses after 2 weeks of IFX treatment [54]. Although the median inflammatory score significantly decreased from 7.0 to 5.0, the obstructive score did not change (3.0 → 3.0) after treatment with IFX. Tielbeek *et al.* demonstrated the usefulness of MRE in examining the treatment effect in patients with CD who were treated with IFX/adalimumab [55]. The mean Crohn's disease activity score in anti-TNF responders significantly improved, whereas the scores did not change significantly in non-responders. Thus, MRE could be used as a complementary approach to measure transmural inflammation in patients with CD and could guide the optimal use of TNF antagonists in daily clinical practice [55]. MRE could evaluate the effects of medical treatments at ileocolonic lesions and at the proximal ileum, where conventional ileocolonoscopy is unable to reach (Figure 5).

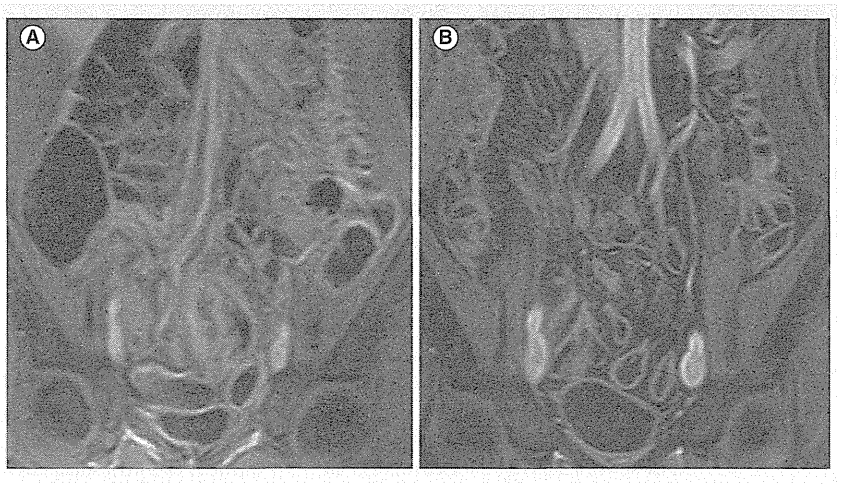


**Figure 5. A case of clinical improvement by infliximab in patients with Crohn's disease.** (**A**) Prior to the administration of infliximab, magnetic resonance enterocolonography could detect deep mucosal lesions in the terminal ileum and the middle ileum. (**B**) Magnetic resonance enterocolonography revealed that inflammation was improved in the colon and in the small intestine.

## Could MRE assess mucosal healing in patients with CD?

Recent studies have indicated that endoscopic improvement after medical treatment reduced hospitalizations and surgeries [56,57]. Endoscopy has been the key device for predicting the long-term prognosis of CD. Because MRE could be repeatedly performed to confirm the effects of medical treatment, a question is raised regarding whether MRE could predict endoscopic remission or ulcer healing.

A recent study demonstrated that the MaRIA score had high sensitivity (85%), specificity (78%) and accuracy (83%) for the diagnosis of mucosal healing with a cutoff of 7. A MaRIA score <11 has a high sensitivity for ulcer healing (90%); however, the specificity is moderate [53]. Another study showed that the CDEIS had a sensitivity of 87% and specificity of 70% for predicting acute inflammation with a cutoff of 3 [52]. These results suggest that MRE might predict endoscopic remission in patients with CD.

## Expert commentary & five-year view

A recent study indicated that the diagnostic ability of MRE was comparable to the diagnostic ability of other devices, such as ileocolonoscopy and CTE. The advantage of MRE is the ability to detect small and large intestinal lesions at the same time

without radiation exposure. MRE is also useful for the simultaneous evaluation of luminal inflammation, transmural lesions and extraintestinal complications in CD. For these reasons, the European Crohn's and Colitis Organisation guidelines recommend MRE as the imaging technique with the highest diagnostic accuracy for the detection of intestinal involvement in CD, including extramural complication [31]. Nevertheless, MRE has not been widely used in actual clinical settings because MRE might be an expensive device and it requires increased time for all sequences to be performed compared with other devices. Moreover, there are few experts who evaluate CD lesions on MRE. If the concerns for expertise and cost could be solved, MRE would be widely used for CD patients in the near future.

Conventional ileocolonoscopy has been performed in most medical institutions; however, only colonic lesions could be assessed with this, and additional diagnostic tools might be required to evaluate the lesions in other parts of the small intestine. BAE could be used to simultaneously assess lesions in the small and large intestines. The advantage of BAE is being able to obtain biopsy specimens of small intestine and to treat for intestinal strictures by endoscopic dilation. BAE can directly observe small intestinal lesions, such as erosions and small ulcerations. BAE is preferred for identifying intestinal damage and strictures [58], although this technique might be operator dependent. Severe adhesions, strictures and fistulas are frequently observed in CD patients and result in technical difficulties of observing the entire small intestine when BAE is performed. MRE is less invasive and is not dependent on the operators' technique. MRE is useful for assessing therapeutic efficacy in the small and large intestine simultaneously. A recent study suggested that endoscopic remission might be predicted by MRE. In our experiment regarding MRE, a transmural lesion with increased wall thickness and hyperintensity could be observed even though endoscopic remission was obtained at the same area. The significance of the discrepancy between endoscopic healing and transmural lesions on MRE [59] should be clarified in a future study.

The question of when MRE should be performed in the clinical setting remains. At the time of diagnosis, conventional colonoscopy is needed, especially for pathological diagnosis. CT procedures provide information regarding extraintestinal complications, such as abscesses or fistulas. In actual clinical setting, conventional CT is more widely used than MRI because CT is less expensive and it does not requires long time for all sequences. CT is useful to detect CD lesion for patients with moderate-to-severe disease because it can be performed on the same day when patients visit the hospital. MRE could be performed repeatedly because there is no radiation exposure. Therefore, MRE is useful as a method of follow-up for younger patients with established CD. MRE is also useful for evaluating the efficacy of medical treatments, such as biologics. MRE could also detect small intestinal lesions even if stenosis is observed. To obtain detailed information of the mucosa in the small intestine, BAE or CE for small intestinal lesions might be more helpful. For each situation, the appropriate diagnostic tools should be selected to ensure the detection of CD lesions in the small intestine.

**Financial & competing interests disclosure**

*The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending or royalties.*

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**Key issues**

- The advantage of magnetic resonance enterography (MRE) for Crohn's disease (CD) patients is that it can evaluate both luminal inflammation and extraintestinal complications of CD in the small intestine.
- Diagnostic accuracy of MRE is comparable with accuracy of ileocolonoscopy and computed tomographic enterography for detecting intestinal lesions of CD.
- MRE is useful as a method of follow-up for younger patients with established CD because of no radiation exposure.
- MRE is also useful for evaluating the efficacy of medical treatments and may predict endoscopic healing in patients with CD.
- The concerns for expertise and cost regarding MRE should be solved to be widely used for CD patients in the near future.

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# Early Intervention with Adalimumab May Contribute to Favorable Clinical Efficacy in Patients with Crohn's Disease

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**Key Words**
Crohn's disease · Adalimumab · Anti-tumor necrosis factor antagonist · Clinical remission · Bowel resection

**Abstract**
***Background:*** We evaluated the clinical efficacy of adalimumab (ADA) for Crohn's disease (CD) and analyzed predictive factors for clinical remission and long-term prognosis. ***Methods:*** We retrospectively reviewed the medical records of 45 patients treated with ADA for CD at Keio University Hospital between October 2010 and March 2014. Clinical remission was defined as a Harvey-Bradshaw index of ≤4. ***Results:*** Twenty-eight of 45 patients (62.2%) achieved clinical remission at week 4. Among these 28 patients, 18 patients (64.3%) maintained clinical remission at week 26, and among these, 16 patients (88.9%) maintained clinical remission at week 52. Absence of a history of bowel resection and absence of prior anti-tumor necrosis factor (anti-TNF) therapy were significant predictive factors for clinical remission at week 4 upon multivariate logistic regression analyses. Younger age and a disease duration of ≤3 years correlated with clinical remission at week 26 upon univariate analyses. Patients without a history of bowel resection showed significantly better long-term prognosis than those with a history of bowel resection ($p = 0.01$). None of the patients contracted a serious infectious disease. ***Conclusions:*** Younger age, shorter duration of disease, being naive to anti-TNF antagonists, and absence of a history of bowel resection were associated with the efficacy of ADA in CD patients.



## Introduction

Crohn's disease (CD) is a chronic inflammatory bowel disease that can lead to progressive and destructive disorders of the alimentary canal. Recent studies have focused upon damage to the digestive tract in CD [1, 2]. It has been reported that (1) up to one third of CD patients have evidence of a stricturing or penetrating intestinal complication at the diagnosis of CD, (2) the annual prevalence of hospitalization due to CD is 20%, (3) half of patients require surgery within 10 years after the diagnosis of CD,

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and (4) the risk of postoperative recurrence is 44–55% after 10 years [3]. In another population-based study, 50% of patients experienced intestinal complications 20 years after the diagnosis of CD, and ileal involvement as well as perianal disease were associated with the development of complications [4]. The therapeutic goal for CD is altering the natural history of the disease to prevent damage to the digestive system. To achieve such disease modification, induction of effective therapy at the correct time is essential.

Anti-tumor necrosis factor (anti-TNF) antagonists are expected to achieve a modification of the course of CD by carrying out mucosal healing [5–8], but some patients are unresponsive to their effects. Hence, how to optimize the use of anti-TNF agents is an important objective. The Study of Biologic and Immunomodulator Naive Patients in Crohn's Disease (SONIC) study [6] as well as an open randomized trial by D'Haens et al. [9] for immunosuppressant- and anti-TNF-naive patients suggested that early induction of infliximab (IFX) combined with immunosuppressants was associated with a high prevalence of corticosteroid-free clinical remission. Analyses of data from the Pegylated Antibody Fragment Evaluation in Crohn's Disease: Safety and Efficacy (PRECiSE) 2 trial using certolizumab pegol demonstrated that patients with CD for <1 year achieved significantly more favorable response rates compared with patients with a disease duration of ≥5 years [10, 11]. These observations suggest the importance of the 'early CD' concept to optimize therapy with anti-TNF agents. Although the definition of early CD has yet to be established, disease duration and previous/current treatment have been proposed as components of the criteria of early CD [12].

The efficacy of adalimumab (ADA) for clinical remission and mucosal healing has been demonstrated in several trials [7, 8, 13–17]. Recent post hoc subgroup analyses of the Crohn's Trial of the Fully Human Antibody Adalimumab for Remission Maintenance (CHARM) [15] and Additional Long-Term Dosing with HUMIRA to Evaluate Sustained Remission and Efficacy in Crohn's disease (ADHERE) [17] trials (which focus on the maintenance of clinical remission with ADA in patients with moderate-to-severe CD) showed that patients with CD of <2 years maintained higher remission rates than patients with a longer duration of up to 3 years of treatment, and that a lack of previous exposure to anti-TNF therapy was a significant prognostic factor [18]. That was the first report to suggest that early CD could be a favorable predictive factor for the efficacy of ADA. However, that post hoc study could not assess the effect of prior bowel resections because surgical histories were not collected in the CHARM trial.

Here, we report for the first time in a Japanese population the optimization of ADA therapy for CD patients. We retrospectively evaluated the clinical efficacy of ADA therapy for CD and analyzed the predictive factors for the induction and maintenance of clinical remission.

## Methods

*Ethical Approval of the Study Protocol*

The study protocol was approved by the ethics committee of the Keio University School of Medicine (Tokyo, Japan).

*Patients and Treatment Protocol*

ADA is approved for the treatment of CD in Japan since October 2010. IFX is the other approved anti-TNF agent for CD in Japan and was approved for treatment in 2002. Between October 2010 and March 2014, 45 patients with CD had been treated with ADA and followed up for ≥52 weeks at Keio University Hospital. The candidates for anti-TNF agents were determined by experienced physicians based on patients' clinical conditions. We explained to the patient about both ADA and IFX equally and decided on the medication according to patient choice. Tuberculosis or other infections were ruled out before induction of ADA therapy. Patients received ADA 160 and 80 mg at weeks 0 and 2, respectively, via the subcutaneous route. After induction therapy, they received ADA (40 mg) every other week. We reviewed their medical records retrospectively.

*Definition and Evaluation of Efficacy*

Clinical response was assessed using the Harvey-Bradshaw index (HBI). 'Clinical remission' was defined as a score of ≤4. We evaluated clinical efficacy at weeks 4 and 26. The HBI is scored using the following 5 items: general wellbeing; abdominal pain; number of liquid stools per day; abdominal mass; complications. The total score is the sum of various scores, and a higher score indicates more severe disease activity [19]. It has been reported that results from the Crohn's Disease Activity Index (CDAI) [20] correlate with those from HBI in analyses of the PRECiSE1 and PRECiSE2 trials [21]. Although the CDAI is widely used to assess disease activity in clinical trials for CD, it requires 7-day data and a calculation that is too complex for use in daily clinical practice. Based on these characteristics, we employed the HBI in this retrospective study. We defined patients who did not need surgery or whose medication was not switched from ADA to other induction therapy as 'event-free survivors'.

*Statistical Analyses*

With respect to predictive factors for clinical remission, univariate analyses for interval scale and comparisons of proportions between groups were undertaken using the Mann-Whitney U test and Fisher's exact test, respectively. Multivariate logistic regression analyses were carried out for variables shown to be significant predictive factors in univariate analyses. The correlation between variables was assessed by Spearman's rank correlation coefficient. The event-free survival rate was examined using the Kaplan-Meier analysis. Factors that contribute to the event-free survival rate were

estimated by the log-rank test. SPSS version 21 (SPSS, Chicago, Ill., USA) was employed for statistical analyses. $p < 0.05$ was considered significant.

## Results

*Demographic Data*

The clinical background of 45 (25 males, 20 females; median age 30 years, range 14–65) patients with CD is shown in table 1. The median duration of disease was 8.0 years (range 0.25–34). Twelve patients had suffered from CD for ≤3 years. Twenty-two patients had bowel stenoses, 7 patients had fistulae and 17 patients had perianal lesions. Fifteen patients had a history of bowel resection and 27 patients had been treated with an anti-TNF agent previously. Forty-two patients showed an HBI score of ≥5 and the median HBI was 6.5 (range 3–16). At base line, 4 (8.9%), 35 (77.8%), 23 (51.1%), and 5 (11.1%) patients were treated with sulfasalazine, 5-aminosalitylate, thiopurines, or prednisolone, respectively.

*Clinical Remission*

Twenty-eight out of 45 patients (62.2%) achieved clinical remission at week 4. Among these 28 patients, 18 patients (64.3%) maintained clinical remission at week 26. Among 17 patients who could not achieve clinical remission at week 4, none was in clinical remission at week 26, regardless of continuance of ADA therapy or due to switching to IFX or surgery. Among the 18 patients who maintained clinical remission at week 26, 16 patients (88.9%) maintained clinical remission at week 52. Finally, 19 out of 45 patients (42.2%) achieved clinical remission at week 52.

*Predictive Factors for the Induction of Clinical Remission*

We analyzed the predictive factors for clinical remission at week 4 in 45 patients. Univariate analyses showed that clinical remission (HBI ≤4) at week 4 was associated with younger age, a disease duration of ≤3 years, absence of a previous history of bowel resection, and absence of prior use of an anti-TNF agent ($p = 0.03$, 0.02, 0.001, and 0.004, respectively; table 2). Multivariate logistic regression analyses revealed that absence of a history of bowel resection and prior use of an anti-TNF agent were significantly correlated with clinical remission at week 4 ($p = 0.03$; odds ratio 9.00, 95% confidence interval 1.30–62.32; $p = 0.04$, 6.95, and 1.07–45.00, respectively; table 3).

**Table 1.** Clinical background of patients treated with ADA

| | |
|---|---|
| Sex | |
| Male | 25 |
| Female | 20 |
| Age, years | 30 (14–65) |
| Disease duration at baseline, years | 8 (0.25–34) |
| ≤3 years | 12 |
| >3 years | 33 |
| Bowel stenosis at baseline | 22 |
| Fistula at baseline | 7 |
| Perianal lesions at baseline | 17 |
| History of bowel resection | 15 |
| Prior use of an anti-TNF agent | 27 |
| HBI | 6.5 (3–16) |
| CRP, mg/dl | 1.34 (0.03–7.00) |
| White blood cells/μl | 6,600 (3,100–12,300) |
| Hemoglobin, g/dl | 11.5 (8.0–16.3) |
| Albumin, g/dl | 3.3 (1.2–4.8) |
| Medications at administration of ADA | |
| Sulfasalazine | 4 |
| 5-Aminosalicylate | 35 |
| Thiopurines | 23 |
| Prednisolone | 5 |

Values are absolute numbers, or medians, with ranges in parentheses.

**Table 2.** Predictive factors for clinical remission at week 4

| | Remission at week 4 | | p |
|---|---|---|---|
| | + | – | |
| Sex, male/female | 15/13 | 10/7 | n.s. |
| Age, years | 29 | 38 | 0.03 |
| Disease duration, ≤3 years/>3 years | 11/17 | 1/16 | 0.02 |
| Stenosis and/or fistula at baseline, yes/no | 14/14 | 10/7 | n.s. |
| Perianal lesions at baseline, yes/no | 12/16 | 12/5 | n.s. |
| History of bowel resection, yes/no | 4/24 | 11/6 | 0.001 |
| Prior anti-TNF agent use, yes/no | 12/16 | 15/2 | 0.004 |
| HBI at baseline | 6 | 7.5 | n.s. |
| CRP, mg/dl | 1.60 | 1.03 | n.s. |
| White blood cells/μl | 6,450 | 6,700 | n.s. |
| Hemoglobin, g/dl | 11.4 | 12.8 | n.s. |
| Albumin, g/dl | 3.4 | 3.2 | n.s. |

n.s. = Not significant.

*Predictive Factors for the Maintenance of Clinical Remission*

Next, we examined the predictive factors for the maintenance of clinical remission at week 26 in the 27 of 28 patients who achieved clinical remission at week 4. We

**Table 3.** Multivariate logistic regression analyses for clinical remission at week 4

| | OR | 95% CI | p |
|---|---|---|---|
| Age, years | 0.98 | 0.90–1.07 | 0.69 |
| Disease duration | 2.33 | 0.19–28.36 | 0.51 |
| History of bowel resection | 9.00 | 1.30–62.32 | 0.03 |
| Prior use of an anti-TNF agent | 6.95 | 1.07–45.00 | 0.04 |

OR = Odds ratio; CI = confidence interval.

**Table 4.** Predictive factors for the maintenance of clinical remission at week 26

| | Maintenance of clinical remission at week 26 | | p |
|---|---|---|---|
| | + | – | |
| Sex, male/female | 10/8 | 5/4 | n.s. |
| Age, years | 24.5 | 38 | 0.03 |
| Disease duration, ≤3 years/>3 years | 10/8 | 0/9 | 0.009 |
| Stenosis and/or fistula at baseline, yes/no | 9/9 | 4/5 | n.s. |
| Perianal lesions at baseline, yes/no | 9/9 | 3/6 | n.s. |
| History of bowel resection, yes/no | 3/15 | 1/8 | n.s. |
| Prior use of an anti-TNF agent, yes/no | 6/12 | 6/3 | n.s. |
| HBI at baseline | 6 | 6 | n.s. |
| CRP, mg/dl | 1.40 | 1.78 | n.s. |
| White blood cells/μl | 6,450 | 6,000 | n.s. |
| Hemoglobin, g/dl | 12.1 | 10.7 | n.s. |
| Albumin, g/dl | 3.3 | 3.7 | n.s. |

n.s. = Not significant.

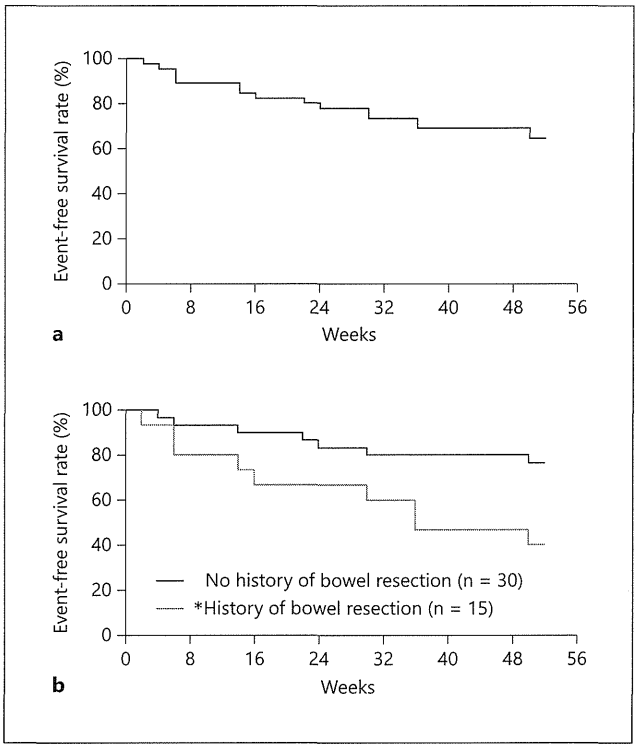


**Fig. 1.** Long-term prognosis of patients treated with ADA. **a** The Kaplan-Meier analysis showed event-free survival in the overall patient population. **b** Long-term prognosis was analyzed in patients without a history of bowel resection and in those with a history of bowel resection. The event-free survival rate was defined as the percentage of patients who had not required surgery or switching to other induction therapy. * p = 0.01 (vs. no history of bowel resection).

excluded 1 patient who discontinued ADA owing to aortitis. Univariate analyses showed that clinical remission at week 26 was associated with younger age and a disease duration of ≤3 years (p = 0.03 and 0.009, respectively; table 4). However, neither of these parameters was significant upon multivariate logistic regression analyses. A significant correlation between age and disease duration was observed (ρ = –0.56, p = 0.002).

*Long-Term Prognosis*

We assessed the long-term prognosis of patients with ADA using Kaplan-Meier analysis. The overall percentage of event-free survivors, who had not required surgery or switching to other induction therapy, was 77.8% at week 26 and 64.4% at week 52 (fig. 1a). We next examined the impact of disease duration of ≤3 years, absence of a previous history of bowel resection, or absence of prior use of an anti-TNF agent on the long-term prognosis using Kaplan-Meier analysis. The overall percentage of event-free survivors in the group without a history of bowel resection was 83.3% at week 26 and 76.7% at week 52. In contrast, the overall percentage of event-free survivors in the group with a history of bowel resection was 66.7% at week 26 and 40.0% at week 52. The group without a history of bowel resection showed a significantly better prognosis than the group with a history of bowel resection (p = 0.01; fig. 1b). The group with a disease duration of ≤3 years or the group without prior use of an anti-TNF agent showed more favorable long-term prognosis than the group with a disease duration of >3 years or the group with prior use of an anti-TNF agent, respectively. However, there was no significant difference between groups, respectively.

*Adverse Events*

One patient discontinued ADA owing to the development of aortitis at week 12. Other causes of withdrawal of ADA were switching to IFX or surgery to control disease activity. Allergic reactions or serious infectious diseases were not observed.

## Discussion

We showed that absence of a history of bowel resection and absence of prior use of an anti-TNF agent were associated with induction of clinical remission. We regarded a history of bowel resection as the indicator of severe bowel damage. In the present study, patients who had strictureplasty also had bowel resection in one operation. In addition, since anal lesion activity is not always correlated with bowel lesion activity, we excluded surgery for anal lesions from the analysis object of surgical history to focus on the bowel damage. We also demonstrated that clinical remission at week 4 was conditional upon remission at week 26. These results suggested that CD patients with less bowel damage and patients naive to an anti-TNF agent could be good subjects for optimizing the efficacy of ADA. Since IFX and ADA were approved in Japan in 2002 and 2010, respectively, the number of patients switching from IFX to ADA has been larger than that of patients who start ADA before IFX. However, it is possible that ADA would be administered as the first-line anti-TNF agent to maximize its efficacy. We also demonstrated that younger age and a disease duration of ≤3 years correlated with clinical remission in ADA therapy upon univariate analyses. Age and disease duration were correlated, so a shorter duration of disease could be associated with a greater likelihood of maintaining clinical remission at week 26. In addition, we revealed that 88.9% of patients who were in clinical remission at week 26 could achieve clinical remission at week 52. Schreiber et al. [18] showed that disease duration was a significant predictive factor for clinical remission at week 56 but not at week 26, and that the baseline level of C-reactive protein (CRP), baseline CDAI and the previous use of an anti-TNF agent were significant predictive factors for clinical remission at weeks 26 and 56 in post hoc analyses of ADA maintenance trials. However, as mentioned in their report, the authors could not assess the impact of bowel damage on clinical remission because surgical history was not documented in the CHARM trial. In the present study, the baseline level of CRP and baseline HBI were not significant predictive factors even at univariate analyses for clinical remission in 45 patients at week 26. These results suggest that the baseline level of CRP or disease activity does not restrict induction of ADA as long as infectious lesions are excluded carefully before ADA administration. Additionally, HBI could have lower sensitivity than CDAI, and we may not have been able to determine the exact effect of baseline disease activity on the induction and maintenance of clinical remission.

The recently proposed definition of early CD for disease modification trials focused on disease duration and previous/current treatment [12]. Indeed, in addition to ADA, Schreiber et al. [11] reported that short duration of disease (<1 year) was a favorable prognostic factor in therapy using certolizumab pegol. Furthermore, Pyerin-Biroulet et al. [22], in recent post hoc analyses of the SONIC study, demonstrated that more patients with a CD duration of ≤2 years achieved mucosal healing compared with patients with longer duration of disease. CD is a progressive, destructive bowel disease, and the speed of progression among patients can vary. Hence, bowel damage at baseline seems to be more important than disease duration. The impact of bowel damage on the effects of anti-TNF therapy has not been assessed thoroughly. However, post hoc analyses of the SONIC study showed absence of previous bowel surgery to be a favorable predictive factor for clinical remission, mucosal healing and remission with mucosal healing [22]. In the present study, we demonstrated lack of a history of bowel resection to be a favorable predictive factor for clinical remission in ADA therapy. Furthermore, we showed that patients without a history of bowel resection had significantly good long-term prognosis. These results suggest the importance of assessment of bowel damage at baseline as well as the usefulness of a multidimensional definition of early CD that considers bowel damage (as in the definition proposed by Peyrin-Biroulet et al. [23]).

Besides maximization of the efficacy of anti-TNF therapy, its safety must also be considered. In the present study, the absence of tuberculosis or other infections was confirmed very carefully before ADA therapy, and no patient contracted severe infectious disease. However, the risk of development of infectious disease or malignancy is a risk during long-term anti-TNF therapy. The ADHERE trial showed that the rates of serious adverse events and malignancies were 33.3 and 1.1 events/100 patient-years, respectively [17]. Lichtenstein et al. [24] examined the long-term safety data for therapies in CD patients in the Crohn's Therapy, Resource, Evaluation, and Assessment Tool Registry. In 2006, they reported

that moderate-to-severe disease activity was associated with serious infections and that IFX was not an independent predictor of serious infections. In that study, the mean length of follow-up was 1.9 years. Then, they assessed long-term safety again and showed IFX treatment to be associated with serious infections. The mean length of patient follow-up at this time was 5.2 years [25]. Their findings suggest that early interventions with anti-TNF therapy for CD could be a 'double-edged sword': anti-TNF agents may contribute to long-term safety by controlling disease activity but could increase the risk of infectious disease.

The present study had several limitations. First, this was a single-center retrospective analysis, so patients were not randomized and the number of patients was relatively small. Second, concomitant use of a corticosteroid, immunomodulator or mesalamine was not uniform in our population. We did not have a sufficient number of patients to analyze those factors separately. Hence, we focused on the history of bowel resection and prior use of an anti-TNF agent as therapeutic factors. Finally, we could not assess mucosal healing in a systematic manner by endoscopy.

In conclusion, we showed that early and bio-naive CD patients without a history of bowel resection could be good candidates for ADA therapy. This finding leads to the concept of early CD as a target of early therapeutic intervention. Nevertheless, the balance between the efficacy and safety of ADA therapy is crucial. Future studies are needed to determine appropriate subjects and the timing of induction of anti-TNF agents.

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