INTRODUCTION

The pathogenic role of *H. pylori* in chronic gastritis and its association with duodenal ulcer (DU) are well established. Therefore, the 1994 NIH Consensus Development Conference recommended eradication of *H. pylori* in all patients with documented peptic ulcer disease. The dramatic effect of *H. pylori*-eradication on the natural course of DU disease has been sufficiently well reported by now. However, published studies on BGU relapse are scarce, and its follow-up periods do not exceed 12 months.

There are a few differences between DU and BGU: positivity rates of *H. pylori* in BGU patients have been reported at 70-90%, lower than that of DU, 95%-99%. The reason for this difference may...
originates from the fact that nonsteroidal anti-inflammatory drugs (NSAIDs) are another major cause of BGU. These facts may play a role in the pattern of recurrence in BGU and DU. However, there is still a considerable lack of knowledge on the post-therapeutic course of BGU disease. We conducted this study to investigate how the BGU recurrence rate is reduced by eradication of H. pylori in a 2 year follow-up.

MATERIALS AND METHODS

This study was performed for H. pylori-positive 65 patients with active BGU, who were enrolled between October 1995 and September 1996, and followed up for 2 years. In forty patients, H. pylori was eradicated by triple therapy: omeprazole 20mg once a day, clarithromycin 500mg twice a day and amoxicillin 1.0g twice a day. The non-eradicated group consisted of 19 patients in whom the triple therapy was not conducted and 6 patients in whom H. pylori was not eradicated with the triple therapy. Patients with pregnancy or lactation, treatment with colloidal bismuth subcitrate or antibiotics within 3 weeks of gastroscopy, severe concomitant diseases and a history of previous gastric surgery were excluded. In addition, patients were excluded if they were under maintenance acid-suppressive therapy.

Six biopsy specimens were taken within 3cm of the pyloric ring before beginning, and 4 weeks after completion of triple therapy. The biopsy specimens were analyzed with CLOtest, microscopy of Gram stained mucosal smear, culture and histology after H&E staining as described in detail elsewhere. A patient was regarded as H. pylori-positive if one or more of the four aforementioned test methods demonstrated H. pylori colonization of the gastric mucosa.

Follow-up gastroscopy was performed 6, 12, 18 and 24 months after treatment, or whenever the ulcer symptom recurred, for evaluation of ulcer recurrence. BGU recurrence was defined as endoscopically confirmed recurrent ulcer after endoscopically proven healing of the initial ulcer. By definition, superficial erosions were not considered to be ulcers. Four H. pylori tests were conducted in the eradicated group whenever follow-up gastroscopy was taken. Clinical factors, such as age, gender, smoking, alcohol, past history of BGU and ingestion history of NSAIDs were evaluated.

For statistical analysis, continuous variables were analyzed by Student's t test, and categorical variables by Chi-square test and Fisher's exact test. A p value of <0.05 was considered to be significant.

RESULTS

The mean age of the non-eradicated group was 51.6 ± 13.0 years and that of the eradicated group 50.6 ± 12.0 years (Table 1). The number of males was 22 (sex ratio, 7.3:1) in 25 patients of the non-eradicated group, and 33 (sex ratio, 4.7:1) in the 40 patients of the eradicated group. Smoking history was found in 16 patients (64%) of the non-eradicated group, and in 20 patients (50%) of the eradicated group. Alcohol history was found in 11 patients (44%) of the non-eradicated group and in 26 patients (65%) of the eradicated group. Past BGU history was found in 17 patients (68%) of the non-eradicated group and in 18 patients (45%) of the eradicated group. Ingestion

Table 1. Clinical characteristics

|                | Non-eradicated group | Eradicated group |
|----------------|----------------------|-----------------|
| No.            | 25                   | 40              |
| Age(year)      | 51.6 ± 13.0          | 50.6 ± 12.0     |
| MF (ratio)     | 22:3 (7.3:1)         | 33:7 (4.7:1)    |
| Smoking(%)     | 16 (64%)             | 20 (50%)        |
| Alcohol(%)     | 11 (44%)             | 26 (65%)        |
| Past BGU history(%) | 17 (68%)         | 18 (45%)        |
| NSAIDs history(%)  | 6 (24%)              | 6 (15%)         |
| BGU recurrence(%)  | 15 (60%)             | 4 (10%)         |

*p < 0.001

BGU, benign gastric ulcer; NSAIDs, nonsteroidal anti-inflammatory drugs.
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-A 24 MONTH FOLLOW-UP STUDY-

A history of NSAIDs was found in 6 patients (24%) of the non-eradicated group and in 6 patients (15%) of the eradicated group. There was no statistical difference between these two groups in age, gender, smoking, alcohol, past history of BGU and ingestion history of NSAIDs. BGU recurrence was found in 15 patients (60%) of the non-eradicated group; 12 of 19 patients (63.2%) in whom triple therapy was not conducted and 3 of 6 patients (50%) in whom \(H. pylori\) was not eradicated with triple therapy. In comparison, BGU recurrence was found in 4 patients (10%) of the eradicated group, which was significantly lower than that of the non-eradicated group \(p<0.001\), Table 1.

In the 25 non-eradicated patients, the BGU recurrence rate was 16% (4 patients) within 6 months, 40% (10 patients) within 1 year, 56% (14 patients) within 18 months and 60% (15 patients) within 2 years (Fig. 1). The respective recurrence rates in the 40 eradicated patients were 0%, 7.5% (3 patients), 10% (4 patients) and 10%, respectively (Fig. 1). The recurrent ulcer sites in the 15 BGU patients of the non-eradicated group were the same as the ulcer sites of the initial diagnosis. In two patients, the number of ulcers increased to 3 and 5, including the initial one. The recurrent ulcer sites in the 4 recurred patients of the eradicated group were the same as those of the initial ulcer.

The mean age of the recurred group was 65.3 ± 15.2 years, which is significantly older than that of the non-recurred group, 49.1 ± 10.9 years \(p<0.05\), Table 2. The two female patients who had BGU recurrence and NSAIDs history were very old (67 and 83 years old), and this brought about a significant increase of the mean age for the recurrence group. Two patients were male (sex ratio, 1:1) in the recurred group, and 31 patients (sex ratio, 6:2:1) in the non-recurred group. Smoking history was found in 3 patients (75%) of the recurred group and 17 patients (47.2%) of the non-recurred group. Smoking history was found in 3 patients (75%) of the recurred group and 17 patients (47.2%) of the non-recurred group. Past BGU history was found in 3 patients (75%) of the recurred group and 15 patients (41.7%) of the non-recurred group. Ingestion history of NSAIDs was found in 3 patients (75%) of the recurred group and 3 patients (8.3%) of the non-recurred group. There was no statistical

| Table 2. Comparison according to benign gastric ulcer recurrence for the eradicated group |
|---------------------------------------------------------------|
| Recurred group | Non-Recurred group |
|----------------|-------------------|
| No.            | 4                 | 36               |
| Age(year)      | 65.3 ± 15.2       | 49.1 ± 10.9      |
| M:F (ratio)    | 2.2 (1:1)         | 3.15 (6.2:1)     |
| Smoking(%)     | 3 (75%)           | 17 (47.2%)       |
| Alcohol(%)     | 1 (25%)           | 25 (69.4%)       |
| Past BGU history(%) | 3 (75%) | 15 (41.7%) |
| NSAIDs history(%) | 3 (75%) | 3 (8.3%) |
| H. pylori reappearance(%) | 1 (25%) | 1 (2.8%) |
| NSAIDs ingestion history before BGU recurring(%) | 2 (50%) | |

\[ p < 0.05 \]
BGU, benign gastric ulcer; NSAIDs, nonsteroidal anti-inflammatory drugs

Fig. 1. Recurrence rate of benign gastric ulcer according to the eradication of \(H. pylori\).

Within 6 months
Within 12 months
Within 18 months
Within 24 months
difference between these two groups in gender, smoking, alcohol, past history of NSAIDs. When BGU recurrence was found in the 4 patients of the eradicated group, one patient (25%) was found to be *H. pylori* positive and two patients (50%) irregularly took NSAIDs due to arthritis before BGU recurring. The BGU recurrence in these 3 patients occurred within 1 year. In the remaining one patient, *H. pylori* was still negative and he denied ingestion history of NSAIDs when BGU recurring within 18 months. In the 36 non-recurred patients, only one patient (2.8%) was found to be *H. pylori* positive again in 1 year.

**DISCUSSION**

*H. pylori* infection and NSAIDs are very important risk factors for peptic ulcer	extsuperscript{12}. The positivity rates of *H. pylori* in patients with DU and BGU were somewhat different: that is, they have been reported to be 95-99% in DU	extsuperscript{15}, but 70-90% in BGU	extsuperscript{13}, which is lower than in DU and shows a wider variation than in DU. These results suggest that NSAIDs as the cause of BGU might be more significant than DU	extsuperscript{13}. We have previously shown that the *H. pylori* infection rate and the rate of NSAIDs history were 82.8% and 26.1% of BGU patients, respectively, and 91.1% of the DU patients had either *H. pylori* infection or NSAIDs history	extsuperscript{13}. In contrast, *H. pylori* infection rate of patients with DU was 94.2%	extsuperscript{13}, higher than that of BGU patients. In addition, even though the major cause of DU and BGU is *H. pylori*, their pathogenesis is thought to be different. That is, if the *H. pylori* infection occurs when the gastric acid secretion from parietal cell is high, *H. pylori* resides and multiplies in the antrum, avoiding the body, causing chronic antral gastritis and DU	extsuperscript{13}. However, if *H. pylori* infection occurs in the low acid secretory state, such as malnutrition, immaturity, and intercurrent infection, pangastritis and multifocal gastric atrophy occur, and BGU or stomach cancer may develop	extsuperscript{13}. Actually, *H. pylori* density was higher in the antrum than in the body for DU patients, but it was somewhat reversed for BGU patients	extsuperscript{13}. In addition, the body is more adequate for *H. pylori* detection in BGU and stomach cancer patients, but it was reversed in DU patients	extsuperscript{13}. These differences between DU and BGU may cause a difference in their pattern of recurrence.

Combined data from 30 pilot and controlled studies show an overall DU relapse rate of 61% (range, 20-100%) in patients who remain *H. pylori*-positive, compared with 3% (range, 0-22%) in patients free of *H. pylori*	extsuperscript{12, 14-29, 34-36}. This wide variance in the study results may be caused by several factors: absence of documented initial ulcer disease and ulcer healing; unknown *H. pylori* status at the time of ulcer relapse or at the conclusion of the study	extsuperscript{30, 37-39}, and the assessment for cure of the infection by *H. pylori* clearance instead of *H. pylori* eradication, leading to high rates of *H. pylori* recrudescence and ulcer relapse rates	extsuperscript{10, 29-32}. Only a few studies have reported gastric ulcer relapse rate in relation to *H. pylori* status with a follow-up period of 1 year	extsuperscript{22-24}. Gastric ulcer relapsed in 47-55.6% of patients who remained *H. pylori*-positive compared with 3-7% of the cured patients	extsuperscript{10, 14}. Because *H. pylori* infection is associated with ulcer disease, ulcer relapses will also be related to recurrent infection	extsuperscript{12, 14, 29}. It is therefore crucial that *H. pylori* eradication is documented accurately. Nevertheless, studies performed with appropriate diagnostic accuracy still report *H. pylori*-negative ulcer relapses	extsuperscript{10, 12, 14, 29, 32}

In these cases, the (occult) use of aspirin or NSAIDs may account for recurrent ulcers in the absence of *H. pylori* infection	extsuperscript{12, 30-34}. In one study where patients taking aspirin or NSAIDs were excluded, recurrence of DU or BGU was completely prevented by successful *H. pylori* eradication for up to 9.8 years (mean follow-up: 2.5 years)	extsuperscript{12}. In the present study, the BGU recurrence rates in the 25 non-eradicated group were 16% within 6 months, 40% within 1 year, 56% within 18 months and 60% within 2 years (Fig. 1). The respective recurrence rates in the 40 eradicated patients were 0%, 7.5% (3 patients), 10% (4 patients) and 80%, respectively (Fig. 1), which were significantly lower than those of the non-eradicated group (p<0.001).

We also investigated the similar study in DU patients with a 4 year follow-up	extsuperscript{37}. When BGU recurrence pattern is compared with that of DU, there were two kinds of difference between BGU and DU. One is that the recurrence rate of BGU patients in the non-eradicated group looked lower than that of DU patients. That is, in a control group, comprising 31 patients with DU who were not treated with *H. pylori* eradication regimen, the DU recurrence rate was 61% within 1 year, 81% within 2 years, 84% within 3 years and 90% within 4 years	extsuperscript{13}. The recurrence rate of BGU
in the non-eradicated group in the present study shows 40% within 1 year and 60% within 2 years, and these rates are lower than those of the DU group. The other is that the main cause of recurrence looks different in DU and BGU. In the 45 patients with DU in whom bacteria had been eradicated, DU recurrences were 0% within 1 year, 4% within 2 years, 13% within 3 years and 18% within 4 years, and all of them were found to be *H. pylori* positive again. Moreover, no DU recurrence was found in the patients who remained *H. pylori* negative. In BGU patients, the recurrence rate of the eradicated group was 7.5% (3 patients) within 1 year and 10% (4 patients) within 2 years, which looks like slightly higher than that of the DU group. Among these 4 recurred BGU patients, only one patient was found to be *H. pylori* positive again within 1 year, and two patients had NSAIDs ingestion history. In the remaining one patient in whom BGU was found to recur within 18 months after eradication, *H. pylori* was still negative and there was no history of NSAIDs ingestion. These results suggest that BGU recurrence is caused by NSAIDs or *H. pylori* reinfection, although DU recurrence after eradication of *H. pylori* nearly depends on *H. pylori* reinfection. In the present study, most of the recurrent ulcer sites in the 19 recurred BGU patients were the same as the ulcer sites of the initial diagnosis, regardless of eradicated (4 patients) or not (15 patients). In two cases of BGU-recurred patients of the non-eradicated group, the number of ulcers increased to 3 and 5, including the initial one. These results suggest that the original weak mucosal point, which had already appeared as an ulcer, is the persistent weak site where BGU can easily recur even after healing, regardless of whether the reattacking cause is *H. pylori* or NSAIDs.

In conclusion, the eradication of *H. pylori* in patients with BGU reduces the recurrence of BGU similar to DU. However, the major causes of BGU appearance to be NSAIDs ingestion and reinfection of *H. pylori*, which is different from DU in which *H. pylori* reinfection is the main cause.

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