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ORIGINAL ARTICLE

Risk factors for the development of gastric mucosal lesions in rheumatoid arthritis patients receiving long-term nonsteroidal anti-inflammatory drug therapy and the efficacy of famotidine obtained from the FORCE study

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Abstract The objective of this study was to investigate the prevalence of gastric mucosal injury induced by nonsteroidal anti-inflammatory drugs (NSAIDs) in patients with rheumatoid arthritis (RA). Upper gastrointestinal endoscopy was performed on 100 RA patients treated with NSAIDs. Patient factors potentially contributing to the development of NSAID-induced gastric mucosal injury were identified by logistic regression analysis; gastric mucosal injury and ulcers were used as objective variables. Gastric mucosal injury was detected in 62 of 100 patients, and eight of these patients had ulcers. Previous history of ulcers, lifestyle, NSAID dosage, and body mass index were associated with the development of gastric mucosal injury, and the use of diclofenac and steroid dose were associated with the development of ulcers. Disease-modifying antirheumatic drugs (DMARDs) did not appear to influence the risk of NSAID-induced gastric mucosal injury. RA patients treated for long periods with NSAIDs for RA symptoms should be controlled with DMARDs, without consideration of increased doses of steroids, in terms of risk for NSAID-induced gastric mucosal injury. Simultaneously, concomitant use of histamine-2 receptor antagonists (H2RA) such as famotidine should be considered.

Keywords NSAID · Steroid · Rheumatoid arthritis · Famotidine · Mucosal lesion

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Introduction

In drug therapy for rheumatoid arthritis (RA), nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used as symptomatic treatment for swelling and pain of the joints from very early stages of the disease [1]. Whereas NSAIDs exert immediate anti-inflammatory and analgesic effects by inhibiting cyclooxygenase (COX) activity and thereby suppressing prostaglandin (PG) production [2, 3], they are also known to cause gastric mucosal injury as an adverse effect [4]. NSAID-induced gastric mucosal injury is often associated with no subjective symptoms due to the analgesic effect of the drugs [5–7], and the damage often becomes apparent only with abrupt hematemesis. Furthermore, other drugs that may exacerbate NSAID-induced gastric mucosal injury, such as steroids and disease-modifying antirheumatic drugs (DMARDs), are commonly used to treat RA. RA patients may thus be expected to be at a higher risk of NSAID-induced gastric mucosal injury than patients with other diseases. In Japan, however, the last epidemiological study of NSAID-induced gastric mucosal injury in RA patients was conducted by Shiokawa et al. [8] in 1991, and no such study has been conducted since.

The famotidine or rebamipide in comparison by endoscopy (FORCE) study examined the prevalence of gastric mucosal injury based on upper gastrointestinal endoscopic findings in 261 patients receiving long-term NSAID therapy and evaluated the efficacy of famotidine and rebamipide for the treatment of such gastric mucosal injury. The study has already been published in detail elsewhere [9, 10]. For this report, we selected 100 RA patients from the FORCE study population and examined the prevalence of gastric mucosal injury in RA patients receiving long-term NSAID therapy to identify patient factors contributing to the development of such mucosal

injury and compare the effects of famotidine and rebamipide in the treatment of NSAID-induced gastric mucosal injury of RA patients.

Materials and methods

A multicenter study was conducted from May 2004 to July 2005 by gastroenterologists and orthopedists from the Nara Medical University and its four affiliated institutions, namely, Nara Prefectural Nara Hospital, Nara Prefectural Gojo Hospital, Kokuho Central Hospital, and Nishi Nara Chuo Hospital. The protocol was approved by the institutional review boards of all participating institutions. The study was conducted in compliance with the standards of Good Clinical Practice, and written informed consent was obtained from each of the study participants.

Materials

Subjects were RA outpatients ranging in age from 20 and 74 years who were under oral treatment with any NSAID other than aspirin for at least the previous 4 weeks. Patients receiving any histamine-2 receptor antagonists (H2RA), proton pump inhibitors (PPIs), muscarinic receptor antagonists, or PGs within 4 weeks prior to the endoscopy were excluded from the study. In addition, patients with any changes in the treatment regimen with NSAIDs or DMARDs within 4 weeks prior to the endoscopy, including any changes in the dosage or administration schedule, were also excluded. Also, patients with any changes in the treatment regimen with adrenocortical hormones, excluding external application, within 14 days prior to the endoscopy were excluded.

Methods

After a complete medical history was obtained from the patients who had provided their consent for participation in the study, a urinary anti-*Helicobacter pylori* (*H. pylori*) antibody test [enzyme-linked immunosorbent assay (ELISA)] was conducted, followed by upper gastrointestinal endoscopy, regardless of whether symptoms were present. The modified Lanza score (hereafter referred to as the Lanza score) [11], determined based on a scoring system reported by Lanza [12], was estimated for evaluation of endoscopic findings. In this scoring system, the severity of gastric mucosal injury as viewed by endoscopy is graded on a scale of 0–5, as follows: absence of gastric mucosal injury is assigned a score of 0, with the score increasing with severity of mucosal injury to a maximum score of 5, which represents the presence of mucosal ulcers.

Investigations and statistical analyses

The prevalence of gastric mucosal injury was estimated based on the Lanza scores as determined by endoscopy. In addition, patient factors potentially contributing to the development of gastric mucosal injury were identified by logistic regression analysis. Gastric mucosal injury (Lanza score 0 or 1–5) and ulcers (Lanza score 0–4 or 5) were used as objective variables. Patient background factors, including gender, age, *H. pylori* infection, type of NSAIDs, and subjective symptoms, were used as explanatory variables. In logistic regression, the odds ratio (OR) and 95% confidence interval (95% CI) were calculated in a stepwise manner for selected explanatory variables according to the inclusion criteria for the explanatory variable as $p < 0.1$. The p value was calculated using the Wald test, and $p < 0.05$ was considered statistically significant.

Scores were assigned to the DMARDs, one of the explanatory variables, based on the intensity of their antirheumatic effects as specified in the *Treatment Manual for Rheumatoid Arthritis* [13] and were used as continuous variables (Table 1). When multiple drugs were used, the scores for each drug were added together. For steroids, the doses listed in Table 2 were used as continuous variables.

Patient background factors contributing to the development of gastric mucosal injury were analyzed by primarily examining the prevalence of gastric mucosal injury in relation to patient background factors that would be expected to play a particularly important role in the development of gastric mucosal injury in RA patients, such as NSAID dose, steroid dose, and concomitant DMARD use.

Patients with a Lanza score of 1–4 (gastric hemorrhage or erosion) were considered eligible for treatment, whereas those with Lanza scores of 0 (no gastric mucosal lesion) or 5 (gastric ulcer) were excluded from the treatment group. Eligible patients were randomly assigned to receive either

Table 1 Details of concomitantly used drugs [disease-modifying antirheumatic drugs (DMARDs)]

Drug	Antirheumatic effect	Score[a]	No. of patients
Methotrexate	High	3	44
Bucillamine	Moderate	2	53
Salazosulfapyridine	Moderate	2	6
Actarit	Low	1	13
Auranofin	Low	1	9
Mizoribine	Low	1	2
None		0	9

[a] The DMARDs were assigned scores based on the intensity of their antirheumatic effects as specified in the *Treatment Manual for Rheumatoid Arthritis: Manual for Diagnosis and Treatment Guidelines* based on evidence-based medicine issued by the Japan Rheumatism Foundation. When multiple drugs were used, the scores for each drug were added together

Table 2 Details of concomitantly used drugs (steroids, 47/100)

Dose (mg)[a]	No. of patients
0.25	1
1	1
2	1
2.5	15
3	1
4	1
5	19
7.5	5
10	3

[a] Prednisolone equivalent

famotidine 20 mg/day (group F) or rebamipide 300 mg/day (group R). Changes in the Lanza scores and the rate of complete cure (percentage of patients showing reversal to a Lanza score of 0 after treatment with either drug) after 4 weeks of treatment with either drug under continuation of NSAID therapy were examined in each group. To objectively evaluate the results, again, a third party unaware of which drug was administered or when endoscopy would be performed examined the Lanza scores before and after the treatment. Within-group and between-group comparisons of changes in the Lanza scores estimated before and after treatment with the drugs under investigation were analyzed by the Wilcoxon signed rank test and Wilcoxon rank test, respectively, and the rates of complete cure were compared by Fisher's exact probability test, with the significance level set at $p < 0.05$, respectively.

Results

Patient background factors

The background factors of the 100 RA patients examined in this study are shown in Table 3. The mean age of patients was 57.7 years; female patients accounted for 80% of the study population. Only 35.0% of patients reported subjective abdominal symptoms. A previous history of ulcers was reported by 10.0% of patients, of which 57.0% were positive for antibody to *H. pylori*. In regard to the NSAID used for the treatment, loxoprofen was the most commonly used NSAID (33 patients), followed by a sustained-release preparation of diclofenac. DMARDs were used concomitantly in 91 patients and steroids in 47 patients. Ninety-eight patients were prophylactically administered mucoprotective drugs.

Details of gastric mucosal injury

The prevalence and severity of gastric mucosal injury in the patients at the first endoscopy are shown in Fig. 1. Gastric mucosal injury was found in 62 patients (62.0%), of which eight patients (8.0%) had ulcers. Analysis by the Lanza score showed that grade 3 was the most frequently observed, with a mean score of 2.8 in the patients with mucosal injury.

In the FORCE study, the prevalence of gastric mucosal injury and ulcers in the 161 patients with underlying diseases other than RA, such as osteoarthritis and lumbar spinal canal stenosis, were 63.4% and 11.8%, respectively, which were similar to the incidence in RA patients.

Results of logistic regression analysis

The following are the results of the logistic regression analysis where the criterion variables were gastric mucosal lesions and ulcers, and the factors in the medical history shown in Table 3, were candidates for explanatory variables. The analysis identified a previous history of ulcers, lifestyle, NSAIDs dose, and body mass index (BMI) as patient factors that were significantly associated with the development of gastric mucosal injury. The OR (95% CI, p value) was 7.53 (1.29–44.06, $p = 0.025$) for a previous history of ulcers, 4.00 (1.60–10.03, $p = 0.003$) for worsening of the lifestyle from good or fair to poor, 3.15 (1.35–7.36, $p = 0.008$) for an increase in NSAIDs dose from half dose or standard dose to double dose or multiple drugs, and 1.30 (1.08–1.58, $p = 0.006$) for every one increase in BMI (Fig. 2).

The use of diclofenac and steroid dose were identified as patient factors significantly associated with the development of ulcers. The OR (95% CI) was 14.15 (2.15–93.32, $p = 0.006$) for the use of diclofenac instead of other NSAIDs and 1.56 (1.15–2.12, $p = 0.005$) for an increase in steroid dose by 1 mg, suggesting that the use of diclofenac is a major risk factor for the development of ulcers (Fig. 3).

Prevalence of gastric mucosal injury in relation to patient background factors

The prevalence of gastric mucosal injury by NSAID dose, NSAID type, steroid dose, and concomitant DMARD use were as follows: In relation to NSAIDs, prevalence was 57.6% with half to standard doses, 57.1% with the standard dose, and 92.3% with twice the standard dose or the use of multiple drugs, including aspirin; a high prevalence of gastric mucosal injury was observed in patients administered double the standard dose or multiple NSAIDs, including aspirin (Fig. 4). Analysis by NSAID type showed gastric mucosal injury in 90.0% of patients receiving diclofenac and 60.6% of those receiving loxoprofen. Gastric mucosal injury was also found in 71.4% of patients receiving meloxicam and etodolac, which have high selectivity for COX-2, with no difference in the incidence compared with conventional NSAIDs.

Table 3 Patient background factors ($n = 100$ patients)

Factors in medical history	Number	Percent
Gender		
Female	80	80.0
Anti-*Helicobacter pylori* antibody		
Positive	57	57.0
Peptic ulcer history		
Yes	10	10.0
Subjective symptoms		
Yes	35	35.0
Smoking habit		
Yes	17	17.0
Alcohol habit[a]		
No	70	70.0
Occasionally	26	26.0
Daily	4	4.0
Coffee habit		
Yes	88	88.0
Lifestyle[a]		
Regular	28	28.0
Almost regular	65	65.0
Irregular	7	7.0
Particular stress		
Yes	20	20.0
Unknown	1	1.0
Type of NSAIDs[b]		
Loxoprofen	33	33.0
Preferential COX-2 inhibitor [c]	14	14.0
Diclofenac	10	10.0
Diclofenac SR	16	16.0
Others	38	38.0
NSAIDs administration		
1–3 months	7	7.0
>3 months	93	93.0
Dosage of NSAIDs[a]		
Below usual dose	28	28.0
Usual dose	59	59.0
Double or combination[d]	13	13.0
Type of mucosal protective agents[b]		
Teprenone	47	47.0
Rebamipide	26	26.0
Score of DMARDs[a]		
0	9	9.0
1–3	66	66.0
4–7	25	25.0
Bisphosphonate		
Yes	17	17.0
Dosage of steroids[a]		
0	53	53.0
<5 mg	39	39.0
<7.5 mg	8	8.0

The mean and range of all patients' ages are 57.7 years and 29.0–74.0 years, respectively; the mean and range of all patients' body mass index (kg/m^2) are 22.0 and 14.7–30.0, respectively

NSAIDs nonsteroidal antiinflammatory drugs, *DMARDs* disease-modifying antirheumatic drugs, *COX* cyclooxygenase

[a] Factors used as continuous variables in multilogistic regression analysis (the rest are discrete variables)

[b] Including duplication due to combination

[c] Meloxicam ($n = 13$) + Etodolac ($n = 1$)

[d] Combination between NSAIDs, including aspirin

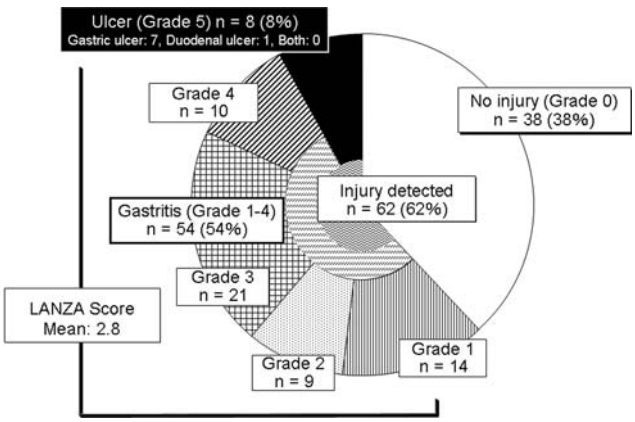

Fig. 1 Detailed findings of gastric mucosal injury at the first endoscopy

Whereas no substantial differences were found in the prevalence of gastric mucosal injury analyzed according to steroid dose, the prevalence of ulcers was 1.9% in patients who did not receive steroids, 10.3% in those treated with steroids at 5 mg or less, and 37.5% in those treated with steroids at 7.5 mg or more, with a particularly high prevalence in those administered high doses (≥7.5 mg) of steroids. Exclusion from the analysis of patients treated with diclofenac, which was considered as the strongest risk factor for the development of ulcers based on the results of the logistic regression analysis, did not affect results on the prevalence of ulcers, which was 2.0% in patients who did not receive steroids, 3.0% in those treated with steroids at 5 mg or less, and 28.6% in those treated with steroids at 7.5 mg or more (Fig. 5).

Analysis of the prevalence of gastric mucosal injury in relation to the concomitant use of DMARDs, which were assigned scores according to the potency of their anti-rheumatic effects, showed that gastric mucosal injury and ulcers and the mean Lanza scores were higher in patients receiving DMARDs assigned higher scores. However, the

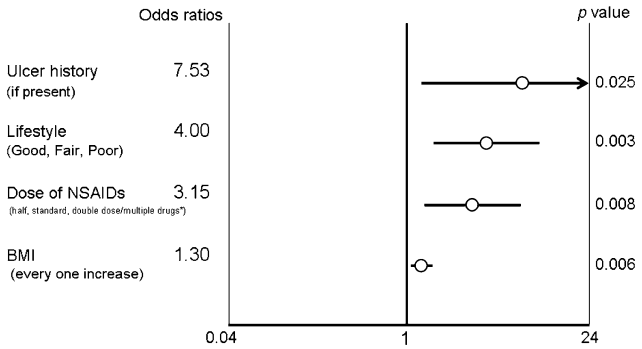

Fig. 2 Patient factors associated with the development of gastric mucosal injury. *Asterisk* including concomitant aspirin

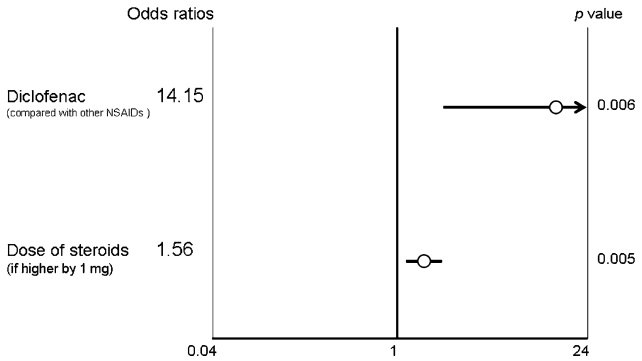

Fig. 3 Patient factors associated with the development of ulcers

trend became less when patients treated with diclofenac, the strongest risk factor for ulcers, was excluded from the analysis (Fig. 6).

The prevalence of gastric mucosal injury and ulcers analyzed in relation to other patient background factors were as follows: 62.3% in patients aged ≤64 years and 60.9% in those aged ≥65 years, 62.8% in those negative and 61.4% in those positive for *H. pylori* infection, 55.4% in those without subjective symptoms and 74.3% in those with subjective symptoms, 57.1% in those administered NSAIDs for 1–3 months and 62.4% in those administered NSAIDs for ≥3 months, and 53.8% in those treated with rebamipide and 63.8% in those treated with teprenone used as a mucoprotective drug.

Evaluation of therapeutic effect

Of the 54 patients with hemorrhage or erosion (Lanza score 1–4), one was not randomized because of the need for treatment for esophageal cancer. Of the 53 randomized patients, one refused to undergo the second endoscopy, and five patients were excluded from the analysis because of a change in NSAID dose, leaving 47 patients (21 in group F and 26 in group R) whose endoscopic findings after completion of treatment were available for analysis. The characteristics of each group are shown in the Table 4. No

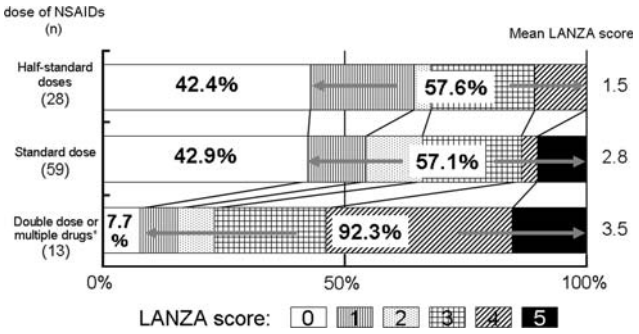

Fig. 4 Presence/absence of gastric mucosal injury in relation to nonsteroidal anti-inflammatory drugs (NSAIDs) dose. *Asterisk* including concomitant aspirin

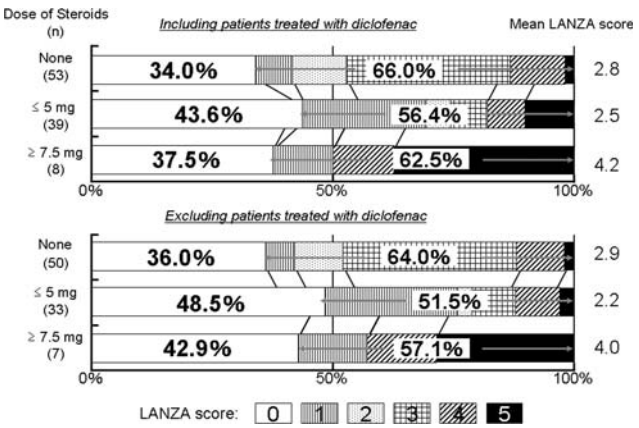

Fig. 5 Presence/absence of gastric mucosal injury in relation to the steroid dose

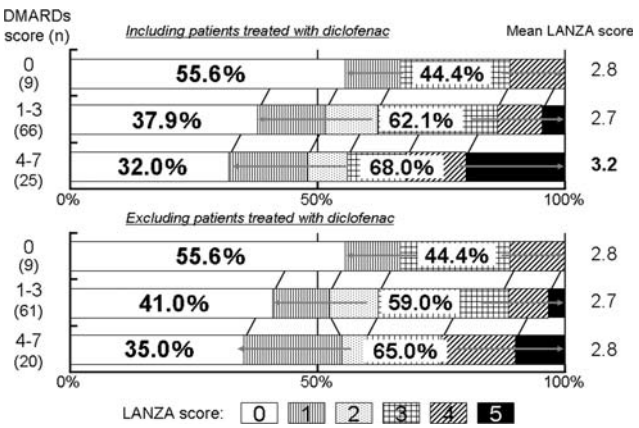

Fig. 6 Presence/absence of gastric mucosal injury in relation to concomitant disease-modifying antirheumatic drug (DMARD) use

significant differences were found in the patient background factors between the two groups, except for the higher mean age of group R than group F. The changes in Lanza scores in both groups are shown in Fig. 7. The mean Lanza score in group F decreased significantly from 2.1 to 1.1 ($p = 0.014$), whereas the score in group R increased,

Table 4 Patient characteristics by treatment

Factors in medical history	Group F ($n = 21$)	Group R ($n = 26$)	p value
Age (Years)	55.19 ± 9.08	61.00 ± 8.14	0.026
Gender			
Female	19	20	0.402
Anti-*Helicobacter pylori* antibody			
Positive	9	17	0.212
Peptic ulcer history			
Yes	19	24	0.763
Smoking habit			
Yes	20	22	0.485
DMARDs			
Yes	21	24	0.567
Bisphosphonate			
Yes	4	1	0.288
Steroids			
Yes	6	12	0.352

DMARDs disease-modifying antirheumatic drugs

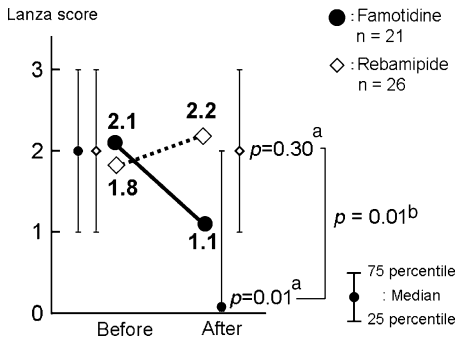

Fig. 7 Changes in the Lanza scores following treatment with famotidine/rebamipide. *a* Wilcoxon's signed rank test. *b* Wilcoxon's rank test

although not statistically significantly ($p = 0.298$), from 1.8 to 2.2. There was a significant difference in the change in the Lanza scores between groups ($p = 0.003$). The rate of complete cure was 57.1% (12/21 patients) in group F, whereas it was as low as 19.2% (5/26 patients) in group R ($p = 0.014$). In regard to adverse drug reactions, mild back pain was reported in one patient in group F, whereas all the other reported events were mild abnormalities in laboratory test values, with no report of any serious adverse drug reactions.

Discussion

The incidence of gastrointestinal lesions in patients receiving long-term NSAID therapy was reported by the Japan Rheumatism Foundation in 1991 [8] to be 62.2%, which is similar to the incidence determined in our study. An incidence of gastric mucosal injury associated with NSAID use of >60% was unexpected with the current availability of NSAIDs that are highly selective for COX-2, such as meloxicam and etodolac, which are considered to be less likely to cause gastric mucosal injury. Meanwhile, celecoxib—a COX-2-selective inhibitor demonstrated in foreign clinical studies to be less likely to cause gastrointestinal damage than conventional NSAIDs—has also become available in Japan. Celecoxib, which was not included in our study, is shown to be less likely to cause gastrointestinal damage in clinical trials of celecoxib in Japan, and it is therefore necessary to evaluate the incidence of gastric mucosal injury associated with the use of this drug by accumulating clinical data in Japanese patients. Similar to the results obtained in previous studies, our study also identified a previous history of ulcers and a high NSAID dose as significant risk factors for gastric mucosal injury associated with long-term NSAID therapy and steroid dose as a significant risk factor for the development of ulcers associated with NSAID use [14, 15].

In our study, diclofenac, which is known to have potent anti-inflammatory effects, was selected as the drug associated with the greatest risk for the development of mucosal ulcers. As the drug has also been reported to be associated with a higher risk of upper gastrointestinal bleeding than other NSAIDs [16], diclofenac must be used with care.

Analysis of prevalence of gastric mucosal injury by patient background factors revealed higher incidence of injury associated with higher doses of NSAIDs; prevalence was especially high in those administered double the usual doses or multiple NSAIDs, including aspirin. Studies from abroad have also reported that the relative risk of developing NSAID-induced peptic ulcers is particularly high in patients administered high doses of NSAIDs [17].

Ulcers caused by steroid treatment alone were first reported by Sandweiss in 1954 [18]. Since then, both positive [19, 20] and negative [21, 22] relationships between steroids and peptic ulcers have been reported. Possible reasons for the controversy include ambiguous definitions of steroid-induced ulcers; endoscopy not performed in all patients; differences in the type, dose, and duration of use of steroids; differences in concomitantly used drugs; and underlying diseases. On the other hand, it is almost universally agreed that concomitant NSAID use with steroids increases the risk of ulcers [14, 15]. In this study, ulcers were observed at a high frequency in patients taking steroids at doses of 7.5 mg or higher; exclusion from the analysis of patients administered diclofenac, which is considered to pose the greatest risk for ulcers, did not affect the result.

The efficacy of DMARDs has recently been reconfirmed. These agents are administered from an early stage after the diagnosis of RA [12], often concomitantly with

NSAIDs even before the definitive diagnosis. Although some DMARDs are associated with a high risk of gastrointestinal adverse effects, gastrointestinal mucosal damage induced by DMARDs has not been reported as frequently as that induced by NSAIDs or steroids. It is also unclear whether the concomitant use of DMARDs with NSAIDs might increase the risk of gastric mucosal injury. In this study, the prevalence and severity of gastric mucosal injury, including ulcers, was higher in patients administered DMARDs with more potent antirheumatic effects; however, the trend became less significant when patients treated with diclofenac, the NSAID associated with the greatest risk of gastric mucosal ulcers, were excluded. The results might suggest that RA patients administered DMARDs with highly potent antirheumatic effects tend to have severe RA and, therefore, also tend to be administered NSAIDs with potent anti-inflammatory and analgesic effects, consequently being at a higher risk of gastric mucosal injury. In the final analysis, concomitant DMARD administration is considered to have little effect on NSAID-induced gastric mucosal injury.

In Japan, mucoprotective drugs are commonly used to treat gastric mucosal injury during NSAID therapy. However, in this study, rebamipide had no therapeutic effect on NSAID-induced gastric mucosal injury in RA patients, whereas famotidine (20 mg/day), which is covered by health insurance, was an effective drug. These results indicate the involvement of gastric acid [23] and the inhibitory effect of NSAIDs on PG biosynthesis [24]—which has been considered to be the cause of NSAID-induced gastric mucosal injury—in NSAID-induced gastric mucosal injury. The efficacy of acid suppressors against NSAID-induced gastric mucosal injury has actually been demonstrated [25–27], lending support to the proposed mechanism above of the effects of these NSAIDs.

In Japan, the use of PPIs, PG preparations, and high doses of H2RA is recommended in the *Treatment Manual for Rheumatoid Arthritis* [13] and the *Treatment Guidelines for Gastric Ulcer*, Ver. 2., for the treatment/prevention of NSAID-induced ulcers [28], and PPI therapy is restricted in Japan. In our study, evaluation included the therapeutic effect of famotidine on preulcer lesions of the gastric mucosa, such as erosions and bleeding, which may explain why the drug exhibited therapeutic effects at a lower dose than that specified in the guidelines (80 mg). In addition, most of the evidence to date has been adopted from guidelines developed in the United States and Europe. Thus, the lower acid-secretory capacity of the Japanese people compared with that of people from the United States or Europe [29–31] and the consequently lower doses of NSAIDs approved in Japan (one half to one third of those approved in the United states and Europe) may also explain the phenomenon. For patients at high risk because of a previous history of upper gastrointestinal bleeding, however, the use of COX-2-selective inhibitors that are expected to rarely cause gastrointestinal damage, such as celecoxib, may be recommended concomitantly with a PPI.

In this study, we examined RA patients selected from the population of the FORCE study but found that the risk factors and prevalence of gastric mucosal injury, and also the efficacy of famotidine (20 mg/day), were similar to the respective results obtained for the entire FORCE study population [9, 10]. Our results suggest that treatment with famotidine (20 mg/day) is effective even in RA patients, who are often administered steroids or DMARDs concomitantly with NSAIDs. As mild gastric mucosal injury, such as erosion, is at a high risk of developing into ulcers even after long-term follow-up [32], there will be an increasing need to manage patients receiving long-term NSAID therapy to prevent gastric mucosal damage.

Conclusion

The prevalence of NSAID-induced gastric mucosal injury in RA patients in this study was similar to that reported by the Japan Rheumatism Foundation in 1991 [5], suggesting that the incidence of gastric mucosal injury remains high even after the relatively recent introduction of NSAIDs considered to be highly selective for COX-2. Risk factors for gastric mucosal injury in the patients were also similar to those reported in previous studies, with higher doses of NSAIDs being associated with a higher risk of gastric mucosal injury and higher doses of steroids administered concomitantly with NSAIDs being associated with a higher risk of ulcers. On the other hand, concomitant use of DMARDs did not appear to significantly influence the risk of NSAID-induced gastric mucosal injury. The efficacy of famotidine (20 mg/day) in the treatment of gastric mucosal injury associated with NSAID use was also confirmed.

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Conflict of interest statement There are no competing interests.

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