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Eiichi Tanaka · Shigeo Kamitsuji · Eisuke Inoue
Toru Yamada · Ayako Nakajima · Etsuko Takeuchi
Akiko Yanagisawa · Ryouichi Misaka · Mutsuo Shigemoto
Katsuko Yamashita · Tetsuo Imamura · Masako Hara
Taisuke Tomatsu · Terunobu Saito · Gerson Lauren
George Triadafilopoulos · Naoyuki Kamatani
Gurkirpal Singh · Hisashi Yamanaka

Nonsteroidal anti-inflammatory drug use does not affect short-term endoscopic and histologic outcomes after *Helicobacter pylori* eradication in patients with rheumatoid arthritis

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Abstract We evaluated the effects of the use of nonsteroidal anti-inflammatory drugs (NSAIDs) on endoscopic and histological findings in patients with rheumatoid arthritis (RA) before and after the eradication of *Helicobacter pylori* infection. *Helicobacter pylori* (*H. pylori*) eradication using lansoprazole 30 mg, amoxicillin 750 mg, and clarithromycin 200 mg twice daily for 1 week was conducted in 44 patients (mean age: 56.5 years) with RA. Using the updated Sydney system, endoscopic and histological findings of the greater curvature of the antrum, the greater curvature of the upper corpus, and the lesser curvature of the lower corpus were compared before and after eradication, for a mean follow-up period of 3.5 months. Overall, *H. pylori* eradication was successful in 32 patients (72.7%). Of these 32 patients, 23 were NSAID users. In the successful eradication group, (1) there was no significant change on endoscopic findings, including gastric erythema and erosion in all three regions irrespective of NSAIDs use; (2) of 17 active ulcers before eradication in NSAIDs users, all healed except for one duodenal ulcer that persisted, where one patient newly developed a gastric ulcer, one developed erosive duodenitis, and two developed reflux esophagitis, all in NSAID users; (3) neutrophil infiltration and chronic inflammation were significantly improved in all three regions after *H. pylori* eradication irrespective of use of NSAIDs, while atrophic change and intestinal metaplasia did not change. In the eradication failure group; (1) there was no significant change on endoscopic and histological findings in the three regions; (2) two of three ulcers present before eradication on NSAID users persisted even after eradication, and no new cases of gastric ulcer or erosive duodenitis occurred. In conclusion, over a mean follow-up period of 3.5 months, use of NSAIDs in Japanese patients with RA did not impair the healing process of gastric and duodenal ulcers nor did it affect the endoscopic and histological improvements associated with *H. pylori* eradication.

Key words *Helicobacter pylori* eradication · Nonsteroidal anti-inflammatory drug · Peptic ulcer disease · Rheumatoid arthritis

E. Tanaka (✉) · S. Kamitsuji · E. Inoue · T. Yamada · A. Nakajima · M. Hara · T. Tomatsu · N. Kamatani · H. Yamanaka
Institute of Rheumatology, Tokyo Women's Medical University, 10-22 Kawada-cho, Shinjuku-ku, Tokyo 162-0054, Japan
Tel. +81-3-5269-1725; Fax +81-3-5269-1726
e-mail: e-tanaka@tkg.att.ne.jp

E. Takeuchi · A. Yanagisawa · R. Misaka · M. Shigemoto · K. Yamashita
Institute of Geriatrics, Tokyo Women's Medical University, Tokyo, Japan

T. Imamura
Department of Surgical Pathology, Teikyo University School of Medicine, Tokyo, Japan

T. Saito
Tokyo Hokubu Hospital, Tokyo, Japan

E. Tanaka · G. Lauren · G. Triadafilopoulos · G. Singh
Division of Gastroenterology and Hepatology, Department of Medicine, Stanford University School of Medicine, Stanford, CA, USA

Introduction

Upper gastrointestinal (UGI) ulcer disease is a potentially life-threatening event in rheumatoid arthritis (RA) patients, especially in those who are being treated with nonsteroidal anti-inflammatory drugs (NSAIDs). It is widely recognized that both *Helicobacter pylori* (*H. pylori*) infection[1,2] and NSAID use[3–5] are major causes of UGI ulcers. Recently, a meta-analysis showed that both *H. pylori* infection and NSAID use independently and significantly increase both the risk of UGI ulcers and ulcer bleeding, and that these two risk factors affect UGI ulcer formation and ulcer bleeding synergistically.[6]

Several controversies regarding *H. pylori* eradication in patients using NSAIDs still prevail.[7–14] Whether to attempt *H. pylori* eradication in patients receiving long-term treatment with NSAIDs remains controversial. Some reports advocate *H. pylori* eradication before NSAID therapy in order to reduce NSAID-induced peptic ulcer.[8,10–12] On the other hand, some reports claim that *H. pylori* eradication should be avoided because it may delay healing of NSAID-induced peptic ulcers[9] and because of the improved effectiveness of omeprazole therapy in healing and preventing of ulcers in *H. pylori*-positive patients regularly using NSAIDs.[15,16] The occurrence of gastric erosions, erosive duodenitis, and reflux esophagitis after *H. pylori* eradication under chronic NSAIDs use is still a matter of debate.

The association of *H. pylori* infection and NSAID use with UGI damage is an important issue in Japanese patients since the gastric acid milieu in such patients is believed to be unique. This is because the prevalence of severe atrophic gastritis and its associated decrease of gastric acid secretion is especially high in Japanese *H. pylori*-positive subjects.[17–21] Further, the prevalence of *H. pylori* infection in Japan is quite different from that of other advanced and developed countries.[22,23] Hence, original clinical UGI research in Japanese patients is warranted.

A large observational cohort study of RA patients, IORRA (Institute of Rheumatology Rheumatoid Arthritis), using physicians' and patients' assessments together with laboratory data, has been established in our Institute since 2000.[24] In this patient cohort, the various types of patient information including disability index, disease activity, comorbidity, and the medication use are collected from patient questionnaire sheets for more than 4500 RA patients every 6 months. Using this cohort, we previously examined the prevalence of *H. pylori* infection and the association of such infection and NSAID use with the risk of UGI ulcers.[25] Among such patients with RA in this study, we evaluated the effects of NSAID use on endoscopic and histological findings before and after the eradication of *H. pylori*.

Patients and methods

Rheumatoid arthritis patients for *H. pylori* eradication

Forty-four patients with RA evaluated at the outpatient clinic of the Institute of Rheumatology, Tokyo Women's Medical University, received *H. pylori* eradication therapy using lansoprazole 30 mg, amoxicillin 750 mg, and clarithromycin 200 mg, twice daily, for 1 week. All patients were Japanese, were seen between September 2002 and April 2004, and had been diagnosed with RA according to the 1987 ACR criteria.[26] Before *H. pylori* eradication, all patients had been already diagnosed as *H pylori*-positive because of the following: (1) histological examination at 3 points (the greater curvature of the antrum, the greater curvature of the upper corpus, and the lesser curvature of the lower corpus); (2) positive rapid urease test at 2 points (antrum and upper body of the stomach); (3) positive serology for *H. pylori*. Seropositivity for *H. pylori* antibody was examined using microplate enzyme immunoassay, using the E Plate kit (E Plate Eiken *H. pylori* Antibody, Eiken Chemical, Tokyo, Japan), which was made on the basis of strains of *H. pylori* as antigens to prepare E plates isolated from Japanese patients with UGI ulcers.[27,28]

Use of NSAIDs

Patients who took NSAIDs for more than 30 days during the 3-month period before eradication were defined as NSAID users based on the patient self-reports in the large observational cohort study of RA patients in our Institute, IORRA. The percentage use for each NSAID is listed in Table 1.

Definition of UGI ulcers

We defined an UGI ulcer as a circumscribed mucosal break that was at least 2 mm in diameter and had a perceptible depth in either the gastric or duodenal mucosa.

Successful eradication of *H. pylori*

We defined *H. pylori* successful eradication as both negative ^{13}C-urea breath test and absence of the bacterium on histological examination during the follow-up period.

Follow-up endoscopy after eradication

All patients underwent endoscopy after a mean follow-up period of 3.5 months after eradication. (115.1 ± 59.6 days, median: 99 days). For both NSAID and non-NSAID users, the following three parameters were compared before and after successful (or unsuccessful) eradication therapy: (1) endoscopic findings (neutrophil infiltration, chronic inflammation, atrophy and intestinal metaplasia) and histological findings (gastric erythema, erosions, nodularity, vascular pattern, edema, friability, exudations, rugal hyperplasia, rugal atrophy and intramural bleeding spots) of the greater curvature of the antrum, the greater curvature of the upper corpus, and the lesser curvature of the lower corpus according to the updated Sydney system;[29,30] (2) the effect of eradication on healing of gastric and duodenal ulcers using number and diameter of ulcers in the cases who had already had UGI ulcers before eradication, and the effect of eradication on the occurrence and the recurrence of gastric and duodenal ulcers; (3) the effect of eradication on the occurrence of erosive duodenitis and reflux esophagitis.

Statistical analysis

SAS software (Version 8: SAS Institute, Cary, NC, USA) was used for database management and the Mann–Whitney test ($P < 0.001$) was used for statistical analysis.

Table 1. Clinical characteristics

	NSAID users	Non-NSAID users
Number of patients	30	14
Successful eradication (%)	23 (76.7%)	9 (64.3%)
Age (years)[a,c]	57.2 ± 9.3	56.5 ± 14.7
% Female	83.3	78.6
RA duration (years)[a,c]	12.9 ± 9.5	11.5 ± 13.9
% Positivity of rheumatoid factor[a,c]	73.3	76.9
Swollen joints/tender joint counts (per 67/68 joints)[b]	2.7/8.5	2.4/2.9
Physicians' VAS (mm)[b,c]	19.8 ± 16.4	10.1 ± 17.2
Patients' general VAS (mm)[b,c]	42.8 ± 25.5	23.3 ± 26.9
Patients' pain VAS (mm)[b,c]	42.6 ± 29.3	19.4 ± 23.4
CRP (mg/dl)[b,c]	1.2 ± 1.1	1.1 ± 1.4
ESR (mm/h)[b,c]	31.3 ± 16.4	24.5 ± 23.5
HAQ score[b,c]	0.9 ± 0.7	0.2 ± 0.4
% NSAID use[a]	100.0	0.0
% Combination of NSAIDs use[a]	16.7	–
Ampiroxicam (%)[a]	3.3	–
Diclofenac sodium (%)[a]	36.7	–
Etodolac (%)[a]	10.0	–
Indomethacin (%)[a]	6.7	–
Lornoxicam (%)[a]	3.3	–
Loxoprofen sodium (%)[a]	16.7	–
Meloxicam (%)[a]	6.7	–
Nabumetone (%)[a]	6.7	–
Sulindac (%)[a]	6.7	–
Zaltoprofen (%)[a]	3.3	–
% DMARD use[a]	96.7	85.7
% MTX use[a]	56.7	21.4
Dosage of MTX per week (mg)[a]	6.2	6.7
% Steroid use[a]	53.3	35.7
Dosage of steroid per day (mg)[a]	4.6	7.4
% Antiulcer drug use[a]	93.3	92.9
Cytoprotective drug (%)[a]	76.7	78.6
Misoprostol (%)[a]	16.7	0.0
H2 receptor antagonist (%)[a]	30.0	21.4
Proton pump inhibitor (%)[a]	26.7	7.1
With active UGI ulcers before the treatment of eradication (%)[b]	36.7	28.6
With multiple UGI ulcers before the treatment of eradication (%)[b]	13.3	0.0

NSAID, nonsteroidal anti-inflammatory drug; RA, rheumatoid arthritis; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; DMARD, disease-modifying antirheumatic drug; MTX, methotrexate; UGI, upper gastrointestinal
[a] Data when *Helicobacter pylori* eradication therapy was conducted
[b] Data before *H. pylori* eradication (within at least 6 months)
[c] Mean ± standard deviation

Results

Helicobacter pylori eradication

This was successful in 32 patients (Success group) and unsuccessful in 12 patients (Failure group), yielding a successful eradication rate of 72.7%. All patients were divided into four groups depending on the eradication results and NSAID use. *Helicobacter pylori* eradication was successful in 23 patients who were NSAID users (Success-NSAID group) and 9 patients who were non-NSAID user (Success-non-NSAID group). Eradication failed in 7 patients who were NSAID user (Failure-NSAID group) and 5 patients who were non-NSAID user (Failure-non-NSAID group) (Table 1).

Baseline clinical features of RA patients received *H. pylori* eradication

The clinical features of our study patients are shown in Table 1. Overall disease activity in both groups was relatively low, although the patients' general VAS (visual analog scale), patients' pain VAS, physicians' general VAS, and erythrocyte sedimentation rate (ESR) titers in NSAID users were higher than those in non-NSAID users. The overall disability index, HAQ (Health Assessment Questionnaire) score was relatively higher in NSAID users than that in non-NSAID users. Percentage use of disease-modifying antirheumatic drugs and anti-ulcer drugs were high in both groups, while percentage use of methotrexate, steroids, misoprostol, and proton pump inhibitors were relatively high in NSAID users.

Endoscopic findings of the stomach before and after eradication therapy (Table 2)

In the Success group, there was no significant change on endoscopic findings, including gastric erythema, erosions, nodularity, vascular pattern, edema, friability, exudations, rugal hyperplasia, rugal atrophy, and intramural bleeding spots in all three regions, irrespective of NSAID use. Simi-

Table 2. Endoscopic findings (mean score) before and after *H. pylori* eradication therapy in the Success and the Failure groups according to the updated Sydney system

	No. of patients *H. pylori* eradication	Success group						Failure group	
		All patients		Success: NSAID group		Success: non-NSAID group			
		32		23		9		12	
		Before	After	Before	After	Before	After	Before	After
Greater curvature of the antrum	Edema	0	0.08	0	0.06	0	0.14	0.22	0.11
	Gastric erythema	0.24	0.08	0.33	0.11	0	0	0	0
	Friability	0	0	0	0	0	0	0	0
	Exudation	0	0	0	0	0	0	0	0
	Erosions	0.32	0.36	0.28	0.28	0.43	0.57	0.67	0.22
	Nodularity	0.76	0.72	0.72	0.67	0.86	0.86	0.56	0.67
	Rugal hyperplasia	0	0	0	0	0	0	0	0
	Rugal atrophy	0.04	0.04	0	0	0.14	0.14	0	0
	Visibility of vascular pattern	0.12	0.12	0.06	0.11	0.29	0.14	0.67	0.56
	Intramural bleeding spots	0	0.04	0	0	0	0	0	0
Greater curvature of the upper corpus	Edema	0	0	0	0	0	0	0	0
	Gastric erythema	0.16	0	0.11	0	0.29	0	0.44	0.33
	Friability	0	0.04	0	0	0	0	0	0
	Exudation	0.12	0.04	0.11	0.06	0.14	0	0.11	0.11
	Erosions	0.04	0.12	0.06	0.17	0	0	0	0
	Nodularity	0.44	0.72	0.50	0.72	0.29	0.71	0.33	0.44
	Rugal hyperplasia	0.16	0	0.17	0	0.14	0	0.11	0.11
	Rugal atrophy	0	0	0	0	0	0	0	0
	Visibility of vascular pattern	0.04	0.08	0.06	0.11	0	0	0.22	0.11
	Intramural bleeding spots	0	0	0	0	0	0	0	0
Lesser curvature of the lower corpus	Edema	0.20	0.28	0.22	0.33	0.14	0.14	0.22	0.11
	Gastric erythema	0.24	0.08	0.33	0.11	0	0	0	0.22
	Friability	0	0	0	0	0	0	0	0
	Exudation	0.08	0.04	0.11	0.06	0	0	0.11	0.22
	Erosion	0.12	0	0.17	0	0	0	0.11	0
	Nodularity	0.32	0.44	0.33	0.33	0.29	0.71	0.56	0.67
	Rugal hyperplasia	0	0	0	0	0	0	0	0
	Rugal atrophy	0	0	0	0	0	0	0	0
	Visibility of vascular pattern	0.52	0.60	0.44	0.56	0.71	0.71	0.78	0.78
	Intramural bleeding spots	0	0	0	0	0	0	0	0

larly in the Failure group, none of the endoscopic findings change before and after *H. pylori* eradication (Table 2).

Histological findings before and after the treatment of eradication (Table 3)

In the Success group, neutrophil infiltration and chronic inflammation in histological examination were significantly improved in all three regions after eradication, while atrophy and intestinal metaplasia did not change. These improvements in neutrophil infiltration and chronic inflammation were observed irrespective of use of NSAIDs. On the other hand, in the Failure group, there was no significant change on the histological findings in any of the three regions after eradication (Table 3).

UGI ulcers after eradication therapy

Before eradication therapy, there were 23 active UGI ulcers (14 gastric ulcers including 10, 3, and 1 ulcers in the Success-NSAID group, the Failure-NSAID group and the Failure-non-NSAID group, respectively, and 9 duodenal ulcers, including 7 and 2 ulcers in the Success-NSAID group and the Success-non-NSAID group, respectively) in 15 patients (Fig. 1), and multiple ulcers were observed in 4 patients. In regard of ulcer sites, gastric ulcers were most commonly observed at the lesser curvature of the antrum (9 ulcers), followed by the posterior wall of the middle portion of corpus (2 ulcers), and the greater curvature of the antrum, the greater curvature of the lower corpus and the lesser curvature of the lower corpus (1 ulcer in each location), while duodenal ulcers were all observed in the duodenal bulb. After eradication therapy, of 17 active UGI ulcers in the Success-NSAID group, duodenal ulcer remained (though became smaller from 10 mm to 2 mm) in one patient, but all other ulcers healed (Fig. 1), while 1 gastric ulcer was newly observed at the anterior wall of the middle portion of corpus in the Success-NSAID group. On the other hand, 2 of 3 active UGI ulcers, located at the lesser curvature of the antrum in the Failure -NSAID group persisted despite eradication therapy (Fig. 1).

Table 3. Histological findings (mean score) before and after *H. pylori* eradication therapy in the Success and Failure groups according to the updated Sydney system

	No. of patients *H. pylori* eradication	Success group						Failure group	
		All patients		Success: NSAID group		Success: non-NSAID group			
		32		23		9		12	
		Before	After	Before	After	Before	After	Before	After
Greater curvature of the antrum	Neutrophil infiltration	1.25*	0.10*	1.22*	0.09*	1.33*	0.13*	1.25	1.17
	Chronic inflammation	1.81*	1.03*	1.83*	1.17*	1.78*	0.63*	1.75	1.67
	Atrophic change	0.71	0.77	0.61	0.78	1.00	0.75	1.17	1.08
	Intestinal metaplasia	0.22	0.31	0.22	0.30	0.22	0.33	0.42	0.42
Greater curvature of the upper corpus	Neutrophil infiltration	1.25*	0.19*	1.26*	0.22*	1.22*	0.11*	1.42	1.25
	Chronic inflammation	1.72*	0.84*	1.78*	0.91*	1.56*	0.67*	1.83	1.83
	Atrophic change	0.34	0.13	0.30	0.04	0.44	0.33	0.17	0.17
	Intestinal metaplasia	0.16	0.09	0.09	0.04	0.33	0.22	0.17	0.00
Lesser curvature of the lower corpus	Neutrophil infiltration	1.28*	0.31*	1.26*	0.39*	1.33*	0.11*	1.33	1.25
	Chronic inflammation	1.81*	1.16*	1.83*	1.22*	1.78*	1.00*	1.75	1.75
	Atrophic change	1.10	0.94	1.05	0.96	1.22	0.89	1.00	1.42
	Intestinal metaplasia	0.69	0.72	0.65	0.70	0.78	0.78	0.92	1.25

*There was significant change in the score before and after *H. pylori* eradication therapy by the Mann–Whitney test ($P < 0.001$)

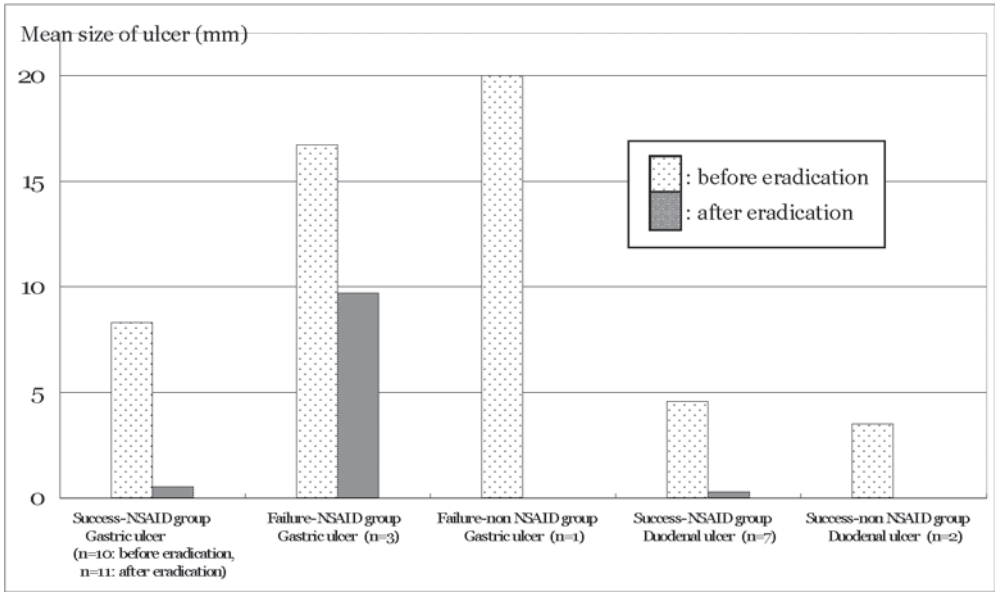

Fig. 1. Upper gastrointestinal ulcers after the treatment of eradication. After eradication therapy, of 17 active upper gastrointestinal ulcers in the Success-NSAID group, duodenal ulcer remained (though became smaller from 10 mm to 2 mm) in one patient, but all other ulcers healed, while one gastric ulcer was newly observed in the Success-NSAID group. On the other hand, 2 of 3 active UGI ulcers in the Failure-NSAID group persisted even after the treatment of eradication. *NSAID*, nonsteroidal anti-inflammatory drug

Erosive duodenitis and reflux esophagitis after eradication therapy

Before therapy, one patient in the Success-NSAID group had erosive duodenitis. After treatment, this case improved, but erosive duodenitis occurred in another patient of the Success-NSAID group and one in the Success-non-NSAID group. Before eradication therapy, one patient of the Success-NSAID group and two patients of the Failure-non-NSAID group had reflux esophagitis. After eradication therapy, one patient with esophagitis improved in the Success-NSAID group, but two new patients developed reflux esophagitis. In the Failure-non-NSAID group, one patient with esophagitis improved, but another deteriorated. In the Failure-NSAID group, one patient developed new reflux esophagitis.

Discussion

It remains controversial whether *H. pylori* eradication should be done or not in patients on long-term treatment with NSAIDs.[7–14] Chan et al. proposed *H. pylori* eradication in these patients,[8,10–12] since they reported that this approach, used before NSAID therapy, reduced the occurrence of NSAID-induced peptic ulcers,[8] and *H. pylori* eradication significantly reduced the risk of ulcers for patients starting long-term NSAID treatment.[12] By contrast, Hawkey et al. argued that *H. pylori* eradication in long-term users of NSAIDs led to impaired healing of gastric ulcers and did not affect the rate of peptic ulcers over 6 months.[9] Several other reports also indicated that *H. pylori* eradication should be avoided from a standpoint of prevention, healing,

and recurrence of UGI ulcers for arthritis patients.[7,13,14] The difference in the methodology and study design may help to explain the contrasting results among these studies according to several reviews.[6,31,32] Since there are few reports on the effect of NSAIDs on endoscopic and histological findings before and after *H. pylori* eradication, we compared these findings before and after the treatment of eradication between successful and unsuccessful eradication groups of NSAID users with RA.

In both the Success and the Failure groups in our study, all endoscopic findings, including gastric erythema, erosions, nodularity, and vascular pattern did not change before and after *H. pylori* eradication in any of the three gastric regions examined, irrespective of NSAIDs use (Table 2). Further, there was no significant change of the histological findings in all three regions in the Failure group after eradication after a mean follow-up period of 3.5 months using the updated Sydney system (Table 3). However, neutrophil infiltration and chronic inflammation were significantly improved in all three regions after eradication irrespective of use of NSAIDs in the Success group (Table 3), suggesting that the histological improvement of neutrophil infiltration and chronic inflammation in those who achieved successful eradication could not be observed on endoscopy. In addition, atrophy and intestinal metaplasia did not change in all three regions after eradication, irrespective of use of NSAIDs in both the Success and the Failure groups (Table 3). Hence, NSAID use neither affected the improvement of histological findings nor deteriorated the endoscopic findings, such as gastric erythema and erosions associated with *H. pylori* eradication.

Although 3.5 months may be a short observation period in our study, of the 17 active ulcers present before eradication in the Success-NSAID group, most healed except for one duodenal ulcer that remained, while 2 of 3 active UGI ulcers remained after the treatment of eradication in the Failure-NSAID group (Fig. 1), indicating that NSAID use did not affect the healing process of gastric and duodenal ulcers for a mean follow-up period of 3.5 months after eradication.

Several reports have suggested that *H. pylori* eradication should be avoided in patients chronically using NSAIDs. Median prostaglandin E2 synthesis by gastric mucosa, which may prevent superficial mucosal injury, was significantly higher in *H. pylori*-positive subjects than in *H. pylori*-negative subjects using NSAIDs.[33] Both Yeomans et al. and Hawkey et al. have shown that omeprazole healed and prevented ulcers more effectively in *H. pylori*-positive patients than in *H. pylori*-negative patients regularly using NSAIDs.[15,16] In our study, one gastric ulcer was newly observed on the anterior wall of the middle portion of corpus in the Success-NSAID group after eradication. Since el-Omar et al. reported that approximately 1 year will be needed in *H. pylori*-positive subjects after eradication to recover acid secretion, similar to *H. pylori*-negative subjects,[34] further longer-term observational studies will be required to examine the recurrence of UGI ulcers in patients chronically using NSAIDs.

The gastric mucosa and acid secretory mechanisms are quite unique in Japanese cohorts as compared to those in the West. First, a high prevalence of severe atrophic gastritis and decreased gastric acid secretion have been reported in Japanese *H. pylori*-positive subjects,[17–21] suggesting that UGI damage by NSAIDs may be likely to occur after the acid recovery that follows *H. pylori* eradication. Second, the prevalence of *H. pylori* infection in Japan increased at approximately 1% per year until 50 years of age, as in other advanced countries in younger individuals (about 20%–30% under 30 years of age), while it was constantly high as in developed countries in older individuals (about 80% over 50 years of age).[22,23] Third, the NSAID dosage in Japan is 50% less than that in Western countries. Finally, other factors, such as the frequent use of anti-ulcer drugs in conjunction with NSAIDs in Japan may play a role.[35]

Because of the improvement of gastric acid secretion after *H. pylori* eradication in Japanese *H. pylori*-positive subjects, the occurrence of erosive duodenitis and reflux esophagitis[36] after eradication would not be surprising. Although several reports indicate that duodenitis does not deteriorate after *H. pylori* eradication,[37,38] in the Success-NSAID group of our study, one patient developed erosive duodenitis and two developed reflux esophagitis without any associated GI symptoms, indicating that a long-term follow-up study may also will be needed.

Limitations of our study include a possible selection bias in the patients with *H. pylori* eradication and a small sample size. We also did not consider details of NSAID use, such as the type and dose of NSAID, and the follow-up period in this study was short. In conclusion, over a mean follow-up period of 3.5 months, NSAID use in Japanese patients with RA neither impaired the healing process of UGI ulcers nor deteriorated UGI damage after *H. pylori* eradication.

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