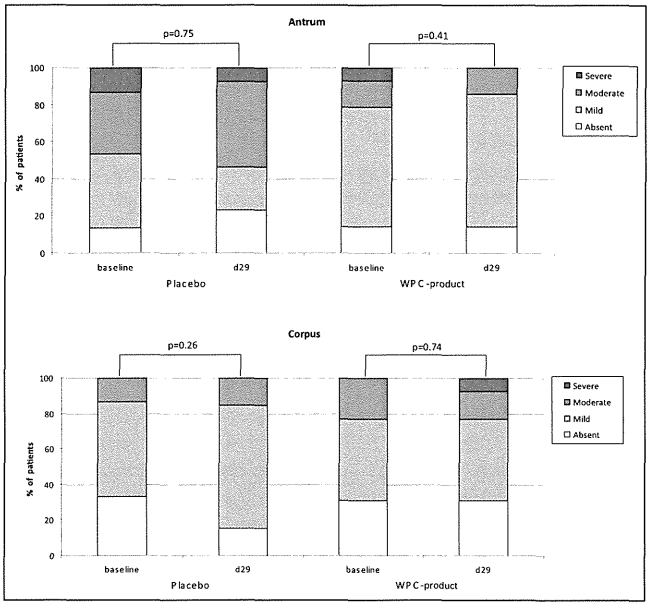

Figure 4) *Histological grade of active gastritis in antrum and corpus in patients randomly assigned to placebo or whey protein concentrate (WPC) preparation. d Day*

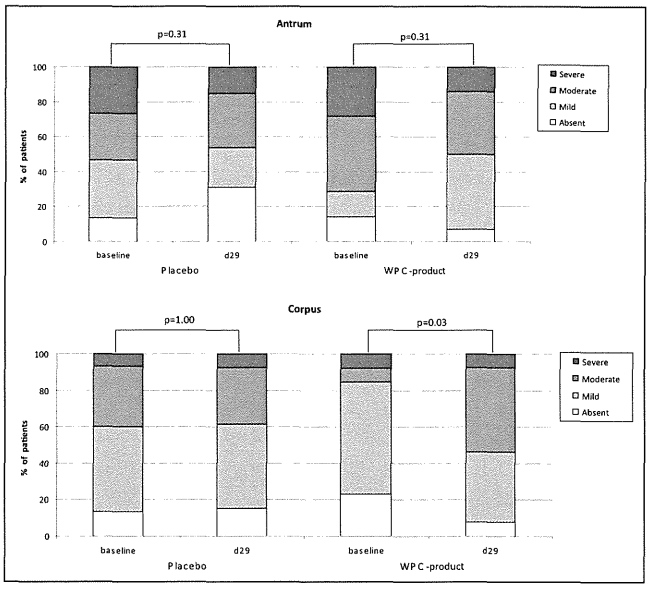

Figure 5) *Histological grade of* Helicobacter pylori *colonization in antrum and corpus in patients randomly assigned to placebo or whey protein concentrate (WPC) preparation. d Day*

Analysis of general blood test parameters revealed no significant changes in either treatment group, nor were there changes in serum liver enzymes or additional serological parameters (eg, hemoglobin, leukocytes, etc) (P>0.05 for all).

DISCUSSION

The present clinical study did not demonstrate a positive effect on *H pylori*-associated gastritis or colonization density following administration of a polyclonal antibody-enriched (sIgA) WPC-80 preparation in humans. No significant reduction was demonstrated in urea breath test levels determined on days 0, 29 and 56. Treatment in either arm had no effects on serum *H pylori* IgG antibody titres, gastrin, pepsinogen I and II levels, or on the pepsinogen I/II ratio. Correcting for the use of PPIs did not influence differences in the outcomes. However, we demonstrated that WPC-80 was well tolerated and did not cause any adverse effects or a decrease in quality of life scores.

H pylori infection is widespread in humans. Although it can be cured by antimicrobial therapy, large-scale use of antibiotics has led to the increasing emergence of antibiotic-resistant strains. Furthermore, side effects of current eradication treatments, although partially preventable by the coadministration of probiotics, limit their efficacy by induction of early treatment withdrawal (23). This has prompted investigators to focus on several alternatives. These alternatives must be effective; however, considerations such as costs, side effects and ease of administration should also be taken into account.

Because previous studies have shown protection against early acquisition of *H pylori* through breastfeeding in breastfed infants (14), the concept of passive immunization (ie, mimicking mechanisms of natural protection) as a logical approach has emerged. An in vitro study conducted in 2001 confirmed the possible effectiveness of antibodies by showing a complement-dependent bactericidal effect of WPC with *H pylori*-specific antibodies. The WPC prevented adherence of *H pylori* to the gastric mucosa (24,25). In addition, an early clinical study in 1991 (19) demonstrated *H pylori* eradication in 20 patients receiving an *H pylori*-specific bovine Ig. The outcomes of more recent studies with *H pylori*-infected patients (16-18,20) have shown modest, albeit encouraging, results. However, one of these studies was open labelled (18) and used a treatment period of only two days, while two others included children only (16,17). Furthermore, the methodology of the other studies were unclear (16-18,20).

A possible limitation of the present analysis was the size of the study population, which may have been too small to demonstrate significant reductions in intragastric bacterial load or gastritis activity by treatment with bovine antibody-based oral immunotherapy. Furthermore, because the optimal length of treatment remains unknown, our study may have been limited by the relatively short duration of WPC-80 treatment. Previously conducted studies (15) used a duration of between two days and four weeks. However, given the total absence of any effect after four weeks in the population studied, we consider it unlikely that an increase in the study population or prolongation of treatment with the same dose would have led to measurable changes.

We cannot exclude the possibility that an increase in dose and/or dosing frequency would have led to an effect on *H pylori* colonization. The dose and administration frequency used in the present study were chosen on the basis of previous experience with similar products, particularly those against *C difficile* (11). Finally, our study may have been limited by the fact that intragastric antibody availability has yet to be clarified (25). Therefore, future research in human subjects is necessary to obtain additional information regarding the optimal antibody dose, frequency of administration and ratio.

The strengths of the present study were the strictly defined outcome parameters, the double-blinded design with repeated follow-up assessments and the exclusion of a possible concomitant antibiotic effect. Except for one subject, all patients completed the four-week treatment course and no adverse effects linked to treatment were identified.

Current research has focused on several alternatives to replace antibiotic eradication therapy. In contrast to our study of bovine-derived IgA antibodies, Japanese researchers have described positive effects of egg yolk-derived IgY, demonstrating a decrease in urea breath test parameters in patients treated with IgY (26,27). Similar studies examining the natural antimicrobial properties of colostrum and egg yolk have focused on the possible use of lactoferrin and lysozyme, which are also components of the humoral immune reaction. Positive effects of bovine antibodies were demonstrated in vitro and in animal models, but conflicting results were obtained in human studies (28). Some studies described a suppressive effect of lactoferrin and lysozyme on *H pylori* colonization (28,29), while others even described an increase in *H pylori* growth and gastric inflammation (30). However, supplementing current eradication therapy with lactoferrin appears to increase eradication rates and could be helpful in patients who fail

eradication therapy. Furthermore, addition of lactoferrin may also have a positive impact on *H pylori* therapy-related side effects (31).

Several studies examining the effects of probiotics, especially in combination with current therapies, have been conducted (23,32-35), and have demonstrated positive effects and trends. A combination of antibiotics and probiotics seems to improve eradication rates primarily by decreasing side effects, resulting in increased adherence.

Another possible alternative to current therapy are DNA vaccines. DNA vaccines are constructed by inserting DNA encoding a pathogen's antigen into a bacterial plasmid, thus inducing both humoral and cell-mediated immunity (36). A recent study by Sun et al (37) has shown a protective effect of DNA vaccines on *H pylori* infection in mice. In addition, vaccination to both prevent and treat infection appears to be a very cost-effective alternative in *H pylori* treatment (38).

Monotherapy with bovine antibodies may not be the optimal alternative to current eradication therapies. Recent studies have described positive effects of combination therapy, for example, the addition of *Lactobacillus* to the current standard treatment. Such a positive effect could also be expected from adding WPC-80 to current eradication therapies. This adjunct to antibiotic therapy requires further investigation while the search for alternatives continues. The prevention of *H pylori* infection is a subject of interest, particularly in the developing world and could be another focus of research, especially because this effect has been described in vitro (15).

Due to increases in the current failure rates of antibiotic-based eradication therapy, the goal of future immunotherapy should focus on replacing antibiotic-based treatment entirely, instead of searching for adjunctive therapies. Presently, the most hopeful alternatives are preventive or therapeutic vaccination therapy. A recent study (39) demonstrated the cost-effectiveness of preventive vaccination in children.

A recent review article (40) reported that *H pylori* vaccination prevents, reduces and eliminates *H pylori* infection in animal models, and that vaccines based on multiple virulence factors cure and prevent infection. A phase I study with a vaccine based on virulence factors in healthy volunteers (39) demonstrated a strong antibody response and was well tolerated, and currently appears to be the most promising alternative for *H pylori* treatment. Unfortunately, significantly more funding and research is needed before this particular alternative treatment is fully developed.

CONCLUSION

Monotherapy with bovine antibody-based oral immunotherapy does not reduce intragastric *H pylori* bacterial load, nor does it have an effect on *H pylori*-associated gastritis. However, WPC-80 is well tolerated and does not cause any adverse effects, nor does it have a negative influence on quality of life scores. Further research into the possible use of WPC-80 as a supplement to current eradication regimens is necessary.

ACKNOWLEDGEMENTS: This study was designed and conducted to meet internationally accepted ethical standards and complies with the CONSORT statement. The authors acknowledge Muco Vax BV, Leiden, the Netherlands and DMV International, Veghel, The Netherlands, for the development of the platform technique and the production of the immune WPC-80 preparation and the placebo.

DISCLOSURE: This study was funded, in part, by Muco Vax BV, Leiden, The Netherlands.

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J Gastroenterol (2011) 46:1267–1272
DOI 10.1007/s00535-011-0447-1

ORIGINAL ARTICLE—ALIMENTARY TRACT

Effect of lansoprazole versus roxatidine on prevention of bleeding and promotion of ulcer healing after endoscopic submucosal dissection for superficial gastric neoplasia

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Received: 7 May 2011 / Accepted: 27 June 2011 / Published online: 30 July 2011

Abstract
Background Proton pump inhibitors have been reported to be more useful than histamine-2 receptor antagonists for the prevention of bleeding after endoscopic submucosal dissection (ESD) for superficial gastric neoplasia. The aim of this study was to assess the effects of the proton pump inhibitor lansoprazole and the histamine-2 receptor antagonist roxatidine for the prevention of bleeding and the promotion of ulcer healing after ESD and to compare the cost-effectiveness of these two drugs.
Methods The study subjects were 129 patients who underwent ESD for superficial gastric neoplasia. The patients were randomly assigned to the lansoprazole group (L group) or the roxatidine group (R group). Either drug was administered intravenously from the morning of the ESD day to the day after the ESD, followed by oral treatment for an additional 8 weeks. A second-look endoscopy was performed on the day after the ESD, and a repeat endoscopy was performed at 8 weeks after the ESD. The incidence of bleeding and the ulcer-healing rate at 8 weeks after the ESD were analyzed, as well as the total cost of treatment with these antisecretory agents.
Results Three patients in each group were excluded from the analysis, leaving 62 patients in L group and 61 in R group. Two of the 62 patients (3.2%) in L group and three of the 61 patients (4.9%) in R group showed bleeding after ESD ; there was no significant difference between the two groups ($P = 0.68$). The ulcer-healing rate was 93.5% (58/62) in L group and 93.4% (57/61) in R group ($P = 1$). The total cost of treatment with the antisecretory agent from the day of the ESD to day 56 after the ESD was Yen 13,212 for lansoprazole and Yen 5,841 for roxatidine.
Conclusions Roxatidine appears to have high cost-effectiveness in the prevention of bleeding and in the promotion of ulcer healing after ESD for superficial gastric neoplasia.

Keywords Bleeding · Ulcer healing · Endoscopic submucosal dissection · Gastric neoplasia · Roxatidine · Lansoprazole · H_2-receptor antagonist · Proton pump inhibitor

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Introduction

Endoscopic mucosal resection (EMR) has been established as a minimally invasive treatment for early-stage gastric cancer (EGC) [1, 2]. Bleeding after EMR has been reported to occur in 1.2–11.6% of patients [3]. Following conventional EMR, proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H_2RAs) have been reported to show equivalent efficacy in preventing bleeding from the ulcer and promoting ulcer healing [4]. Of note, en-bloc resection is often not achieved by EMR, such as for a strip biopsy or EMR using a cap. Recently, endoscopic submucosal dissection (ESD) has been developed for EGC, and this procedure enables larger lesions to be resected, thereby yielding improved rates of successful en-bloc resection [5].

Although ESD has been established as a standard treatment for EGC, it is associated with a higher incidence of complications, such as bleeding and perforation, than EMR [6]. PPIs or H_2RAs have been administered for the prevention of bleeding after ESD as well as after EMR. PPI therapy has been reported to be more useful than H_2RA treatment for the prevention of delayed bleeding from the ulcer after ESD [7, 8].

Roxatidine is a second-generation six-membered-ring H_2RA that not only suppresses gastric acid secretion, but also increases mucus secretion from the gastric mucosa [9, 10]. It is as effective and safe as the other H_2RAs with a five-membered ring (cimetidine, ranitidine, famotidine, and nizatidine) in the treatment of gastric and duodenal ulcers, and may also be useful for the treatment of five-membered-ring H_2RA-resistant ulcers, especially duodenal ulcers [11].

The first aim of this pilot study was to evaluate the efficacy of lansoprazole, as compared with that of the second-generation H_2RA, roxatidine, for the prevention of bleeding and promotion of ulcer healing after ESD for superficial gastric neoplasia. The second aim of the study was to compare the cost-effectiveness of these two drugs.

Patients and methods

This prospective pilot study was performed at Keio University Hospital. Written informed consent was obtained from all patients, and patient enrollment started from March 2008 and finished in March 2010. The inclusion criteria were patients with EGC, gastric adenoma, or suspected gastric neoplasia who were referred to our hospital for the purpose of ESD. Patients who had received acid-suppressant treatment within 1 week prior to the procedure, or those who had a history of gastrectomy, major organ failure, or drug allergy were excluded. Patients were admitted on the day before the ESD and remained hospitalized for 4 days with a defined clinical path. All patients were randomly assigned to either the lansoprazole group (L group) or the roxatidine group (R group). A randomization table was generated using Excel 2007. Patients in the L group received lansoprazole 30 mg twice a day intravenously for 2 days from the morning of the ESD procedure, and then 30 mg once a day orally for 8 weeks. Patients in the R group received roxatidine 75 mg twice a day intravenously for 2 days from the morning of the ESD procedure, and then 75 mg twice a day orally for 8 weeks. The doses of both drugs were standard according to the health insurance system in Japan. A second-look endoscopy was performed on the day after the ESD. If there was bleeding or a visible vessel in the ulcer bed, argon plasma coagulation (ICC-200; ERBE, Tübingen, Germany) and/or endoscopic hemoclipping (HX-610-090S; Olympus Medical Systems, Tokyo, Japan) was performed. Oral intake of meals was started on the evening of the second-look endoscopy, except in patients with massive bleeding and patients who were discharged on the same day as the second-look endoscopy.

Any anticoagulant or antiplatelet drugs that the patients were being treated with were stopped at least 7 days before the ESD and restarted 7 days after the ESD, and any mucosal protectant agents and antacids were discontinued during the treatment period. Venous blood samples were analyzed for IgG *Helicobacter pylori* antibodies by the E-plate test (Eiken Kagaku, Tokyo, Japan) using an enzyme-linked immunosorbent assay (ELISA) kit. If the test for IgG *H. pylori* antibodies was negative, the urea breath test was performed (Otsuka Pharmaceutical, Tokyo, Japan).

Major bleeding was defined as hematemesis, melena, and/or decrease of blood hemoglobin by more than 2 g/dL necessitating endoscopic hemostasis. The incidence of bleeding after the ESD was evaluated in the two groups. Minor bleeding was defined as type 1b according to the Forrest classification, i.e., bleeding that necessitated endoscopic hemostasis at the second-look endoscopy, except for major bleeding [12].

The endoscopists who performed the ESD were unaware of the group allocation of the subjects. This study was approved by the ethics committee at Keio University Hospital, and was registered through the registries approved by the International Committee of Medical Journal Editors (UMIN000001069).

ESD procedure

The indications for ESD for EGC included intramucosal differentiated-type EGC of any size without ulceration, intramucosal differentiated-type EGC measuring <3 cm in diameter with ulceration or scar formation, submucosal differentiated-type EGC showing invasion up to a depth of no more than 500 μm and <3 cm in diameter, and gastric adenoma of any size suspected by preoperative diagnostic examinations. The absence of lymph node and distant metastases was confirmed by contrast-enhanced computed tomography (CT) of the thorax and abdomen and/or abdominal ultrasonography. The ESD procedure was performed using a flex knife (Olympus Medical Systems). An ICC-200 (ERBE) or VIO300D (ERBE) was used as the electrosurgical unit. The ulcer created after the resection was carefully examined, and any visible vessels were coagulated by the flex knife in the soft coagulation mode with 80-W current or treated by hemoclipping. The resected specimen was immediately pinned flat to a rubber plate for measurement of its size, and then it was sent to the

department of pathology for gross and histopathological examinations.

Follow-up and monitoring of adverse events

During the patients' periods of hospitalization, the occurrence of any adverse events was evaluated daily by history-taking and physical examination. A complete blood cell count was assessed on the day after the ESD. Follow-up endoscopy was scheduled for the day after the ESD, for the evaluation of bleeding, and a repeat endoscopy was performed at 8 weeks after the ESD for the evaluation of ulcer healing. When the ulcer appeared to be closed, it was defined as having healed fully. All adverse events after discharge were verified by history-taking at the time of consultation. Patients were asked to bring all remaining tablets to the outpatient clinic at the end of the 8-week study period, and if they did not exceed 10% of the prescribed number, the patients were regarded as showing good compliance with the treatment. The rate of ulcer healing at 8 weeks after the ESD was also evaluated in the two groups.

Sample size calculation

The primary variable was the major bleeding rate. First, we hypothesized that bleeding rates in the two groups would not be significantly different. The sample size calculation was based on non-inferiority of the H_2RA with a significance level of 0.05, a power level of 0.9, and an inferiority margin of 10%, and bleeding rates of 6.0% with a PPI and 17.2% with a first-generation-H_2RA [7]. The required sample size was more than a hundred thousand. Of note, there were no available data on the bleeding rate with the use of a second-generation H_2RA. Uedo et al. [7] reported that a PPI was superior to an H_2RA in preventing bleeding after ESD in 130 patients. Taking into account the feasibility of the sample size, we conducted a pilot study to compare a second-generation-H_2RA with a PPI by using 65 samples in each group, for a total of 130, the same as the sample size reported by Uedo et al.

Statistical analysis

All statistical analyses were performed on a per-protocol basis. Statistical comparisons were performed using the χ^2 test or Fisher's exact test for categorical data, and Student's *t*-test for numerical data. The cumulative non-bleeding rates in the two groups were estimated using the Kaplan–Meier method, and the log-rank test was used for analysis of the differences between the two curves. Multivariate analysis was performed using Cox's proportional hazard model. Candidate covariates included the stratification factors, age, sex, smoking status, presence/absence of *H. pylori* infection, history of use of anticoagulant or antiplatelet drugs, identity of the endoscopists, location of the tumor, presence/absence of scar formation in the tumor, and the tumor size and depth. Computer software (SAS version 9.1; SAS Institute, Cary, NC, USA) was used for the data analysis. *P* values of <0.05 were considered to denote statistical significance.

Results

A total of 129 patients were enrolled in the study, consisting of 103 men and 26 women, all of whom fulfilled the inclusion criteria. The patients ranged in age from 46 to 86 years (mean 60.9). As shown in Fig. 1, 65 patients were enrolled in the L group (two of whom were referred for surgery and one had massive submucosal gastric cancer) and 64 patients were enrolled in the R group (in three of whom gastric neoplasia was not confirmed pathologically). Finally, 62 patients in the L group and 61 patients in the R group were followed up for 8 weeks and showed good compliance with the treatment.

The baseline data in the patients of the two treatment groups are shown in Table 1. There were no significant differences between the groups in the distribution of age, sex, smoking status, *H. pylori* infection status, history of anticoagulant or antiplatelet drug use, identity of the endoscopists, mean tumor size, mean artificial ulcer size, depth of the tumor, location of the tumor, or scar-forming tumors.

ESD was performed successfully in all patients and there were no cases of complication by perforation. Major bleeding occurred in two of the 62 patients (3.2%) in the L group and three of the 61 patients (4.9%) in the R group;

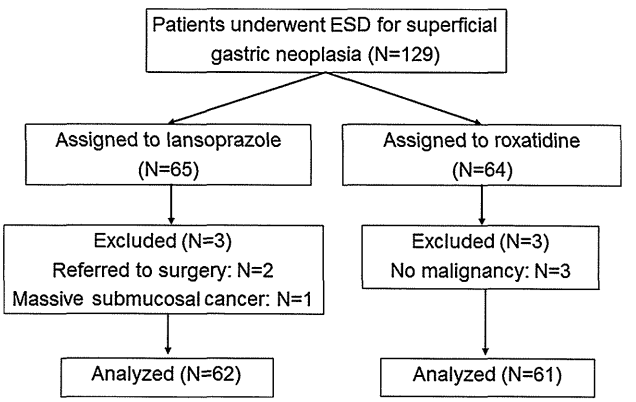

Fig. 1 Flow diagram of the participants in the study. *ESD* endoscopic submucosal dissection

Table 1 Baseline data of the treatment groups

	Lansoprazole	Roxatidine	*P*
No. of patients	62	61	
Mean age (years ± SD)	68.4 ± 8.0	67.6 ± 8.5	0.57
Sex			
M/F	47/15	52/9	0.27
Smoking			
Yes/no	36/26	30/31	0.42
Helicobacter pylori			
Positive/negative	38/24	38/23	1
Anticoagulants			
Positive/negative	9/53	8/53	1
Endoscopist			
H.I.	24	20	
N.H.	23	26	
R.N.	11	11	
Y.I.	4	4	0.93
Mean tumor size (mm, ±SD)	13.7 ± 9.0	16.3 ± 11.7	0.17
Mean artificial ulcer size (mm, ±SD)	32.8 ± 10.3	34.2 ± 12.7	0.50
Depth of tumors			
M/SM1	59/2	61/0	0.24
Location of tumors			
Body/antrum	42/20	36/25	0.41
Tumor with scar			
Positive/negative	12/50	8/53	0.49

M mucosal, *SM* submucosal

Table 2 Incidence of bleeding and ulcer healing after endoscopic submucosal dissection (ESD) for superficial gastric neoplasia

	Lansoprazole	Roxatidine	*P*
No. of patients	62	61	
Major bleeding after ESD			
Positive/negative	2/60	3/58	0.68
Minor bleeding after ESD			
Positive/negative	6/56	6/55	1
Ulcer healing			
Positive/negative	58/4	57/4	1

there was no significant difference in the incidence between the two groups ($P = 0.68$; Table 2). Endoscopic hemostasis was performed successfully in all 5 of the patients who developed major bleeding after ESD; none of these patients required blood transfusion or surgery. As shown in Fig. 2, the cumulative non-bleeding rate assessed using the Kaplan–Meier method was not significantly different between the two groups ($P = 0.64$). After adjustments for the potential factors influencing the risk of bleeding, treatment with roxatidine was not found to be a significant risk factor for bleeding (adjusted hazard ratio 3.42, 95% confidence interval [CI] 0.24–48.5, $P = 0.36$). Minor bleeding occurred in six of the 62 patients (9.7%) in the L group and six of the 61 patients (9.8%) in the R group; there was no significant difference in the incidence between the two groups.

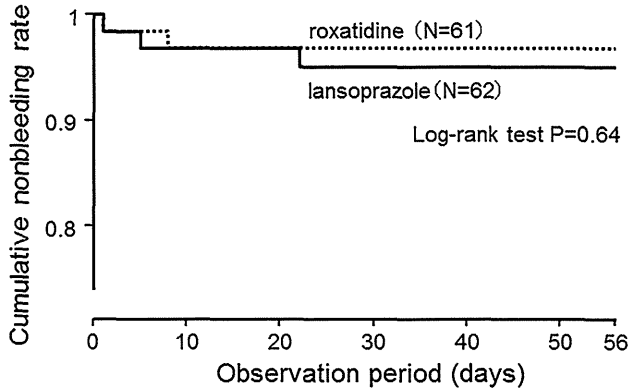

Fig. 2 The cumulative nonbleeding rates of the two treatment groups, determined using the Kaplan–Meier method

The ulcer-healing rate at 8 weeks after the ESD was 93.5% (58/62) in the L group and 93.4% (57/61) in the R group; there was no significant difference in the rate between the two groups ($P = 1$). After adjustments for the potential factors influencing the risk of ulcer healing, treatment with roxatidine was not found to have any significant effect of decreasing the ulcer-healing rate (adjusted odds ratio 0.61, 95% CI 0.10–3.83, $P = 0.60$).

No bleeding or perforation happened after ESD in any of the three patients with no neoplasm excluded from the R group. Ulcer healing occurred at 8 weeks after ESD in all of these patients.

The total cost of treatment with the antisecretory agents from the day of the ESD to day 56 (8 weeks) after the ESD was Yen 13,212 for lansoprazole and Yen 5,841 for roxatidine in our study, demonstrating a significantly higher cost-benefit ratio for roxatidine. During the follow-up period, no side-effects induced by drug administration were found in either treatment group.

Discussion

In ESD, a relatively large area of the gastric mucosa can be resected by electrocautery. However, bleeding occurs frequently during the procedure, and postoperative bleeding occurs in approximately 5% of all patients who undergo gastric ESD [6, 13, 14]. The size of the resected tumor has been reported as a significant risk factor for postoperative bleeding after ESD [7, 15]. Gastric pH affects the efficiency of blood coagulation and platelet aggregation at the

site of bleeding. Pepsin is active below pH 5.0 and accelerates clot digestion. In vitro, platelet functions are severely impaired at low pH [16]. Thus, a reduction in gastric acidity towards neutral would stabilize the clotting mechanism and prevent bleeding. PPIs are known to be more potent at elevating the intragastric pH than H_2RAs. Uedo et al. [7] reported that the intragastric pH was significantly higher in patients administered a PPI than in those administered an H_2RA on the day before the ESD. PPIs have also been reported to be superior to H_2RAs in preventing bleeding after ESD [7, 8]. According to the report by Uedo et al. [7], bleeding after ESD was seen in four of 66 patients (6.1%) treated with rabeprazole and 11 of 64 patients (17.2%) treated with cimetidine. Jeong et al. [8] reported that the incidence of bleeding after ESD was significantly lower in a group treated with pantoprazole than in a group treated with famotidine (3.5 vs. 12.7%, $p < 0.05$).

In the present pilot study, there was no significant difference between the lansoprazole and roxatidine groups in the prevention of bleeding after ESD. Roxatidine is a second-generation-H_2RA and has been reported to not only suppress gastric acid secretion, but also to activate gastric mucosal defense mechanisms [9, 10]. Although the exact mechanisms involved in the mucosal defense system are unknown, at least one or more of the naturally occurring gastric mucosal defense factors such as increase of the gastric blood flow and promotion of bicarbonate secretion and mucin metabolism are involved. Roxatidine has been reported to prevent the formation of gastric mucosal lesions induced by necrotizing agents in rats [17], and it has also been shown to be as effective and safe as the other H_2RAs for the treatment of gastric ulcers and duodenal ulcers. Particularly in duodenal ulcers, switching from H_2RAs with a five-membered ring to roxatidine may be useful in the treatment of ulcers resistant to treatment with five-membered-ring agents [11]. Therefore, roxatidine might be as efficacious as lansoprazole in preventing bleeding after ESD.

The rate of major bleeding in the present study was 4.1% (5/123) in all patients, which seemed to be lower than that reported from many previous studies. In patients undergoing ESD, the risk of delayed bleeding is highest within 24 h of the procedure [14]. We always perform a second-look endoscopy on the day after the ESD, and we also carry out endoscopic hemostasis for any minor bleeding, so as to prevent major bleeding from the ulcer after ESD. Ono et al. [18] also reported a very low rate of major bleeding (one of 155 patients), likely attributable to the second-look endoscopy performed to prevent bleeding after ESD.

In our study, the ulcer-healing rate at 8 weeks after ESD was similar in the lansoprazole and roxatidine groups. In the study reported by Uedo et al. [7] also, the ulcer-healing rate in the PPI group (83%) was similar to that in the H_2RA group (89%). However, Ye et al. [19] reported that fewer patients in their omeprazole group than in their famotidine group showed active ulcers at 28 days after ESD. Kato et al. [20] reported that combined PPI plus rebamipide treatment yielded a higher gastric ulcer healing rate at 4 weeks after ESD (68%) as compared with PPI treatment alone (36%). PPIs in combination with mucosal protectant drugs have been reported to be more useful than PPIs alone for the healing of ulcers after ESD [20, 21]. Mucosal protectant drugs may have an important role in promoting the healing of ulcers after ESD. In our study, we checked on ulcer healing only at 8 weeks after ESD; therefore, further studies are required to determine both the optimum duration of PPI therapy and the usefulness of follow-up endoscopy. Kakushima et al. [22, 23] reported that ulcer healing after ESD was delayed in patients with tumors showing ulceration or scar formation, while the presence/absence of *H. pylori* infection had no effect on ulcer healing. In our study, there was no significant difference between the two treatment groups in the number of tumors showing ulceration or scar formation, or in the prevalence of *H. pylori* infection. After adjustments for the potential contributors to ulcer healing, treatment with lansoprazole was not identified as a significant factor in increasing the ulcer-healing rate. Our study was, however, a single-center study and the sample size was so small that the difference between two groups might not have become apparent. We therefore hope to perform a multi-center trial with a larger study population in the future.

With respect to the costs and benefits, the total cost of treatment with the antisecretory agents from the day of the ESD to day 56 (8 weeks) after the ESD was Yen 13,212 for lansoprazole and Yen 5,841 for roxatidine. The cost-benefit ratio was thus significantly higher for roxatidine as compared with that for lansoprazole, and successful ulcer healing could be obtained in the roxatidine group at only 44.2% of the cost incurred in the lansoprazole group.

In conclusion, there was no significant difference in the incidence of bleeding or in the ulcer-healing rate after ESD for superficial gastric neoplasia between lansoprazole and roxatidine. Roxatidine appears to have high cost-effectiveness in the prevention of bleeding and promotion of ulcer healing after ESD for superficial gastric neoplasia.

Conflict of interest The authors declare that they have no conflict of interest.

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Antimicrobial Agents and Chemotherapy

Helicobacter pylori Resistance to Rifabutin in the Last 7 Years

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Antimicrob. Agents Chemother. **2011, 55(11):5374. DOI: 10.1128/AAC.05437-11.**
Published Ahead of Print 6 September 2011.

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Nov. 2011, p. 5374–5375 Vol. 55, No. 11
0066-4804/11/$12.00 doi:10.1128/AAC.05437-11

Helicobacter pylori Resistance to Rifabutin in the Last 7 Years▽

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Received 1 August 2011/Returned for modification 22 August 2011/Accepted 24 August 2011

A low rate of resistance (0.24%) to rifabutin was noted in *Helicobacter pylori* strains isolated from 414 Japanese patients. The only rifabutin-resistant strain detected showed a point mutation in the *rpoB* gene and was isolated from a patient with a history of rifampin treatment for pulmonary tuberculosis.

Resistance to antibiotics is a major cause of failure of *Helicobacter pylori* eradication therapy (4, 5, 8), and alternative regimens need to be developed to overcome this problem (6). One of the candidate antibiotics for a third-line eradication regimen is a fluoroquinolone, such as levofloxacin or sitafloxacin (13). We previously examined the resistance of *H. pylori* to gatifloxacin (8-methoxy fluoroquinolone) and showed high rates of resistance (43%) to gatifloxacin of *H. pylori* strains isolated from Japanese patients after unsuccessful eradication therapy (10).

Another candidate antibiotic for a third-line eradication regimen is rifabutin, which is an antituberculous agent derived from rifamycin-S, which is structurally similar to rifampin. Rifabutin inhibits the beta-subunit of DNA-dependent RNA polymerase of *H. pylori*, which is encoded by the *rpoB* gene (2). Van der Poorten and Katelaris designed a prospective study to assess the efficacy of rifabutin-based triple therapy. Of 67 patients, eradication of *H. pylori* was achieved in 76% (48/63) in the per protocol analysis and 72% (48/67) in the intention-to-treat analysis (15). Adverse events were reported in 10% of the patients. This study demonstrated that rifabutin triple therapy as third-line therapy is well tolerated and yields an acceptable eradication rate.

We previously investigated the MICs of rifabutin and also the point mutations of the *rpoB* gene in 48 strains of *H. pylori* isolated from patients of a general hospital (Keio University Hospital) and 46 strains isolated from patients at a specialized hospital for chronic respiratory diseases (Minami-Yokohama Hospital) (14). Although all the strains isolated from the patients at the general hospital were susceptible to rifabutin, 8 of the 46 strains (17.4%) isolated from the patients at the specialized hospital for chronic respiratory diseases showed resistance to rifabutin; 6 of these 8 strains also showed point mutations of the *rpoB* gene. In particular, the MICs were high for the strains isolated from patients with a history of treatment with rifampin. The present study was aimed at analyzing the resistance pattern to rifabutin of *H. pylori* strains isolated from the patients at the general hospital (Keio University Hospital) during the last 7 years.

The present study was conducted with the approval of the Ethics Committee of Keio University School of Medicine. A total of 414 patients with *H. pylori* infection (233 males and 181 females; mean age, 55.9 years) were enrolled between September 2004 and July 2011. *H. pylori* infection was defined as *H. pylori* culture positivity in this study. All patients underwent esophagogastroduodenoscopy and gastric biopsy for bacterial culture at Keio University Hospital. Of the total, 19 patients had no history of *H. pylori* eradication therapy, 263 patients had had one treatment failure, 116 patients had had two treatment failures, and 16 patients had had three treatment failures (first-line treatment was triple therapy with 800 mg/day clarithromycin, 1,500 mg/day amoxicillin, and a proton pump inhibitor [PPI] for 7 days; second-line treatment was triple therapy with 500 mg/day metronidazole, 1,500 mg/day amoxicillin, and a PPI for 7 days; and third-line treatment was triple therapy with a fluoroquinolone [400 mg/day levofloxacin, gatifloxacin, or sitafloxacin], 2,000 mg/day amoxicillin, and a PPI for 7 days) (3, 9, 11). Among the 386 patients, the 48 strains isolated between September 2004 and June 2005 that were used in the present study had been previously examined, and a comparison of the rifabutin resistance rates between isolates from the general hospital patients and patients at the specialized hospital for chronic respiratory diseases was reported (14).

The susceptibility of *H. pylori* isolates to rifabutin was determined by the agar dilution method, according to the guidelines established by the Clinical and Laboratory Standards Institute (CLSI) (1, 7). Isolates were considered resistant to rifabutin if the MIC of the drug was ≥0.25 μg/ml (14). The MIC of rifabutin for one of the 414 (0.24%) strains was high (MIC = 2 μg/ml), whereas the MIC values for the other strains were low (MIC < 0.015 μl/ml). The rifabutin-resistant strain was from a patient who had a history of one *H. pylori* eradication failure and a history of treatment with rifampin for pulmonary tuberculosis.

We performed PCR amplification and sequencing of the resistance-determining regions of the *rpoB* gene (from codon 511 to 612; forward, 5′-AAATGATCACAAGCACCATC-3′, and reverse, 5′-ACCTTGCCATCCACAACC-3′) (2) of 43 strains isolated between June 2008 and May 2010. The *rpoB* sequences obtained were compared with the published *rpoB*

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▽ Published ahead of print on 6 September 2011.

TABLE 1. MIC of rifabutin and substitution in the resistance-determining region of the *rpoB* gene

Strain(s)	Rifabutin MIC (μg/ml)	Substitution in the *rpoB* gene	History of treatment with rifampin
KSO513	2	D530N	Yes
42 other strains	<0.015	Not detected	No

data of rifabutin-susceptible *H. pylori* strain 26695 (GenBank accession number AE000511). The rifabutin-resistant strain had a point mutation of the *rpoB* gene with a substitution at amino acid 530 (D530N). On the other hand, no such mutations were seen in the remaining 42 rifabutin-susceptible strains (Table 1).

In conclusion, the prevalence of resistance of *H. pylori* to rifabutin has fortunately remained low. It has been suggested that the use of rifabutin be reserved for the treatment of multiresistant *Mycobacterium tuberculosis* strains (12). Although rifabutin may be a promising candidate for third-line therapy, careful consideration should be given to the results of the history of treatment with rifampin or of drug susceptibility testing prior to the inclusion of rifabutin in treatment regimens for eradication of *H. pylori*.

The present study was supported by a Grant-in-Aid for Scientific Research (B) from the Japan Society for the promotion of Science (No. 22300169, to H.S.), a grant of the Adaptable and Seamless Technology Transfer Program through target-driven R&D (A-STEP) (AS231Z00132G to H.S.) from the Japan Science and Technology Agency (JST), and grants from the Smoking Research Foundation (to H.S.), the Keio Gijuku Academic Development Fund (to H.S.), and the Nateglinide Memorial Toyoshima Research and Education Fund (to H.S.).

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EXPERT REVIEWS

Metronidazole-based quadruple versus standard triple therapy: which is better as first-line therapy for *Helicobacter pylori* eradication?

Expert Rev. Clin. Pharmacol. 4(5), 579–582 (2011)

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Evaluation of: Malfertheiner P, Bazzoli F, Delchier JC *et al. Helicobacter pylori* eradication with a capsule containing bismuth subcitrate potassium, metronidazole, and tetracycline given with omeprazole versus clarithromycin-based triple therapy: a randomised, open-label, non-inferiority, Phase III trial. *Lancet* 377, 905–913 (2011).

The eradication rate of 7-day standard triple therapy for *Helicobacter pylori* eradication (a proton pump inhibitor combined with amoxicillin and clarithromycin) has decreased as a consequence of the increase in the resistance rates to clarithromycin. The authors of the article under evaluation conducted a multicenter, randomized, noninferiority, Phase III trial in Europe to compare the efficacy and safety of a 10-day treatment with omeprazole plus a single capsule containing bismuth subcitrate potassium, metronidazole and tetracycline (quadruple therapy) versus a 7-day treatment with omeprazole, amoxicillin and clarithromycin (standard triple therapy) in adults, and demonstrated that the quadruple therapy yielded superior *H. pylori* eradication rates compared with the standard triple therapy. The results suggest that quadruple therapy merits consideration as first-line eradication therapy for *H. pylori* in regions with high resistance rates to clarithromycin. However, several issues need to be considered, such as the optimal doses of bismuth and amoxicillin, as well as the treatment duration, before quadruple therapy can be established as the standard first-line therapy for *H. pylori* eradication.

Keywords: bismuth • clarithromycin • *Helicobacter pylori* • metronidazole

Helicobacter pylori (*H. pylori*) infection affects more than half of the world's population and is a significant cause of morbidity and mortality worldwide. *H. pylori* plays a critical role in the development of many gastroduodenal disorders, including peptic ulcer disease and gastric adenocarcinoma [1–3]. Eradication of *H. pylori* is advocated to prevent the development of gastric adenocarcinoma, especially in regions with high incidence rates of this disease [4,5]. The identification of highly effective and well-tolerated treatment regimens is therefore crucial.

Traditionally, 7 days of triple therapy with a proton pump inhibitor combined with amoxicillin and clarithromycin is recommended as the first treatment of choice for eradicating *H. pylori* [4,6,7]. However, the success rate of this triple therapy has recently fallen to 80% or less because of the increasing *H. pylori* resistance rates to clarithromycin [4,8]. Since a first-line treatment regimen should yield an eradication rate of at least 80% [9], clarithromycin-based triple therapy should not be used, or a clarithromycin susceptibility test should be performed, in regions with clarithromycin resistance rates of 20% or more [6].

Recent management guidelines from the Maastricht consensus conference (Maastricht III) and the American College of Gastroenterology have proposed 10–14 days of quadruple therapy with a proton pump inhibitor, bismuth, metronidazole and tetracycline as another potential first-line regimen for *H. pylori* eradication [6,10]. A previous international study which assessed

 10.1586/ECP.11.34 ISSN 1751-2433

the efficacy and safety of 10-day quadruple therapy for *H. pylori* eradication reported an overall eradication rate of greater than 90% [11]. Therefore, to evaluate the efficacy and safety of bismuth-containing metronidazole-based quadruple therapy versus the standard clarithromycin-based triple therapy as the first-line treatment for *H. pylori*, Malfertheiner *et al.* conducted a randomized controlled trial and elegantly demonstrated the significant effectiveness of quadruple therapy [12].

Summary of the methods & results

The study by Malfertheiner and colleagues (the Pylera Study Group) was a multicenter, randomized, noninferiority, Phase III trial conducted in Europe to compare the efficacy and safety of 10-day treatment with omeprazole plus a single capsule containing bismuth subcitrate potassium, metronidazole and tetracycline (quadruple therapy) versus 7-day treatment with omeprazole, amoxicillin and clarithromycin (standard triple therapy) in adults with documented *H. pylori* infection [12]. The primary outcome was *H. pylori* eradication, established by two negative ^{13}C urea breath tests at a minimum of 18 and 56 days after the end of treatment. The eradication rates were 80% in the quadruple-therapy group versus 55% in the standard triple-therapy group in the intention-to-treat population ($n = 440$; $p < 0.0001$), and 93% in the quadruple-therapy group versus 70% in the standard triple-therapy group in the per-protocol population ($n = 339$; $p < 0.0001$). The side-effect profile of both treatments was similar, with gastrointestinal disorders, such as dyspepsia, abdominal pain and diarrhea, and CNS disorders, such as headache and dysgeusia, being the main adverse events reported.

Discussion

The results of this study show that 10 days of quadruple therapy yields *H. pylori* eradication rates superior to 7 days of standard triple therapy. There were no significant differences in the side-effect profile between the quadruple and triple therapies. The authors comment that this is the first large-scale study of metronidazole-based quadruple therapy for *H. pylori* eradication in almost a decade. On the basis of their findings, they suggest that quadruple therapy merits consideration as a first-line treatment regiment for the eradication of *H. pylori*, especially in view of the rising prevalence rates of clarithromycin resistance [13–16].

The interesting aspect of this study is that the authors also tested the pretreatment prevalence of *H. pylori* resistance to clarithromycin and metronidazole, and assessed the effect of resistance on treatment efficacy. The baseline resistance rates to metronidazole and clarithromycin were similar between the quadruple- and standard triple-therapy groups (metronidazole: 29 vs 31%; clarithromycin: 23 vs 19%). While metronidazole resistance did not significantly affect the efficacy of the quadruple therapy, clarithromycin resistance significantly affected the efficacy of the triple therapy in the per-protocol population set.

Previous studies have demonstrated that the clinical impact of metronidazole resistance on bismuth-containing quadruple therapy differs from that on clarithromycin-based triple therapy [17–20]. The discrepancy has been partly explained by metronidazole resistance being overcome by metronidazole–bismuth synergism [21,22]. However, the precise molecular mechanism of metronidazole–bismuth synergism is still unclear. Several studies have suggested that bismuth action might produce competitive interference of iron transport [23,24], which is essential for the activation of of bacterial superoxide dismutase, one of the key enzymes for the development of metronidazole resistance [25]. Another reason proposed to explain the discrepancy is that it may be derived from the Etest method currently used for the assessment of metronidazole resistance: according to one study, Etest yields a significantly higher prevalence of *H. pylori* resistance to metronidazole than the National Committee for Clinical Laboratory Standards-approved agar dilution method when isolates from different parts of the same stomach are compared [26]. Although concerns have often been raised about the toxic effects of bismuth, a recent systematic review and meta-analysis of adverse events of bismuth used for *H. pylori* eradication showed that dark stools was the only significant adverse event associated with bismuth ingestion [27].

The higher eradication rate in the quadruple-therapy group and lower rate in the triple-therapy group in the present study as compared with the corresponding rates reported in a recent systematic review and meta-analysis of quadruple versus triple therapy for *H. pylori* eradication [20] is a cause for concern and further discussion. According to the systematic review of intention-to-treat eradication rates reported by Luther *et al.*, quadruple therapy yielded an eradication rate of 78% and triple therapy an eradication rate of 77%, while in this study by Malfertheiner *et al.*, the corresponding rates were 80 and 55%, respectively [12]. This might be partly related to the doses of bismuth and amoxicillin used. In this study, relatively high doses of bismuth (1680 mg/day) were used in the quadruple-therapy group. Moreover, the dose of amoxicillin used in the triple-therapy group was significantly lower (1 g/day), since amoxicillin doses of 1.5–2 g/day have been used routinely in most previous trials. Although it is unclear whether the eradication rates might differ depending on the dose of amoxicillin, the eradication rate in the group of patients with clarithromycin-susceptible *H. pylori* in this study (85%) appears to be lower than the rates reported previously [17,28–30]. Unfortunately, resistance to amoxicillin was not examined in this study. Although *H. pylori* has been thought to rarely become resistant to amoxicillin, a recent study conducted by Nishizawa *et al.* showed that resistance to amoxicillin can be induced gradually after unsuccessful eradication therapy, suggesting that resistance to amoxicillin would also need to be taken into consideration in order to assess the efficacy of triple therapy in the next era [31].

The optimal duration of the present quadruple therapy also needs to be discussed. It could be suggested that it is unfair to compare 10 days of quadruple therapy with 7 days of triple therapy. The authors described that international guidelines advocate a treatment duration of 10 days for quadruple therapy [4,10]. Previous reports have demonstrated that quadruple therapy should be given for more than 7 days, since metronidazole resistance can be overcome by increasing the dose of metronidazole and prolonging the duration of metronidazole-containing treatment [32,33]. However,

Laine *et al.* only showed a marginal difference in a similar study of 10-day quadruple therapy: the eradication rate was 80.4% in the group with metronidazole-resistant *H. pylori* and 91.7% in the group with metronidazole-susceptible *H. pylori* (p = 0.067) [17]. Moreover, a recent systematic review and meta-analysis showed that the treatment duration did not influence the efficacy of quadruple therapy [20]. Therefore, the duration of quadruple therapy (10 days vs 7 days or 14 days) needs to be rigorously assessed before quadruple therapy can be introduced as a first-line eradication regimen for *H. pylori*.

Five-year view

The gold standard for first-line *H. pylori* eradication therapy is changing drastically as a result of the impact of this study. Primary clarithromycin resistance has been reported to be greater than 20% in Spain, Italy, Turkey and Japan [34]. Therefore, in these regions, quadruple therapy might be appropriate as the first-line therapy. On the other hand, in regions with high resistance rates to metronidazole such as Korea, Malaysia, Chile and Cameroon, the efficacy rates of metronidazole-based quadruple therapy might differ from those in Europe, and should be examined individually.

Despite good treatment results, quadruple therapy also has disadvantages. The efficacy of quadruple therapies containing bismuth is often limited by poor patient compliance due to the number of tablets that need to be taken and the dose frequency per day (quadruple therapy needs to be taken four times a day) [35,36]. A single three-in-one capsule is an innovative drug formulation from this point of view. Unfortunately, however, bismuth is still not available in some countries, including Japan. Direct clinical evidence of metronidazole–bismuth synergism must be provided before bismuth-containing regimens can be introduced worldwide.

The *H. pylori* resistance rates to various antibiotics have gradually increased worldwide [34]. It is therefore important to monitor the antimicrobial resistance patterns regularly and reassess the best choice regimen for first-line eradication therapy every few years.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, grants or patents or pending, and royalties.

No writing assistance was utilized in the production of this manuscript.

Key issues

- 10-day treatment with omeprazole plus a single capsule containing bismuth subcitrate potassium, metronidazole and tetracycline (quadruple therapy) merits consideration as the first-line eradication therapy for *Helicobacter pylori* in regions with clarithromycin resistance rates greater than 20%.
- However, the duration of quadruple therapy needs to be rigorously assessed before quadruple therapy can be introduced as a first-line eradication regimen for *H. pylori*.
- The antimicrobial resistance patterns of *H. pylori* must be monitored regularly, and the best choice regimen for first-line eradication therapy should be assessed every few years.

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JNM
J Neurogastroenterol Motil, Vol. 17 No. 4 October, 2011
pISSN: 2093-0879 eISSN: 2093-0887
http://dx.doi.org/10.5056/jnm.2011.17.4.360
Journal of Neurogastroenterology and Motility

Review

Overlap Syndrome of Functional Dyspepsia and Irritable Bowel Syndrome - Are Both Diseases Mutually Exclusive?

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Among functional gastrointestinal (GI) disorders, functional dyspepsia (FD) and irritable bowel syndrome (IBS) are important to public health around the world and are frequently encountered in general practice. Upper GI symptoms such as heartburn, postprandial fullness, early satiety, epigastric pain or burning and lower GI symptoms such as constipation and diarrhea often coexist. Although the prevalence of FD-IBS overlap would be influenced by the selection of the study population, the overlap rate of FD-IBS could be in the range of 11%-27%. Specifically, FD-IBS overlap is associated with more severe symptoms than FD alone or IBS alone. Since clinical overlap, especially FD-IBS overlap, is very common, the 2 syndromes should not be treated in a mutually exclusive fashion.

(J Neurogastroenterol Motil 2011;17:360-365)

Key Words

Dyspepsia; Epigastric pain syndrome; Health-related quality of life; Irritable bowel syndrome; Postprandial distress syndrome

Introduction

Epidemiological studies suggest a considerably high rate of overlap between functional dyspepsia (FD) and irritable bowel syndrome (IBS). According to the recent systematic review and metanalysis,[1] the prevalence of IBS in subjects with dyspepsia is 37% (95% CI, 30%-45%) as compared to 7% (95% CI, 5%-10%) in those without. The pooled odds ratio for IBS in subjects with dyspepsia was 8 (95% CI, 5.74-11.16) as compared to that in those without dyspepsia. However, the original studies used an older classification such as Manning's, Rome I or II, than Rome III and also did not exclude organic diseases, possibly resulting in the contamination with peptic ulcer diseases or reflux esophagitis.

Prevalence of Overlap Between Functional Dyspepsia and Irritable Bowel Syndrome

There are a few evaluations of overlap between FD and IBS

Received: June 29, 2011 Revised: July 9, 2011 Accepted: July 14, 2011

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Financial support: This work was supported by a Health and Labour Sciences Research Grant (Clinical Research Promotion No. 47) for Research on Health Technology Assessment (to H.S.), a grant (11035231-000061) from the JSPS Bilateral Joint Projects with Belgium, a grant from the Smoking Research Foundation (to H.S.), the Keio Gijuku Academic Development Fund (to H.S.) and a Nateglinide Memorial Toyoshima Research and Education Fund (to H.S.).
Conflicts of interest: The contents of this article had been lectured as a special lecture in the 12th Recent Update of Neurogastroenterology and Motility Symposium, held on June 11, 2011 at Novotel Ambassador Busan Hotel.

based on the Rome III classification. Kaji et al[2] conducted a cross-sectional study to examine the prevalences of gastroesophageal reflux, FD and IBS, their overlap rates, and the health-related quality of life (HRQOL) for each disease and each overlap syndrome, as compared with the corresponding values in healthy controls in a Japanese health check-up population. Of the 2,680 eligible subjects, 269 (10.0%) were diagnosed as having FD, and 381 (14.2%) as having IBS. Overlaps between FD and IBS were found in 92 patients (3.4%). Overlap significantly worsened the HRQOL in most domains, except in the "role emotional" domain. The HRQOL was particularly poor in the mental component summary for overlapping IBS.[2] On the other hand, Nakajima et al[3] conducted a survey in a general gastroenterology outpatient clinic of 1,378 consecutive patients. Among them, 29 (2.1%) were diagnosed as having FD, and 33 (2.4%) as IBS. Overlaps between FD and IBS were found in 12 (0.9%).

Wang et al[4] investigated 3,014 patients who responded to their questionnaires (male:female = 47.2:52.8, response rate 89%) at a general gastroenterology outpatient clinic. FD-IBS overlap was observed in 151 (5.0%) patients, while 457 (15.2%) and 329 (10.9%) were classified as having FD alone and IBS alone, respectively.[4] As compared with that in the non-IBS cohorts, the OR of having FD among IBS was 2.09 (95% CI, 1.68-2.59). Patients with FD-IBS overlap had higher severity scores for the symptom of postprandial fullness (2.4 ± 1.5 vs 1.7 ± 1.6, $P < 0.001$) and overall FD symptoms (6.7 ± 2.9 vs 5.8 ± 2.8, $P < 0.05$) than those with FD alone. The only independent risk factor for FD-IBS overlap versus FD alone was the presence of postprandial fullness (OR, 2.67; 95% CI, 1.34-5.31).[4]

Lee et al[5] investigated the differences in depressive mood and quality of life (QOL) among Korean patients with FD, IBS and FD-IBS overlap diagnosed by the Rome III definition. According to their report,[5] out of 279 subjects, 70 (25.1%) and 124 (44.4%) were diagnosed as having FD and IBS, respectively. Patients with FD-IBS overlap and those with FD alone showed higher Beck Depressive Inventory scores than normal subjects ($P < 0.001$ and $P = 0.02$, respectively), whereas those with IBS alone showed no differences in scores from normal subjects ($P = 0.17$). All of the SF-36 (the 36-item Short Form general health survey) subscores of the FD-IBS overlap cohorts were significantly lower than those in normal subjects ($P < 0.05$). Depressive mood was significantly related to FD and FD-IBS overlap, but not to IBS alone. Patients with FD-IBS overlap had a worse QOL than patients with FD alone or IBS alone.[4] Furthermore, according to the recent report by Park,[6] the sensitivity and specificity of the Rome III classification in discriminating functional gastrointestinal disorders (FGIDs) from organic diseases of the upper gastrointestinal (GI) tract were 60% and 53%, respectively, while the values of the lower GI tract were 80% and 50%, respectively, partially supporting the use of the Rome III criteria in Korea.[5]

Data on the impact of FD on the HRQOL in the general population are scarce. Aro et al[7] explored the impact of FD based on the Rome III classification on the HRQOL in the general population. Among 1,001 cohorts, 202 (20%) individuals reported uninvestigated dyspepsia (UID), and 157 (16%) reported FD. FD-IBS overlap had a significant impact on bodily pain ($P < 0.01$) and general health ($P < 0.05$).[7]

Although Hori et al[8] used the Rome II criteria, they examined concurrent GI symptoms in FD and IBS in a total of 186 college students who filled out a questionnaire administered to determine whether they had UID or IBS. The diagnosis of UID, IBS and UID + IBS overlap was made in 12 (6.7%), 40 (22.1%) and 8 (4.4%) patients, respectively and a significant prevalence of UID + IBS overlap was observed (66.7% IBS in UID; 20.0% UID in IBS).[8] Although Corsetti et al[9] also used Rome II criteria for the diagnosis of FD in their questionnaire survey of 309 consecutive FD patients to assess the dyspepsia and IBS symptom patterns, 54% of the patients had FD alone, whereas 46% had FD + IBS. FD-IBS overlap patients were more likely to be female (75% vs 60%, $P < 0.01$) and to have greater weight loss (5.4 ± 0.6 vs 3.5 ± 0.4 kg, $P < 0.05$). Coexisting IBS did not increase the risk of dyspepsia, however, the overall symptom severity was significantly higher in the patients with FD-IBS overlap (12.4 ± 0.4 vs 9.8 ± 0.3, $P < 0.01$). FD-IBS overlap patients had a lower threshold for first perception (2.9 ± 0.3 vs 3.8 ± 0.3 mmHg, $P < 0.05$) and for discomfort (7.9 ± 0.4 vs 9.5 ± 0.5 mmHg, $P < 0.05$) and a greater prevalence of hypersensitivity to gastric distention (44% vs 28%, $P < 0.05$).[9]

Recently, we performed a web-based survey comprised of Rome III criteria for FD, the Gastrointestinal Symptom Rating Scale, and questions to determine demographic information among subjects registered for Japanese clinical trial programs.[10] Cluster analysis revealed 3 distinct clusters: cluster associated with diarrhea, cluster associated with constipation and cluster associated with neither diarrhea nor constipation. Cluster associated with constipation and cluster associated with diarrhea were significantly linked to the presence of FD, suggesting that FD was more prevalent among participants with bowel symptoms than in those without. Furthermore, FD patients with bowel

symptoms had more severe dyspepsia symptoms than those without.

Although GI symptoms are quite common in the general population, different methods for the survey show different epidemiologies, and the effects of psychosocial and behavioral factors on the symptoms have been studied, mainly by subgroup analysis. According to the Japanese questionnaire survey focusing on GI symptoms and the psycho-behavioral background in members of a registered panel via e-mail and postal mail, despite the difference in the prevalence of GI symptoms, that is, 47% in the electronic survey and 25% in the postal one, similar proportions of symptom subtypes and patterns of overlaps were obtained with such 2 methods.[11] While 56% were diagnosed as having FD, and 58% as having IBS in the electronic survey, 57% were diagnosed as having FD, and 55% as having IBS in the postal one. FD-IBS overlap was found in 24% in the electronic survey and in 23% in the postal one. Subjects who have higher scores for psycho-behavioral problems had a higher prevalence of FD and IBS symptoms. The data suggest that psycho-behavioral conditions may affect the development of functional GI symptoms, regardless of the subtype of GI disorders, and can explain the high proportion of overlap among the subtypes.[11]

Taken together, the above-mentioned prevalence of FD-IBS overlap would be altered depending on the selected study population. The rate of FD-IBS overlap could be in the same range, such as 11.4%,[6] 16.5%,[2] 23.8%,[4] 24.0%[3] and 27.6%[5] (Table).

Influence of Each Subtype of Functional Dyspepsia or Irritable Bowel Syndrome on the Presence of Functional Dyspepsia-Irritable Bowel Syndrome Overlap

A general definition of FD, to be used mainly for clinical purposes, and although further research on more specific definitions is ongoing, is provided under category B1: functional dyspepsia (FD) in Rome III classification. However, particularly for pathophysiological and therapeutic approach, it is recommended in Rome III that new entities of meal-induced dyspeptic symptoms as postprandial distress syndrome (PDS): B1a, and epigastric pain and burning as epigastric pain syndrome (EPS): B1b, should be used.[12] These 2 subcategories such as PDS and EPS seem very useful in clinical practice as well as in the investigative settings. According to the report by Wang et al,[4] more patients with PDS alone had IBS than those with EPS alone. Patients with FD-IBS overlap were more likely to be classified as the PDS + EPS subtype, had more frequent presence of the postprandial fullness symptom, one of major symptoms of PDS ($P < 0.001$), and overall FD symptom ($P < 0.01$) than those with FD alone. Furthermore, patients with FD-IBS overlap were less likely to be classified as the EPS alone ($P < 0.01$) compared to those classified as FD alone. By the multivariate logistic regression analysis, only the presence of postprandial fullness (OR, 2.67; 95% CI, 1.34-5.31; $P < 0.01$) had a statistically significant and independent effect on the probability of FD-IBS overlap. On the other hand, subtypes of IBS did not differ between patients with constipation type-IBS (IBS-C) and diarrhea-type IBS (IBS-D). In addition, neither IBS-D (OR, 1.44; 95%CI, 0.93-2.22; $P = 0.10$) nor mixed-type IBS (IBS-M) (OR, 1.62; 95% CI, 0.77-3.40; $P = 0.21$) was identified as risk factor for FD-IBS overlap versus IBS alone in the multivariable analysis. Aro et al[7] reported the data on the impact of PDS and EPS on QOL. The impact of PDS is statistically significant compared with controls except for Role Emotional and the results are consistently the same when analyzing for the possible confounders such as anxiety, depression and use of proton pump inhibitors. Patients with EPS had a statistically relevant impairment of HRQOL only in 2 domains such as Bodily Pain and Vitality compared with nondyspeptic cohorts. Namely, PDS seems to damage HRQOL in all SF-36 domains more than EPS.

In addition, non-erosive relux disease is more frequently overlapped with FD, especially with EPS and presents with significantly increased frequency of IBS.[13]

Table. Prevalence of Overlap Between Functional Dyspepsia and Irritable Bowel Syndrome

	FD alone (n [%])	IBS alone (n [%])	FD-IBS overlap (n [%])
Wang et al[4]	306 (48.2)	178 (28.0)	151 (23.8)
Nakajima et al[3]	17 (34.0)	21 (42.0)	12 (24.0)
Kaji et al[2]	177 (31.7)	289 (51.8)	92 (16.5)
Lee et al[5]	28 (18.4)	82 (53.9)	42 (27.6)
Park[6]	72 (43.1)	76 (45.5)	19 (11.4)

FD, functional dyspepsia; IBS, irritable bowel syndrome.

Pathophysiology Leading to Functional Dyspepsia-Irritable Bowel Syndrome Overlap

FD and IBS are common functional disorders without de-

fined pathophysiology and are known as multifactorial syndromes. The pathophysiological factors for the generation of FD or IBS would be listed as visceral hypersensitivity, central abnormal deregulation for sensory perception, GI dysmotility, and abnormal alteration of the intestinal flora, GI inflammation, and psychosocial factors. Although such a mechanistic investigation is further preceded in the research field in IBS, the detail of pathophysiology in FD-IBS overlap has not been fully explored. However, as these 2 syndromes (FD and IBS) would have common causative factors, the high prevalence of FD-IBS overlap is considered to be easily acceptable.

Abnormalities of psychosocial or central nervous factors, which would affect the whole GI tract, could be a possible causative factor in the pathogenesis of FD-IBS overlap. Savas et al[14] examined the 1-year prevalence of IBS and dyspepsia symptoms and their associations with depression, anxiety and post-traumatic stress disorder (PTSD) among women veterans receiving primary care at a Women's Clinic, Veteran Affairs (VA) Medical Center. They reported that women with IBS-dyspepsia overlap showed higher scores of anxiety (IBS: 24 vs 12, $P < 0.001$ and dyspepsia: 26 vs 12, $P < 0.001$), depression (IBS: 22 vs 11, $P < 0.001$ and dyspepsia: 23 vs 11, $P < 0.001$) and PTSD (IBS: 87 vs 69, $P < 0.001$ and dyspepsia: 86 vs 69, $P < 0.0005$), and age- and ethnicity-adjusted logistic regression analyses revealed a 3- to 46-fold increase in the OR of IBS and dyspepsia among women with depression, anxiety or PTSD.[14] Although gastric sensorimotor dysfunction, psychosocial factors and somatization are all implicated in the development of FD symptoms according to the report by Van Oudenhove et al,[15] symptom severity and weight loss in FD are determined by psychosocial factors (depression or history of abuse) and somatization, and to a lesser extent by gastric sensorimotor function, but not by FD-IBS overlap. On the other hand, Kindt et al[16] in Belgium investigated the 5-year evolution of symptoms in a clinical FD population to identify factors associated with the outcome and indicated that the dyspepsia symptom score (DSS) at the initial visit and trait anxiety were longitudinally associated with the DSS at follow-up, with a trend found for weight loss; depression, chronic fatigue and IBS at follow-up were cross-sectionally associated with DSS.

On the other hand, GI inflammation and altered immune responses could be another candidate as the cause of FD-IBS overlap. Patients with IBS show a greater degree of inflammatory cell infiltration than healthy controls. Mast cells and eosinophils interact with T lymphocytes and may alter the enteric nerve and smooth muscle functions. Examination of 48 IBS patients with either diarrhea or constipation,[17] 12 patients with microscopic colitis, 20 patients with ulcerative colitis, and 24 healthy controls, indicated that as compared to male IBS patients, female IBS had greater numbers of mast cells ($P = 0.066$), but lesser numbers of CD3+ and CD8+ T cells ($P < 0.01$ and $P < 0.001$, respectively). Such mucosal mast cell infiltration in IBS patients was significantly associated with the frequency of abdominal bloating ($P < 0.05$) and with dysmotility-like dyspepsia ($P = 0.001$), but not with ulcer-like dyspepsia.[17] According to the report by Walker et al,[18] intraepithelial lymphocytes in IBS-C were significantly increased ($P = 0.005$) and mast cells were significantly increased in the second part of the duodenum in IBS ($P < 0.001$), while eosinophils were significantly increased in the duodenal bulb and second part of the duodenum in FD ($P < 0.001$), suggesting that duodenal mast cell hyperplasia is linked to IBS, and eosinophilia to FD.

Recently, it has been revealed that previous infectious gastroenteritis is often followed by postinfectious FD (PI-FD)[19] or postinfectious IBS (PI-IBS).[20] Porter et al[21] recently conducted a matched, case-control study describing the epidemiology and risk determinants of IBS, functional constipation, functional diarrhea and dyspepsia using electronic medical encounter data in active-duty US military personnel, and demonstrated a significant association between infectious gastroenteritis and all FGIDs (OR, 2.64; $P < 0.001$), with the highest frequency of functional diarrhea (OR, 6.28; $P < 0.001$) and IBS (OR, 3.72; $P < 0.001$), and a moderate frequencies of functional constipation (OR, 2.15; $P < 0.001$) and FD (OR, 2.39; $P < 0.001$). According to Kindt et al[22] and Suzuki[23], PI-FD is associated with persistent focal T cell aggregates, decreased CD4+ cells and increased macrophage counts surrounding the crypts, indicating an impaired ability of the immune system to terminate the inflammatory response after an acute insult.

Since the etiology of FD is still uncertain, it is not surprising that *Helicobacter pylori*, a major pathogen in the stomach,[24-26] has been implicated in the pathophysiology of so called dyspepsia. Many trials reporting the efficacy of *H. pylori* eradication therapy for FD including non-ulcer dyspepsia have given conflicting results but there is a clear indication that *H. pylori* eradication treatment is effective in at least a subset of patients with FD or non-ulcer dyspepsia.[27,28] The recent meta-analysis also suggests that *H. pylori* eradication at 12 months has a small but statistically significant benefit in the treatment of FD (relative risk [RR] of remaining dyspepsia with *H. pylori* eradication therapy = 0.91; 95% CI, 0.87-0.99). While statistically significant, the clinical