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ORIGINAL ARTICLE

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Prevalence of *Helicobacter pylori* infection and risk of upper gastrointestinal ulcer in patients with rheumatoid arthritis in Japan

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Abstract We evaluated the prevalence of *Helicobacter pylori* infection and the association of *H. pylori* infection and/or nonsteroidal anti-inflammatory drug (NSAID) use with upper gastrointestinal (UGI) ulcers in a cohort of Japanese patients with rheumatoid arthritis (RA). Using the clinical database of the cohort of RA patients and the serum titers of *H. pylori* antibody, 1815 patients were analyzed. Clinical data were successfully collected for 1529 patients over 2 years, and the history of NSAID use and the occurrence of newly diagnosed UGI ulcer were ascertained by patient self-reports and confirmed by their medical records. A total of 871 patients (49.3%) were *H. pylori* antibody-positive. Rates of positivity for *H. pylori* in patients with and without NSAID use were 47.5% and 54.7%, respectively (odds ratio = 0.75, 95% confidence intervals [CI]: 0.58–0.96). The incidence of newly diagnosed UGI ulcer was 0% in the *H. pylori*–/NSAID– group, 1.24% in the *H. pylori*–/NSAID+ group, 1.06% in the *H. pylori*+/NSAID– group, and 3.46% in the *H. pylori*+/NSAID+ group. The odds ratios of *H. pylori* infection and NSAID for the occurrence of new UGI ulcers after adjusting for age and sex were 2.97 (95% CI: 1.19–7.38) and 4.31 (95% CI: 0.57–32.4), respectively. Although the prevalence of *H. pylori* antibody was low in patients with RA compared with that in healthy Japanese individuals, *H. pylori* infection was a significant risk factor for UGI ulcer in patients with RA.

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Introduction

Upper gastrointestinal (UGI) ulcer disease is a potential life-threatening event in rheumatoid arthritis (RA) patients, especially in those who are being treated with nonsteroidal anti-inflammatory drugs (NSAIDs). *Helicobacter pylori* infection[1,2] and NSAID use[3–5] are among the major causes of UGI ulcers. The clinical course of *H. pylori* infection varies, and is influenced by both microbial and host factors.[2] Although some patients suffer from the UGI ulcers and gastric cancer, 80%–90% of *H. pylori*-positive individuals will never have gastrointestinal (GI) symptoms.[2] The overall prevalence of *H. pylori* infection in Japan is approximately 50%, but is low in younger individuals and higher in older individuals, consistent with findings in other developed countries. Approximately 2%–3% of *H. pylori*-positive Japanese individuals develop UGI ulcer and 0.4% develop gastric cancer.[6,7]

In 1991, the Epidemiological Research Committee for UGI Injury in Patients with Rheumatoid Arthritis (author's translation) of the Japan Rheumatism Foundation reported the results of endoscopy study in 1008 patients with RA who had been taking NSAIDs for more than 3 months.[8] This report revealed that 627 (62.2%), 156 (15.5%), and 19 (1.9%) patients had GI disorders, gastric ulcer and duodenal ulcer, respectively, and suggested that the frequency of NSAID-induced UGI ulcer was high in Japanese RA patients.[8] However, since the influence of *H. pylori* infection on GI events was not considered at that time, it is not known whether *H. pylori* infection or NSAID use was the major cause of the high frequency of UGI ulcers in Japanese patients with arthritis. Recently, a meta-analysis showed that both *H. pylori* infection and NSAID use independently and significantly increased the risk of UGI ulcer and ulcer bleeding, and that these two risk factors affected

UGI ulcer and ulcer bleeding synergistically.[9] However, most of the reports included in the analysis came from populations with comparatively low prevalences of *H. pylori* infection. For analysis of the association of *H. pylori* infection and NSAID use in chronic NSAID users such as RA patients, data from a large-scale cohort in a population with high prevalence of *H. pylori* infection are needed.

A large observational cohort study of RA patients using physician's assessment, patient's assessment, and laboratory data has been established in our institute since 2000.[10] In this 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. In this study, we evaluated the prevalence of *H. pylori* infection and investigated the association of *H. pylori* infection and NSAID use with risk of UGI ulcer in Japanese patients with RA enrolled in the cohort study.

Materials and methods

Patients and measurement of *H. pylori* antibody

Among RA patients who consulted the outpatient clinic of the Institute of Rheumatology, Tokyo Women's Medical University, 4451 participated in the prospective observational cohort study in April and May 2002. All of these 4451 patients were asked to undergo measurement of serum *H. pylori* antibody by the self-report questionnaire, and 1815 of 4451 patients agreed to be tested. All patients were of Japanese origin and had been diagnosed with RA according to the 1987 ACR criteria.[11] Those who had already been treated for eradication of *H. pylori* were excluded from the analysis. Seropositivity for *H. pylori* antibody was examined by 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.[12,13] Patients with *H. pylori* antibody titer above 10 U/ml were defined as *H. pylori*-positive.

Use of NSAIDs

Frequencies of NSAID use were estimated based on the patient self-reports in the cohort study from April 2000 to March 2002. Patients who took NSAIDs more than 10 days per month were defined as NSAID users. For the purposes of this study, NSAIDs included suppositories as well as oral medications.

Incidence of newly diagnosed UGI ulcers

The incidence of newly diagnosed UGI ulcers from April 2000 to March 2002 was ascertained based on the patient self-reports in the cohort study and was confirmed by examination of medical records. The presence of UGI ulcer was confirmed by endoscopy and/or gastrography, and excluded scar-stage ulcers, but neither size nor bleeding of ulcers was considered.

We divided the RA patients into three groups, A, B, and C. Group A patients had newly diagnosed UGI ulcer in this period, group B patients had no UGI ulcer either in this period or previously, and group C patients had no newly diagnosed UGI ulcer in this period and had a history of UGI ulcer from before the study period.

Use of antiulcer drugs in the three groups

The frequencies of use of antiulcer drugs, including cytoprotective drugs, misoprostol, H_2 receptor antagonists, and proton pump inhibitors (PPI) in the three groups were estimated based on the patient self-reports in the cohort study from April 2000 to March 2002.

Statistical analysis

SAS software (Version 8; SAS Institute, Cary, NC, USA) was used for database management and for statistical analysis, with performance of the χ^2 test and multiple logistic regression analysis.

Results

Percentages of H. pylori positivity

Of 1815 patients with RA, 871 (49.3%) were *H. pylori* antibody-positive. The rate of positivity increased with age from 24.5% in individuals less than 30 years of age to 56.5% in those over 60 years of age. The percentage of patients who were *H. pylori*-positive exceeded that of patients who were *H. pylori*-negative in age group of the 50s and 60s (Fig. 1).

The percentages of *H. pylori* positivity in patients with and without NSAID use were 47.5% (720/1517) and 54.7% (163/298), respectively (odds ratio = 0.75, 95% confidence intervals [CI]: 0.58–0.96). However, after adjustment for age, the significance of this difference disappeared (odds ratio = 0.85, 95% CI: 0.66–1.09), since the mean ages of patients with and without NSAID use were 54.7 ± 12.2 and 58.7 ± 11.4, respectively.

Clinical features in the three groups

Of the 1815 patients enrolled in this investigation, data for 286 were incomplete either in the patient questionnaire or in the clinical data set, and these were excluded from further analysis. The remaining 1529 RA patients were divided into 3 groups: group A (24 patients) with new ulcer diagnosed during this period, group B (1180 patients) without both new ulcer during this period and previous history of ulcers, and group C (325 patients) with previous history of

ulcers (Table 1). Patients in group C were older and had had RA for a longer period of time compared with the other groups, but were otherwise similar. The rates of use of disease-modifying antirheumatic drugs (DMARDs) and methotrexate (MTX) were over 95% and over 50%, respectively, in each group. The percentage of NSAID users was high in each group, especially in group A. Use of antiulcer drugs in group A (79.2%) was lower than in group B (91.0%) and group C (95.4%). Among antiulcer drugs, cytoprotective drugs were frequently used (>70%) in all three groups. Misoprostol, H_2 receptor antagonists, and PPIs were more frequently used in group C than in the other groups.

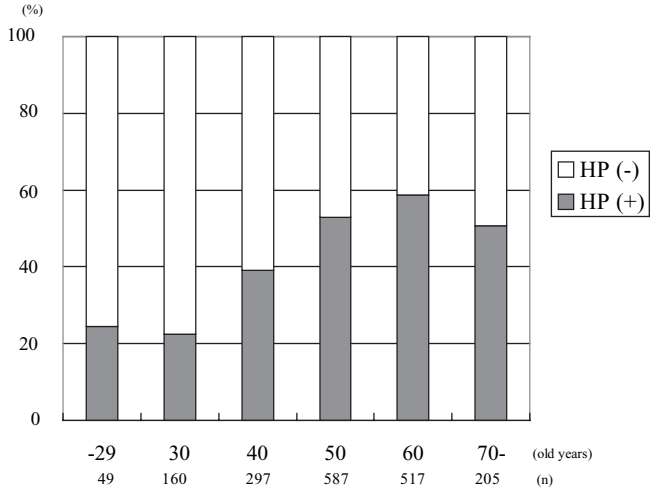

Fig. 1. Prevalence of *Helicobacter pylori* (*HP*) antibody positivity and negativity in Japanese patients with rheumatoid arthritis by age group. The rate of positivity increased with age from 24.5% in individuals younger than 30 years of age to 56.5% in those over 60 years of age. The percentage of patients who were *H. pylori*-positive exceeded that of patients who were *H. pylori*-negative in the 50s and 60s age-groups

Association of H. pylori infection and NSAID use with risk of UGI ulcer

The association between *H. pylori* infection and NSAID use and risk of new UGI ulcer is shown in Table 2. The incidence of newly diagnosed UGI ulcer was 0/82 patients (0%) in the *H. pylori*–/NSAID– group, 7/566 patients (1.24%) in the *H. pylori*–/NSAID+ group, 1/94 patients (1.06%) in the *H. pylori*+/NSAID– group, and 16/462 patients (3.46%) in the *H. pylori*+/NSAID+ group. The odds ratios of *H. pylori* infection and NSAID use for the occurrence of new UGI ulcer after adjustment for age and sex were 2.97 (95% CI: 1.19–7.38) and 4.31 (95% CI: 0.57–32.4), respectively.

Discussion

Our investigation of 1815 RA patients concerning the prevalence of *H. pylori* infection demonstrated that 49.3% of Japanese patients with RA were seropositive for *H. pylori* antibody, and that the percentage of patients who were *H. pylori*-positive exceeded that of patients who were *H. pylori*-negative in the 50s and 60s age groups (Fig. 1).

Although the prevalence of *H. pylori* infection in Japan has been reported to be relatively high in older individuals compared with other advanced countries,[7] it has not previously been determined for Japanese RA patients. Asaka et al. reported in 1992 that seropositivity for *H. pylori* antibody in Japan measured by the high-molecular-weight,

Table 1. Comparison of rheumatoid arthritis patient background factors among groups

	Group A with ulcer	Group B without ulcer	Group C with history of ulcer
No. of patients	24	1180	325
Age (years)	55.8 ± 11.2	54.5 ± 12.3	59.4 ± 10.4
% Female	75.0	85.8	72.0
RA duration (years)	8.9 ± 6.9	10.1 ± 8.5	11.7 ± 8.4
Positivity of HP antibody (%)	70.8	45.7	59.7
Swollen/tender joint counts	2.4/2.9	3.4/4.0	3.3/4.6
Physician's VAS (mm)	18.4 ± 15.2	20.5 ± 17.5	18.9 ± 16.7
Patient's general VAS (mm)	41.7 ± 21.2	38.3 ± 25.6	39.7 ± 24.9
CRP (mg/dl)	1.3 ± 1.4	1.4 ± 1.8	1.4 ± 1.8
HAQ score	0.6 ± 0.5	0.8 ± 0.7	0.9 ± 0.7
% NSAID use	95.8	85.2	81.2
% DMARD use	95.8	95.7	96.3
% MTX use	58.3	51.3	55.4
Dosage of MTX per week (mg)	5.7	4.2	4.5
% Steroid use	62.5	61.0	64.0
Dosage of steroid per day (mg)	4.4	4.8	4.6
% Antiulcer drug use	79.2	91.0	95.4
Cytoprotective drug (%)	70.8	82.0	82.2
Misoprostol (%)	4.2	5.7	10.5
H_2 receptor antagonist (%)	12.5	30.0	55.4
Proton pump inhibitor (%)	0.0	2.3	11.7

RA, rheumatoid arthritis; HP, *Helicobacter pylori*; VAS, visual analogue scale; HAQ, Health Assessment Questionnaire; NSAID, non-steroidal anti-inflammatory drug; DMARD, disease-modifying antirheumatic drug; MTX, methotrexate

Table 2. Association between *H. pylori* infection and NSAID use with the occurrence of new UGI ulcer

	NSAID use	Occurrence of new UGI ulcer	
HP antibody-positive	+	16/462	(3.46%)
	–	1/94	(1.06%)
HP antibody-negative	+	7/566	(1.24%)
	–	0/82	(0%)

HP, *Helicobacter pylori*; NSAID, nonsteroidal anti-inflammatory drug; UGI, upper gastrointestinal

cell-associated protein (HM-CAP) enzyme-linked immunosorbent assay (ELISA) increased with age, and that for persons born after 1950 it increased at approximately 1% per year, as in other advanced countries (about 20%–30% under 30 years of age, and about 40%–50% in the 30s); while for persons born before 1950 it was constantly high, as in developed countries (about 80% over 40 years of age).[7] According to their report, seropositivity for *H. pylori* antibody in 2002 would increase at approximately 1% until 50 years of age and remain high over 50 years of age. Thus, seropositivity for *H. pylori* antibody would be predicted to be about 20%–30% under 30 years of age, about 40%–50% in the 30s, about 50%–60% in the 40s, and about 80% over 50 years of age in our study population. Therefore, the prevalence of *H. pylori* in patients with RA was low compared with that of healthy Japanese individuals in each age group.

We now discuss the difference between the ELISA kit used in our study in 2002 and that in the healthy Japanese population study in 1992. In this study, seropositivity was examined with the E Plate kit, which was made on the basis of strains of *H. pylori* as antigens to prepare E plates isolated from Japanese patients with UGI ulcers. Interestingly, Miwa et al. reported that the diagnostic accuracy of serum antibody detection kits imported from Western countries, such as the HM-CAP, was insufficient for the Japanese population,[14] suggesting as reasons for this, the presence of strain heterogeneity in different geographic regions,[15] differences in cross-reactivity to other intestinal pathogens among various geographic regions,[16] and differences in immunological responses to *H. pylori* antigen in different patient populations.[17] In fact, the validity of the E Plate kit used for the measurement of *H. pylori* antibody in this study has already been confirmed in the diagnosis and evaluation of eradication of *H. pylori* in the Japanese population.[12,13] These findings suggest that *H. pylori* seropositivity could have been low in the previous study of healthy Japanese individuals. Hence, bias due to differences in ELISA kit used could not have affected our study results. Furthermore, the sensitivity of our study could have been improved if the ELISA kit had been used in combination with other methods such as histologic examination and the rapid urease test for diagnosis of *H. pylori* infection. Although the use of antibody for the diagnosis of *H. pylori* infection might be disadvantageous, it could not have led to overestimation of *H. pylori* seropositivity in our study.

It might be argued that effects of immunosuppressants and/or corticosteroids existed on production of antibodies to *H. pylori*, since many patients with RA in this population took MTX and/or prednisolone, and these drugs might reduce antibody production.[18,19] However, the average doses of MTX and prednisolone were 4.3 mg/week and 4.8 mg/day, respectively, in this study, which would not be expected to have any protective effects on antibody production. Indeed, the prevalences of *H. pylori* antibody in patients taking MTX (49.4%) or not taking it (47.9%), and those taking prednisolone (48.7%) or not (48.6%), were equivalent.

One possible explanation of the lower incidence of *H. pylori* infection in RA patients is that chronic use of NSAIDs may decrease the prevalence of *H. pylori* infection. Several reports have suggested that the rate of *H. pylori* infection was low among NSAID users.[20–23] Mizokami et al. reported that some NSAIDs have antibacterial effects against *H. pylori*.[24] Our findings indicated that the prevalence of *H. pylori* infection was lower in patients with NSAID use (47.5%) than in those without NSAID use (54.7%), although the difference between these groups was not significant after adjustment for age. Since our study is non-interventional and observational, we cannot exclude bias in analysis. One possible bias is that use of NSAIDs is less in the older than in the younger population, since aging is an established risk factor for NSAID-induced ulcer.[4,25] The average durations of RA in patients over and under 60 years of age in this study were 12.6 ± 9.8 years and 9.5 ± 7.1 years, respectively. Thus, patients over 60 years of age with RA could have been exposed to NSAIDs for a longer period, and this might have affected the prevalence of *H. pylori*. Indeed, fewer patients over 60 years of age used NSAIDs (80.2%) than those under 60 years of age (85.8%) in our study. Therefore, NSAID use cannot completely explain the low *H. pylori* seropositivity in patients with RA observed in this study.

Our findings clearly demonstrated that *H. pylori* infection is a risk for UGI ulcer in Japanese patients with RA (odds ratio = 2.97, 95% CI: 1.19–7.38). On the other hand, the odds ratio for NSAID use (4.31, 95% CI: 0.57–32.4), while numerically similar to that reported by Offman et al.[3] and ARAMIS data,[25] did not reach statistical significance. This may be explained by the small number of UGI ulcers in our study. However, we may have to consider the possibility of lower risk of NSAIDs for UGI ulcer in Japanese patients with RA. This finding might conflict with the report from

the Committee of the Japan Rheumatism Foundation in 1991, which noted that the frequency of NSAID-induced ulcers was high.[8] A decade has passed since that report, and the circumstances surrounding NSAID-induced ulcers have been altered dramatically. These include the introduction of COX-2 selective inhibitors,[26–28] and the development of antiulcer drugs such as PPIs[29–31] and misoprostol.[32] In addition, the development of DMARDs and anticytokine agents has reduced the opportunity for the use of NSAIDs in RA management.[33] It would not be surprising if these factors had reduced the frequency of NSAID-induced ulcer. Recently, Yanagawa et al. reported that the prevalence of NSAID-induced ulcer in Japan had decreased to less than 0.5% after 1998.[34] On the other hand, in the United States, Singh and Triadafilopoulos reported that NSAID-induced ulcers were still major causes of death in patients with arthritis,[35] and that the likelihood of hospitalization or death due to a GI event was about 1.3%–1.6% per year in patients with RA.[36] There are many possible explanations of the difference in frequency of NSAID-induced ulcers in the United States and Japan. The difference in dose of NSAID for RA patients may be one, since the dose of NSAIDs in Japan is limited to approximately half that in Western countries. Another is the frequent use of antiulcer drugs with NSAIDs in Japan. In Japan, most patients were traditionally coprescribed NSAIDs with antiulcer drugs, such as cytoprotective drugs or H_2 receptor antagonists, for prophylaxis of GI symptoms.[8] Surprisingly, 1403 of 1529 patients (91.8%) were prescribed these antiulcer agents. In addition, the high frequency of DMARD use in our population (95.8%) may have reduced the likelihood of NSAID use. These factors may explain the lower frequency of NSAID-induced ulcer in Japan.

The incidence of newly diagnosed UGI ulcer increased from 0% in the *H. pylori*–/NSAID– group to 3.46% in the *H. pylori*+/NSAID+ group, as shown in Table 2. *H. pylori* infection and NSAID use were each confirmed to be independent and significant risks for UGI ulcer and ulcer bleeding in a previous study.[9] According to our study, patients with *H. pylori* have 2.97 times greater risk for a new UGI ulcer than those without *H. pylori*, and patients with NSAID use have 4.31 times greater risk for a new UGI ulcer than those without NSAID use, although the latter difference was not statistically significant. Thus, patients who were *H. pylori*-positive and took NSAIDs might have been 12.8 times more likely to develop a new UGI ulcer than patients not exposed to either in this study. Since the significance of eradication of *H. pylori* in patients with long-term use of NSAIDs is controversial,[37,38] further study with eradication of *H. pylori* should be performed to determine the significance of *H. pylori* infection and NSAID use in the pathogenesis of GI events in our observational cohort.

The design of the present study has been that of a case-control study. Thus, there is a possibility of patient selection bias. For example, our study was done based on a patient questionnaire, thus some patients in group B might have a silent GI ulcer without any symptoms. Also, concomitant use of other agents such as corticosteroids and DMARDs may influence the results in our cohort. Hence, further study should be done by well-designed, randomized control study to clarify the relationship between *H. pylori* infection and NSAID use for UGI ulcer in patients with RA.

In conclusion, although the prevalence of *H. pylori* antibody was low in patients with RA compared with that in healthy Japanese individuals, *H. pylori* infection was a significant risk factor for UGI ulcer in Japanese patients with RA.

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