in inflammatory bowel disease and is frequently measured in routine practice. A correlation between CRP and disease activity or clinical course in CD has been described [20, 21]. Early normalization of CRP levels was related to long-term response during maintenance therapy with infliximab. Consistent with our present results, Jürgens et al. [20] also stated that CRP levels were increased prior to clinical relapse in nearly 70 % of patients. However, both authors did not mention a relationship to serum infliximab level. Our present study is the first to clarify the relationship between a CRP level increase and decrease in serum infliximab level, and that both precede relapse. These results suggest that a decrease in serum trough infliximab level below the effective level, i.e., 1 μg/mL, results in insufficient suppression of TNF-α and IL-6, which subsequently results in an increase in CRP level and exacerbation of clinical symptoms. These findings highlight the critical importance of inducing a constant decrease in inflammation by maintaining serum infliximab levels above the effective level in patients receiving maintenance therapy with infliximab.

Assuming patients with a trough infliximab level below 1 μg/mL to be positive, the accuracy, sensitivity, and specificity of CRP level using the threshold value of normal levels as a cut-off were markedly high. Patients with a trough infliximab level of <1 μg/mL at weeks 14, 22, 30, 38, 46, and 54 were clearly detected by an elevated CRP level. We, therefore, suggest that CRP is a useful marker of a decrease in trough infliximab level to <1 μg/mL.

Fourteen patients showed a clinical response despite an elevated CRP level at week 14; of these, however, 9 (64 %) proceeded to LOR by week 54. A CRP level increase preceded LOR in 7 patients (78 %). This result was similar to that of patients with a decrease in serum infliximab level to <1 μg/mL prior to a LOR. In addition, the timing of LOR, a decrease in trough infliximab level, and an increase in CRP level were compared in patients showing LOR in whom the trough infliximab level decreased to <1 μg/mL. Findings confirmed that the timing of a decrease in the trough infliximab level closely coincided with that of an increase in the CRP level, which were both observed prior to LOR.

The LOR to anti-TNF-α agents is partly explained by antibody formation [5]. Because detectable antibodies to infliximab were not seen in any of our LOR patients ($n = 22$), we were unable to describe the relation between LOR and antibodies to infliximab.

Several limitations of our study warrant mention. The first concerns the threshold of the effective serum level of infliximab and CRP level. Clinical response was lost in 10 patients even when the serum trough infliximab level was ≥1 μg/mL. Of the 7 patients whose infusion interval was shortened and whose CDAI was then subsequently measured, clinical response was achieved in 5 (71 %) and no response in 2 (29 %) at week 54. The threshold of an effective serum level in these 5 responders was considered to be higher than 1 μg/mL and 2 non-responders might show LOR due to factors other than serum infliximab level, which indicates that monitoring using the normal CRP level as a threshold level is not applicable to all patients. The CRP level is normal in some patients with active CD, and was in fact ≤0.5 mg/dL before infliximab treatment in 11 of our 57 patients. Three of these patients experienced LOR, but CRP did not increase, and CRP monitoring in such patients would not be useful. It has been reported that the CRP level at diagnosis was associated with disease location in CD [22], however, in the present study, the disease location did not differ between the 11 patients with normal CRP level and the others (data not shown). Future studies are required to elucidate factors that predict LOR in patients with a higher effective infliximab serum level threshold, in patients with LOR due to factors other than infliximab level, and in patients with normal CRP levels. Second, CRP levels can also be increased by other factors, such as infection [19]. Some patients experienced a transient increase in CRP without a decrease in serum trough infliximab level. Thus, monitoring of CRP level should be performed with caution. Third, our study was a subanalysis with a relatively small number of patients, indicating the need for a larger prospective study on this topic.

In this study, we clarified that a decrease in serum trough infliximab level precedes LOR. Further, a decrease in trough infliximab level to below 1 μg/mL could be easily detected by an elevation in CRP level above the normal range. Our findings suggest that CRP is an indicator of serum infliximab level in predicting LOR. Intensive treatment, such as infliximab dose escalation, by monitoring the CRP level is expected to produce effective and persistent remission in CD. Our results also indicate the need for care in relying on the CDAI, and that this score might require the incorporation of an inflammatory marker such as CRP.

Acknowledgments This study was sponsored by Mitsubishi Tanabe Pharma Corporation. The authors thank the patients, investigators, and study personnel who made the trial possible. We also thank the following investigators for their involvement: Noriaki Watanabe (Department of Internal Medicine, Kitasato Institute Hospital, Tokyo, Japan), Tomoe Katsumata (Department of Gastroenterology, Kitasato University East Hospital, Sagamihara, Japan), Hidemi Goto (Department of Gastroenterology, Nagoya University Graduate School of Medicine, Nagoya, Japan), Akiyoshi Nishio (Department of Gastroenterological Endoscopy, Kyoto University Hospital, Kyoto, Japan).

Conflict of interest T. Hibi has received grant/research support from Ajinomoto Pharmaceuticals, JIMRO, and Mitsubishi Tanabe Pharma. M. Watanabe has received grant/research support and lecture fees from Abbott Japan, Ajinomoto Pharmaceuticals, Asahi Kasei

Medical, Astellas Pharma, AstraZeneca, Chugai Pharmaceutical, DAIICHI SANKYO, Eisai, JIMRO, Kyorin Pharmaceutical, Kyowa Hakko Kirin, Mitsubishi Tanabe Pharma, MSD, Otsuka Pharmaceutical, UCB Japan, and Zeria Pharmaceutical. H. Ito has received lecture fees from Mitsubishi Tanabe Pharma. N. Sato and T. Yoshinari are employees of Mitsubishi Tanabe Pharma. Y. Suzuki has received lecture fees from Mitsubishi Tanabe Pharma. T. Matsumoto has received grant/research support from Asahi Kasei Medical, Ajinomoto Pharmaceuticals, Astellas Pharma, Eisai, EN Otsuka Pharmaceutical, Kyorin Pharmaceutical, Mitsubishi Tanabe Pharma, Otsuka Pharmaceutical, Otsuka Pharmaceutical Factory, UCB Japan, and Zeria Pharmaceutical. The other authors have no conflict of interest.

References

1. Peyrin-Biroulet L, Loftus EV Jr, Colombel J-F, Sandborn WJ. The natural history of adult Crohn's disease in population-based cohorts. Am J Gastroenterol. 2010;105:289–97.
2. Targan SR, Hanauer SB, van Deventer SJ, Mayer L, Present DH, Braakman T, et al. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor α for Crohn's disease. N Engl J Med. 1997;337:1029–35.
3. Hanauer SB, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. Lancet. 2002;359:1541–9.
4. Gisbert JP, Panés J. Loss of response and requirement of infliximab dose intensification in Crohn's disease: a review. Am J Gastroenterol. 2009;104:760–7.
5. Allez M, Karmiris K, Louis E, Assche GV, Ben-Horin S, Klein A, et al. Report of the ECCO pathogenesis workshop on anti-TNF therapy failures in inflammatory bowel diseases: definitions, frequency and pharmacological aspects. J Crohns Colitis. 2010;4:355–66.
6. Sandborn WJ, Hanauer SB. Infliximab in the treatment of Crohn's disease: a user's guide for clinicians. Am J Gastroenterol. 2002;97:2962–72.
7. Hibi T, Sakuraba A, Watanabe M, Motoya S, Ito H, Motegi K, et al. Retrieval of serum infliximab level by shortening the maintenance infusion interval is correlated with clinical efficacy in Crohn's disease. Inflamm Bowel Dis. 2012;18:1480–7.
8. Maini RN, Breedveld FC, Kalden JR, Smolen JS, Davis D, Macfarlane JD, et al. Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor α monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. Arthritis Rheum. 1998;41:1552–63.
9. Maser EA, Villela R, Silverberg MS, Greenberg GR. Association of trough serum infliximab to clinical outcome after scheduled maintenance treatment for Crohn's disease. Clin Gastroenterol Hepatol. 2006;4:1248–54.
10. Afif W, Loftus EV Jr, Faubion WA, Kane SV, Bruining DH, Hanson KA, et al. Clinical utility of measuring infliximab and human anti-chimeric antibody concentrations in patients with inflammatory bowel disease. Am J Gastroenterol. 2010;105:1133–9.
11. Guerra I, Chaparro M, Bermejo F, Gisbert JP. Utility of measuring serum concentrations of anti-TNF agents and anti-drug antibodies in inflammatory bowel disease. Curr Drug Metab. 2011;12:594–8.
12. Sartor RB. Mechanisms of disease: pathogenesis of Crohn's disease and ulcerative colitis. Nat Clin Pract Gastroenterol Hepatol. 2006;3:390–407.
13. Louis E, Belaiche J, van Kemseke C, Franchimont D, de Groote D, Gueenen V, et al. A high serum concentration of interleukin-6 is predictive of relapse in quiescent Crohn's disease. Eur J Gastroenterol Hepatol. 1997;9:939–44.
14. Song L, Hanlon DW, Chang L, Provuncher GK, Kan CW, Campbell TG, et al. Single molecule measurements of tumor necrosis factor α and interleukin-6 in the plasma of patients with Crohn's disease. J Immunol Methods. 2011;372:177–86.
15. Kato K, Fukunaga K, Kamikozuru K, Kashiwamura S, Hida N, Ohda Y, et al. Infliximab therapy impacts the peripheral immune system of immunomodulator and corticosteroid naïve patients with Crohn's disease. Gut Liver. 2011;5:37–45.
16. Charles P, Elliott MJ, Davis D, Potter A, Kalden JR, Antoni C, et al. Regulation of cytokines, cytokine inhibitors, and acute-phase proteins following anti-TNF-α therapy in rheumatoid arthritis. J Immunol. 1999;163:1521–8.
17. Knudsen LS, Ostergaard M, Baslund B, Narvestad E, Petersen J, Nielsen HJ, et al. Plasma IL-6, plasma VEGF, and serum YKL-40: relationship with disease activity and radiographic progression in rheumatoid arthritis patients treated with infliximab and methotrexate. Scand J Rheumatol. 2006;35:489–91.
18. Dain L, Braun-Moscovici Y, Baum E, Nahir AM, Hoffer E. Modification of neutrophil function by plasma of rheumatoid arthritis patients treated with infliximab. Clin Exp Rheumatol. 2006;24:38–44.
19. Vermeire S, Van Assche G, Rutgeerts P. Laboratory markers in IBD: useful, magic, or unnecessary toys? Gut. 2006;55:426–31.
20. Jürgens M, Mahachie John JM, Cleynen I, Schnitzler F, Fidder H, van Moerkercke W, et al. Levels of C-reactive protein are associated with response to infliximab therapy in patients with Crohn's disease. Clin Gastroenterol Hepatol. 2011;9:421–7.
21. Reinisch W, Wang Y, Oddens BJ, Link R. C-reactive protein, an indicator for maintained response or remission to infliximab in patients with Crohn's disease: a post-hoc analysis from ACCENT I. Aliment Pharmacol Ther. 2012;35:568–76.
22. Kiss LS, Papp M, Lovasz BD, Vegh Z, Golovics PA, Janka E, et al. High-sensitivity C-reactive protein for identification of disease phenotype, active disease, and clinical relapses in Crohn's disease: a marker for patient classification? Inflamm Bowel Dis. 2012;18:1647–54.

Potential Utility of a New Ulcerative Colitis Segmental Endoscopic Index Combining Disease Severity and the Extent of Inflammation

Yasuo Suzuki, MD, PhD, Kan Uchiyama, MD, PhD,† Masahisa Kato, MD, PhD,‡ Keigo Matsuo, MD, PhD,§ Tomoo Nakagawa, MD, PhD,‖ Hiroshi Kishikawa, MD, PhD,¶ Norio Kimura, MD,# Junji Kasanuki, MD, PhD,** and Soetsu Ino, MD††*

Goal: To investigate the potential utility of a new scoring system, the Ulcerative Colitis Segmental Endoscopic Index (UCSEI), which combines measures of disease severity and extent of inflammation.

Background: Intestinal mucosal healing (MH) is a new therapeutic goal for ulcerative colitis (UC). Discontinuous lesions are common in UC and endoscopic observation of the entire colon is important.

Study: Patients with active mild-to-moderate UC received daily treatment with oral mesalazine (4 g/d) and mesalazine enemas (1 g/d) for 8 weeks. Endoscopic evaluations, using the UCSEI and Mayo Endoscopic Score (MES), were performed in 5 colonic segments at baseline and week 8. The UCSEI criteria included erythema, vascular pattern, friability, and erosion/ulcer. The sum of 5 subscores, determined for each segment, was calculated as the UCSEI. Disease activity was also assessed using the UC Disease Activity Index (UCDAI). MH was defined as MES = 0 to 1.

Results: Of 58 patients, 51 completed the scheduled endoscopic evaluations. At week 8, the UCDAI score had significantly decreased from 6.63 (baseline) to 2.73 ($P < 0.001$). The remission and MH rates were 35.3% and 55.3%, respectively. Segmental endoscopic evaluation, using UCSEI, showed that baseline inflammation tended to be more severe in the distal colon. The baseline UCSEI increased with the extent of disease, which was not seen in MES. Improvements in UCSEI were observed, even in the patients without decreases in the MES.

Conclusions: UCSEI, reflecting disease severity and extent of inflammation, provides useful information for UC management that is not available with MES.

Key Words: mucosal healing, segmental endoscopic evaluation, ulcerative colitis, mesalazine

(*J Clin Gastroenterol* 2014;00:000–000)

Ulcerative colitis (UC), a chronic inflammatory bowel disease, is characterized by rectal mucosa involvement with continuous proximal extension. Several exceptions, such as skip lesions,[1–5] rectal sparing,[3,4,6] or right-sided inflammation,[7,8] have been described in patients with non-extensive UC in both new-onset and treated patients. In addition, the extent and pattern of inflammation distribution in UC may vary significantly after 1 year of treatment.[9] These reports suggest that endoscopic observation of the entire colon is important for choosing the appropriate treatment strategy and for evaluating therapeutic efficacy.

Mucosal healing (MH) is regarded as a new treatment goal for the management of UC because of the accumulating evidence that MH is associated with lower rates of relapse, hospitalization, and surgery.[10] In addition, macroscopically normal colons are reported to have a colorectal cancer risk similar to that of the general population.[11] However, there is no fully validated scoring system for evaluating MH in clinical practice.[12] According to the International Organization for the Study of Inflammatory Bowel Disease (IOIBD), MH in UC is defined as the absence of friability, blood, erosions, and ulcers in all visualized segments of the intestinal mucosa.[12] Although methods to evaluate MH defined by IOIBD have not been developed, this definition highlights the importance of endoscopic observation of the entire colon.

At least 9 different scoring systems, including the Mayo Endoscopic Score (MES), have been used to measure endoscopic outcomes in clinical trials.[13] The Ulcerative Colitis Endoscopic Index of Severity was recently reported as a validated scoring system to improve interobserver variation (IOV).[14] These endoscopic scores are usually determined from the disease severity in the most active site of a limited observation area. They evaluate the severity, but not changes in disease extent. As a result, we have occasionally observed discrepancies between changes in endoscopic scores and perceived improvements based on total colonoscopy. Regueiro et al[15] also reported that physicians' clinical impressions of UC activity agree poorly with endoscopy results.

The appropriate treatment strategy for UC should be decided according to the severity and extent of disease.[16,17] Hence, a new scoring system for MH that can evaluate both the severity of inflammation throughout the colon and the extent of the disease needs to be developed. In this study, we conducted segmental endoscopic examinations in patients with mild-to-moderate UC who were treated with a combination of oral Pentasa and Pentasa enemas to

Received for publication December 4, 2013; accepted July 9, 2014.
From the *Sakura Medical Center, Toho University, Sakura; †The Jikei University Kashiwa Hospital, Kashiwa, ‡Tsudanuma Central General Hospital, Narashino; §Tokatsu-Tsujinaka Hospital, Abiko; ‖Chiba University Hospital, Chiba; ¶Tokyo Dental College, Ichikawa General Hospital, Ichikawa; #Secomedic Hospital; **Social Insurance Funabashi Central Hospital, Funabashi; and ††Narita Red Cross Hospital, Narita, Japan.
Clinical trial registration number: UMIN000010168.
Presented in part at Annual Meeting of the American Gastroenterological Association (DDW 2012), May 19–22, 2012, San Diego, CA.
The authors declare that they have nothing to disclose.
Reprints: Yasuo Suzuki, MD, PhD, Sakura Medical Center, Toho University, 564-1, Shimoshizu Sakura, Chiba 285-8741, Japan (e-mail: yasuo-suzuki@sakura.med.toho-u.ac.jp).

develop the Ulcerative Colitis Segmental Endoscopic Index (UCSEI) as a new endoscopic scoring system for clinical practice, and to evaluate its potential utility as an index of therapeutic efficacy.

MATERIALS AND METHODS

Study Patients

UC patients were recruited from 9 hospitals in the Chiba (Japan) prefecture, between February 2011 and February 2012. The local hospital ethics committees approved this study, and all patients provided written informed consent before participation in the study. Male and female outpatients were eligible to participate if they were 15 to 75 years old and had been diagnosed with active, mild-to-moderate UC. Exclusion criteria included: oral treatment with total doses >4.5 g of sulfasalazine or >4.0 g of mesalazine; treatment with topical mesalazine, topical sulfasalazine, or steroids; cytapheresis within 14 days of study entry; immunosuppressive drugs or antitumor necrosis factor-α antibody therapy within 90 days before study enrollment; a history of severe adverse effects to mesalazine; salicylate allergy; possible or documented pregnancy; malignant disease; or any other condition that might interfere with study assessments, in the judgment of the investigator.

METHODS

Patients received daily treatment with oral mesalazine (Pentasa, 4 g/d; Kyorin, Tokyo, Japan) and with mesalazine enemas (1 g/d) for 8 weeks.

Endoscopic examinations were performed at baseline and week 8; the findings were scored using both the UCSEI and MES systems.[18] The UCSEI reflects the sum of the severity subscores, determined in each of the 5 colonic segments (ascending colon/cecum, transverse colon, descending colon, sigmoid colon, and rectum). The severity was graded by 4 different parameters of mucosal inflammation, erythema, vascular pattern, friability, and ulceration, on a scale of 0 to 10, as shown in Table 1. MH was defined as MES = 0 to 1. Although this definition does not reflect the IOIBD definition, it is widely used in clinical studies. MES was determined at the most affected colon site.

Disease activity was also assessed at baseline and week 8 using the UC Disease Activity Index (UCDAI), with clinical[19] and endoscopic signs.[18] Remission and improvement were defined as a UCDAI score <2 and as a decrease in the UCDAI score by ≥2 points from baseline, respectively. An abbreviated UCDAI (aUCDAI) score, reflecting stool frequency, rectal bleeding, and physician's global assessment, was assessed at baseline, week 4, and week 8.[20] Clinical remission was defined as an aUCDAI≤2 and a rectal bleeding score of 0.

TABLE 1. Ulcerative Colitis Segmental Endoscopy Index (UCSEI) Observation

Item	Score
Erythema	0: none, 1: mild, 2: marked
Vascular pattern	0: normal, 1: decreased, 2: absent
Friability	0: none, 1: mild, 2: contact bleeding, 3: spontaneous bleeding
Erosions/ulcers	0: absent, 2: erosion, 3: ulcer
UCSEI subscore range, segment	0-10
UCSEI range patient	0-50

For each of the 5 colon segments (ascending colon cecum, transverse colon, descending colon, sigmoid colon, rectum), a severity subscore is given, according to the above scale, for the 4 observation items. The sum of 5 subscores, determined for each segment, is calculated as the Ulcerative Colitis Segmental Endoscopic Index (UCSEI) score

Statistical Analysis

The Wilcoxon signed-rank test (paired test) was used to compare clinical signs and endoscopic scores at baseline and at week 8. All analyses were performed using StatMate IV (ATMS, Tokyo, Japan). Data are expressed as means ± SD, medians (ranges), or frequencies, as appropriate.

RESULTS

A total of 58 patients were recruited into the study. Seven patients were excluded because of a decision not to participate, loss to follow-up, or refusal of colonoscopy at week 8. The remaining 51 patients completed both baseline and week 8 endoscopic evaluations. Demographic and baseline characteristics of the patients are shown in Table 2.

At week 8, the UCDAI scores had significantly decreased from 6.63 ± 1.68 at baseline to 2.73 ± 2.19 ($P < 0.001$). The remission, clinical remission, and improvement rates were 35.3%, 78.4%, and 82.4%, respectively. The aUCDAI score also decreased significantly over the course of treatment (baseline, 4.53 ± 1.51; week 4, 1.62 ± 1.66; week 8, 1.39 ± 1.72; $P < 0.001$) and each of the subscores for stool frequency, rectal bleeding, and physician's global assessment were also significantly decreased at weeks 4 and 8, compared with baseline ($P < 0.001$, Fig. 1).

The UCSEI significantly decreased from 17.41 ± 8.96 at baseline to 7.39 ± 6.78 at week 8 (−57.6%, $P < 0.001$) and the MES significantly decreased from 2.10 ± 0.50 at baseline to 1.37 ± 0.74 at week 8 (−34.8%, $P < 0.001$). The MH rate after treatment was 55.3%. The UCSEI subscore for each segment, indicating segmental disease severity, decreased significantly at week 8 ($P < 0.01$, Fig. 2). Inflammation at baseline tended to be more severe in the

TABLE 2. Characteristics of Patients Completing Baseline and Week 8 Endoscopies

Clinical Parameters	Values
Age (y)*	44.1 ± 14.0 (43, 17-75)
Male [n (%)]	32 (62.7)
Disease duration (mo)*	78.7 ± 86.4 (48, 1-312)
Type of disease [n (%)]	
Proctitis	13 (25.5)
Left-sided colitis	16 (31.4)
Pancolitis	22 (43.1)
Clinical course [n (%)]	
New onset UC	15 (29.4)
Relapsing remitting UC	36 (70.6)
Disease activity index*	
Ulcerative colitis disease activity index	6.63 ± 1.68 (6, 4-10)
Stool frequency subscore	1.71 ± 0.91 (2, 0-3)
Rectal bleeding subscore	1.24 ± 0.76 (1, 0-2)
Mayo endoscopic subscore	2.10 ± 0.50 (2, 1-3)
Physician global assessment subscore	1.59 ± 0.49 (2, 1-2)

*Age, disease duration, and disease activity index results expressed as mean ± SD (median, range)

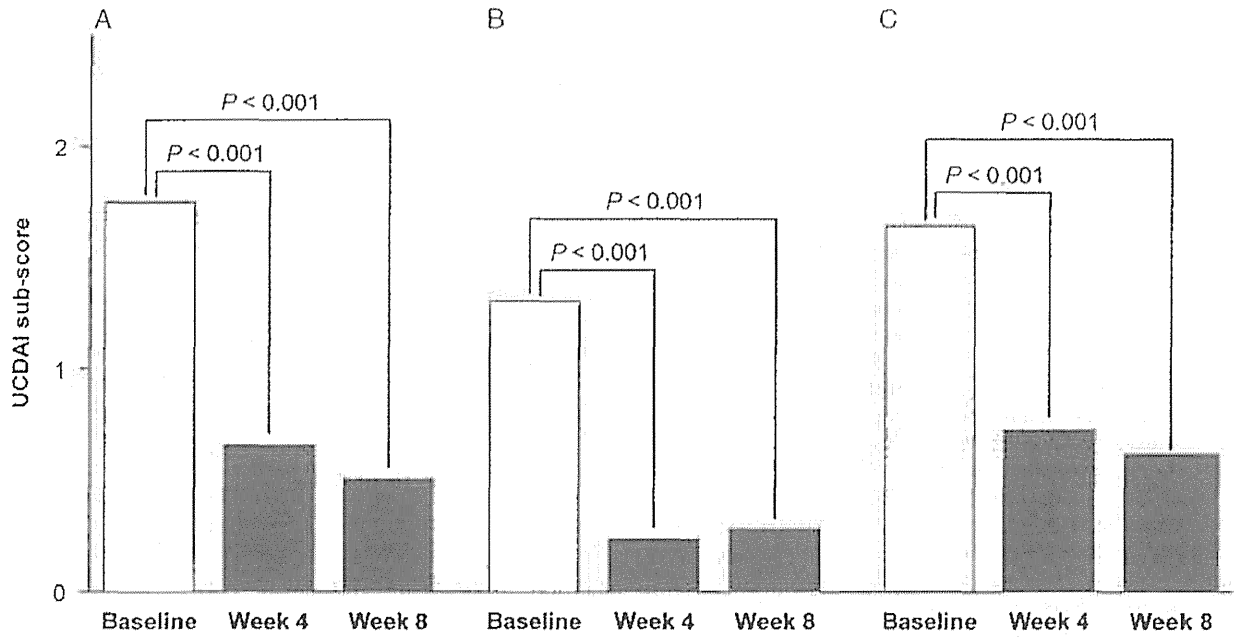

FIGURE 1. Changes in Ulcerative Colitis Disease Activity Index (UCDAI) clinical subscores, based on clinical findings. All scores regarding (A) stool frequency, (B) rectal bleeding, and (C) physician's global assessment were significantly decreased at weeks 4 and 8, compared with baseline (n = 47, Wilcoxon signed-rank test).

distal colon compared with the proximal segments. The baseline and week 8 UCSEI values for proctitis, left-sided colitis, and extensive colitis are shown in Figure 3. The baseline UCSEI increased with the extent of disease, whereas the MES did not. Both the UCSEI and MES scores significantly decreased in all types of UC ($P < 0.001$),

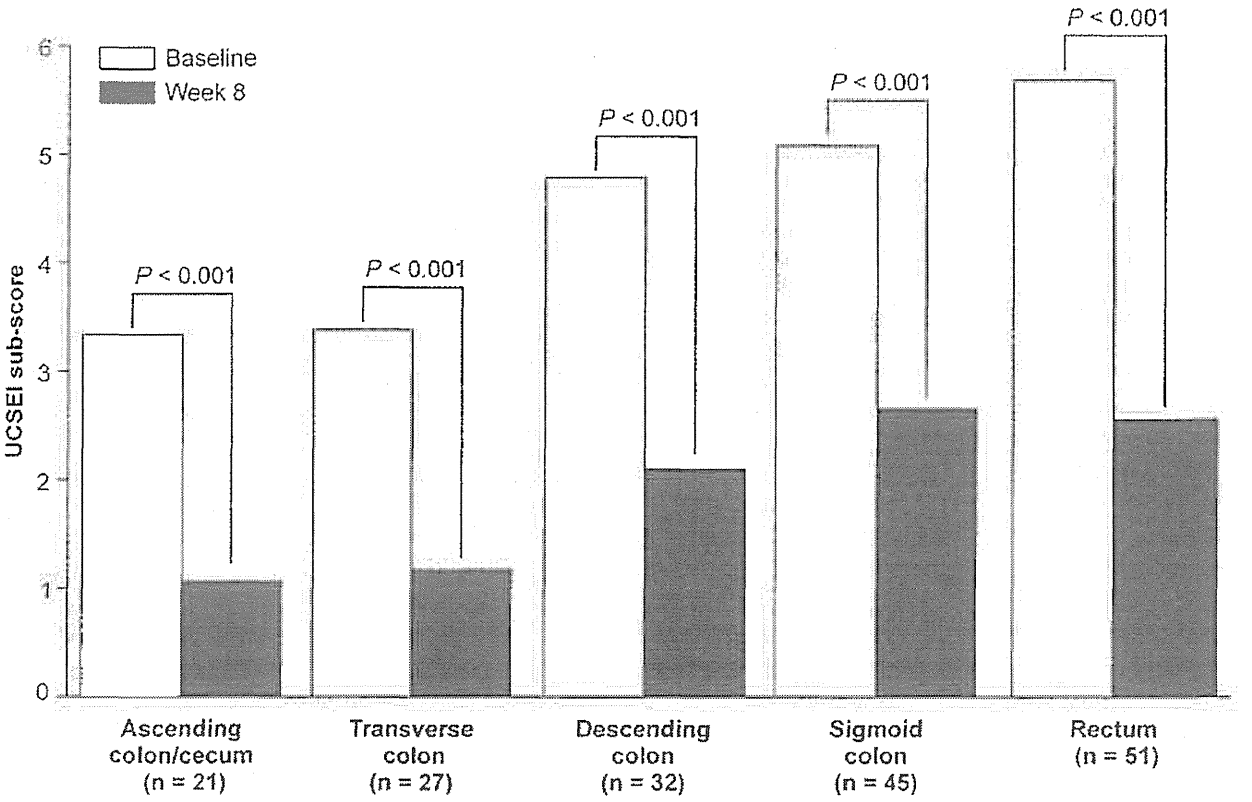

FIGURE 2. Changes in the severity of endoscopic inflammation subscores in each colon segment. The subscores for each segment, at week 8, were significantly decreased, compared with those at baseline (Wilcoxon signed-rank test). Baseline inflammation tended to be more severe in the distal colon than in the proximal segments. UCSEI indicates Ulcerative Colitis Segmental Endoscopic Index.

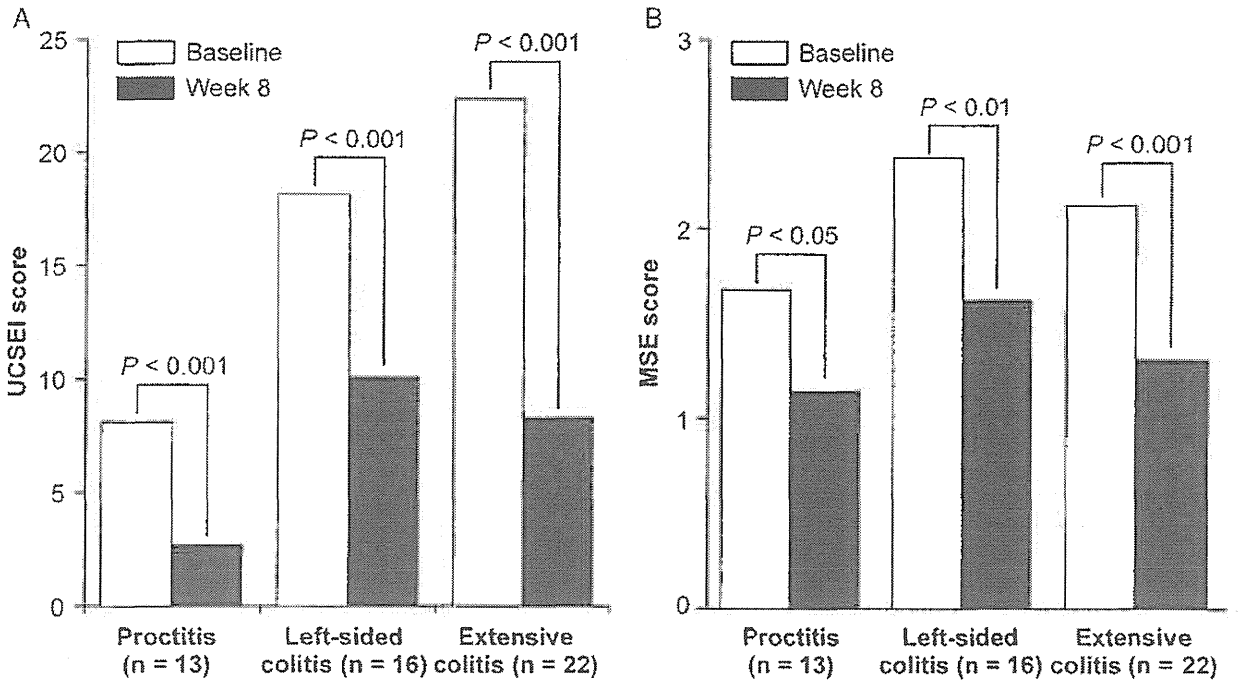

FIGURE 3. Changes in Ulcerative Colitis Segmental Endoscopic Index (UCSEI) and Mayo Endoscopic Score (MES) by disease type. Regardless of disease type, the (A) UCSEI and (B) MES values, at week 8, were significantly lower than at baseline (Wilcoxon signed-rank test). The baseline UCSEI increased with the extent of the disease; a similar trend was not observed in the MES.

indicating that the UCSEI reflected the efficacy of mesalazine therapy.

A comparison of the baseline to week 8 decreases in MES and UCSEI scores in the individual patients is shown in Figure 4. Even patients who had same change in MES showed varied decreases in UCSEI.

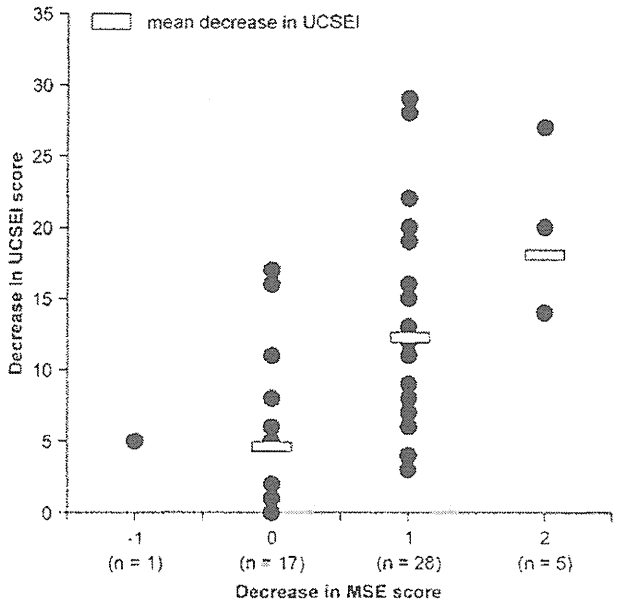

FIGURE 4. Comparison of the decrease in Mayo Endoscopic score (MES) with that in the Ulcerative Segmental Endoscopic Index (UCSEI) in individual patients. Decreases in MES and UCSEI values, from baseline to week 8, for individual patients are shown (•). Even patients with same decrease in MES show variable UCSEI decreases.

DISCUSSION

MH is regarded as an appropriate therapeutic goal for the management of UC, and the importance of whole colon endoscopy has been highlighted. The ulcerative colitis colonoscopic index of severity (UCCIS), recently reported by Samuel et al,[21] emphasized the importance of whole colon evaluation. However, the UCCIS has not yet been applied in clinical trials or clinical practice.

Low interobserver agreement has been noted as a drawback of the conventional scoring systems, with recent studies of the variability in MES and Baron endoscopic scores revealing that the interobserver agreement for the scores was only 27% and 21%, respectively.[14,22] The method used to determine the scores from several findings may account for this low agreement. In the case of MES, for example, physicians must score disease severity from 0 to 3, on the basis of vascular pattern, erythema, friability, and erosion/ulceration. This process is highly dependent on subjective factors, such as physician experience and knowledge. These factors may become more significant as the increasing prevalence of UC in Japan increases the likelihood that UC patients will be examined by non-specialists. Scoring a single finding is easier and the methodology can be more reliably standardized than when assigning a score to a plurality of findings, like in the MES. A one-to-one scoring system can be less susceptible to IOV during assessment of endoscopic activity.

On the basis of previous reports[18,23–25] and our clinical trial experience, we chose the assessment of 4 different parameters of mucosal inflammation: vascular pattern, erythema, erosion/ulceration, and friability. In this study, rates of remission, improvement, and MH were comparable with those in previous reports.[20,26–28] The endoscopic scores for both the UCSEI and MES decreased significantly after 8 weeks of combination therapy. In contrast, increases at

baseline, corresponding with the extent of disease, were only observed in the UCSEI (Fig. 3). This was not surprising because the MES does not take into account the extent of disease. However, this result indicated that the extent of disease was reflected in the UCSEI, as expected. UC is empirically known to typically involve the rectum and to expand to more proximal regions, with inflammation also commonly more severe in the distal parts of the colon than in the proximal regions. However, these have not been shown by the current scoring systems, to the best of our knowledge. The UCSEI is considered to be useful for assessing not only the extent of disease, but also the severity of segmental inflammation (Figs. 2, 3).

The UCSEI may also provide valuable therapeutic decision-making information, not obtainable with the MES. Comparisons of the decreases in the UCSEI and MES, in individual patients, revealed that improvements in the UCSEI were observed even in patients who did not exhibit decreases in the MES (Fig. 4). This suggests that, in some patients, the extent of inflammation was ameliorated, but the severity in the most affected site was unchanged. The UCSEI may be useful for filling the gap between conventional endoscopic scores and physicians' impressions of improvement, on the basis of total colonoscopies.

This study has several limitations to consider. First, we did not perform a validation study of the UCSEI to assess IOV, correlation with other clinical/endoscopic indices, or its relationship with laboratory markers of inflammation. Validation studies are essential to the development of a new, robust scoring system for UC, as previous reports have indicated that only 21% of physicians completely agreed with endoscopic subscores.[21] Although all investigators in this study agreed on the scoring standard to minimize IOV, before the beginning of the study, we gave higher priority to investigating the potential utility of the UCSEI in UC management over a validation study. Additional studies are required to assess the validity of our measurements. Second, a UCSEI subscore cutoff value for determining MH was not determined. This issue has to be resolved. Finally, a clear consensus regarding whether total colonoscopy or sigmoidoscopy should be the first option in the management of UC has not yet been established. The UCSEI requires a total colonoscopy, whereas a flexible sigmoidoscopy is generally used for the MES. Total colonoscopy definitely caused a tremendous patient burden a couple of decades ago; however, recent technological and methodological advancements have reduced this burden. For instance, modalities for total colonoscopy have become thinner, and a small-diameter colonoscope with new functions, such as passive bending, high force transmission, or variable stiffness, has been developed. As a result, the time for total colonoscopy has been shortened and the patient burden has greatly decreased. Therefore, total colonoscopy can be applied to diagnose and monitor the disease, as well as to assess the treatment efficacy in patients with mild-to-moderate and quiescent UC. When the strategy to exactly evaluate the severity and extent of disease is applied, the UCSEI is considered to be useful in clinical practice.

In conclusion, the UCSEI was able to evaluate the efficacy of mesalazine therapy and provided useful clinical information not obtained by MES. Because the UCSEI reflects both the severity and extent of inflammation, improvement in the UCSEI score is potentially a more precise index for evaluating intervention efficacy. Further studies are warranted to develop the UCSEI as a new scoring system and to propose a therapeutic strategy based on the results obtained.

REFERENCES

1. Bernstein CN, Shanahan F, Anton PA, et al. Patchiness of mucosal inflammation in treated ulcerative colitis: a prospective study. *Gastrointest Endosc*. 1995;42:232–237.
2. D'Haens G, Geboes K, Peeters M, et al. Patchy cecal inflammation associated with distal ulcerative colitis: a prospective endoscopic study. *Am J Gastroenterol*. 1997;92:1275–1279.
3. Joo M, Odze RD. Rectal sparing and skip lesions in ulcerative colitis: a comparative study of endoscopic and histologic findings in patients who underwent proctocolectomy. *Am J Surg Pathol*. 2010;34:689–696.
4. Shah SN, Amarapurkar AD, Shrinivas N, et al. Atypical histological features of ulcerative colitis. *Trop Gastroenterol*. 2011;32:107–111.
5. Yang S-K, Jung H-Y, Kang GH, et al. Appendiceal orifice inflammation as a skip lesion in ulcerative colitis: an analysis in relation to medical therapy and disease extent. *Gastrointest Endosc*. 1999;49:743–747.
6. Kim B, Barnett JL, Kleer CG, et al. Endoscopic and histological patchiness in treated ulcerative colitis. *Am J Gastroenterol*. 1999;94:3258–3262.
7. Loftus EV, Harewood GC, Loftus CG, et al. PSC-IBD: a unique form of inflammatory bowel disease associated with primary sclerosing cholangitis. *Gut*. 2005;54:91–96.
8. Mutinga ML, Farraye FA, Wang HH, et al. Clinical significance of right colonic inflammation in patients with left sided chronic ulcerative colitis: a study of 34 patients. *Gastroenterology*. 2001;120:A450–A450.
9. Moum B, Ekbom A, Vatn MH, et al. Change in the extent of colonoscopic and histological involvement in ulcerative colitis over time. *Am J Gastroenterol*. 1999;94:1564–1569.
10. Peyrin-Biroulet L, Ferrante M, Magro F, et al. Results from the 2nd Scientific Workshop of the ECCO (I): impact of mucosal healing on the course of inflammatory bowel disease. *J Crohns Colitis*. 2011;5:477–483.
11. Rutter MD, Saunders BP, Wilkinson KH, et al. Cancer surveillance in longstanding ulcerative colitis: endoscopic appearances help predict cancer risk. *Gut*. 2004;53:1813–1816.
12. D'Haens G, Sandborn WJ, Feagan BG, et al. A review of activity indices and efficacy end points for clinical trials of medical therapy in adults with ulcerative colitis. *Gastroenterology*. 2007;132:763–786.
13. de Chambrun GP, Peyrin-Biroulet L, Lémann M, et al. Clinical implications of mucosal healing for the management of IBD. *Nat Rev Gastroenterol Hepatol*. 2009;7:15–29.
14. Travis SPL, Schnell D, Krzeski P, et al. Developing an instrument to assess the endoscopic severity of ulcerative colitis: the Ulcerative Colitis Endoscopic Index of Severity (UCEIS). *Gut*. 2012;61:535–542.
15. Regueiro M, Rodemann J, Kip KE, et al. Physician assessment of ulcerative colitis activity correlates poorly with endoscopic disease activity. *Inflamm Bowel Dis*. 2011;17:1008–1014.
16. Dignass A, Van Assche G, Lindsay JO, et al. The second European evidence-based consensus on the diagnosis and management of Crohn's disease: current management. *J Crohns Colitis*. 2010;4:28.
17. Kornbluth A, Sachar DB. Ulcerative colitis practice guidelines in adults. American College of Gastroenterology, Practice Parameters Committee. *Am J Gastroenterol*. 1997;92:204–211.
18. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. *N Engl J Med*. 1987;317:1625–1629.
19. Sutherland LR, Martin F, Greer S, et al. 5-Aminosalicylic acid enema in the treatment of distal ulcerative colitis, proctosigmoiditis, and proctitis. *Gastroenterology*. 1987;92:1894–1898.

20. Marteau P, Probert C, Lindgren S, et al. Combined oral and enema treatment with pentasa (mesalazine) is superior to oral therapy alone in patients with extensive mild/moderate active ulcerative colitis: a randomised, double blind, placebo controlled study. *Gut*. 2005;54:960–965.
21. Samuel S, Bruining DH, Loftus EV, et al. Validation of the ulcerative colitis colonoscopic index of severity and its correlation with disease activity measures. *Clin Gastroenterol Hepatol*. 2013;11:49–54.
22. Walsh AJ, Bram O, Keshav S, et al. W1205 how variable is the Mayo Score between observers and might this affect trial recruitment or outcome? *Gastroenterology*. 2009;136: A-677–A-677.
23. Feagan BG, Greenberg GR, Wild G, et al. Treatment of ulcerative colitis with a humanized antibody to the α4β7 integrin. *N Engl J Med*. 2005;352:2499–2507.
24. Hanauer S, Schwartz J, Robinson M, et al. Mesalamine capsules for treatment of active ulcerative colitis: results of a controlled trial. Pentasa Study Group. *Am J Gastroenterol*. 1993;88:1188–1197.
25. Hanauer SB, Robinson M, Pruitt R, et al. Budesonide enema for the treatment of active, distal ulcerative colitis and proctitis: a dose-ranging study. *Gastroenterology*. 1998;115:525–532.
26. Meucci G, Fasoli R, Saibeni S, et al. Prognostic significance of endoscopic remission in patients with active ulcerative colitis treated with oral and topical mesalazine: a prospective, multicenter study. *Inflamm Bowel Dis*. 2012;18:1006–1010.
27. Safdi M, DeMicco M, Sninsky C, et al. A double-blind comparison of oral versus rectal mesalamine versus combination therapy in the treatment of distal ulcerative colitis. *Am J Gastroenterol*. 1997;92:1867–1871.
28. Sandborn WJ, Hanauer S, Lichtenstein GR, et al. Early symptomatic response and mucosal healing with mesalazine rectal suspension therapy in active distal ulcerative colitis–additional results from two controlled studies. *Aliment Pharmacol Ther*. 2011;34:747–756.

J Gastroenterol (2014) 49:1299–1306
DOI 10.1007/s00535-013-0873-3

The Japanese Society of Gastroenterology

ORIGINAL ARTICLE—ALIMENTARY TRACT

Hematologic malignancies in the Japanese patients with inflammatory bowel disease

Norimasa Fukata · Kazuichi Okazaki · Mika Omiya · Mitsunobu Matsushita · Mamoru Watanabe · The Members of the Ministry of Health and Welfare of Japan's Inflammatory Bowel Diseases Study Group

Received: 10 July 2013 / Accepted: 7 August 2013 / Published online: 19 August 2013

Abstract
Background Although attention has been focused for over 20 years on the possible increased risk for hematologic malignancies (HM) in patients with inflammatory bowel diseases (IBD) receiving immune-modulators or anti-TNF-alpha antibodies, the association is still controversial. To understand the actual conditions of HM in the Japanese patients with IBD, the research committee for IBD supported by the Ministry of Health, Welfare and Labor of Japan (IBD-MHWL) conducted a multi-center retrospective study.
Methods Questionnaires for the development of HM in IBD patients were sent to the 70 facilities participating with IBD-MHWL in the first survey, followed by the second survey using a more detailed questionnaire, sent to the 27 members with HM patients.
Results Out of a total of 36,939 IBD patients in 70 facilities, 28 cases of HM related with IBD [12 of 10,500 UC patients (0.11 %), 16 of 6,310 CD patients (0.25 %)] were analyzed. The numbers of UC patients who developed HM were 2 (0.15 %) from the group receiving and 10 (0.13 %) from the group non-receiving thiopurine, without significant differences. The numbers of CD patients who developed HM were 4 (0.39 %) from the group receiving and 12 (0.21 %) from the group non-receiving thiopurine, without significant differences. The odds ratios of developing HM by thiopurine were 1.37 (95 % CI 0.30–6.24) in UC patients and 1.86 (95 % CI 0.60–5.78) in CD patients.
Conclusions Our results suggested that thiopurine therapy may not be a risk factor for HM in Japanese patients with IBD. Further accumulation of cases and prospective studies are necessary to conclude this important issue.

Keywords Inflammatory bowel disease · Ulcerative colitis · Crohn's disease · Hematologic malignancy · Lymphoproliferative disorder · Thiopurine

Introduction

Inflammatory bowel diseases (IBD) such as ulcerative colitis (UC) and Crohn's disease (CD) are chronic intestinal disorders of unknown cause. Since many patients develop these diseases at a young age, the possibility of increased risk for proliferative disorders of hematopoietic cells in patients receiving immune-modulators or anti TNF-alpha antibody preparations over a long-term course of therapy has been a focus of attention for over 20 years [1–3].

In organ transplant recipients, long-term use of immunomodulatory agents or infection with EB virus are known to be risk factors for hematologic malignancies (HM) such as lymphoproliferative disorders (LPD). Similarly, in the patients with rheumatoid arthritis (RA), methotrexate (MTX) and EB virus are risk factors in the development of LPD [4–6]. There is a controversy because some reports show an increased risk of LPD in UC patients, but other reports say there is no relation; an association between the two is not yet clear [7–20].

Recent reports suggested that in IBD patients, especially in CD patients, the use of immunomodulatory agents may relate to the development of LPD [14, 19, 21–27]. The

N. Fukata · K. Okazaki (✉) · M. Omiya · M. Matsushita
Department of Gastroenterology and Hepatology,
Kansai Medical University, Hirakata, Japan
e-mail: okazaki@hirakata.kmu.ac.jp

M. Watanabe
Department of Gastroenterology and Hepatology,
Tokyo Medical and Dental University, Bunkyo, Japan

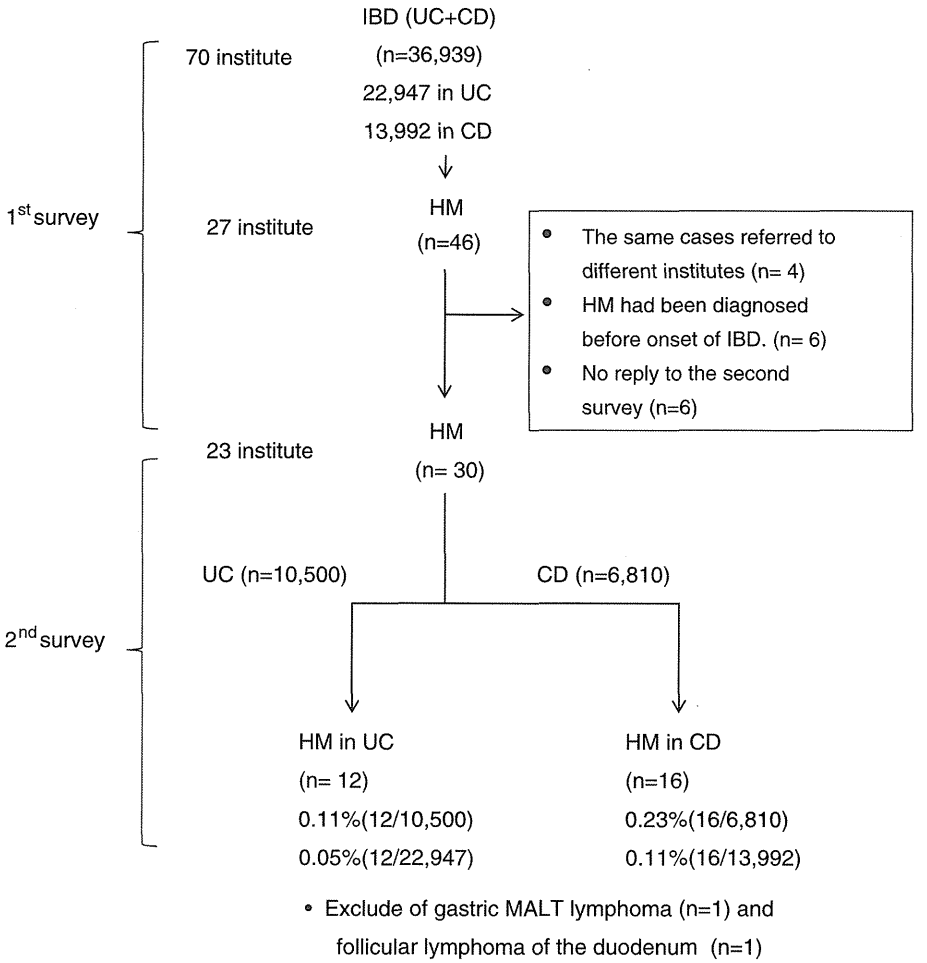

Fig. 1 The first and second surveys for the development of hematologic malignancies (HM) in patients with inflammatory bowel disease in the present study. There were a total of 36,939 IBD patients being treated in 70 facilities, of whom 22,947 were UC (62.1 %) and 13,992 were CD (37.9 %) patients. In 27 out of 70 facilities, there were 46 cases of HM. The second survey was then sent to these 27 facilities, and responses were received from 23 facilities. In 23 facilities, there were 10,500 patients with UC and 6,310 patients with CD. Of the 46 cases reported as having HM in the first survey, except for the same 4 cases referred to different institutes, 6 cases IBD having HM prior to the development of IBD, 6 cases without reply to the second survey, one case of gastric MALT lymphoma, and one case of duodenal follicular lymphoma, 28 cases were studied. In 23 facilities, 12 of 10,500 UC patients (0.11 %) and 16 of 6,310 CD patients (0.25 %) developed HM, respectively. In all facilities, 12 of 22,947 UC patients and 16 of 13,992 CD patients developed HM, respectively. In 23 facilities, 12 of 10,500 UC patients (0.11 %) and 16 of 6,310 CD patients (0.25 %) developed HM, respectively. In all facilities, 12 of 22,947 UC patients and 16 of 13,992 CD patients developed HM, respectively

CESAME study, a prospective study conducted in France, reported that IBD patients receiving thiopurine drugs are at significantly higher risk of developing LPD. Also, a recent report from the Netherlands strongly suggested the association of LPD with EB virus infection as in the case of chronic rheumatoid arthritis [20].

The development of proliferative disorders of hematopoietic cells in IBD patients in Japan is still unclear, although a recent cohort study reported that the risks for colorectal cancer and leukemia in the patients with CD were higher compared with those in the Japanese standard population [28]. The research committee for inflammatory bowel disease supported by the Ministry of Health, Welfare and Labor of Japan (IBD-MHWL) conducted a national survey to understand the development of HM in IBD patients in Japan.

Methods

A questionnaire survey was conducted with 88 medical facilities throughout Japan who are participating in IBD-MHWL. The first survey asked, "How many patients with IBD, ulcerative colitis (UC), and CD have been treated in your facility?" and "How many patients developed HM, such as malignant lymphoma, MALT lymphoma, T cell

lymphoma, Burkitt's lymphoma, leukemia, multiple myeloma, and so on, in your facility?" The facilities who replied in the first survey that there were patients who developed HM were then asked how many cases had been treated with thiopurine drugs and the patients' age, gender, underlying disease, disease type, severity of IBD conditions at the onset of HM, amount of steroids used, amount of immunomodulatory drugs used, duration of usage, and amount of anti-TNFalpha antibodies used.

Data analysis

For each of the cases of UC and CD, the risk of developing HM by treating with immunomodulatory drugs was determined by chi-square test and odds ratio.

Results

The first survey

Responses to the first survey were received from 70 out of 88 facilities (79.5 %). There were a total of 36,939 IBD patients being treated in 70 facilities (Fig. 1), of whom 22,947 were UC (62.1 %) and 13,992 were CD (37.9 %) patients. In 27 out of 70 facilities, there were 46 cases of HM.

The second survey

The second survey was then sent to these 27 facilities, and responses were received from 23 facilities. In 23 facilities, there were 10,500 patients with UC and 6,310 patients with CD. Of the 46 cases reported as having HM in the first survey, except for the same 4 cases referred to different institutes, 6 cases IBD having HM prior to the development of IBD, 6 cases without reply to the second survey, one case of gastric MALT lymphoma, and one case of duodenal follicular lymphoma, 28 cases were studied. In 23 facilities, 12 of 10,500 UC patients (0.11 %) and 16 of 6,310 CD patients (0.25 %) developed HM, respectively. In all facilities, 12 of 22,947 UC patients and 16 of 13,992 CD patients developed HM, respectively.

Table 1 shows the breakdown of HM developed in UC and CD. Of the 12 cases of HM developing in UC (0.11 %), 7 were malignant lymphoma (6 cases of non-Hodgkin lymphoma and one case of MALT lymphoma of large intestine), one was acute leukemia (M1), 3 were multiple myeloma, and one was primary macroglobulinemia. Of the 16 cases of HM developing in CD (0.24 %), 5 were malignant lymphoma (3 cases of non-Hodgkin lymphoma, one case of MALT lymphoma of large intestine, and one unknown case), 9 were leukemia [8 cases of acute myelogenous leukemia (AML) and 2 cases of chronic myelogenous leukemia (CML)], 2 cases of multiple myeloma, and one case of myelodysplastic syndromes (MDS). Table 2 shows the details of each case. Generally, chronic inflammation is supposed to take an important role of malignant transformation in the involved organ. As *Helicobacter pylori* infection is well-known to be the major cause of gastric or duodenal MALT lymphoma, they were excluded in the analysis of the second survey to avoid confusing effects of immunomodulators in the development of the GI tract lymphoma in the patients with IBD.

Table 1 Development of hematologic malignancies in the patients with ulcerative colitis and Crohn's disease

	UC ($n = 12$)	CD ($n = 16$)
Malignant lymphoma	7	5
Non-Hodgkin's	(6)	(3)
Colonic MALToma	(1)	(1)
Unknown		(1)
Acute myelogenous leukemia	1	8
Chronic myelogenous leukemia		2
Multiple myeloma	3	2
Myelodysplastic syndrome		1
Primary macroglobulinemia	1	

UC ulcerative colitis, *CD* Crohn's disease

Table 3 shows comparison of the UC and CD patients who developed HM in the present study. The average ages of patients having UC and CD were 40.33 ± 16.83 and 26.94 ± 12.60 years, respectively. Of those who developed HM, the number of male patients with UC and CD were 4 (33.3 %) and 13 (81.3 %), respectively. The time from the onset of IBD to the development of HM was 12.44 ± 10.34 years for UC and 13.71 ± 8.31 years for CD patients. Two UC patients (16.7 %) and 4 CD patients (25 %) were receiving thiopurine drugs. None of UC patient and 6 CD patients (37.5 %) were receiving infliximab (IFX). There were no relationships between the occurrence of HM and duration of thiopurine or IFX use in each.

In the 23 facilities where the second survey was conducted, 1,341 UC patients (12.8 %) and 1,036 CD patients (16.4 %) were receiving thiopurine drugs, respectively (Table 4). The numbers of UC patients who developed HM were 2 (0.15 %) from the group receiving and 10 (0.13 %) from the group not receiving thiopurine drugs; no significant difference was found between the two. The numbers of CD patients who developed HM were 4 (0.39 %) from the group receiving and 12 (0.21 %) from the group not receiving thiopurine drugs; no significant difference was found between the two. The odds ratios of developing hematopoietic malignancy by the use of thiopurine drugs were 1.37 (95 % CI 0.30–6.24) in UC patients and 1.86 (95 % CI 0.60–5.78) in CD patients; thiopurine therapy was not found to be a contributing factor for developing hematopoietic malignancy.

Table 2 Profiles of the patients with hematologic malignancies (HM) in inflammatory bowel disease

Case	Sex	Age at the onset of IBD (years)	Age at the onset of HM (years)	Period from the onset of IBD to HM (years)	Type of IBD	Total doses of steroid (mg)	Period of thiopurine therapy (years)	Use of IFX (times)	Type of HM	Duration after diagnosis of HM (years)	Prognosis
1	F	42	56	14	UC		0.67	0	Multiple myeloma	2.75	Alive
2	F	19	56	37	UC	23725	ND	0	Non-Hodgkin's lymphoma	2	Alive
3	F	46	52	6.75	UC	6000	5.5	0	AML	2.25	Alive
4	M	20	31	10.5	UC	0	ND	0	Non-Hodgkin's lymphoma	2.25	Alive
5	F	51	63	12.08	UC	1000	ND	0	Non-Hodgkin's lymphoma	9.17	Alive
6	M	32	39	7	UC	0	ND	0	Multiple myeloma	7.17	Alive
7	F	24	53	29.75	UC	ND	ND	0	Multiple myeloma	9.92	Alive
8	F	49	52	3	UC	0	ND	0	Colonic MALToma, sigmoid colon cancer	1.5	Alive
9	M	53	63	10	UC	ND	ND	ND	Primary macroglobulinemia	3	Dead
10	F	78	85	6.67	UC	5600	ND	0	Non-Hodgkin's lymphoma	0.33	Dead
11	M	40	46	6	UC	ND	ND	0	Non-Hodgkin's lymphoma	9	Dead
12	F	30	36	6.5	UC	710000	ND	ND	Non-Hodgkin's lymphoma	2.75	Alive
13	M	13	19	6	CD	0	ND	5	Colonic MALToma	1.17	Alive
14	M	17	44	26.83	CD	19000	0.83 (13y ago)	0	AML	2.5	Dead
15	M	30	39	8.42	CD	0	ND	0	AML	2.25	Alive
16	M	18	30	12.17	CD	26148	0.25	3	AML	2.17	Alive
17	M	30	44	14	CD	ND	Unknown	10	Malignant lymphoma	1	Unknown
18	M	52	73	21	CD	2000	ND	0	Non-Hodgkin's lymphoma	3.75	Alive
19	F	44	49	5	CD	4150	ND	38	Non-Hodgkin's lymphoma	10.25	Alive
20	F	24	45	21.83	CD	9240	ND	0	Non-Hodgkin's lymphoma	Unknown	Unknown
21	M	10	32	22	CD	0	7	70	AML	1.25	Alive
22	F	19	21	2.42	CD	0	ND	2	AML	3.33	Alive
23	M	33	52	19	CD	3000	ND	0	Multiple myeloma	4.83	Dead
24	M	21	31	10	CD	0	ND	0	AML	Unknown	Alive
25	M	21	46	25	CD	ND	ND	ND	Multiple myeloma	3.42	Dead
26	M	30	48	18	CD	2015	ND	0	CML	3.08	Alive
27	M	19	24	4.75	CD	ND	ND	ND	CML	6.17	Alive
28	M	50	53	3	CD	0	ND	0	MDS	3	Dead

IBD inflammatory bowel disease, *HM* hematologic malignancies, *ND* not described, *AML* acute myelogenous leukemia, *CML* chronic myelogenous leukemia, *MDS* myelo-dysplastic syndrome

Discussion

In organ transplant recipients or RA patients, long-term use of immunomodulatory agents or infection with EB virus seems to be risk factors for HM such as LPD [4–6]. Interestingly, the rate of immunodeficiency-associated LPD regression in the Japanese patients with RA has been reported to be approximately 30 % following withdrawal of MTX [4]. However, there is a controversy because some reports show an increased risk of HM in UC patients, but other reports say there is no relation; an association between the two is not yet clear [7–20].

Table 3 Comparison of the patients with ulcerative colitis and Crohn's disease who developed hematologic malignancies in the present study

	UC	CD
Age onset IBD		
Mean ± SD (years)	40.33 ± 16.83	26.94 ± 12.60
Median (range, years)	41 (19–78)	22.5 (10–52)
Male (%)	4/12 (33.3 %)	13/16 (81.3 %)
Duration between IBD and HM		
Mean ± SD (years)	12.44 ± 10.34	13.71 ± 8.31
Median (range, years)	8.5 (3–37)	13.01 (2.42–26.83)
Thiopurine use (%)	2/12 (16.7 %)	4/16 (25 %)
IFX use (%)	0/12 (0 %)	6/16 (37.5 %)

UC ulcerative colitis, *CD* Crohn's disease, *IBD* inflammatory bowel disease, *HM* hematologic malignancies

It is still controversial whether IBD is a risk factor for developing HM or not, because some reports show an increased risk of HM in UC patients, but other reports say there is no relation [7]. Although this is the first multi-center study for the incidence of HM in the Japanese patients with IBD, it is limitation to fully clarify whether risks are involved in IBD or not. In Japan, the Japan Cancer Surveillance Research Group is involved in cancer monitoring since 2000 [29, 30] and estimate the cancer incidence every year as part of the Monitoring of Cancer Incidence in Japan (MCIJ) project, on the basis of data collected from 30 population-based cancer registries. Based on the data from the MCIJ project in 2012, the predictive incidence of malignant lymphoma, multiple myeloma and leukemia were 14.6, 3.8, 7.3 in 100,000 general population. Although the population in the present study was different from those in the MCIJ project, IBD might be a risk factor for developing HM in Japan (Table 5).

In the CESAME study conducted in France [19], 19,486 IBD patients, consisting of 7,727 UC and 11,759 CD patients, were analyzed; of which 5,867 patients were continuously receiving, 2,809 had received in the past, and 10,810 had never received thiopurine drugs. During the observation period, 23 (0.11 %) new cases of malignant lymphoma were diagnosed (22 cases of non-Hodgkin lymphoma and one case of Hodgkin lymphoma) in patients under observation. The risk of LPD in patients continuously receiving thiopurine drugs was 5.28 times (95 % CI

Table 4 Risks of hematologic malignancies in patients with IBD receiving immunomodulatory drugs

	AZA/6MP use	AZA/6MP never use	Odds ratio (95 % CI)
UC	2/1341 (0.15 %)	10/9159 (0.13 %)	1.37 (0.30–6.24, $p = 0.97$)
ML in UC	0	7	0
Leukemia in UC	1	0	0
MM in UC	1	2	3.41 (0.30–37.7, $p = 0.83$)
Primary macroglobrinemia		1	
CD	4/1036 (0.39 %)	12/5774 (0.21 %)	1.86 (0.60–5.78, $p = 0.45$)
ML in CD	1	4	1.39 (0.16–12.4, $p = 0.74$)
Leukemia in CD	3	5	3.35 (0.8–14.0, $p = 0.20$)
MM in CD	0	2	0

Table 5 Comparison of development of hematologic malignancies between in the Japanese patients with inflammatory bowel disease and general population

HD	Odds ratio	95 %CI	IBD ($n = 36{,}939$)		Japanese general population in 2006 ($n = 127{,}770{,}000$)	
			No. of HM	Incident rate*	No. of HM	Crude rate*
Malignant lymphoma	2.5991	1.5389–4.3898	14	37.9	18,636	14.6
Multiple myeloma	3.5967	1.4963–8.6456	5	13.5	4,809	3.8
Leukemia	3.3197	1.7266–6.3828	9	24.4	9,379	7.3

HM hematologic malignancies, *IBD* inflammatory bowel disease

* Patient numbers/100,000 population

2.01–13.9) higher than that in those who never received them. In our present study, the incidence rate of lymphoma among all 36,939 IBD patients was 0.03 %. The incidence rates of lymphoma in patients receiving and not receiving thiopurine drugs were 0.04 % (1/2377) and 0.07 % (11/14933), respectively; there was no significant difference in incidence rate between the two.

Pedersen et al. [31], based on meta-analysis results, reported increased risk of leukemia in UC (SIR 2.00, 95 % CI 1.31–3.06) but not in CD (SIR 0.99, 95 % CI 0.50–1.99).

In our present study, new cases of leukemia were diagnosed in one UC and 8 CD patients. Of the 9 cases, 7 were acute myeloid leukemia, 2 were chronic myeloid leukemia, and no lymphocytic leukemia was diagnosed. While the association between leukemia and CD had been reported in the past [32], some recent studies also reported cases of myeloid malignancies in CD patients [33–35]. There was a report suggesting that organ transplant recipients or patients with autoimmune disorder receiving oral azathioprine (AZA) therapy are at an increased risk of developing acute leukemia [33]. In our present study, 5 CD patients were receiving AZA, but we could not obtain results to indicate that the use of AZA increases the risk of leukemia (odds ratio 3.35, 95 % CI 0.8–14.0).

It was reported that the use of anti TNF alpha antibody for CD patients, in rare cases, causes hepatosplenic T-cell lymphoma (HSTCL) as an unfavorable prognosis, which has been drawing attention. Ochenrider et al. [36] analyzed the reported cases of 28 CD patients who developed HSTCL; all 28 patients were receiving thiopurine drugs continuously, of which 22 patients were receiving IFX concurrently. Based on those findings, the US Food and Drug Administration (FDA) has concluded that the use of anti TNF alpha antibody in young patients has an increased risk of lymphoma or other malignant lymphomas and issued an alert: tumor necrosis factor (TNF) Blockers (marketed as Remicade, Embrel, Humira, Cimzia, and Simponi) August 2009 (http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm175843.htm). Our present study did not find any new cases of HSTCL, therefore we cannot say whether IBD patients have higher risk of developing HSTCL or not.

Taken together, our present study indicated that the use of thiopurine drugs in UC patients does not increase the incidence rate of HM. Although the survey we conducted was retrospective and did not provide a high level of evidence, since those surveyed are the leading medical facilities in Japan for the treatment of IBD, we believe the results reflect present situations in Japan. Further accumulation of cases and prospective studies are necessary to conclude this important issue.

Acknowledgments This study was supported by a grant-in-aid for the Intractable Disease Project of the Ministry of Health, Labour, and Welfare of Japan.

The authors thank the 70 members of participating with IBD-MHWL for replying the questionnaires in the 1st and 2nd survey: Department of Gastroenterology and Hepatology, Tokyo Medical and Dental University (Mamoru Watanabe), Department of Human and Environmental Sciences, Kagoshima University Graduate School of Medical and Dental Sciences (Hirohito Tsubouchi), The Institute of Medical Science, The University of Tokyo (Kozo Imai), Department of Surgery, Tohoku University Graduate School of Medicine (Iwao Sasaki), Department of Medicine, Ofuna Chuo Hospital (Fumiaki Ueno), Division of Digestive Endoscopy, Shiga University of Medical Science (Yoshihide Fujiyama), Department of Public Health, Osaka City University Graduate School of Medicine (Yoshio Hirota), Department of Gastroenterology, Fukuoka University Chikushi Hospital (Toshiyuki Matsui), Department of Internal Medicine, National Defense Medical College (Soichiro Miura), Department of Internal Medicine, Keio University School of Medicine (Toshifumi Hibi), Division of Gastroenterology and Hematology/Oncology, Department of Internal Medicine, Asahikawa Medical University (Yutaka Kohgo), Department of Internal Medicine, Sakura Medical Center, Toho University (Yasuo Suzuki), The Third Department of Internal Medicine, Kansai Medical University (Kazuichi Okazaki), Department of Gastroenterology and Hepatology, Graduate School of Medicine, Kyoto University (Tsutomu Chiba), Division of Molecular and Diagnostic Pathology, Niigata University Graduate School of Medical and Dental Sciences (Yoichi Ajioka), Department of Surgery, Teikyo University School of Medicine (Toshiaki Watanabe), Department of Lower Gastroenterology, Hyogo College of Medicine Takayuki Matsumoto

Department of Surgery, Yokohama Municipal Hospital (Akira Sugita), Department of Medicine and Clinical Science, Kyushu University Graduate School of Medical Sciences (Takayuki Matsumoto), First Department of Internal Medicine, Sapporo Medical University (Yoshiaki Arimura), Department of Gastroenterology and Hepatology, Osaka University Graduate School of Medicine (Hideki Iijima), Institute of Gastroenterology, Tokyo Women's Medical University (Bun-ei Iizuka), Akita Health Care Center, Akita Red Cross Hospital (Masahiro Iizuka), Department of Surgery, Hyogo College of Medicine (Hiroki Ikeuchi), Department of Gastroenterology and Hematology, Hirosaki University Graduate School of Medicine (Yoh Ishiguro), Department of Gastroenterology and Hepatology, Shimane University School of Medicine (Shunji Ishihara), Infusion clinic (Hiroaki Ito), Division of Gastroenterology and Hepatology, Department of Internal Medicine, Keio University School of Medicine (Yasushi Iwao), Department of Gastroenterology, Imamura Hospital (Hidehisa Ohi), Department of Gastroenterology, Osaka City Juso Hospital (Kiyotaka Okawa), Department of Gastroenterology and Hepatology, Okayama University Graduate School of Medicine (Jun Kato), Departments of Surgery II, Tokyo Women's Medical University (Shingo Kameoka), Health Administration Center, Center for the Advancement of Higher Education, Tohoku University (Yoshitaka Kinouchi), Department of Gastroenterological Medicine, Wakakusadaiichi Hospital (Atsuo Kitano), Department of Endoscopy, Ryukyu University Hospital (Fukunori Kinjo), Departments of Gastrointestinal and Pediatric Surgery, Mie University Graduate School of Medicine (Masato Kusunoki), Digestive Disease Center, Showa University Northern Yokohama Hospital (Shin-ei Kudo), Department of Gastroenterology, Kitasato University East Hospital (Kiyonori Kobayashi), Department of Gastroenterology, Nagoya University Graduate School of Medicine (Hidemi Goto), Department of Gastroenterology, Aichi Medical University School of Medicine (Makoto Sasaki), Division of Gastroenterology and Hepatology, Department of Internal Medicine, The Jikei University School of Medicine (Masayuki Saruta), Department of Gastroenterology,

Osaka General Hospital of West Japan Railway Company (Seiji Shimizu), Department of Gastroenterology and Metabolism, Nagoya City University Graduate School of Medical Sciences (Takashi Joh), Department of Gastroenterology and Hepatology, Niigata City General Hospital (Kazuhito Sugimura), Departments of Gastroenterology and Hepatology, Niigata University Graduate School of Medical and Dental Sciences (Kenji Suzuki), Department of Gastroenterology and Metabolism, Hiroshima University Graduate School of Biomedical Science (Shinji Tanaka), Department of Gastroenterology, Research Institute, National Center for Global Health and Medicine (Taeko Dohi), Department of Molecular Gastroenterology and Hepatology, Kyoto Prefectural University of Medicine (Yuji Naito), Division of Gastroenterology, Yokohama City University Graduate School of Medicine (Atsushi Nakajima), Division of Digestive and General Surgery, Niigata University Graduate School of Medical and Dental Sciences (Katsuyoshi Hatakeyama), Division of Gastroenterology, Department of Internal Medicine, Kawasaki Medical School (Ken Haruma), Department of Gastroenterology, Fujita Health University School of Medicine (Ichiro Hirata), Department of Endoscopy and Ultrasound, Nara Medical University (Hisao Fujii), Department of Surgery, Fukuoka University Chikushi Hospital (Kitaro Futami), Department of Surgery, Tohoku Rosai Hospital (Yuji Funayama), Division of Gastroenterology, Department of Medicine, Kurume University School of Medicine (Keiichi Mitsuyama), Department of Gastroenterology, Sapporo Kosei General Hospital (Satoshi Motoya), Department of Surgery, Kansai Medical University Kori Hospital (Kazuhiko Yoshioka), Department of Pediatrics, Osaka Medical College (Atsushi Yoden), Department of Gastroenterology, Osaka City University Graduate School of Medicine (Kenji Watanabe), Department of Internal Medicine, Koukann Clinic (Hitoshi Asakura), Department of Gastroenterological Surgery, Cancer Institute Hospital (Tetsuichiro Muto), First Department of Internal Medicine, Hirosaki University School of Medicine (Akihiro Munakata), Department of Medicine and Clinical Oncology, Graduate School of Medicine, Chiba University (Tatsuro Katsuno), Department of Gastroenterology, Graduate School of Medicine, Kanazawa University (Takashi Kagaya), Department of Gastroenterology, St. Luke's International Hospital (Katsuyuki Fukuda), Inflammatory Bowel Disease Center, Yokohama City University Medical Center (Reiko Kunisaki), Department of Pediatrics, Osaka General Medical Center (Hitoshi Tajiri), Department of Pediatrics, Gunma University Graduate School of Medicine (Takashi Ishige), Department of Gastroenterology and Hematology, Faculty of Medicine, University of Miyazaki (Shojiro Yamamoto).

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Jones JL, Loftus EV Jr. Lymphoma risk in inflammatory bowel disease: is it the disease or its treatment? Inflamm Bowel Dis. 2007;13:1299–307.
2. Ueno F, Matsui T, Matsumoto T, et al. Evidence-based clinical practice guidelines for Crohn's disease, integrated with formal consensus of experts in Japan. J Gastroenterol. 2013;48:31–72.
3. Hamilton MJ, Snapper SB, Blumberg RS. Update on biologic pathways in inflammatory bowel disease and their therapeutic relevance. J Gastroenterol. 2012;47:1–8.
4. Hoshida Y, Xu J-X, Fujita S, et al. Lymphoproliferative disorders in rheumatoid arthritis: clinic-pathological analysis of 76 cases in relation to methotrexate medication. J Rheumatol. 2007;34:322–31.
5. Kondo S, Tanimoto K, Yamada K, et al. Mature T/NK-cell lymphoproliferative disease and Epstein-Barr virus infection are more frequent in patients with rheumatoid arthritis treated with methotrexate. Virchows Arch. 2013;462:399–407.
6. Ichikawa A, Arakawa F, Kiyasu J, et al. Methotrexate/iatrogenic lymphoproliferative disorders in rheumatoid arthritis: histology, Epstein-Barr virus, and clonality are important predictors of disease progression and regression. Eur J Haematol. 2013;91:20–8.
7. Sokol H, Beaugerie L. Inflammatory bowel disease and lymphoproliferative disorders: the dust is starting to settle. Gut. 2009;58:1427–36.
8. Ekbom A, Helmick C, Zack M, et al. Extracolonic malignancies in inflammatory bowel disease. Cancer. 1991;67:2015–9.
9. Persson PG, Karlen P, Bernell O, et al. Crohn's disease and cancer: a population-based cohort study. Gastroenterology. 1994;107:1675–9.
10. Karlen P, Lofberg R, Brostrom O, et al. Increased risk of cancer in ulcerative colitis: a population-based cohort study. Am J Gastroenterol. 1999;94:1047–52.
11. Loftus EV Jr, Tremaine WJ, Habermann TM, et al. Risk of lymphoma in inflammatory bowel disease. Am J Gastroenterol. 2000;95:2308–12.
12. Palli D, Trallori G, Bagnoli S, et al. Hodgkin's disease risk is increased in patients with ulcerative colitis. Gastroenterology. 2000;119:647–53.
13. Bernstein CN, Blanchard JF, Kliewer E, et al. Cancer risk in patients with inflammatory bowel disease: a population-based study. Cancer. 2001;91:854–62.
14. Lewis JD, Bilker WB, Brensinger C, et al. Inflammatory bowel disease is not associated with an increased risk of lymphoma. Gastroenterology. 2001;121:1080–7.
15. Winther KV, Jess T, Langholz E, et al. Long-term risk of cancer in ulcerative colitis: a population-based cohort study from Copenhagen County. Clin Gastroenterol Hepatol. 2004;2:1088–95.
16. Jess T, Winther KV, Munkholm P, et al. Intestinal and extraintestinal cancer in Crohn's disease: follow-up of a population-based cohort in Copenhagen County, Denmark. Aliment Pharmacol Ther. 2004;19:287–93.
17. Askling J, Brandt L, Lapidus A, et al. Risk of haematopoietic cancer in patients with inflammatory bowel disease. Gut. 2005;54:617–22.
18. von Roon AC, Reese G, Teare J, et al. The risk of cancer in patients with Crohn's disease. Dis Colon Rectum. 2007;50:839–55.
19. Beaugerie L, Brousse N, Bouvier AM, et al. Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. Lancet. 2009;374:1617–25.
20. Vos AC, Bakkal N, Minnee RC, et al. Risk of malignant lymphoma in patients with inflammatory bowel diseases: a Dutch nationwide study. Inflamm Bowel Dis. 2011;17:1837–45.
21. Kinlen LJ. Incidence of cancer in rheumatoid arthritis and other disorders after immunosuppressive treatment. Am J Med. 1985;78:44–9.
22. Connell WR, Kamm MA, Dickson M, et al. Long-term neoplasia risk after azathioprine treatment in inflammatory bowel disease. Lancet. 1994;343:1249–52.
23. Korelitz BI, Mirsky FJ, Fleisher MR, et al. Malignant neoplasms subsequent to treatment of inflammatory bowel disease with 6-mercaptopurine. Am J Gastroenterol. 1999;94:3248–53.
24. Farrell RJ, Ang Y, Kileen P, et al. Increased incidence of non-Hodgkin's lymphoma in inflammatory bowel disease patients on immunosuppressive therapy but overall risk is low. Gut. 2000;47:514–9.
25. Fraser AG, Orchard TR, Robinson EM, et al. Long-term risk of malignancy after treatment of inflammatory bowel disease with azathioprine. Aliment Pharmacol Ther. 2002;16:1225–32.

26. Kandiel A, Fraser AG, Korelitz BI, et al. Increased risk of lymphoma among inflammatory bowel disease patients treated with azathioprine and 6-mercaptopurine. Gut. 2005;54:1121–5.
27. Glazier KD, Palance AL, Griffel LH, et al. The ten-year single-center experience with 6-mercaptopurine in the treatment of inflammatory bowel disease. J Clin Gastroenterol. 2005;39:21–6.
28. Yano Y, Matsui T, Hirai F, et al. Cancer risk in Japanese Crohn's disease patients: investigation of the standardized incidence ratio. J Gastroenterol Hepatol. 2013;28:1300–5.
29. Matsuda T, Marugame T, Kamo K, et al. Cancer Incidence and Incidence Rates in Japan in 2005: based on Data from 12 Population-based Cancer Registries in the Monitoring of Cancer Incidence in Japan (MCIJ) Project. Jpn J Clin Oncol. 2011;41:139–47.
30. Matsuda T, Marugame T, Kamo K, et al. Cancer incidence and incidence rates in Japan in 2006: based on data from 15 population-based cancer registries in the monitoring of cancer incidence in Japan (MCIJ) project. Jpn J Clin Oncol. 2012;42:139–47.
31. Pedersen N, Duricova D, Elkjaer M, et al. Risk of extra-intestinal cancer in inflammatory bowel disease: meta-analysis of population-based cohort studies. Am J Gastroenterol. 2010;105:1480–7.
32. Caspi O, Polliack A, Klar R, et al. The association of inflammatory bowel disease and leukemia–coincidence or not? Leuk Lymphoma. 1995;17:255–62.
33. Froilan Torres C, Castro Carbajo P, Pajares Villarroya R, et al. Acute spontaneous tumor lysis syndrome in a patient with Crohn's disease taking immunosuppressants. Rev Esp Enferm Dig. 2009;101:288–94.
34. Walker G, Venkatachalam P, Bird J, et al. Mixed fortunes in the treatment of Crohn's disease. Lancet. 2012;379:2212.
35. Mullier F, Rahier JF, Maignen F, et al. A case of therapy-related myeloid neoplasm in a patient with Crohn's disease treated with azathioprine. Acta Haematol. 2012;128:1–6.
36. Ochenrider MG, Patterson DJ, Aboulafia DM. Hepatosplenic T-Cell lymphoma in a young man with Crohn's disease: case report and literature review. Clin Lymphoma Myeloma Leuk. 2010;10:144–8.

Journal of Gastroenterology and Hepatology

JGHF

doi:10.1111/jgh.12411

GASTROENTEROLOGY

Use of capsule endoscopy in patients with Crohn's disease in Japan: A multicenter survey

Motohiro Esaki,* Takayuki Matsumoto,* Kenji Watanabe,† Tetsuo Arakawa,† Yuji Naito,‡ Minoru Matsuura,§ Hiroshi Nakase,§ Toshifumi Hibi,¶ Takayuki Matsumoto,** Sadaharu Nouda,†† Kazuhide Higuchi,†† Naoki Ohmiya,‡‡ Hidemi Goto,‡‡ Sei Kurokawa,§§ Satoshi Motoya§§ and Mamoru Watanabe¶¶

*Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, †Department of Gastroenterology, Osaka City University, Graduate School of Medicine, Osaka, ‡Molecular Gastroenterology and Hepatology, Kyoto Prefectural University of Medicine, §Department of Gastroenterology and Hepatology, Graduate School of Medicine, Kyoto University, Kyoto, ¶Division of Gastroenterology and Hepatology, Department of Internal Medicine, Keio University School of Medicine, ¶¶Department of Gastroenterology, School of Medicine, Tokyo Medical and Dental University, Tokyo, **Division of Lower Gastroenterology, Department of Internal Medicine, Hyogo College of Medicine, Nishinomiya, Hyogo, ††Second Department of Internal Medicine, Osaka Medical College, Takatsuki, ‡‡Department of Gastroenterology, Nagoya University Graduate School of Medicine, Nagoya, and §§Division of Gastroenterology, Sapporo Kosei General Hospital, Sapporo, Japan

Key words
capsule endoscopy, Crohn's disease, diagnosis, retention.

Accepted for publication 29 August 2013.

Correspondence
Dr Motohiro Esaki, Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Maidashi 3-1-1, Higashi-ku, Fukuoka 812-8582, Japan. Email: mesaki@intmed2.med.kyushu-u.ac.jp

Conflicts of interest: The authors declare no potential conflicts of interest with regards to the manuscript.

Abstract

Background and Aim: Until the approval of patency capsule, capsule endoscopy (CE) has not been routinely applied for the diagnosis of Crohn's disease (CD) in Japan. We aimed to survey current situation of CE use for patients with CD in Japan.

Methods: The nationwide survey of 40 Japanese institutions identified 94 patients with established CD (eCD) and 80 patients with suspected CD (sCD), who were examined by CE. Types and positive rates of mucosal injury under CE and capsule retention rate were investigated. In sCD, final diagnosis after CE was also analyzed.

Results: Patients with eCD comprised 82 patients of ileitis or ileocolitis type, while 12 patients had CD of colitis type. CE identified mucosal injuries in 83 of 94 patients. Eight of 12 patients with eCD of colitis type had ileal lesions under CE, thereby being reclassified as ileocolitis type. In patients with sCD, CE detected mucosal injuries in 58 patients. Linear ulceration and cobblestone appearance were depicted in 22 and 3 patients, respectively, thereby resulting in established diagnosis of CD in 23 patients. Mucosal lesion was not found in 22 patients with sCD, who were diagnosed as not having CD. Capsule retention rate was not statistically different between patients with eCD and those with sCD (7.4% *vs* 6.3%, $P = 1.0$).

Conclusions: CE is useful for the evaluation of small bowel mucosal injuries in Japanese patients with sCD and eCD. Possible intestinal stricture needs to be carefully evaluated before CE even in patients with sCD.

Introduction

Capsule endoscopy (CE) is a minimally invasive diagnostic tool that enables complete visualization of the small bowel mucosa. CE obviously allowed major implications for the diagnosis, therapeutic decision-making, and outcomes in the management of obscure gastrointestinal (GI) bleeding.[1–3] Recently, the availability of CE for other clinical conditions, including hereditary polyposis syndrome,[4,5] malabsorption syndrome,[6,7] and inflammatory bowel diseases,[8,9] have been increasingly reported. In Crohn's disease (CD), a growing body of evidence shows a favorable diagnostic yield of CE ranging between 58% and 71%,[10–13] and a recent meta-analysis confirmed significantly higher diagnostic yields of CE when compared with small bowel radiography, computed tomography (CT) enterography, or magnetic resonance enterography.[14] However, the European Crohn's and Colitis Organisation (ECCO) and the Organisation Mondiale d'Endoscopie Digestive (OMED) consensus recommended a rigorous selection for the application of CE because the risk of capsule retention is increased especially in CD patients with intestinal stenosis.[15]

Unlike in Western countries, established CD (eCD) was a contra-indication for CE in Japan until the recent approval of patency capsule. Thus, the clinical role of CE for the diagnosis of CD remains uncertain in Japan, where its original diagnostic

criteria[16] exist. Furthermore, the diagnostic process in Japan may be different from that in Western countries, especially as to the selection of small bowel examinations. We thus conducted a nationwide survey to identify the role of CE for Japanese patients with suspected or eCD.

Methods

Contents of the questionnaire sheet. As a nationwide survey by the Research Committee of Inflammatory Bowel Disease organized by Japanese Ministry of Labour and Welfare, questionnaire sheets were sent to 62 Japanese institutions majoring in inflammatory bowel diseases in October 2010. The study protocol was approved by the ethical committee at Kyushu University Hospital, and the study was conducted in accordance with the Helsinki Declaration. In addition, the study protocol was also approved by the ethical committee at each institution where CE was performed for patients with eCD, since established CE was a contra-indication for CE in Japan at the time of this survey.

The questionnaire comprised three sections. The initial section included a query regarding the total number of patients examined by CE at the time of this survey. The following two sections contained queries for eCD and for suspected CD (sCD). The information collected in both sections included the number of CE cases, positive cases of small bowel mucosal injury, and cases suffering capsule retention. In eCD, queries regarding the reason for the application of CE and possible contribution of CE in the determination of small bowel involvement were added. In sCD, the number of cases who could confirm the diagnosis of CD under CE, as well as the diagnosis and the number of cases achieving subsequent clinical diagnosis other than CD were further evaluated. Clinical information of this retrospective survey was obtained by reviewing medical records of the patients at each institution.

In order to determine the current position of CE in the diagnosis of CD, the priority of five small bowel procedures (CE, small bowel radiography, anterograde balloon endoscopy [BE], retrograde BE, and abdominal CT) was graded separately for eCD and sCD.

Definition of eCD and sCD. eCD was regarded as the condition, which fulfilled Japanese diagnostic criteria for CD.[16] The diagnostic criteria included linear ulceration, cobblestone appearance, and histologically verified granuloma within GI tract. sCD was regarded as a condition suspected of having CD based on clinical symptoms, laboratory data, or other abdominal imaging modalities, which did not fulfill the Japanese diagnostic criteria.

Types of mucosal injury under CE. The types of mucosal injury under CE were classified into four types. A whitish crater surrounded by mucosal erythema presumably measuring over 5 mm was defined as an ulcer (Fig. 1a). A superficial whitish

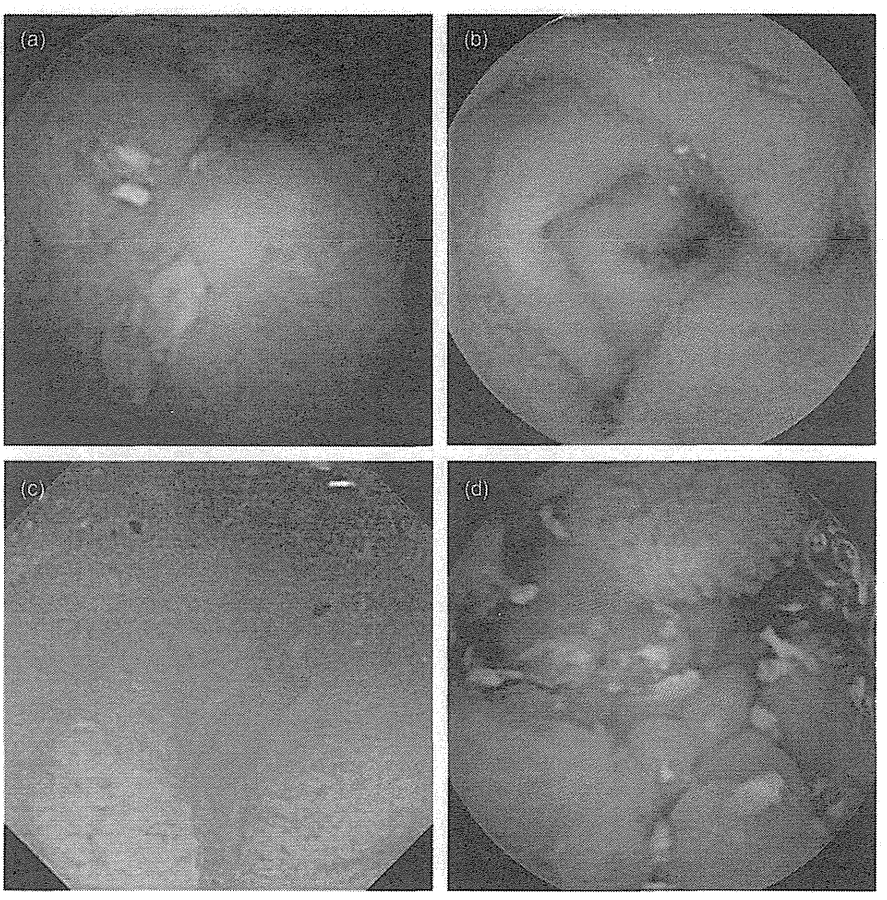

Figure 1 Typical capsule endoscopy (CE) images of mucosal injuries. Mucosal injuries were classified into four types, ulcer (a), erosion (b), linear ulceration (c), and cobblestone appearance (d).

lesion with surrounding erythema less than 5 mm in size was classified as an erosion (Fig. 1b). The diagnosis of linear ulceration (Fig. 1c) and cobblestone appearance (Fig. 1d) was based on the description in the Japanese criteria for the diagnosis of CD. Other types of mucosal injuries included luminal stenosis with or without capsule retention, and an orifice of possible intestinal fistula.

Statistical analysis. All the categorical variables were expressed as frequencies and percentages throughout the manuscript. Capsule retention rates between eCD and sCD were compared using Fisher's exact probability test. A P value of less than 0.05 was regarded as statistically significant.

Results

Of the 62 institutions, 40 institutions (65%) responded to the survey until March 31, 2011, and 5944 cases examined by CE were accumulated. CE was performed in 94 patients with eCD and 80 patients with sCD. All the patients with eCD and sCD underwent CE at the participating institutions after written informed consent for CE was obtained. These patients accounted for 2.9% of all CE examinations. The disease type of eCD was ileocolonic disease in 50 patients (53%), isolated ileal disease in 32 patients (34%), and isolated colonic disease in 12 patients (13%). In eCD, CE was applied for purposes of the possible identification of small bowel mucosal injury in 55 patients (58%), for the evaluation of therapeutic efficacy in 34 patients (36%), and for the determination of bleeding source in 5 patients (6%). In patients with sCD, ileocolonoscopy was performed in 66 patients (83%), esophagogastroduodenoscopy in 61 patients (76%), small-bowel follow-through study in 46 patients (58%), double balloon endoscopy in 6 patients (8%), abdominal CT and ultrasonography each in 5 patients (6%), barium enema examination in 2 patients (3%), and barium meal examination and Ga scintigraphy each in a patient (1%) before CE.

CE findings and capsule retention. Total enteroscopy was achieved under CE in 84 cases (89%) in eCD and 72 cases (90%) in sCD. CE identified small bowel mucosal injuries in 83 cases (88%) in eCD and 58 cases (73%) in sCD. The type and the prevalence of mucosal injury in eCD and sCD are described in Table 1. Erosions and ulcers were frequently identified in both eCD and sCD. CE also detected linear ulcerations in nearly half of the patients with eCD. Furthermore, linear ulceration was found in 22 (28%) of 80 patients with sCD.

In eCD, CE depicted intestinal strictures in 14 patients, seven of whom suffered from subsequent capsule retention. Surprisingly, intestinal strictures were found in six patients with sCD, five of whom manifested capsule retention. Among the 12 patients, the capsule retained in the jejunum in 1, the ileum in 10, and the colon in 1. The retained capsule was collected endoscopically in seven patients; however, surgery was performed in two patients. The retained capsule was naturally excreted in three patients afterwards. Consequently, the incidence of capsule retention in sCD was as high as that in eCD (6.0% *vs* 7.4%, $P = 1.0$). The luminal orifice of intestinal fistula was not found in any patients with eCD or sCD.

Clinical outcomes. CE identified small bowel mucosal injuries in 75 (91%) of 82 patients with eCD of ileitis or ileocolitis type. CD also identified small bowel mucosal injuries in 8 (67%) of 12 patients with eCD of colitis type. By means of CE, the disease type of CD was changed from colitis type to ileocolitis type in eight patients.

Table 2 shows final clinical diagnosis in sCD according to CE results. Of the 58 patients with positive CE, clinical diagnosis was established in 31 patients. The diagnoses included CD, chronic nonspecific multiple ulcers of the small intestine,[17] simple ulcers of the small intestine, intestinal Behçet's disease, and intestinal tuberculosis. However, clinical diagnosis remained obscure in the other 27 patients. The diagnosis of CD was excluded in 22 patients showing negative CE. Consequently, the diagnosis of CD was confirmed in 29% of patients with sCD.

Priority of CE in the diagnosis of CD. Corresponding Japanese gastroenterologists in 28 (70%) of 40 institutions replied that CE is considered to be useful for the evaluation of small bowel mucosal injuries in eCD. However, CE was graded to be unnecessary by 12 institutions. The reasons for such a decision were a lack of clinical advantage ($n = 7$), insufficient inspection ($n = 3$), or possible retention risk ($n = 6$). For sCD, CE was regarded to be useful in 36 (90%) of 40 institutions. However, the diagnostic yield of CE was presumed to be less than that of small bowel radiography and BE in four institutions. The result of the determination for

Table 1 Prevalence of mucosal injury in established or suspected CD

Type of injury	Established CD ($n = 94$)	Suspected CD ($n = 80$)
Erosion	66 (70%)	49 (61%)
Ulcer	53 (56%)	36 (45%)
LU	43 (46%)	22 (28%)
CA	12 (13%)	3 (4%)
Stricture	14 (15%)	6 (8%)
Fistula	0 (0%)	0 (0%)

CA, cobblestone appearance; CD, Crohn's disease; LU, linear ulceration.

Table 2 CE results and final clinical diagnoses in suspected CD

Positive CE	58 (73%)
CD	23
CNSU	3
Simple ulcer	3
Behçet's disease	1
Intestinal tuberculosis	1
Unknown	27
Negative CE	22 (27%)
Ulcerative colitis	2
Irritable bowel syndrome	2
Normal	18

CE, capsule endoscopy; CD, Crohn's disease; CNSU, chronic nonspecific multiple ulcers of the small intestine.[17]

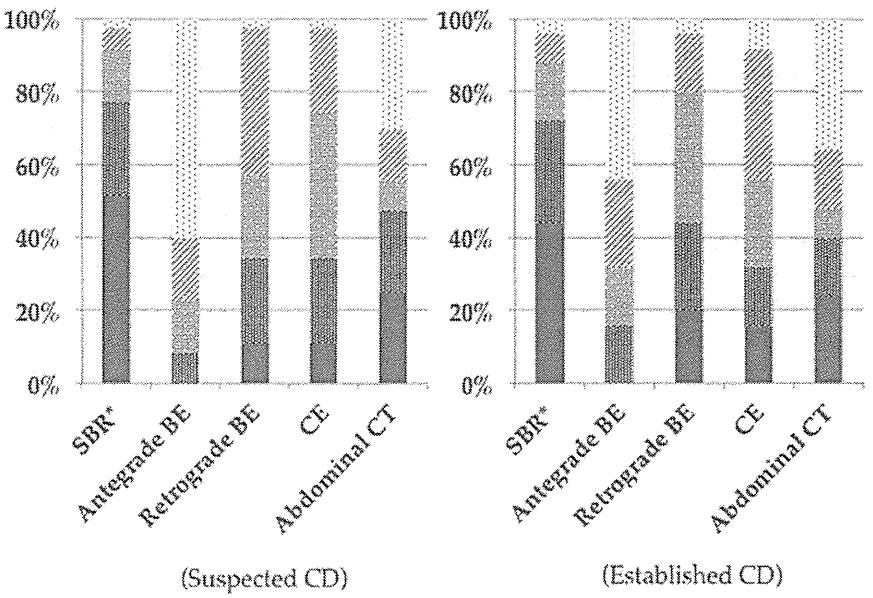

Figure 2 Priority of small bowel procedures in suspected and established Crohn's disease (CD). *SBR; small bowel radiography. †BE; balloon-assisted endoscopy. Priority grade (1 = high to 5 = low): ■, 1; ▩, 2; ▒, 3; ▨, 4; ⁝, 5.

the priority of five procedures in sCD and eCD is shown in Figure 2. The priority of CE was judged to be comparatively low in both sCD and eCD.

Discussion

CD is a chronic inflammatory disorder that may affect any segment of the gastrointestinal tract. Although any part of the gastrointestinal tract can be involved, CD most commonly affects the small bowel, with up to 30% of patients presenting isolated small bowel disease.[18] Because a diagnosis of CD is based on a combination of clinical, biochemical, radiologic, endoscopic, and histologic findings,[1] imaging procedures for the small bowel play a crucial role. With this regard, small bowel radiography (including enteroclysis and double contrast study) has been the most commonly applied in Japan, even though complicated angulation of the small bowel easily interrupts lesion detection, leading possible false negative results. Push enteroscopy and ileocolonoscopy have been also available. However, these procedures can only unveil mucosal lesions of the restricted part of the small bowel.[19,20]

CE enables direct visualization of the entire small bowel. Furthermore because CE also allows the detection of subtle mucosal changes, there has been a growing interest in the use of CE for patients with suspected and eCD.[10–13,20–25] In a recent meta-analysis by Dionisio *et al.*,[14] CE demonstrated a significantly greater diagnostic yield when compared with small bowel radiography, CT enterography, and ileocolonoscopy in patients with suspected or established diagnosis of CD. However, the meta-analysis by Dionisio *et al.*[14] included a larger amount of studies which dealt with small bowel erosions as a positive finding for CD. It thus has been criticized that the result of the meta-analysis is not necessarily representative of the diagnostic ability of CE in CD.[26] In Japan, where the proposed diagnostic criteria of CD are mainly composed of the endoscopic or macroscopic characteristics of the gastrointestinal lesions (linear ulceration and cobblestone appearance),[16] it remains uncertain whether CE is useful for the diagnosis and the evaluation of CD. We thus performed this nationwide survey to clarify the value of CE in Japanese patients with sCD or eCD.

In the present study, CE identified small bowel mucosal injuries in 88% of patients with eCD, while the detection rate of mucosal injuries characteristic of CD was not so high. This was especially the case for patients with known small bowel involvement because the detection rate of mucosal injuries by CE in those patients reached 91%. It thus seems likely that CE has a significant diagnostic yield for Japanese patients with eCD. Of interest, the procedure could identify mucosal injuries even in 67% of CD patients who had been regarded to have an isolated colonic disease. Thus, as has been suggested in an international OMED-ECCO consensus statement,[15] CE may be appropriate for CD patients having apparently isolated colonic disease under other imaging procedures. However, comparative studies with CE and other modalities are required to confirm such indication.

The major role of the imaging procedures in patients with sCD is the detection of characteristic intestinal lesions compatible with the disease. In the present survey, CE identified linear ulcerations or cobblestone appearance, which are two major items in the Japanese diagnostic criteria for CD,[16] in only 28% of the patients. It thus seems possible that the diagnostic value of CE in our patients was apparently lower than that reported previously.[1,14,22,26] However, such a discrepancy is obviously a consequence of obscure criteria for the diagnosis of CD in the previous reports.[1,14,22,26] It thus seems inevitable to evaluate a diagnostic yield of CE for CD under common diagnostic criteria. With this regard, the criteria reported by Mow *et al.*,[27] namely diffuse or multiple (> 3) small bowel ulcerations without a current consumption of nonsteroidal anti-inflammatory drugs, may be a candidate. However, the sensitivity and specificity of the criteria need to be established.

Although CE is a minimally invasive diagnostic tool for small bowel pathology, possible significant complications of the procedure should be considered. In patients with eCD prone to intestinal strictures, capsule retention seems to be a major