Second-Line and Third-Line Trial for *Helicobacter pylori* Infection in Patients with Duodenal Ulcers: A Prospective, Crossover, Controlled Study

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ABSTRACT

Background: Following standard first-line triple therapies for *Helicobacter pylori* infection, up to 20% of patients require further eradication.

Objective: The aim of this study was to assess the effects of second-line triple therapies and third-line quadruple therapies for the eradication of *H pylori*.

Methods: This 7-week, prospective, crossover, controlled, second- and third-line trial was conducted at the Department of Gastroenterology, Ferencváros Health Center (Budapest, Hungary). Patients aged 18 to 80 years with duodenal ulcers and an *H pylori* infection resistant to first-line triple therapy (pantoprazole 40 mg BID + amoxicillin 1000 mg BID + clarithromycin 500 mg BID [PAC] given as tablets) received a different triple therapy regimen (ranitidine bismuth citrate 400 mg BID + metronidazole 500 mg BID + clarithromycin 500 mg BID [RBC-MC]) for 7 days (group 1A), and nonresponders after RBC + 2 antimicrobials received the pantoprazole-based regimen (group 1B). After secondary failure, patients were randomized to receive quadruple therapies: pantoprazole, amoxicillin, tetracycline, and either nitrofurantoin or bismuth subsalicylate (groups 2A and 2B).

Results: One hundred thirty-four patients were enrolled in the second-line study (56 men, 78 women; mean [SD] age, 51.1 [12.4] years; group 1A, 68 patients; group 1B, 66 patients). Subsequently, 41 (30.6%) of these patients were randomized to receive quadruple therapies. Using intent-to-treat (ITT) analysis, the eradication rates did not differ significantly (60.3% and 65.2% in groups 1A and 1B, respectively; 61.9% and 55.0% in groups 2A and 2B, respectively). Per-protocol eradication rates did not differ significantly (66.1% and 68.3% in groups 1A and 1B, respectively); however, the rates were significantly different in group 2A (66.7%) versus group 2B (55.5%) ($P = 0.03$).

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Conclusions: In this study of patients with persistent *H pylori* infection and duodenal ulcer, the PAC and RBC-MC regimens used as second-line therapies and the nonmacrolide, nonimidazole third-line regimens were of moderate efficacy in the eradication of persistent *H pylori*. On ITT analysis, no significant differences were detected between the second-line triple and the third-line quadruple regimens. Due to the high rates of resistance, determination of antimicrobial susceptibility of *H pylori* was of little benefit in this study; instead, empiric, nonmacrolide, nonimidazole combinations were preferred. (*Curr Ther Res Clin Exp.* 2004;65:13–25) Copyright © 2004 Excerpta Medica, Inc.

Key words: antimicrobials, eradication, *Helicobacter pylori*, proton pump inhibitors, ranitidine bismuth citrate.

INTRODUCTION

Helicobacter pylori infection plays a major role in peptic ulcer pathogenesis. Eradicating the bacterium accelerates the healing of the ulcers, reduces the risk for relapse, and prevents complications (eg, rebleeding, gastric outlet obstruction).¹ In European countries, a 7-day triple therapy regimen consisting of a standard dose of a proton pump inhibitor (PPI) BID + clarithromycin BID and either amoxicillin BID or a nitroimidazole BID has been proposed as the first-line regimen in eradicating *H pylori* by the First (1996)² and Second (2000)³ Maastricht Consensus conferences. The efficacy of these regimens has been proved in randomized controlled trials and meta-analyses.^{4–11} Ranitidine bismuth citrate (RBC)–based triple combinations are also efficacious first-line therapies.^{12,13} In 2000, the *H pylori* Working Group of the Hungarian Society of Gastroenterology¹⁴ proposed the same therapies as first-line regimens. As many as 20% of patients require second-line treatment, and an additional 5% undergo a third-line regimen, especially patients with peptic ulcer, in whom eradication is strongly recommended.^{2,3,15}

The aim of this study was to assess the effects of second-line triple therapies and third-line quadruple therapies for the eradication of *H pylori* in patients with duodenal ulcers.

PATIENTS AND METHODS

Study Design

This 7-week, prospective, crossover, controlled, second- and third-line trial was conducted at the Department of Gastroenterology, Ferencváros Health Center (Budapest, Hungary). The study protocol was approved by the local ethics committee and conformed to the Declaration of Helsinki and its amendments.

Patients

Patient selection began in 1999, before the publication of the Second Maastricht³ and Hungarian consensus reports.¹⁴ Patients were selected from a cohort of 686 patients aged 18 to 80 years with duodenal ulcers whose *H pylori*

infection persisted (confirmed using a ^{13}C -urea breath test [UBT]) 4 to 6 weeks after the end of first-line triple therapy with either pantoprazole 40 mg BID + amoxicillin 1000 mg BID + clarithromycin 500 mg BID (PAC) or RBC 400 mg BID + metronidazole 500 mg BID + clarithromycin 500 mg BID (RBC-MC). The results of a randomized study of first-line treatments have been reported elsewhere.¹⁶ The diagnosis of a duodenal ulcer was established by endoscopy (Fujinon UGI FP7 and EGT HR2, Fuji Photo Optical Co., Ltd., Saitama City, Japan) performed before first-line treatment. *H pylori* infection was confirmed by modified Giemsa stain from 2 antral and 2 corporeal biopsies and the rapid urease test (Controloc Test kit, Byk-Gulden, Konstanz, Germany).

Exclusion criteria were gastric bleeding within the 3 months before enrollment, previous gastric surgery (resection, vagotomy), severe concomitant disease (eg, heart failure, chronic obstructive pulmonary disease, type 1 diabetes mellitus, cirrhosis of the liver, renal failure), heavy drinking (>5 alcoholic beverages per day), and regular use (1–3 pills/day or >10 pills/wk) of nonsteroidal anti-inflammatory drugs (NSAIDs) (aspirin, ibuprofen, diclofenac, or naproxen). Pregnant, possibly pregnant, or breastfeeding women were excluded from the study. Women of childbearing age were required to use an effective method of birth control throughout the study.

Written informed consent was obtained from all patients.

Methods

A flow chart of the study design is shown in the **figure**.

Second-Line Triple Therapy

All drugs in this study were self-administered as tablets. For second-line therapy, the patients were allocated in a crossover manner as follows. Patients with an *H pylori* infection resistant to first-line therapy with PAC received RBC-MC for 7 days (group 1A). Patients with infection persistent after RBC-MC treatment received the PAC regimen for 7 days (group 1B). Thus, the type of acid inhibitor (PPI vs RBC) and 1 antibiotic (amoxicillin vs metronidazole) was changed, with clarithromycin remaining as the only drug used in both regimens. In both groups, all patients received ranitidine 150 mg BID or famotidine 40 mg once daily as needed for 1 month after the end of second-line therapy.

Six weeks after the end of the second treatment regimen (ie, after PAC or RBC-MC and a 2-week washout period following H_2 blocker intake), control examinations were performed by a laboratory specialist (ISz) using a UBT with isotope-selective infrared spectrometry (IRIS C13, Wagner Analysentechnik GmbH, Bremen, Germany). No gray zone was used for interpretation. *Eradication* was defined as UBT $\Delta^{13}\text{CO}_2$ 0‰ to 4‰. *Treatment failure* was defined as UBT $\Delta^{13}\text{CO}_2$ >4‰.

Treatment failures were offered either a repeat endoscopy with tissue sampling for *H pylori* culture and antibiotic susceptibility testing or empiric third-line quadruple therapy.

Figure. Study flow chart. PAC = pantoprazole 40 mg BID + amoxicillin 1000 mg BID + clarithromycin 500 mg BID; RBC-MC = ranitidine bismuth citrate 400 mg BID + metronidazole 500 mg BID (M) + clarithromycin 500 mg BID (C); PATN = pantoprazole 40 mg BID + amoxicillin 1000 mg BID + tetracycline 500 mg QID + nitrofurantoin 100 mg TID; PATBS = pantoprazole 40 mg BID + amoxicillin 1000 mg BID + tetracycline 500 mg QID + bismuth subsalicylate 120 mg QID.

During repeat endoscopy, 3 antral specimens were collected by a gastroenterologist (GyMB), placed in modified Stuart broth, and transported to the laboratory. Biopsy specimens were plated on an *H pylori*-selective, 10% agar-horse blood medium containing 10 µg/mL vancomycin at 37°C in a microaerophilic environment. Urease and catalase reactions and Gram stain were performed by a microbiologist (ASz) for *H pylori* identification. Bacterial growth was determined after 1 week. Antibiotic susceptibility was determined using an epilometer test¹⁷ (E-Test, AB Biodisk, Solna, Sweden).

Third-Line Quadruple Therapy

Patients rejecting repeat endoscopy were randomized using a computer-generated randomization schedule to receive empiric therapy with pantoprazole 40 mg BID + amoxicillin 1000 mg BID + tetracycline 500 mg QID and either nitrofurantoin 100 mg TID (PATN; group 2A) or bismuth subsalicylate 120 mg QID for 7 days (PATBS; group 2B). Because the number of patients was too small to constitute a separate therapeutic group, patients with infection resistant to metronidazole and/or clarithromycin (based on susceptibility testing), together with the few susceptible patients, also were randomized to receive PATN or PATBS. UBT was performed again 6 weeks after the end of the third-line regimen to determine treatment failures.

Compliance and Tolerability

To ensure compliance, the patients were informed about the expected adverse effects (AEs) (abdominal pain, bloating, constipation, diarrhea, fatigue, headache, itching, loss of appetite, nausea, rash, stomatitis, stool and tongue discoloration, vaginitis, vomiting, and possible allergic reactions). Compliance was assessed using pill count. AEs were recorded based on patients' self-reporting.

Statistical Analysis

The sample size of 65 patients was calculated to have a power of 80% to detect a 15% difference between the efficacy of the 2 second-line regimens. The results were expressed based on intent-to-treat (ITT) and per-protocol (PP) analyses. Differences between the groups were calculated using the chi-square test. $P \leq 0.05$ was considered significant; 95% CIs were calculated. The statistical work was performed using Statistica software version 9 (StatSoft, Inc., Tulsa, Oklahoma).

RESULTS

One hundred thirty-four patients were enrolled in the second-line study (56 men, 78 women; mean [SD] age, 51.1 [12.4] years; group 1A, 68 patients; group 1B, 66 patients). The baseline demographic characteristics of the 2 treatment groups were similar (Table I).

Table I. Baseline demographic characteristics of the study patients (N = 134).*

Characteristic	Second-Line Triple Therapy		Third-Line Quadruple Therapy	
	Group 1A (RBC-MC) (n = 68)	Group 1B (PAC) (n = 66)	Group 2A (PATN) (n = 21)	Group 2B (PATBS) (n = 20)
Age, y				
Mean (SD)	50.3 (12.6)	51.9 (12.3)	46.3 (9.8)	51.4 (10.2)
Range	19–80	25–79	36–67	40–75
Sex, no. (%)				
Women	34 (50.0)	31 (46.9)	14 (66.7)	12 (60.0)
Men	34 (50.0)	35 (53.0)	7 (33.3)	8 (40.0)
Duration of complaints, mean (SD), y	9.1 (8.1)	8.1 (6.1)	10.8 (8.3)	9.2 (6.6)
Smokers, no. (%)	37 (54.4)	32 (48.5)	9 (42.9)	10 (50.0)
Alcohol users, no. (%) [†]	16 (23.5)	15 (22.7)	4 (19.0)	5 (25.0)
NSAID users, no. (%) [‡]	8 (11.8)	11 (16.7)	3 (14.3)	4 (20.0)

RBC-MC = ranitidine bismuth citrate + metronidazole + clarithromycin; PAC = pantoprazole + amoxicillin + clarithromycin; PATN = pantoprazole + amoxicillin + tetracycline + nitrofurantoin; PATBS = pantoprazole + amoxicillin + tetracycline + bismuth subsalicylate; NSAID = nonsteroidal anti-inflammatory drug.

*No significant between-group differences were found.

[†]Heavy drinkers (>5 alcoholic beverages per day) were excluded.

[‡]Only regular (1–3 pills/day or >10 pills/wk) users of aspirin, ibuprofen, diclofenac, and naproxen were included.

Efficacy of Second-Line Triple Therapy

The eradication rates of the second-line treatment are shown in **Table II**. Second-line treatment failed to eradicate *H pylori* in 41 patients (30.6%) (22 [32.4%] in the RBC-MC group and 19 [28.8%] in the PAC group).

Efficacy of Third-Line Quadruple Therapy

All 41 second-line treatment failures received third-line treatment (**Table III**). Of these patients, 22 (53.7%) underwent repeat endoscopy, and *H pylori* culture was successful in 14 patients (63.6%); 8 of the 14 patients (57.1%) were metronidazole resistant, 5 patients (35.7%) were clarithromycin resistant, and 6 patients (42.9%) had double resistance. No amoxicillin, tetracycline, or nitrofurantoin resistance was observed. On an ITT basis, no significant difference in eradication rate between the third-line quadruple regimens was found. The cumulative eradication rates after 3 consecutive treatments were 88.6% and 94.2% in ITT and PP analyses, respectively.

Tolerability

AEs occurred in 19 patients (27.9%) in group 1A, 9 (13.6%) in group 1B, 7 (33.3%) in group 2A, and 8 (40.0%) in group 2B (**Table IV**). The most common AEs were stool discoloration (32.4%, 0.0%, 0.0%, and 20.0% of patients in groups 1A, 1B, 2A, and 2B, respectively), tongue discoloration (23.5%, 0.0%, 0.0%, and 10.0% of

Table II. Eradication of *Helicobacter pylori* after second-line triple therapy.

Analysis	Group 1A (RBC-MC)	Group 1B (PAC)
Intent-to-treat population	(N = 68)	(N = 66)
No. (%)	41 (60.3)	43 (65.2)
95% CI	48.4%–72.2%	53.3%–77.0%
Per-protocol population	(N = 40)	(N = 42)
No. (%)	26 (65.0)	25 (69.0)
95% CI	54.0%–78.2%	56.4%–80.1%
Withdrawals, no. (%)*	6 (8.8)	3 (4.5)
Treatment discontinuations, no. (%)	2 (2.9)	1 (1.5)

RBC-MC = ranitidine bismuth citrate + metronidazole + clarithromycin; PAC = pantoprazole + amoxicillin + clarithromycin.

*Withdrawals were due to lack of cooperation (5 cases), loss to follow-up (2 cases), and life events (2 cases).

patients in groups 1A, 1B, 2A, and 2B, respectively), and nausea (5.9%, 6.1%, 9.5%, and 5.0% of patients in groups 1A, 1B, 2A, and 2B, respectively). Two patients (2.9%) in group 1A and 1 patient (1.5%) in group 1B discontinued treatment because of AEs (stomatitis, severe fatigue, and vaginitis, respectively). One patient developed an esophageal ulcer after 2 days of PATBS treatment, which was immediately discontinued, and the lesion healed during PPI treatment.

DISCUSSION

According to the European^{2,3} and the Hungarian¹⁴ national consensus reports, 1 week of therapy with a standard dose of any of the available PPIs plus cla-

Table III. Eradication of *Helicobacter pylori* after third-line quadruple therapy.

Analysis	Group 2A (PATN)	Group 2B (PATBS)
Intent-to-treat population	(N = 21)	(N = 20)
No. (%)	13 (61.9)	11 (55.0)
95% CI	52.6%–71.2%	46.3%–63.7%
Per-protocol population	(N = 20)	(N = 17)
No. (%)	13 (65.0)	12 (70.6)*
95% CI	56.2%–77.2%	47.8%–62.8%
Withdrawals, no. (%)†	1 (4.8)	2 (10.0)
Treatment discontinuations, no. (%)	0 (0.0)	1 (5.0)

PATN = pantoprazole + amoxicillin + tetracycline + nitrofurantoin; PATBS = pantoprazole + amoxicillin + tetracycline + bismuth subsalicylate.

* $P = 0.03$ versus group 2A.

†Withdrawals were due to lack of cooperation (2 cases) and life events (1 case).

Table IV. No. (%) of patients who experienced adverse effects (AEs) with *Helicobacter pylori* treatment.*

Parameter	Second-Line Triple Therapy		Third-Line Quadruple Therapy	
	Group 1A (RBC-MC) (n = 68)	Group 1B (PAC) (n = 66)	Group 2A (PATN) (n = 21)	Group 2B (PATBS) (n = 20)
AE				
Stool discoloration	22 (32.4)	0 (0.0)	0 (0.0)	4 (20.0)
Tongue discoloration	16 (23.5)	0 (0.0)	0 (0.0)	2 (10.0)
Nausea	4 (5.9)	4 (6.1)	2 (9.5)	1 (5.0)
Constipation	4 (5.9)	2 (3.0)	1 (4.8)	3 (15.0)
Loss of appetite	3 (4.4)	1 (1.5)	0 (0.0)	1 (5.0)
Bloating	3 (4.4)	1 (1.5)	0 (0.0)	0 (0.0)
Stomatitis	2 (2.9) [†]	3 (4.5)	0 (0.0)	0 (0.0)
Abdominal pain	2 (2.9)	2 (3.0)	1 (4.8)	1 (5.0)
Fatigue	2 (2.9) [†]	2 (3.0)	0 (0.0)	1 (5.0)
Vaginitis	2 (2.9)	2 (3.0) [†]	0 (0.0)	0 (0.0)
Vomiting	2 (2.9)	1 (1.5)	1 (4.8)	0 (0.0)
Headache	1 (1.5)	2 (3.0)	0 (0.0)	1 (5.0)
Diarrhea	0 (0.0)	3 (4.5)	0 (0.0)	0 (0.0)
Itching	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)
Rash	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)
Patients experiencing AEs	19 (27.9)	9 (13.6) [‡]	7 (33.3)	8 (40.0)

RBC-MC = ranitidine bismuth citrate + metronidazole + clarithromycin; PAC = pantoprazole + amoxicillin + clarithromycin; PATN = pantoprazole + amoxicillin + tetracycline + nitrofurantoin; PATBS = pantoprazole + amoxicillin + tetracycline + bismuth subsalicylate.

*Some patients experienced >1 AE.

[†]This AE caused treatment discontinuation in 1 patient in this group.

[‡]P = 0.04 versus group 1A.

rithromycin and amoxicillin has been identified as the first-line regimen for *H. pylori* eradication; alternatively, regimens based on RBC plus 2 antimicrobials could be used.^{12,13} However, even with these triple therapies, the eradication rate does not reach 100%. Although no ideal therapy for *H. pylori* infection has yet been found, ~20% of patients need second-line treatment and a further 5% need third-line or rescue therapy.^{1-3,15}

Several methods of second-line treatment have been proposed. First, the efficacy of repeat administration of the initial therapy for the same (1 week¹⁸) or for an extended (10- to 14-day¹⁵) period has been assessed by several investigators. Regimens based on omeprazole + clarithromycin and either amoxicillin or metronidazole achieved eradication rates of 25% to 100% on an ITT and PP basis^{15,19}; and according to a meta-analysis,¹⁸ the pooled eradication rate for repeat omeprazole + amoxicillin + clarithromycin treatment was 76.5% and that

of omeprazole + amoxicillin + metronidazole was 69.2%, which are lower than the rates obtained in randomized controlled trials^{4–7} using the same combinations as first-line treatment.

A second method of second-line treatment involves switching from the PPI-based triple therapy to RBC-based triple therapy. This method was shown to be promising.²⁰ In most studies, RBC was substituted for the PPI, and so the more marked acid inhibitory effect of the PPI was replaced by the less profound antisecretory action of RBC, which has the potential advantage of in vivo interaction with clarithromycin²¹ and the ability to overcome nitroimidazole resistance.²² In a study²³ of multistep treatment of *H. pylori* infection, a 79% eradication rate was achieved in a group of 2413 patients receiving PPI + tinidazole and clarithromycin as first-line treatment; RBC + amoxicillin + clarithromycin was given as a second-line regimen to 507 patients and was efficacious in 77% and 82% of the cases on ITT and PP analysis. Other investigators^{19,20} have found that RBC + 2 antimicrobials given for 14 days after failed Maastricht triple therapy led to eradication rates of 62% to 86%. In another study,¹⁸ the pooled eradication rate of second-line RBC-based triple therapies was 80.2%. In our study, the RBC-MC regimen given after failed PAC treatment led to eradication rates of 60.3% and 66.1% based on ITT and PP analyses, respectively; these rates were ~20% less than that obtained with first-line treatment of the same population (78.7% and 90.5% for ITT and PP analyses, respectively).¹⁶

There have been fewer studies of a third method of second-line treatment, which involves giving PPI-based triple regimens after failure of first-line RBC-based therapies. The rationale of our choice was to achieve a more profound suppression of the acid secretion and to substitute the imidazole component of the first-line regimen with amoxicillin. The prevalence of primary metronidazole resistance in Hungary is 38.0%, and 3.9% and 1.0% of the population is resistant to clarithromycin and amoxicillin, respectively.¹⁴ In our study, PAC eradicated the infection in 65.2% and 68.3% of patients in the ITT and PP analyses, respectively; these rates also were ~20% less than that found with first-line treatment (80.8% and 88.3% for ITT and PP analyses, respectively).¹⁶

Finally, according to the Maastricht Consensus, quadruple therapies are the regimens of choice after the failure of the triple treatment.³ Although quadruple therapies have proved to be efficacious in >85% to 90% of patients as first-line therapies,¹⁵ they entail poorer compliance and an increased incidence of AEs compared with triple therapies. A meta-analysis¹⁸ of 30 studies involving 669 patients found a pooled eradication rate of 75.8% with quadruple therapy used as second-line treatment, whereas the eradication rates using quadruple therapies as first-line treatment with the same regimens were well over 90%.

The prevalence of treatment failure is increasing worldwide as more patients are treated for *H. pylori* infection. The second-line regimens used in the present study were less efficacious than the first-line treatments used in the same population, a finding that is in agreement with other studies.¹⁸ An eradication rate of 80% in the ITT population is generally accepted as the lower limit for

regimens used in clinical practice.³ However, no such cutoff value has been proposed for second-line therapy. Antibiotic resistance has repeatedly proved to be the primary cause of first-line treatment failure.^{24,25} Antibiotic susceptibility testing is available in only some centers in Hungary. The Hungarian consensus¹⁴ recommends that antimicrobial susceptibility testing be used only after the failure of the second-line therapy; this recommendation is in opposition to the European statement, which recommends this testing after the failure of first-line treatment.³ High rates of nitroimidazole/macrolide resistance could at least in part explain the failure rates after second-line treatment found in the present study. A longer duration (10–14 days) of the given regimens would probably be of more benefit.

Following second-line therapy, 20% to 40% of patients need third-line eradication or rescue therapy.^{15,26,27} Third-line therapy is particularly reserved for patients in whom eradication is strongly recommended, such as in patients with duodenal ulcer.^{2,3,14} There is considerable debate about which are the best rescue regimens. The results of papers assessing failures of first- and second-line therapies are difficult to analyze because of the small number of patients included (5–30/group),¹⁵ unknown circumstances, and the variability of dose and duration of first-line treatments. The utility of antibiotic susceptibility testing is controversial, and the susceptibility of *H pylori* in vitro often differs from the susceptibility in vivo, and even in susceptible cases, eradication rates do not reach 100%.¹⁵ In the patients in the present study, high rates of metronidazole and clarithromycin resistance were observed (57.1% and 35.7%, respectively), and we do not know whether this was primary or secondary because pretreatment cultures were not performed. The *H pylori* cultures had a low diagnostic yield and were of limited practical utility. Therefore, we chose non-imidazole, nonmacrolide quadruple regimens that included amoxicillin, tetracycline, and either nitrofurantoin or bismuth subsalicylate. Nitrofurantoin has fairly good antibiotic activity, even in metronidazole-resistant cases.^{28–31} The eradication rates obtained with our quadruple therapies are in agreement with some studies,^{15,26} whereas much higher rates were obtained in other studies.^{23,32} Although no patients resistant to amoxicillin, tetracycline, and nitrofurantoin were encountered, the reason for the lower rates of eradication might be the short treatment regimen (7 days). Regimens of 10 to 14 days instead of 7 days have been proposed as rescue therapies.¹⁵ A multivariate analysis³³ of 2751 patients revealed that a short treatment duration was a risk factor for failure of eradication therapy. In the present study, the cumulative eradication rates in patients with duodenal ulcer after 3 consecutive therapies were 88.6% and 94.2% based on ITT and PP analyses, respectively. All of the regimens were well tolerated, with the incidence of the AEs being comparable to those described in other studies.^{15,19,20,23,26,27} In groups 1A and 2B, the higher incidences of the AEs were probably due to the bismuth component of the regimens.

Selection bias could be a limitation of this study. Assignment of patients to the second-line regimens was done in a crossover manner. Also, in the assign-

ment to third-line regimens, randomization was not standardized; approximately half of the patients were selected based on endoscopy/culture results, whereas the others were treated empirically, based on positive UBT tests.

CONCLUSIONS

In this study of patients with persistent *H pylori* infection and duodenal ulcer, the PAC and RBC-MC regimens used as second-line therapies and the nonmacrolide, nonimidazole third-line regimens were of moderate efficacy in the eradication of persistent *H pylori*. On ITT analysis, no significant differences were detected between the second-line triple and the third-line quadruple regimens. Due to the high rates of resistance, determination of antimicrobial susceptibility of *H pylori* was of little benefit in this study; instead, empiric, nonmacrolide, nonimidazole combinations were preferred. Nevertheless, new agents that are active against the multidrug-resistant strains of *H pylori* must be found.

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REFERENCES

1. Chiba N, Hunt RH. Ulcer disease and *Helicobacter pylori* infection: Etiology and management. In: McDonald JWD, Burroughs AK, Feagan B, eds. *Evidence-Based Gastroenterology and Hepatology*. London: BMJ Books; 1999:66–90.
2. The European *Helicobacter pylori* Study Group. Current European concepts in the management of *Helicobacter pylori* infection. The Maastricht Consensus Report. *Gut*. 1997;41:8–13.
3. Malfertheiner P, Mégraud F, O'Morain CO, et al, for the European *Helicobacter pylori* Study Group. Current concepts in the management of *Helicobacter pylori* infection—The Maastricht 2-2000 Consensus Report. *Aliment Pharmacol Ther*. 2002;16:167–180.
4. Lind T, van Zanten VSJ, Unge P, et al. Eradication of *Helicobacter pylori*: Using one-week triple therapies combining omeprazole with two antimicrobials: The MACH I study. *Helicobacter*. 1996;1:138–144.
5. van Zanten VSJ, Bradette M, Farley A, et al. The DU-MACH study: Eradication of *Helicobacter pylori* and ulcer healing in patients with acute duodenal ulcer using omeprazole-based triple therapy. *Aliment Pharmacol Ther*. 1999;13:289–295.
6. Misiewicz JJ, Harris AW, Bardhan KD, et al, for the Lansoprazole *Helicobacter* Study Group. One week triple therapy for *Helicobacter pylori*: A multicentre comparative study. *Gut*. 1997;41:735–739.
7. Unge P. Antimicrobial treatment of *H. pylori* infection—a pooled efficacy analysis of eradication therapies. *Eur J Surg Suppl*. 1998;86:16–26.

8. Laheij RJ, Rossum LG, Jansen JB, et al. Evaluation of treatment regimens to cure *Helicobacter pylori*—a meta-analysis. *Aliment Pharmacol Ther.* 1999;13:857–864.
9. Gisbert JP, Gonzalez L, Calvet X, et al. Proton pump inhibitor, clarithromycin and either amoxicillin or nitroimidazole: A meta-analysis of eradication of *Helicobacter pylori*. *Aliment Pharmacol Ther.* 2000;14:1319–1328.
10. Leodolter A, Kulig M, Brasch H, et al. A meta-analysis comparing eradication, healing and relapse rates in patients with *Helicobacter pylori*-associated gastric or duodenal ulcer. *Aliment Pharmacol Ther.* 2001;15:1949–1958.
11. Schmid CH, Whiting G, Cory D, et al. Omeprazole plus antibiotics in the eradication of *Helicobacter pylori* infection: A meta-regression analysis of randomized, controlled trials. *Am J Ther.* 1999;6:25–36.
12. Sung JJ, Chan FK, Wu JC, et al. One-week ranitidine bismuth citrate in combinations with metronidazole, amoxicillin and clarithromycin in the treatment of *Helicobacter pylori* infection: The RBC-MACH study. *Aliment Pharmacol Ther.* 1999;13:1079–1084.
13. Gisbert JP, Gonzalez L, Calvet X, et al. *Helicobacter pylori*: Proton pump inhibitor vs. ranitidine bismuth citrate plus two antibiotics for 1 week—a meta-analysis of efficacy. *Aliment Pharmacol Ther.* 2000;14:1141–1150.
14. Rác I, Bajtai A, Lonovics J, Simon L. *Helicobacter pylori* Consensus Report of the *Helicobacter pylori* Working Group of the Hungarian Society of Gastroenterology [in Hungarian]. Budapest, Hungary: Hungarian Society of Gastroenterology–Medicom, 2000;4–95.
15. Gisbert JB, Pajares JM. Review article: *Helicobacter pylori* ‘rescue’ regimen when proton pump inhibitor-based triple therapies fail. *Aliment Pharmacol Ther.* 2002;16:1047–1057.
16. Buzás GM, Illyés G, Székely E, Széles I. Six regimens for the eradication of *Helicobacter pylori* (Hp) in duodenal ulcer patients: Three consecutive trials (1995–1999). *J Physiol (Paris).* 2001;95:437–441.
17. Glupczynski Y. Culture of *Helicobacter pylori* from gastric biopsies and antimicrobial susceptibility testing. In: Lee A, Mégraud F, eds. *Helicobacter pylori: Techniques for Clinical Diagnosis and Basic Research*. London: WB Saunders; 1996:17–33.
18. Hojo M, Miwa H, Nagahara A, Sato N. Pooled analysis on the efficacy of the second-line treatment regimens for *Helicobacter pylori* infection. *Scand J Gastroenterol.* 2001;36:690–700.
19. Zullo A, Hassan C, Campo SM, et al. A triple therapy regimen after failed *Helicobacter pylori* treatments. *Aliment Pharmacol Ther.* 2001;15:1193–1197.
20. Perri F, Villani MR, Quitadamo M, et al. Ranitidine bismuth citrate-based triple therapies after failure of the standard ‘Maastricht triple therapy’: A promising alternative to the quadruple therapy? *Aliment Pharmacol Ther.* 2001;15:1017–1022.
21. Mégraud F, Roberts P, Williamson R. Ranitidine bismuth citrate can help to overcome *Helicobacter pylori* resistance to clarithromycin in vivo. *Helicobacter.* 2000;5:222–226.
22. Van der Wouden EJ, Thijs JC, Zwet AA, et al. The influence of metronidazole resistance on the efficacy of ranitidine bismuth citrate triple therapy regimens for *Helicobacter pylori* infection. *Aliment Pharmacol Ther.* 1999;13:297–302.
23. Gasbarrini A, Ojetti V, Armuzzi A, et al. Efficacy of a multistep strategy for *Helicobacter pylori* eradication. *Aliment Pharmacol Ther.* 2000;14:79–83.
24. Houben MH, van de Beek D, Hensen EF, et al. A systematic review of *Helicobacter pylori* eradication therapy—the impact of antimicrobial resistance on eradication rates. *Aliment Pharmacol Ther.* 1999;13:1047–1055.

25. Dore MP, Leandro G, Realdi G, et al. Effect of pretreatment antibiotic resistance to metronidazole and clarithromycin on outcome of *Helicobacter pylori* therapy: A meta-analytical approach. *Dig Dis Sci*. 2000;45:68–76.
26. Perri F, Festa V, Clemente R, et al. Randomized study of two ‘rescue’ therapies for *Helicobacter pylori*-infected patients after failure of standard triple therapies. *Am J Gastroenterol*. 2001;96:58–62.
27. Boixeda D, Bermejo F, Martin-De-Argila C, et al. Efficacy of quadruple therapy with pantoprazole, bismuth, tetracycline and metronidazole as rescue treatment for *Helicobacter pylori* infection. *Aliment Pharmacol Ther*. 2002;16:1457–1460.
28. Coudron PE, Stratton CW. In-vitro evaluation of nitrofurantoin as an alternative agent of metronidazole in combination antimicrobial therapy against *Helicobacter pylori*. *J Antimicrob Chemother*. 1998;42:657–660.
29. Graham DY, Saeed MA, Hoffman J, et al. Nitrofurantoin quadruple therapy for *Helicobacter pylori* infection: Effect of metronidazole resistance. *Aliment Pharmacol Ther*. 2001;15:513–518.
30. Kwon DH, Lee M, Kim JJ, et al. Furazolidone- and nitrofurantoin-resistant *Helicobacter pylori*: Prevalence and role of genes involved in metronidazole resistance. *Antimicrob Agents Chemother*. 2001;45:306–308.
31. Sisson G, Goodwin A, Raudonikienė A, et al. Enzymes associated with reductive activation and action of nitazoxanide, nitrofurans, and metronidazole in *Helicobacter pylori*. *Antimicrob Agents Chemother*. 2002;46:2116–2123.
32. Gomollón F, Sicilia B, Ducons JA, et al. Third line treatment for *Helicobacter pylori*: A prospective, culture-guided study in peptic ulcer patients. *Aliment Pharmacol Ther*. 2000;14:1335–1338.
33. Broutet N, Tchamgoué S, Pereira E, et al. Risk factors for failure of *Helicobacter pylori* therapy—results of an individual data analysis of 2751 patients. *Aliment Pharmacol Ther*. 2003;17:99–109.

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