

## Novel endoscopic activity index is useful for choosing treatment in severe active ulcerative colitis patients

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### Abstract

**Aim** Clinical symptoms are the most important factors used by physicians to evaluate the severity and extent of ulcerative colitis (UC). In this context, colonoscopy is also a useful diagnostic tool. We have recently developed an endoscopic activity index (EAI) to assess the severity of UC. Here, we assess the correlations among the EAI, other endoscopic indices, and clinical scores. The usefulness of the EAI for choosing treatment options, such as intravenous corticosteroid or cyclosporine A (CsA), in severe UC patients was also evaluated.

**Methods** Clinical symptoms and endoscopic finding were evaluated in 396 patients with UC (454 colonoscopies). The EAI was scored using the following six items: ulcer size, ulcer depth, redness, bleeding, edema, and mucus exudates. The patients were also scored using Matts' grade, Rachmilewitz's endoscopic index, and the Lichtiger index.

**Results** Our results showed that (1) the EAI scores were closely correlated with those of the Lichtiger index, Matts' grade, and Rachmilewitz's endoscopic index; (2) the EAI scores significantly decreased in patients who responded to treatment, while Matts' grade did not change in some

responders treated with intravenous CsA and steroid; (3) patients with a higher EAI (14–16) tended to be refractory to corticosteroid therapy (responders 19%) compared to CsA (77%), while steroid treatment was effective in 58% of patients with EAI scores of 11–13.

**Conclusions** The EAI is equivalent to other endoscopic indices and relatively more useful in choosing a treatment for patients with severe UC.

**Keywords** Cyclosporine A · Endoscopic activity index · Ulcerative colitis

### Introduction

Ulcerative colitis (UC) is an inflammatory bowel disease of unknown aetiology. It is characterized by severe inflammation of the colonic mucosa and by periods of remission and acute episodes of relapse. Corticosteroid treatment is considered to be the treatment of choice in patients with more severe symptoms who do not respond to initial therapy. Severe UC is a serious condition that is accompanied by diarrhea, abdominal pain, fever, dehydration, and tachycardia, and patients with this condition require hospitalization and intensive treatment. For many years, the standard therapy has been the administration of intravenous corticosteroids, which promotes remission in up to 60% of patients [1]. However, 20% of patients treated with intravenous steroid show no improvement of symptoms [1, 2] and require further therapy with intravenous cyclosporine A (CsA) or infliximab (IFX) or a total colectomy. Lichtiger et al. [3] demonstrated that intravenous CsA therapy is rapidly effective in more than 80% of steroid-refractory UC patients, and this result has been confirmed by a number of additional clinical trials [4–7]. The efficacy

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of IFX for steroid-refractory UC patients has also been demonstrated in a small controlled trial [8].

While total colonoscopy should not be performed at a time when it carries the risk of inducing toxic megacolon [9], sigmoidoscopy can be attempted by expert colonoscopists to assess the severity of the disease and rule out other causes of severe colitis. Sigmoidoscopy is a useful tool for evaluating the severity of UC because it allows the clinician to observe the inflamed mucosa directly and to take biopsies. The evaluation of disease activity based on endoscopy findings has been described in several articles. Truelove and Witts were the first to report the use of sigmoidoscopic assessment in an evaluation of the efficacy of steroid treatment in patients with active UC. Based on their results, they classified their patients into four categories: normal, improved, no change, and worse [1]. The Baron score, the Powell–Tuck sigmoidoscopic assessment, and the Mayo score for proctosigmoidoscopy have also been reported. These scores define patients into three or four categories based on specified findings. However, although these scores are easy for investigators to use, they do not show short-term changes because mucosal improvement and healing take a relatively long time compared to clinical responses. Rachmilewitz's endoscopic index uses four items, namely, granulation, vascular pattern, vulnerability of the mucosa, and mucosal damage [10], and the scores range from 0 to 12 points. Rachmilewitz's endoscopic index was used as an assessment tool in a controlled trial of mesalamine and sulfasalazine and the findings indicate that this index may be considered for use in patients with mild to moderate UC. When Rachmilewitz's endoscopic index is applied, most cases treated with IFX or CsA have the highest score (12 points).

We have recently developed an endoscopic activity index (EAI) to assess the severity of UC from remission to the most severe cases. Among patients with severe UC, this score may be able to distinguish more severe cases from moderate to severe cases. The aim of the study reported here was to analyze the correlations among EAI, other endoscopic indices, and clinical scores. The utility of the EAI in facilitating the treatment decision process in severe UC patients was also assessed.

## Patients and methods

### Scoring UC with the EAI

Clinical symptoms and endoscopic findings were evaluated in 396 UC patients who underwent 454 colonoscopies between 2006 and 2007. Total colonoscopies could not be performed in 28 (6.2%) patients due to the severity of the disease symptoms or reports of unbearable pain by the

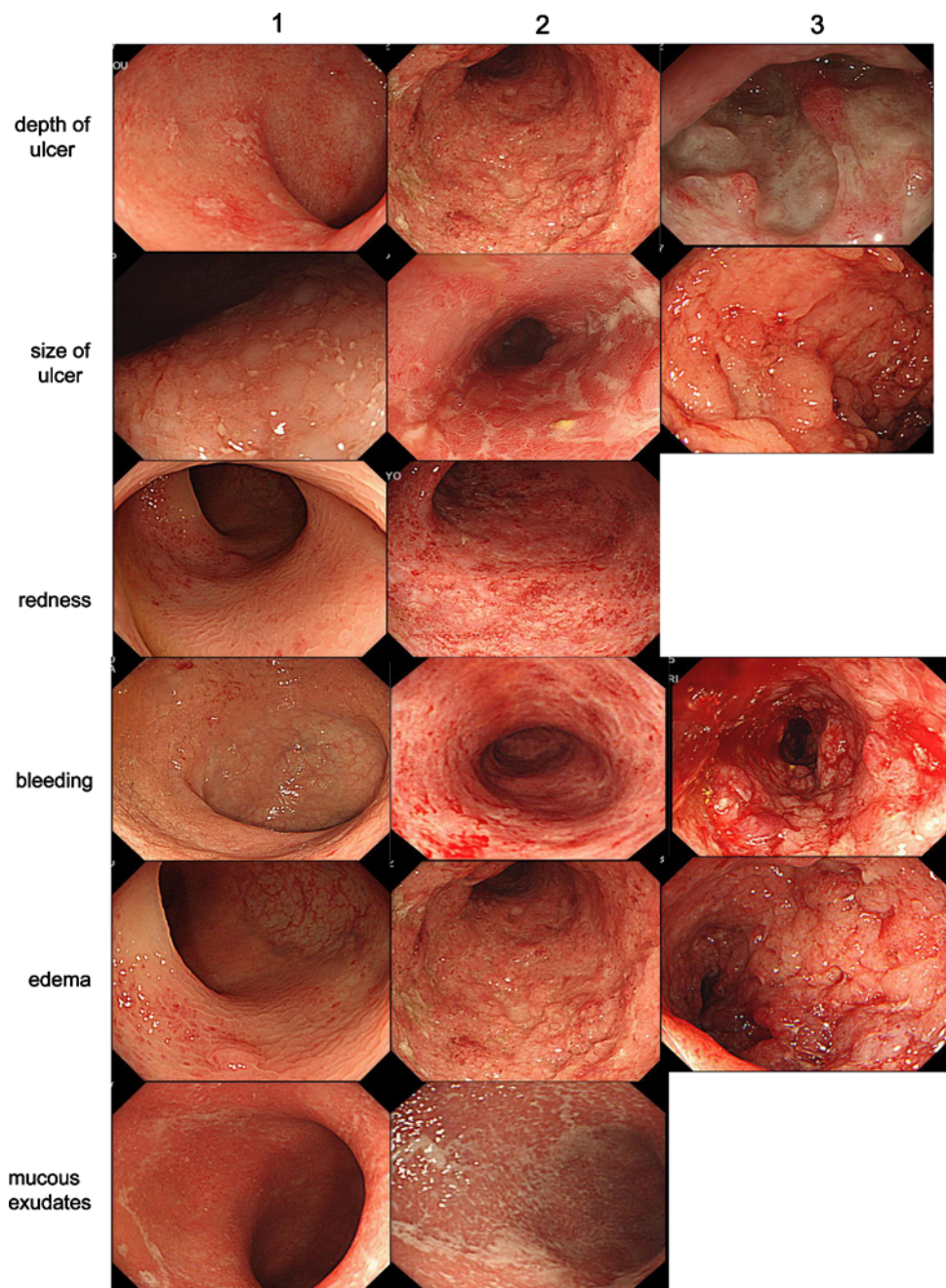
patient during the colonoscopy. These patients underwent a sigmoidoscopy. Inpatients and outpatients from the gastroenterology clinic between the ages of 13 and 71 years with active moderate to severe UC confirmed by colonoscopy were eligible for enrollment. At the time of diagnosis, infectious colitis, radiation colitis, ischemic colitis, Crohn's disease, and intestinal Behcet's disease were excluded. Table 1 shows the scoring system for the EAI. The EAI was scored using the following six items: (1) ulcer size, (2) ulcer depth, (3) redness, (4) bleeding, (5) edema, and (6) mucus exudates. Typical endoscopic findings for each sub-score are shown in Fig. 1. Scores using Matts' classification (1–4) [11] and Rachmilewitz's endoscopic index (0–12) [6] were also determined. The EAI was compared with the other endoscopic scores and the Lichtiger's clinical activity index (CAI) (0–21).

**Table 1** Items included in the endoscopic activity index (EAI)

Items 1–3 of the EAI	
Size of ulcers	
0	None
1	Erosion/small ulcer
2	Intermediate
3	Wide-ranged mucosal defects
Depth of ulcers	
0	None
1	Shallow
2	Intermediate
3	Deep
Redness	
0	None
1	Mild
2	Marked
Items 4–6 of the EAI	
Bleeding	
0	None
1	Contact bleeding
2	Spontaneous bleeding
3	Massive bleeding
Mucosal edema	
0	None
1	Mild
2	Moderate
3	Severe
Mucous exudate	
0	None
1	Mild
2	Marked

For each of the six items, scores of zero to two/three can be given, depending on the severity of the item, with a higher score indicating the more severe condition

**Fig. 1** The endoscopic activity index (EAI) was scored using the following six items: ulcer size (0 none, 1 erosion/small ulcers, 2 intermediate, 3 wide-ranging mucosal defect), ulcer depth (0 none, 1 shallow, 2 intermediate, 3 deep), redness (0 none, 1 mild, 2 severe), bleeding (0 none, 1 contact bleeding, 2 spontaneous, 3 massive), edema (0 none, 1 mild, 2 moderate, 3 severe), and mucus exudates (0 none, 1 mild, 2 marked)



Among our patient cohort, 25 colonoscopies were repeated within 30 (range 16–29) days to evaluate the efficacy of the chosen therapy. Seven patients were treated with CsA, 12 with steroid, three received apheresis therapy [12], and four were received other treatments, such as IFX and immunomodulators. The relationships between the changes in the CAI and the endoscopic severities (EAI and Matts' grade) were evaluated. The efficacy of the therapies for active UC was assessed as: remission (CAI <4 after treatment), clinical response (CAI <10 and decreased by at

least 4 points with treatment, but remission was not induced), and non-response. The changes in the EAI and the Matts' scores in the remission, response, and non-response groups were compared. The CAI was scored at the start of treatment and on the day that the second colonoscopies were performed.

We reviewed and assessed the colonoscopic findings and the medical records. The EAI was scored by a single colonoscopist (M.N.). Inter-observer variations are often observed when sigmoidoscopy/colonoscopy activity

indices are used, and since the EAI has six different items, with scores ranging from 0 to 16 points, the EAI may also be sensitive to inter-observer variation. To assess this possibility, two colonoscopists (M.N. and H.O.) scored the 40 colonoscopic findings of UC patients with various disease activities. A difference of more than 2 points in the EAI between the assessment of the two colonoscopists was defined as “variation”. The variations in the change in the EAI ( $\Delta$ EAI) following 25 treatments (described above) were also assessed. For example, if one colonoscopist gave a score of 12 points before treatment and 6 points after treatment ( $\Delta$ EAI 6) and the other colonoscopist gave scores of 13 and 4, respectively ( $\Delta$ EAI 9), variation was considered to be present.

Usefulness of the EAI for patients with severe active UC

The usefulness of the EAI for making treatment decisions for patients with severe active UC was also reviewed by analyzing the clinical and endoscopic efficacy of intravenous steroid therapy and CsA. Patients who were treated with CsA or intravenous steroid from 1998 to 2006 were analyzed, and the EAI was determined in each of the patients. Only patients who received sigmoidoscopy before and after treatments were selected for study. Of these, 48 patients treated with intravenous steroid and 43 treated with CsA had an EAI >10 (EAI 11–16). UC patients with relapses were hospitalized, sigmoidoscopy was performed to confirm the presence of active inflammation before CsA therapy or steroid therapy was initiated. Patients treated with intravenous CsA were given a continuous infusion for 14 days, with an initial dosage of 4 mg/kg daily [3], followed by dosage adjustments to maintain blood CsA levels in the range of 350–600 ng/ml. Blood samples for CsA

measurement were taken every other day or more frequently, as necessary. Patients treated with steroid therapy received the same dose for 7 days. If they responded well and achieved remission, the steroid dose was tapered. If the patients did not achieve remission, the same dose was continued for 7 more days (total 14 days). Clinical efficacy was assessed 15 days from the initiation of CsA/steroid therapy and classified as remission, response, and non-response, respectively, as described above.

The rates of remission and response to intravenous steroid/CsA treatment were compared in the highest EAI group (EAI 14–15) and the moderate EAI group (EAI 11–13).

Statistics

Statistical analysis of the data was performed using Statcel (Tokyo, Japan). The data were analyzed using the Wilcoxon signed ranks test and the chi-square test at a statistical significance level of 5%.

Results

Development of EAI for UC patients

Table 2 shows the clinical features of the UC patients in this study. More than half of the patients maintained remission or did not complain of any abdominal symptoms. Endoscopic activity was assessed in UC patients using the EAI, Matts’ classification, and Rachmilewitz’s endoscopic index. The relationship between the EAI and clinical activity was also analyzed. The CAI ranged from 0 to 19, while the EAI ranged from 0 to 15. The EAI was closely correlated with clinical activity (CAI,  $r = 0.77, p < 0.001$ )

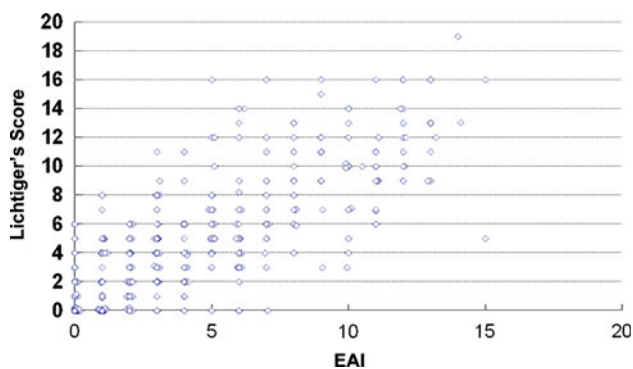
**Table 2** Patients’ clinical background

Clinical parameters	Values	Clinical parameters	Values
Gender, <i>n</i> (male:female)	264:190	Treatment at sigmoidoscopy	
Age (years)	42.8 (13–71)	SASP/5-ASA	389 (169/220)
Duration of disease (years)	8.4 (0–36)	5-ASA enema	52
Extension of disease, <i>n</i> (number of patients)		PSL enema	15 (5/10)
Total colitis	182	PSL	30
Left sided colitis	81	Apheresis	9
Procto-sigmoiditis	75	6-Mercaptopurine/azathioprine	54
Proctitis	79	Cyclosporine A	7
Others	37	Others	11
Purpose of colonoscopy, <i>n</i> (number of patients)		None	21
New patients	28		
Flare up	155		
Surveillance	169		
Evaluation of efficacy for treatment	84		

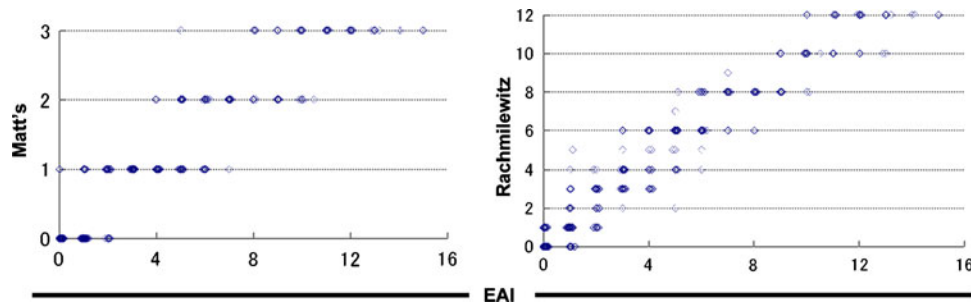
SASP/5-ASA sulphasalazine/  
5-aminosalicylic acid, PSL  
prednisolone



as Fig. 2 indicates. Discrepancies between the EAI and CAI were observed in 25 patients (5.5%). The CAI Hi group (CAI 6 or more points higher than the EAI) consisted of 18 patients, while the EAI Hi group (EAI 6 or more points higher than the CAI) consisted of eight patients. Rectal severity was mild in six of the eight patients in the EAI Hi group. In these patients, blood in the stool was not present or was not frequently observed, and endoscopic severity was relatively higher in the descending colon or right-sided colon. Thus, the EAI was relatively high with low clinical activity. In the CAI Hi group, eight patients had a CAI <12 (mild to moderate colitis), even though all patients received oral 5-aminosalicylic acid (5-ASA; CAI <11). Of these eight patients, five achieved spontaneous remission according to the colonoscopic findings, with no or mild endoscopic severity, without additional treatment; the remaining three patients were given only 5-ASA enemas or sulfasalazine. No patients needed steroid therapy.



**Fig. 2** Relationship between clinical activity and the EAI. The EAI was scored patients with active ulcerative colitis (UC) to assess endoscopic activity. A total of 454 colonoscopies were performed in 393 patients; 47 patients underwent repeat colonoscopy at 12 months (repeated two to five times). The EAI was closely correlated with Lichtiger's score ( $r = 0.77$ ,  $p < 0.001$ )



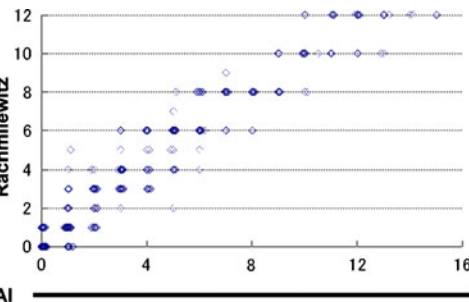
**Fig. 3** The EAI is equivalent to other endoscopic indices. A total of 454 colonoscopies were performed in 393 patients. The EAI is closely correlated with Matt's grade ( $r = 0.91$ ,  $p < 0.001$ ) and the Rachmilewitz's endoscopic index score ( $r = 0.87$ ,  $p < 0.001$ ). Rachmilewitz's endoscopic index was scored using the following four items:

The EAI is equivalent to other endoscopic indices and closely correlated to the CAI

We then assessed whether the EAI is equivalent to earlier endoscopic activity indices and found that the EAI score was closely correlated with Matt's grade ( $r = 0.91$ ,  $p < 0.001$ ) and the Rachmilewitz's endoscopic index score ( $r = 0.87$ ,  $p < 0.001$ ) (Fig. 3). However, there was a fairly wide range of EAI scores for patients with the highest Matt's grade or the highest Rachmilewitz endoscopic index score. Figure 4 shows examples of endoscopic findings with the same Matt's score (grade 4) with different EAI scores. It is apparent that more severe activity is present in the right panel of Fig. 4. In fact, patients on the left side of Fig. 4 responded to steroid treatment, while those on the right did not. These results suggest that EAI scores may be more useful for assessing patients with severe UC than Matt's score.

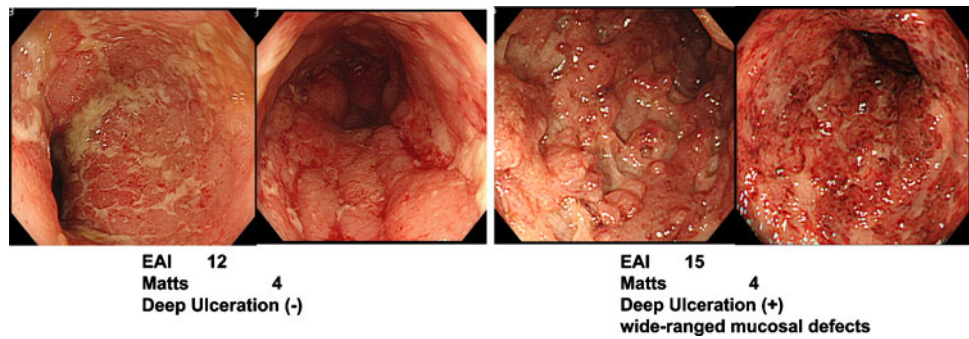
Whether the EAI score changed with improvement of the clinical symptoms was also assessed. The changes in the EAI score and Matt's grade before/after treatment were compared in the clinical remission, response, and non-response groups. With treatment, the EAI significantly decreased in the remission group (from  $8.7 \pm 1.0$  to  $2.7 \pm 1.7$ ,  $p < 0.001$ ) and the response group (from  $10.2 \pm 2.1$  to  $6.5 \pm 3.2$ ,  $p < 0.01$ ). As expected, it did not decrease in the non-response group (from  $10.3 \pm 1.7$  to  $10.0 \pm 2.1$ ) (Fig. 5). Interestingly, Matt's grade did not significantly decrease in the response group (from  $3.7 \pm 0.5$  to  $3.3 \pm 0.8$ ,  $p = 0.27$ ), though the EAI scores did decrease significantly.

Since the EAI has more items (six items) and a wider range than the other indices/grades, it was expected that greater inter-observer variation would be present compared to these other scores. The EAI scores between the two colonoscopists were completely matched in only six (15%) of 40 patients. However, the difference in EAI scores between two observers was within 2 points in 35 cases (87.5%).

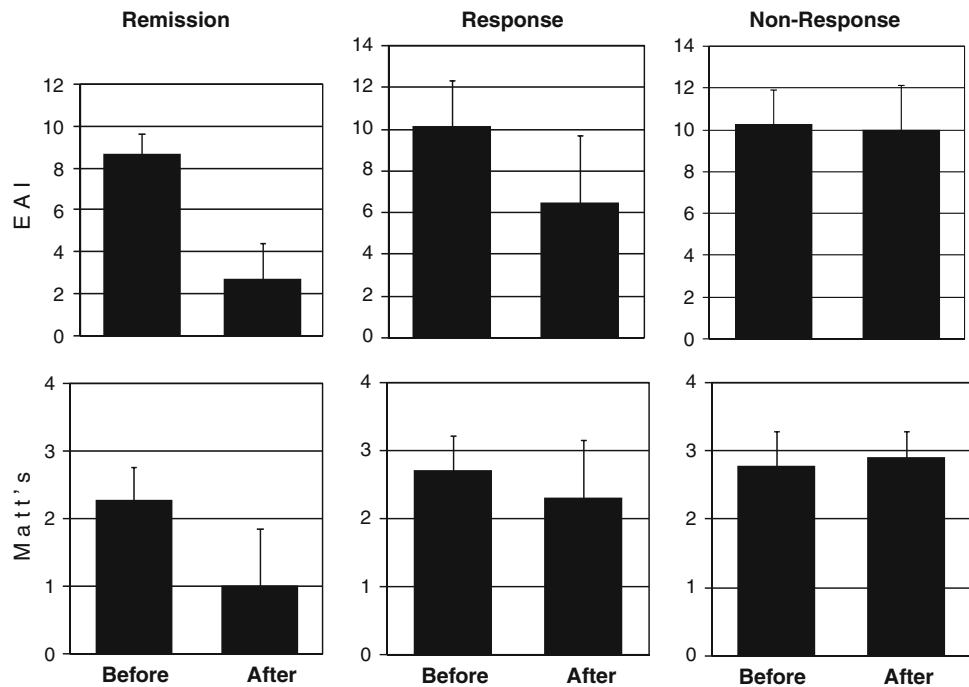


granulation scattering reflected light (0 no, 2 yes); vascular pattern (0 normal, 1 faded/disturbed, 2 completely absent); vulnerability of mucosa (0 none, 2 contact bleeding, 4 spontaneous bleeding); mucosal damage (0 none, 2 slight, 4 pronounced)

**Fig. 4** Both panels show severe endoscopic findings; severe ulcerations are present in both (Matts' score = 4). The findings in the left panel were scored as 12 points according to the EAI, while those in the right panel were scored as 15 points



**Fig. 5** The EAI is significantly decreased in the remission ( $p = 0.03$ ) and response groups ( $p = 0.01$ ). Matts' grade shows a tendency to decrease in the remission group, but the difference is not significant ( $p = 0.07$ ). There were eight, ten, and seven patients in the remission, response, and non-response group, respectively



Variation for  $\Delta$ EAI by treatment was also assessed. Interestingly, only two variations (8%) were observed in the 25 patients who had repeated colonoscopies after a short period.

The EAI is a useful tool for determining the initiation of intensive treatment in patients with severe UC

The EAI varied from 10 to 15 even in patients with the highest Rachmilewitz endoscopic index score (12 points). Whether the EAI can predict the efficacy of steroid/CsA was assessed by comparing the efficacy of steroid/CsA in the highest EAI (14–15) group with those in the moderate EAI (11–13) group. In patients with the highest EAI scores, 16 patients were treated with intravenous steroid therapy and 30 were given CsA, while in the moderate EAI group, 32 patients were given steroid therapy and 13 patients were received CsA. Patients with the highest EAI (14–15) tended to be refractory to corticosteroid therapy (responders 3/16; 18.8%), compared to CsA (responders:23/30; 76.7%). However, steroid therapy was effective in 59.3% (19/32) of

**Table 3** The efficacy of prednisolone/cyclosporine A in patients with EAI >10

Treatment	EAI >14		EAI 11–13	
	Responder	Non-responder	Responder	Non-responder
Prednisolone	3	13	19	13
Cyclosporine A	23	7	10	3

patients in the moderate EAI group (Table 3). These results suggest that the EAI is useful for making treatment decisions in patients with severe UC.

**Discussion**

The results of this study confirm that the newly developed EAI is comparable to other endoscopic activity scores and is closely correlated with clinical activity. Discrepancies

between the EAI and clinical activity were observed in <5% of the UC patients participating in this study. In some cases, psychological factors lead to frequent diarrhea with mild to moderate abdominal pain. If sigmoidoscopy/colonoscopy had not been performed, unnecessary treatment, such as steroid therapy, may have been given to these patients since their clinical activities were moderate and they did not respond to initial treatment. Therefore, sigmoidoscopy/colonoscopy is needed to avoid unnecessary steroid therapy when clinical activity flares and additional treatment, such as steroid therapy, is being considered.

There are several endoscopic indices for assessing the severity of colitis (for review, see D'Haens et al. [13]). The Mayo score for flexible proctosigmoidoscopy assessment is one of the most common endoscopic scores. It was originally used in a placebo-controlled trial of mesalamine by Schroeder et al. [14]. This score, as well as other clinical scores, such as blood in the stool, daily diarrhea, and physician's assessment, has been widely used in recent clinical trials. The Mayo score is easy to score and accurately reflects both the clinical and endoscopic activities of UC. The Sutherland mucosal appearance assessment index was used in a placebo-controlled trial of mesalamine enemas in patients with distal UC [15]; it also has a 4-point scale. Both of these scores consist of four categories. However, during short-term observation periods, endoscopic severities did not markedly change in some severe cases.

Prior to initiating this study, we noticed that mucosal edema and friability changed rapidly, consistent with decreasing C-reactive protein (CRP) levels and improving clinical symptoms, while deep ulceration remained, even though clinical remission was obtained. At that time, endoscopic scores, such as Matts' score, did not change in some cases. Consequently, we categorized six items based on endoscopic findings of UC patients and developed the EAI in 1996 to assess the severity of UC. By the beginning of this study, we had confirmed that the EAI score rapidly decreased in patients who achieved clinical response to intravenous steroid treatment even though Matts' score had not decreased. The data obtained in this study indicate that the EAI decreased in the remission group, while Matts' score was unchanged in some patients who actually did achieve clinical remission. Furthermore, the EAI was helpful in distinguishing between moderate to severe UC patients and those who would not respond to steroid and need rescue treatment, such as CsA, IFX, or surgery.

CsA is reported to be a lymphocyte-specific agent that inhibits interleukin-2 and, hence, the function of T-helper cells. During the past 10 years, CsA has been given to patients with severe steroid refractory UC with the intention of avoiding colectomy. Little information is currently available on factors predictive of response to

intravenous CsA [16]. Cacheux et al. identified [17] higher body temperature, heart rate, and CRP at the initiation of CsA as predictive criteria for colectomy. Severe endoscopic findings were also an independent predictive factor of colectomy. Conversely, our data indicate that CsA was effective in patients with severe endoscopic findings (EAI 14–16), while patients with higher EAI scores did not respond to steroids. These discrepancies between our results and those of Cacheux et al. can be explained by the CsA concentration: we maintained CsA at 350–600 ng/ml, which was higher than that reported by Cacheux et al. Colectomy was defined as the clinical endpoint in Cacheux's study, while we focused on clinical response using Lichtiger's index. Our data indicate that 77% of our patients with severe inflammation and deep ulceration and edema responded to intravenous CsA. We also confirmed that colectomy within 12 months could be predicted by the endoscopic findings after 2–3 weeks of CsA treatment (data not shown).

It is difficult to state whether, in terms of EAI evaluation, a total colonoscopy is always needed or whether sigmoid colonoscopy is sufficient. Among most of our patients, severe lesions existed in the sigmoid colon, while the appearance of moderate to severe lesions in the right sided-colon without inflammation of the rectum and sigmoid colon was rare (6/454 cases). Furthermore, a total colonoscopy has the effect of negatively affecting disease deterioration in severe cases. Therefore, sigmoidoscopy may be both advisable and sufficient to evaluate EAI in most cases.

Since the EAI score has six items, inter-observer variation may occur. If there were a 1-point difference in each item, the difference in the total EAI would be 6 points. Our data indicate that variations in the EAI score do occur, we found that the variation was relatively minimal in patients with endoscopic findings of severe activity. Of note, the change in the EAI before/after treatment ( $\Delta$ EAI) did not vary between observers. These results suggest inter-observer variations may be less when delta EAI is calculated to assess endoscopic improvement by intensive treatment (e.g., intravenous steroid or CsA).

In conclusion, the EAI score is closely correlated with scores obtained using other endoscopic and clinical indices. The EAI score decreases rapidly according to the clinical response, while other scores, such as the Matts' score, do not change in some cases. Since a higher EAI is a predictive factor for steroid-refractory UC, the EAI is a useful score for severe patients who require CsA or surgery to decrease the use of inappropriate intravenous steroid therapy.

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