Can magnetic resonance enterocolonography reflect the presence of partial mucosal healing in patients with Crohn's disease?

Poster No.: C-1853
Congress: ECR 2016
Type: Scientific Exhibit
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Keywords: Abdomen, Small bowel, Colon, MR, Colonography MR, Inflammation
DOI: 10.1594/ecr2016/C-1853

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Aims and objectives

Mucosal healing (MH), defined as the absence of ulceration at follow-up endoscopy in patients who had previous ulcerative lesions, is increasingly considered as the therapeutic goal in patients with Crohn's disease (CD) (1, 2). Magnetic resonance enterocolonography (MREC) has been reported to be useful for monitoring response to therapy and detecting MH in patients with CD (3, 4).

Partial mucosal healing (pMH) of CD was defined as endoscopic improvement of lesions with residual ulceration in one report (2). The healing process of ulcers has been described classically for peptic ulcer disease and is classified into three stages: active, healing, and scarring (5). Healing stage is defined as presence of ulcer covered by regenerating epithelium, and lesions at this stage should be included in pMH classification.

It is clinically important to evaluate whether ulcers have partially healed by in order to optimize the therapeutic strategy. However, ulcers at this stage were not distinguishable from non-healed or active lesions in previous studies that included computed tomography or MR imaging for CD.

Recently, magnetic resonance activity index for CD (MaRIA) has emerged as a validated score system, which is developed from the regression model by using the endoscopic activity score as reference standard (6). This score consists of quantitative and qualitative variables, and it might reflect the differences between the active and healing stage.

The purpose of this study was to assess whether MREC reflects pMH in patients with CD by comparing the validated MR activity score of deep ulcers in the healing stage and other conditions.
Methods and materials

This study was approved by our institutional review board and the requirement for informed consent was waived for this retrospective study.

Patients

From June 2014 to February 2015, 89 consecutive patients with CD (57 men, 32 women; mean age 33 years; range 17-70 years) who had undergone MREC and ileocolonoscopy (22 procedures) or balloon-assisted enteroscopy (67 procedures) within one month apart were enrolled in our study. 21 patients (24%) had the ileal type, 56 (63%) had the ileocolonic type, and 12 (13%) had the colonic type. Mean Crohn's disease Activity Index (CDAI) was 89.2, and 13 patients (14.6%) had active disease (CDAI > 150). Mean C-reactive protein (CRP) was 0.53 mg/dl.

MREC imaging and Endoscopy

MREC and endoscopy were performed on the same day in 82 patients (92%). In patients who underwent MREC and endoscopy on the same day, MREC was performed before endoscopy.

On the day before MR imaging, bowel cleansing was performed by oral ingestion of 50 g of magnesium citrate with 200 mL of water at 7 PM. Within 60 minutes and before MR imaging, all patients were instructed to drink 1000 mL of polyethylene glycol. MR imaging was performed using a 1.5-T scanner (Excelart Vantage powered by Atlas; Toshiba Medical Systems, Tokyo, Japan). All MR images were acquired with the patient in the supine position. After intravenous injection of 20 mg of scopolamine butylbromide, coronal and axial single-shot fast-spin echo sequences, a coronal True Steady State Free Precession (True SSFP) and a coronal 3-dimensional T1-weighted gradient echo sequence, termed quick dimensional dynamic diagnostic scan (Quik3Ds), were acquired. After 60 seconds of intravenous administration of gadolinium chelate at a dose of 0.2 mL/kg body weight, a Quick3Ds was performed in axial and coronal orientations. Finally, transverse diffusion-weighted (DW) imaging with b-value 800 sec/mm² was performed. All imaging covered the entire small and large intestines.

Single ballon-assissted enteroscopy (SBE) in 67 patients and ileocolonoscopy (ICS) in 22 patients were subsequently performed by experienced endoscopists. In patients who underwent endoscopy on another day of MREC, bowel cleaning was performed according to the same method as that of MREC. A retrograde approach was used and the endoscope was advanced as deep as possible. Total insertion time was limited to 90 minutes.
Bowel Segmentation and characterization of CD lesions for MREC and Endoscopies

For comparison of MREC and endoscopic findings, the large bowel was divided into five segments instead of 4 used in conventional Crohn's Disease Endoscopic Activity Index of Severity (CDEIS): the rectum, sigmoid colon, descending colon, transverse colon, and ascending colon, and the small bowel was divided into three segments: terminal ileum, proximal ileum, and jejunum (7). For MREC analyses, the ileum was defined as generally occupying the right middle and lower portions of the abdominal cavity and the jejunum, the left upper and middle portions (8). For endoscopic analyses, the ileum was defined as the distal part of the small bowel extending 300 cm or less from the ileocecal valve, and the jejunum was defined as the proximal part of the small bowel (9). In MREC and endoscopic analyses, the terminal ileum was defined as the distal part of the ileum 10 cm or less from the ileocecal valve and proximal ileum was defined as the proximal part of the ileum. In addition, in case of an ileocolonic anastomosis, the terminal ileum included the distal part of the small bowel 10 cm or less from the anastomotic site.

MR and Endoscopy evaluations

Radiologists and physicians blinded to the result of another studies, evaluated MREC and endoscopies.

Radiologists scored MREC using MaRIA for each bowel segment (6). In order to calculate MaRIA score, quantitative and qualitative variables were recorded for each segment. Pre- and post-contrast wall signal intensity (WSI) at 60 seconds in Quick3Ds was quantitatively analyzed to calculate relative contrast enhancement (RCE). WSIs were quantitatively measured using the average of three regions of interest (ROIs) placed on the area within the intestinal wall presenting the largest thickness. RCE was calculated according the following formula: RCE = [(WSI postgadolinium - WSI pregadolinium)/ (WSI pregadolinium)] × 100 × (SD noise pregadolinium/SD noise postgarolinium). The MaRIA was calculated with the following formula: MaRIA = 1.5 × wall thickening (mm) + 0.02 × RCE + 5 × edema + 10 × ulceration.

Endoscopy was considered as the reference standard, and physicians classified each bowel segment into one of four conditions: deep ulcer, superficial ulcer, non-active lesion, and no lesion. Moreover, deep ulcers were sub-classified into two conditions: active and healing stages, according to endoscopic staging system of peptic ulcers (5).

Statistical analysis

We performed statistical analysis with the R software (version 3.2.2, R Foundation for Statistical Computing, Vienna, Austria).
The variables were compared among these five conditions using multiple comparison analysis. Tukey's honestly significant difference test was used for the quantitative variables: MaRIA, wall thickness, and RCE, and Tukey's wholly significant difference test was performed for the qualitative variables: ulceration and edema. A p value < 0.05 was considered statistically significant.
Results

In 89 patients, 607 bowel segments (88 rectums, 89 sigmoid colons, 86 descending colons, 87 transverse colons, 83 ascending colons, 85 terminal ileums, 65 proximal ileums, and 24 jejunums) were evaluated by endoscopy. MaRIA of deep ulcers (n = 98; mean ± standard deviation, 20.1 ± 9.4) was shown to be higher than that of superficial ulcers (n = 88; 10.43 ± 8.2), non-active lesions (n = 111; 8.8 ± 6.6) and no lesions (n = 311; 6.7 ± 4.2). Of the 98 deep ulcers, 78 were revealed to be in the active stage and 20 in the healing stage. MaRIA of the active stage (21.6 ± 9.1) was higher than that of the healing stage (14.55 ± 8.9).

Multiple comparison analysis revealed statistically significant differences between the active and healing stage in MaRIA (p < 0.001), RCE (p < 0.001), wall thickness (p < 0.0001) and edema (p < 0.05).

Significant differences between the active stage and other conditions (no lesions, no active lesions or superficial ulcers), were found for MaRIA (all, p < 0.001), RCE (no lesions, p < 0.001), wall thickness (all, p < 0.0001), ulceration (all, p < 0.0001), and edema (all, p < 0.0001).

Significant differences between the healing stage and other conditions were observed for MaRIA (no lesions, p < 0.001; non-active lesions, p < 0.01), ulceration (no lesions, p < 0.0001; non-active lesions, p < 0.01; superficial ulcers, p < 0.05), and edema (no lesions, p < 0.0001; non-active lesions, p < 0.01).

Typical cases of active and healing stages are demonstrated in figure 1, and the results of MaRIA and each variable for the five conditions are shown in figure 2.
Fig. 1: Magnetic Resonance images and endoscopic images: 23-year-old man with deep ulcers of the terminal ileum in the active stage (a, b and c); 21 year-old woman with deep ulcers of the descending colon in the healing stage (d, e and f). Each lesion is shown on gadolinium-enhanced T1 weighted images (a and d) and coronal T2 weighted single-shot fast-spin echo images (b and e).

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Fig. 2: Boxplots of MaRIA for the five conditions of the bowel segments: no lesion (NoLesion), non-active lesion (NonActive), superficial ulcer (Superficial), deep ulcer in the healing stage (DeepHealing) and deep ulcer in the active stage (DeepActive).

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**Fig. 3:** Boxplots of relative contrast ratio (a) and wall thickness (b) and 100% stacked column chart of edema (c) and ulceration (d) for the five conditions of each bowel segment.

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Conclusion

This study revealed that deep ulcers in the healing stage showed significantly lower values of MaRIA than those in the active stage, and higher values of MaRIA than those of non-active lesions and no lesions. Therefore, deep ulcers in the healing stage could be described as a milder active lesion than the active stage on MR images.

Wall thickness and RCE was considered to be important to differentiate deep ulcers in the active stage from those in the healing stage. However, significant differences in wall thickness and RCE were not observed between the healing stage and other conditions. Significant differences were observed in ulceration and edema between the healing stage and the other conditions. Therefore, reduction of wall thickness or RCE might be related to the change from the active to healing stage and disappearance of ulceration or edema might suggest complete mucosal healing.

In previous literature, the ulcer stage has not been assessed by endoscopy in the studies regarding CT and MR imaging for CD. One rationale for this is that healing stage is not included in either validated endoscopic activity scores (CDEIS or simplified endoscopic score for CD) (7, 10). The ulcer stage should be described in studies on diagnostic accuracy of cross-sectional imaging for CD because the healing stage is reflected on MR imaging findings.

In ECCO-ESGAR evidence-based consensus guidelines it was mentioned that MR imaging shows a delayed timeline for therapeutic response as compared to clinical or endoscopic changes (11). However, our study suggested that findings on MR images might correlate with early endoscopic responses.

This study has some limitations. First, the study was retrospective in design. Second, mucosal healing is usually diagnosed by using at least two endoscopies on two different days (4). Comparison of therapeutic responses between endoscopy and MREC should be assessed by repeated examinations.

In conclusion, magnetic resonance enterocolonography reflected the presence of partial mucosal healing in patients with Crohn's disease. Assessment of wall thickness, relative contrast enhancement, ulceration, and edema on MR images are important to evaluate the healing process of ulcerative lesions.
References


