



# Seven days triple therapy for eradication of *Helicobacter pylori* does not alter the disease activity of patients with inflammatory bowel disease

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**Background/Aims:** The influences of *Helicobacter pylori* eradication therapy on the disease course of inflammatory bowel disease (IBD) are still unclear. We therefore conducted a multicenter, retrospective cohort study to evaluate the safety of *H. pylori* eradication therapy for IBD patients. **Methods:** IBD patients with *H. pylori* eradication from 2005 to 2015 (eradication group) and control patients (non-eradication group; 2 paired IBD patients without *H. pylori* eradication matched with each eradicated patient) were included. IBD exacerbation (increased/additional IBD drug or IBD-associated hospitalization/surgery) and disease improvement based on the physicians' global assessment were investigated at baseline, and at 2 and 6 months after eradication or observation. **Results:** A total of 429 IBD (378 ulcerative colitis, 51 Crohn's disease) patients, comprising 144 patients in the eradication group and 285 patients in the non-eradication group, were enrolled at 25 institutions. IBD exacerbation was comparable between groups (eradication group: 8.3% at 2 months [odds ratio, 1.76; 95% confidence interval, 0.78–3.92;  $P=0.170$ ], 11.8% at 6 months [odds ratio, 1.60; 95% confidence interval, 0.81–3.11;  $P=0.172$ ]). Based on the physicians' global assessment at 2 months, none of the patients in the eradication group improved, whereas 3.2% of the patients in

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the non-eradication group improved ( $P=0.019$ ). Multivariate analysis revealed that active disease at baseline, but not *H. pylori* eradication, was an independent factor for IBD exacerbation during 2 months' observation period. The overall eradication rate was 84.0%—comparable to previous reports in non-IBD patients. **Conclusions:** *H. pylori* eradication therapy does not alter the short-term disease activity of IBD. (*Intest Res* 2018;16:609-618)

**Key Words:** *Helicobacter pylori* eradication; Proton pump inhibitor; Clarithromycin; Metronidazole

## INTRODUCTION

Although the cause of IBD is not clear, recent progress in the analysis of intestinal microflora suggests that changes in the intestinal microflora are associated with IBD onset and exacerbation.<sup>1</sup> Many exogenous microorganisms, such as *Clostridium difficile* and cytomegalovirus potentially induce acute and/or chronic intestinal inflammation, which can alter the intestinal microflora and affect the clinical course of IBD.<sup>2-4</sup>

*Helicobacter pylori*, a Gram-negative, spiral-shaped, microaerophilic bacterium that colonizes the gastric mucosa of humans and non-human primates, is a major cause of exogenous infection, and is closely associated with atrophic gastritis,<sup>5</sup> gastroduodenal ulcers,<sup>6</sup> gastric cancer,<sup>7,8</sup> mucosa-associated lymphatic tissue lymphoma,<sup>9</sup> and idiopathic thrombocytopenic purpura.<sup>10</sup> *H. pylori* eradication therapy to treat or prevent these diseases is generally performed by administering triple therapy with a proton pump inhibitor, amoxicillin, and clarithromycin or metronidazole for 7 days, with eradication rates ranging from 80% to 90%.<sup>8,11,12</sup> Although 10% to 30% of patients experience some complications such as diarrhea and loose stool, the benefits of eradication regimens are fully acknowledged for patients without complicated diseases.<sup>13</sup> *H. pylori* infection and its eradication can alter gastric microflora,<sup>14</sup> but analyses of the intestinal microflora have not been reported, except for one study of eradicated patients with an altered microbiome in which *Bacteroides* was decreased and *Firmicutes* was increased.<sup>15</sup> The incidence of concomitant *H. pylori* infection is lower in IBD patients than in a non-IBD cohort,<sup>16</sup> suggesting that *H. pylori* infection protects against IBD and thus eradication therapy could be harmful for IBD by altering the gastric acid content and changing the intestinal microbiota. In contrast, the efficacy of 3 kinds of antibiotics (amoxicillin, tetracycline, and metronidazole) for 2 weeks was reported for patients with UC,<sup>17</sup> suggesting that *H. pylori* eradication therapy can be safely performed for UC patients without inducing disease exacerbation, but direct evidence of the effect of *H.*

*pylori* eradication on the disease course of IBD patients has not been reported. In addition, the *H. pylori* eradication rate for IBD patients has not yet been reported. We performed a multicenter, retrospective cohort study to elucidate the safety and efficacy of *H. pylori* eradication therapy for IBD patients.

## METHODS

### 1. Ethical Considerations

The overall study meets the intent and requirements of the Declaration of Helsinki, Ethical Guidelines for Medical and Health Research Involving Human Subjects by the Ministry of Health, Labour, and Welfare-Japan and by the Japanese Ministry of Education, Culture, Sports, Science and Technology-Japan. The institutional ethics committees of each participating institution approved this study.

### 2. Patients

This was a multicenter, retrospective cohort study conducted at 25 institutions in Japan. Outpatients with IBD (UC or CD) who underwent eradication therapy for *H. pylori* with acid-suppressive drugs and amoxicillin-based triple-therapy from March 2005 to July 2015 were included (eradication group). After searching patients by prescription history and/or International Classification of Diseases (ICD)-10 codes, basically all eradicated IBD patients were enrolled except ones whose detailed medical records during eradication could not be obtained. To establish a non-eradication control group (non-eradication group), 2 paired IBD patients without *H. pylori* eradication in the same institution were included by selecting the next 2 consecutive outpatients after the date of prescribing eradication drugs for each eradicated patient, and matching them by sex, age (within 10 years), and disease location and severity. We did not have any standard values to establish the number of enrolled patients. The infection rate of *H. pylori* in all Japanese population is around 20% in their 50's,<sup>18</sup> and the rate in IBD patients was reported to be almost half of that in non-IBD cohort.<sup>16</sup> And we hypothesized

that the detailed clinical courses after eradication therapy could be obtained in 20% of IBD patients for whom *H. pylori* infection was checked. Overall, we estimated that 2% (100 patients) in 5,000 IBD patients in participating institutions could be enrolled as eradication group. And we used 1:2 design to enhance the reliability of the present study as much as possible. Prior to the patient enrollment, we had set the above study design and the ethics committee approved the design. Patient inclusion was decided by the IBD specialists or gastroenterologists at each institution, and the patients were given the right to opt out the study.

### 3. Medical Records

Baseline clinical information for all patients was obtained, including sex, age, BMI, disease duration and location, blood type, smoking and drinking status, history of abdominal surgery for IBD, medications, and disease activity. In the eradication group, detailed information of the *H. pylori* eradication was obtained, such as the modality of diagnosing *H. pylori* infection and eradication, indications for eradication therapy, number of eradication treatments, eradication regimen, and success of eradication. The *H. pylori* status of the non-eradication group was also determined. In both groups, disease activity of IBD at baseline, and at 2 and 6 months after eradication/observation was obtained, and severe adverse events were collected. The survey forms were retrospectively collected and submitted from the participating institutions to the Department of Gastroenterology and Hepatology, Osaka University Graduate School of Medicine.

### 4. Definition of Disease Exacerbation

To ensure maximum objectivity and measurability for assessing disease exacerbation in this retrospective study design, we obtained information for all participants regarding “increase or addition of IBD drug,” “IBD-associated hospitalization,” and “IBD-associated surgery” after 2 and 6 months of eradication/observation, and cases meeting any of the above conditions were defined as IBD exacerbation. The physician’s global assessment was applied to all participants for analysis of disease exacerbation and improvement. Disease activity indices such as the clinical activity index (CAI) for UC<sup>19,20</sup> and the CDAI for CD<sup>21</sup> were also obtained, and higher and lower scores from a baseline CAI score of  $\geq 3$  and a baseline CDAI score of  $\geq 70$  were considered disease exacerbation or improvement, respectively.

### 5. Endpoints

Prior to the approval of the ethics committee and subse-

quent patient enrollment, we established the primary endpoint of the study as the difference in the IBD exacerbation rate (defined) after 2 months of observation between the eradication group and the non-eradication group. Secondary endpoints were the difference in the exacerbation rate at 6 months of observation, the physicians’ global assessment, and disease activity indices between groups. In the eradication group, the eradication success rate, difference in IBD exacerbation between eradication success and failure, and adverse events after eradication were also set as secondary endpoints.

### 6. Statistical Analysis

Statistical analyses were performed using Pearson chi-square test, and univariate and multivariate logistic regression analyses were performed with factors associated with disease exacerbation. All data obtained from the study were analyzed using JMP Pro version 12.1.0 (SAS Institute Inc, Cary, NC, USA) and a *P*-value of less than 0.05 was considered statistically significant.

## RESULTS

### 1. Characteristics of the Participants

A total of 437 IBD patients were enrolled in this study. Eight patients were excluded due to incomplete data, and thus 429 participants were included in the analysis (Supplementary Fig. 1). Participants comprised 144 patients in whom *H. pylori* was eradicated (eradication group) and 285 control patients (non-eradication group); 88.1% of the patients had UC and the others had CD. One hundred thirty-eight patients (32.2%) had limited disease (proctitis in UC [E1] and terminal ileitis in CD [L1] in Montreal classification<sup>22</sup>), and 380 patients (88.6%) were in remission at baseline. There were no significant differences in the baseline clinical parameters between the eradication group and non-eradication group, except for the lower use of 5-aminosalicylic acid in the eradication group (*P*=0.012). Detailed characteristics are provided in Table 1.

### 2. Disease Activity after *H. pylori* Eradication

We first analyzed the primary endpoint of the study by comparing the rate of IBD exacerbation between the eradication group and non-eradication group at 2 months. The IBD exacerbation rate in the eradication group was 8.3%, and did not differ significantly from that in the non-eradication group (4.9%; OR, 1.76; 95% CI, 0.78–3.92, *P*=0.170) (Fig. 1). The IBD exacerbation rate at 6 months was also not signifi-

Table 1. Patient Characteristics

Characteristic	Total (n=429)	Eradication (n=144)	Non-eradication (n=285)	P-value
Sex (female/male) <sup>a</sup>	186/243	64/80	122/163	NS
Age (yr) <sup>a</sup>	51.5±13.8	52.6±13.9	51.0±13.8	NS
Disease (CD/UC) <sup>a</sup>	51/378	17/127	34/251	NS
Location (CD, ileum/colon/ileocolon) <sup>a</sup>	9/12/30	3/4/10	6/8/20	NS
Location (UC, rectum/left/total) <sup>a</sup>	126/77/175	42/27/58	84/50/117	NS
Disease activity (active/remission) <sup>a</sup>	49/380	17/127	32/253	NS
Duration of disease (yr)	10.6±9.1	10.5±9.4	10.7±9.0	NS
BMI (kg/m <sup>2</sup> )	22.5±3.6	22.6±3.5	22.5±3.6	NS
Smoking (yes/no/unknown)	57/291/81	17/90/37	40/201/44	NS
Alcohol (yes/no/unknown)	111/177/133	41/50/53	70/127/88	NS
Behavior (CD, inflammatory/structuring/penetrating)	24/17/10	8/6/3	16/11/7	NS
Behavior (UC, initial/recurrent/chronic/unknown)	39/294/37/8	18/94/10/5	21/200/27/3	NS
5-Aminosalicylic acid (yes/no)	384/45	121/23	263/22	0.012
Corticosteroids (yes/no)	32/397	12/132	20/265	NS
Immunomodulators (yes/no)	90/339	23/121	67/218	NS
Biologic agents (yes/no/unknown)	43/385/1	9/135/0	34/250/1	NS
Tacrolimus (yes/no)	6/423	0/144	6/279	NS
CDAI (CD)	96±50	97±42	96±54	NS
CAI (UC)	1.2±1.1	1.1±1.1	1.2±1.1	NS
Interval days between the matched cases	NA	NA	131±450	
<i>H. pylori</i> infection (non-eradication group, yes/eradicated/no/unknown)	NA	NA	7/2/89/187	

Values are presented as number or mean±SD.

<sup>a</sup>Matched item between the groups.

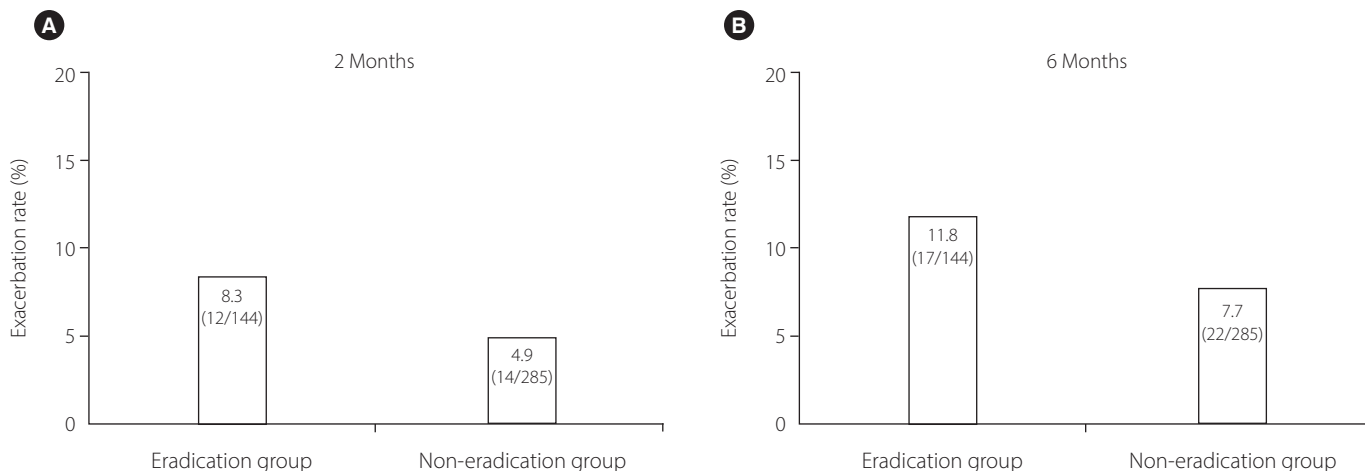
CAI, clinical activity index; NA, not applicable.

cantly different between groups: 11.8% in the eradication group and 7.7% in the non-eradication group (OR, 1.60; 95% CI, 0.81–3.11;  $P=0.172$ ) (Fig. 1). We also investigated the IBD exacerbation rates in UC and CD. In both diseases, the differences were also not observed between 2 groups (Supplementary Table 1). Next, changes in disease activity following *H. pylori* eradication were analyzed by the physicians' global assessment. Analysis of patient outcomes according to 3 categories (exacerbated, unchanged, and improved disease) at 2 months revealed that none of the patients in the eradication group had improved whereas 3.2% (9/285) of patients in the non-eradication group had improved, and the difference between groups was significant ( $P=0.019$ ) (Table 2). Moreover, changes in the disease activity indices were investigated. Analysis of 82.7% (350/423) of patients analyzed at 2 months and 81.1% (343/423) of patients analyzed at 6

months revealed no significant differences in disease activity between groups (Supplementary Table 2). Together, these results indicate that *H. pylori* eradication therapy does not exacerbate IBD or improve disease activity.

### 3. Factors Associated with IBD Exacerbation after *H. pylori* Eradication

We next investigated the factors associated with disease exacerbation by *H. pylori* eradication. Univariate analysis including all participants indicated that female and active disease at baseline tended to be risk factors of definition-based exacerbation at 2 months (Table 3). We then performed a multivariate analysis using a logistic regression model for these 2 categories above, as well as *H. pylori* eradication, which identified active disease an independent factor of exacerbation (OR, 3.57; 95% CI, 1.37–8.61;  $P=0.011$ ). We also



**Fig. 1.** Definition-based disease exacerbation 2 and 6 months after *Helicobacter pylori* eradication or observation in IBD patients. Disease exacerbation rates in the eradication group and the non-eradication group were shown. ORs of disease exacerbation were 1.76 (95% CI, 0.78–3.92;  $P=0.170$ ) at 2 months (A) and 1.60 (95% CI, 0.81–3.11;  $P=0.172$ ) at 6 months (B), respectively. In 39 patients exacerbated in 6 months after eradication or observation, there were 37 patients with increased/additional IBD drugs, 6 patients with IBD-associated hospitalization, and 2 patients with IBD-associated surgery.

**Table 2.** Changes in IBD Disease Activity after *Helicobacter pylori* Eradication by the Physicians' Global Assessment

	Exacerbated	Unchanged	Improved	<i>P</i> -value
2 Months				0.019
Eradication	14	130	0	
Non-eradication	14	262	9	
6 Months				0.362
Eradication	17	125	2	
Non-eradication	23	255	7	

analyzed the factors of exacerbation in only the eradication group. Univariate analysis was performed by additionally including eradication-associated factors, such as frequency of eradication treatment, eradication regimen, and success of eradication. The analysis identified use of corticosteroids as a significant risk for exacerbation, and biologic agents and active disease tended to be risks for exacerbation (Table 4). Although multivariate analysis was not performed because of the small number of exacerbated patients, these findings suggest that active disease, but not *H. pylori* eradication, is an independent risk for disease exacerbation, and that use of corticosteroids can be associated with disease exacerbation after *H. pylori* eradication.

**4. Disease Course after IBD Exacerbation**

Next, the detailed disease courses of exacerbated patients were investigated. In 12 patients experiencing disease exacerbation within 2 months in the eradication group, exacerbation occurred 33±21 days after *H. pylori* eradication, but the exacerbation was mild in all patients and 11 patients recovered while 1 remained unchanged by medical therapy. At the 6-month observation in all patients, the rates of overall IBD-related hospitalization, IBD-related surgery, and severe adverse events other than IBD exacerbation were 1.4% (6/421), 0.5% (2/421), and 0.2% (1/421), respectively, with no significant differences between the eradication group and non-eradication group.

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**5. H. pylori Eradication Regimen and IBD Exacerbation**

Finally, *H. pylori* status and *H. pylori* eradication success rates were investigated in the eradication group. Characteristics at *H. pylori* eradication are shown in Supplementary Table 3. Overall eradication success rate was 84.0% (121/144). Among 144 eradicated patients, 123 patients (85.4%) received primary eradication therapy, and the eradication success rates of primary and secondary therapy were 82.9% (102/123) and 90.4% (19/21), respectively (Fig. 2). Differences in the acid-suppressive drugs used at eradication were not associated with exacerbation of IBD (Table 5). We also investigated the exacerbation rates in clarithromycin and metronidazole. Disease exacerbation rates in 2 months were 9.2% (11/120) in clarithromycin group and 4.6% (1/22) in metronidazole group, and differences were not significant (OR, 2.12; 95% CI, 0.26–17.3;  $P=0.474$ ). The rates in 6 months were 11.7% (14/120) in clarithromycin group and 13.6% (3/22) in metronidazole group, with no significance between 2 groups (OR, 0.84; 95% CI, 0.22–3.22;  $P=0.794$ ). These data

**Table 3.** Factors Associated with IBD Exacerbation in 2 Months in all Participants

	Univariate analysis				Multivariate analysis	
	Exacerbation (n=26)	Non-exacerbation (n=403)	OR (95% CI)	P-value	OR (95% CI)	P-value
<i>H. pylori</i> eradication treatment, +	12 (46)	132 (33)	1.76 (0.79–3.91)	0.161	1.78 (0.78–4.01)	0.170
Female sex	16 (61)	170 (42)	2.19 (0.97–4.95)	0.054	1.95 (0.86–4.61)	0.101
Age >50 yr	15 (58)	189 (47)	1.54 (0.69–3.44)	0.285		
Disease, UC	25 (96)	353 (88)	3.54 (0.47–26.7)	0.191		
Smoking, +	4 (15)	53 (13)	1.14 (0.37–3.52)	0.870		
Alcohol, +	5 (19)	106 (26)	0.71 (0.24–2.10)	0.690		
Disease location, extensive	21 (81)	270 (67)	2.07 (0.76–5.61)	0.145		
Disease activity, active	8 (31)	41 (10)	3.92 (1.61–9.59)	0.001	3.57 (1.37–8.61)	0.011
5-Aminosalicylic acid, +	23 (88)	361 (90)	0.89 (0.26–3.10)	0.857		
Corticosteroids, +	4 (15)	28 (7)	2.44 (0.78–7.56)	0.113		
Immunomodulators, +	5 (19)	85 (21)	0.89 (0.33–2.43)	0.821		
Biologic agents, +	2 (8)	41 (10)	0.73 (0.17–3.21)	0.680		

Values are presented as number (%).

*H. pylori*, *Helicobacter pylori*.

**Table 4.** Factors Associated with Disease Exacerbation in 2 Months in the Eradication Group (n=144)

Variable	Exacerbation (n=12)	Non-exacerbation (n=132)	OR (95% CI)	P-value
Female sex	5 (42)	59 (45)	0.88 (0.27–2.93)	0.840
Age >50 yr	7 (58)	54 (41)	2.02 (0.61–6.71)	0.242
Disease, UC	11 (92)	116 (88)	1.52 (0.18–12.5)	0.697
Smoking, +	2 (25)	15 (15)	1.87 (0.34–10.1)	0.464
Alcohol, +	3 (50)	38 (45)	1.23 (0.24–6.48)	0.801
Disease location, extensive	8 (67)	90 (68)	0.93 (0.27–3.27)	0.914
Disease activity, active	3 (25)	14 (11)	2.81 (0.68–11.6)	0.139
5-Aminosalicylic acid, +	10 (83)	111 (84)	1.05 (0.22–5.17)	0.945
Corticosteroids, +	3 (25)	9 (7)	4.56 (1.05–19.8)	0.029
Immunomodulators, +	2 (17)	21 (15)	1.05 (0.22–5.17)	0.945
Biologic agents, +	2 (17)	7 (5)	3.57 (0.65–19.5)	0.120
Frequency of eradication, primary	11 (92)	112 (85)	1.96 (0.24–16.1)	0.522
Non-penicillin antibiotics, CAM	11 (92)	109 (82)	2.11 (0.26–17.3)	0.474
Eradication success, +	9 (75)	112 (86)	0.51 (0.13–2.05)	0.335

Values are presented as number (%).

CAM, clarithromycin.

indicate that eradication regimen was not associated with IBD exacerbation at least amoxicillin-based triple therapy during 6 months period.

## DISCUSSION

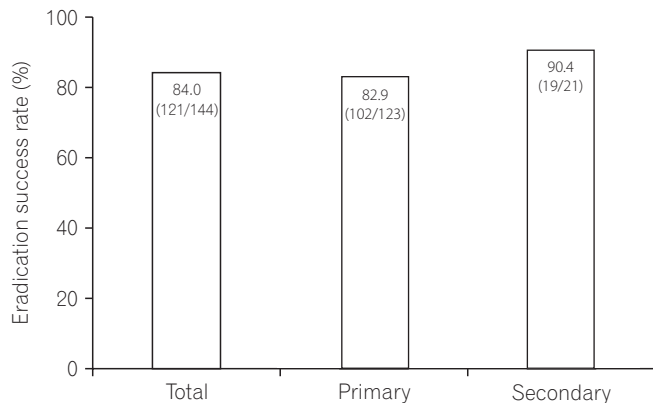
Here, we report the results from a multicenter retrospective cohort on the disease activity of IBD patients who underwent *H. pylori* eradication therapy. Our data clearly demon-

**Table 5.** IBD Exacerbating and Acid-Suppressive Drugs used in *Helicobacter pylori* Eradication (n=144)

	EPZ (n=19)	LPZ (n=70)	OPZ (n=9)	RPZ (n=39)	VPZ (n=5)	Unknown (n=2)	P-value
Exacerbation, +	2 (10.5)	3 (4.3)	1 (11.1)	5 (12.8)	1 (20.0)	0	0.577

Values are presented as number (%).

EPZ, esomeprazole; LPZ, lansoprazole; OPZ, omeprazole; RPZ, rabeprazole; VPZ, vonoprazan.



**Fig. 2.** *Helicobacter pylori* eradication success rate in IBD patients. A total of 144 patients in the eradication group was analyzed. Among 123 patients who received primary therapy, clarithromycin was used in 121 patients (98.4%) and unknown in 2 patients. All patients who received secondary therapy were treated with metronidazole.

stated that *H. pylori* eradication did not exacerbate IBD and induced no severe adverse events. On the other hand, we revealed that *H. pylori* eradication therapy did not improve IBD. Moreover, the eradication success rate was comparable to that in previous reports in which eradication therapy was performed for patients without IBD.<sup>23</sup> Although the influence of eradication therapy was prospectively observed in only 6 CD patients and unchanged disease activity was reported,<sup>24</sup> this was small study without control arm and no UC patients were included. Our present report clearly described the disease activity of both CD and UC patients after *H. pylori* eradication in larger cohort with control arm.

The prevalence of concomitant *H. pylori* infection is low in IBD patients compared with non-IBD populations,<sup>16,25</sup> suggesting that *H. pylori* infection itself might be protective against IBD. *H. pylori* infection mainly occurs in early childhood in countries with a high-prevalence,<sup>26</sup> and IBD can generally develop after *H. pylori* has colonized in the stomach. In the present study, *H. pylori* eradication did not affect the disease activity of IBD, suggesting that the association between IBD and *H. pylori* infection may be weak at least in short-term disease course. Additional study is needed to clarify whether long-time *H. pylori* infection can affect dis-

ease course of IBD.

Eradication of *H. pylori* using acid-suppressive drugs and antibiotics can alter intestinal microflora,<sup>27,28</sup> which could potentially affect the disease activity in IBD patients with reduced microbial diversity.<sup>29</sup> In addition to the report that triple antibiotic combination therapy using amoxicillin, tetracycline, and metronidazole for 2 weeks improves UC,<sup>17</sup> a systematic review of studies of adult patients receiving any dose of antibiotic therapy for at least 7 days and up to 16 weeks for active disease also demonstrated a statistically significant benefit of antibiotic treatment for inducing remission in patients with active UC.<sup>30</sup> In the present study, however, we did not observe a better outcome of IBD following *H. pylori* eradication therapy. A 1-week treatment with 2 types of antibiotics may not provide enough of a therapeutic effect, such as reducing relapse, for quiescent IBD patients. The safety of antibiotic treatment for patients with quiescent UC, which comprised 90% of patients in the present study, has not been reported. Further analysis is needed to evaluate the safety of antibiotic therapy for patients with quiescent UC.

Although the number of CD patients enrolled in the present study was small, there were no differences in the disease course after eradication therapy between CD and UC patients (Tables 3, 4 and Supplementary Table 1). Moreover, additional detailed investigation of patients whose disease exacerbated within 2 months after eradication revealed no severe adverse events, and almost all cases recovered with appropriate treatment. These results indicate that *H. pylori* eradication therapy is generally feasible even for IBD patients. Moreover, the multivariate analysis indicated that high disease activity, but not *H. pylori* eradication, was an independent factor for IBD exacerbation (Table 3). Analysis for the only eradicated patients also showed that use of corticosteroids was significantly associated with disease exacerbation after *H. pylori* eradication (Table 4). Although the direct association between corticosteroids and intestinal microflora has not been reported, our present results suggest that patients who receive immunosuppressant therapy such as corticosteroids have a potentially high risk for disease exacerbation by *H. pylori* eradication. Additional study

is needed to clarify whether corticosteroids have a unique role in exacerbating IBD at eradication therapy. Emergent *H. pylori* eradication therapy may be unnecessary in clinical practice, and physicians can therefore avoid *H. pylori* eradication therapy in IBD patients who receive immunosuppressant drugs. Actually, among patients in the eradication group from whom clinical activity indices were obtained, no severe active patients were included with maximum CDAI and CAI of 176 and 4, respectively. If eradication is necessary for patients with active disease, even though it is mild, careful observation after eradication is advised.

The *H. pylori* eradication rates in IBD patients in the present study were comparable to previously reported rates for non-IBD patients.<sup>23,31,32</sup> Different acid-suppressive drugs and non-penicillin antibiotics also did not affect the eradication rate, and primary and secondary eradication rates were comparable to previously reported rates for non-IBD patients. These data strengthen our findings that IBD does not affect *H. pylori* eradication, and provide important information to help physicians select an *H. pylori* eradication regimen. Moreover, a previous report showed that IBD-related upper gastric lesions, such as focally enhanced gastritis, were not associated with *H. pylori* infection.<sup>33</sup> Although detailed upper endoscopic findings were not analyzed in the present study, our data strongly indicate that *H. pylori* infection independently affects upper gastrointestinal lesions associated with IBD.

This study has some limitations. First, as this was a retrospective study, we did not adopt validated disease activity indices for investigating disease exacerbation as the primary endpoint. Second, the analyses for eradicated patients were underpowered due to the limited population under stringent criteria. We then established rigorous inclusion criteria to select patients comprising the non-eradication group, however, a selection bias based on the retrospective study design could not be completely eliminated. And the number of CD patients was considerably smaller than that of UC, which might influence some results. Third, we selected patients in the non-eradication group regardless of *H. pylori* infection. In the present study we focused on the short-term influences on *H. pylori* eradication therapy, but not on the long-term effect of IBD patients who succeeded in eradication. To elucidate the long-term influences of *H. pylori* eradication, another study should be needed to compare more than 1 year clinical courses of *H. pylori*-infected IBD patients who succeeded in eradication therapy with those who failed in eradication. Finally, in the present study we did not analyze the extent of gastric mucosal atrophy, the *H. pylori* strain

and fecal microbiota. *H. pylori* strain is broadly divided into Western and East-Asian types based on differences in the cytotoxin associated gene A protein Glu-Pro-Ile-Tyr-Ala motif, which is strongly associated with gastric inflammation and carcinogenesis.<sup>34</sup> A well-designed study in a Western cohort is needed to confirm our results.

In conclusion, we demonstrated that *H. pylori* eradication therapy does not exacerbate IBD, and does not improve disease activity. Careful observation after eradication therapy is necessary, especially for IBD patients with active disease that undergo eradication therapy.

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### CONFLICT OF INTEREST

SS received lecture fees from Mitsubishi-Tanabe Pharma, Kyorin Pharmaceutical, Abbvie, EA Pharma, Mochida Pharmaceutical, Zeria Pharmaceutical, Eisai, Mylan, advisory/consultancy fees from Janssen, Kyorin Pharmaceutical, and research grant from Mitsubishi-Tanabe Pharma. TK received lecture fees from Mitsubishi-Tanabe Pharma, Eisai, Kyorin Pharmaceutical, Abbvie, Janssen, JIMRO, Ajinomoto Pharma, EA Pharma, Astellas, Mochida Pharmaceutical, Asahi Kasei Medical, Takeda Pharmaceutical, Gilead Sciences, Celltrion, Nippon Kayaku, Alfresa Pharma, Thermo Scientific, advisory/consultancy fees from Janssen, Pfizer, Kyorin Pharmaceutical, Mochida Pharmaceutical, Takeda Pharmaceutical, Eli Lilly, Ferring Pharmaceuticals, Nippon Kayaku, and research grants from EA Pharma, Thermo Scientific, and Alfresa Pharma. AY, TY, HT, and SR received lecture fees from EA Pharma. TF received research support from Eisai and lecture fees from EA Pharma. KO received research support from EA Pharma, Takeda and Daiichi Sankyo. KKak received research support from EA pharma. MN received research support from EA Pharma, Takeda, AstraZeneca and Daiichi Sankyo. TH received lecture fees from Mitsubishi-Tanabe Pharma, Kyorin Pharmaceutical, Abbvie, GK, Janssen, Mochida Pharmaceutical, JIMRO, Takeda Pharmaceutical,



Gilead Sciences, Miyarisan Pharmaceutical, Kissei Pharmaceutical, Zeria Pharmaceutical, Ferring Pharmaceutical, Nippon Kayaku, advisory/consultancy fees from Mitsubishi-Tanabe Pharma, Takeda Pharmaceutical, EA Pharma, Janssen, Eli Lilly, and research grants from Abbvie, JIMRO, and Zeria Pharmaceutical. Other authors have no financial relationship to disclose. The manuscript was edited by SciTechEdit International, LLC (7012 East Mountain Brush Circle, Highlands Ranch, CO 80130, USA) without funding source.

## AUTHOR CONTRIBUTION

The authors' contributions to the study were as follows: SS, TE, SB, TK, HT, AY, YT, NK designed the study. The data were collected by SS, TE, SB, MOg, TK, MOs, HT, KO, ST, HK, KKan, SN, TS, YS, TI, KKak, AY, HY, YY, TY, AM, MN, TT, RS. SS analyzed the data and SS, TE, SB, TK, HT, AY, YT, NK interpreted the data. SS drafted the manuscript. TH made critical revisions to the manuscript. All authors reviewed and approved the final version of the manuscript.

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