Alimentary Pharmacology & Therapeutics

Efficacy and safety of rifabutin-containing 'rescue therapy' for resistant *Helicobacter pylori* infection

T. J. BORODY*†, G. PANG*†, A. R. WETTSTEIN*, R. CLANCY†, K. HERDMAN*, R. SURACE*, R. LLORENTE* & C. NG*

*Centre for Digestive Disease, NSW; †Discipline of Immunology and Microbiology, School of Health Sciences, University of Newcastle, NSW, Australia

Correspondence to:
Dr T. J. Borody, Centre for Digestive Disease, 144, Great North Road, Five Dock, NSW 2046, Australia.
E-mail: tborody@zip.com.au

Publication data
Submitted 27 February 2005
First decision 29 March 2005
Resubmitted 3 December 2005
Accepted 9 December 2005

SUMMARY

Background
Current 'rescue' therapies provide inadequate *Helicobacter pylori* eradication rates because of antibiotic resistance.

Aim
To test the efficacy of a modified triple regimen combining rifabutin, pantoprazole and amoxicillin as rescue therapy for patients in whom eradication of *H. pylori* had failed standard clarithromycin-based triple therapy.

Methods
One hundred and thirty patients (mean age 51.7 ± 14.8 years) who had failed one or more eradication attempts with omeprazole, clarithromycin and amoxicillin were treated for 12 days with rifabutin 150 mg daily, amoxicillin 1 g or 1.5 g t.d.s, and pantoprazole 80 mg t.d.s.

Results
The intention-to-treat and per-protocol eradication rates were 90.8/90.8%. Metronidazole or/and clarithromycin resistance had no significant impact on *H. pylori* eradication rates. A higher overall eradication rate of 96.6% (95% CI: 92.1–101%) was obtained in patients treated with a regimen containing 1.5 g amoxicillin t.d.s compared with 90.7% (95% CI: 82–98.6%) using a regimen with 1 g amoxicillin t.d.s but the difference was not significant. Side-effects reported in 40% of patients were mild.

Conclusion
A 12-day course of low dose of rifabutin with an increased dose of amoxicillin and pantoprazole is well-tolerated and highly effective against dual-resistant *H. pylori* infection after failure of triple therapy.

Aliment Pharmacol Ther **23**, 481–488

doi:10.1111/j.1365-2036.2006.02793.x

INTRODUCTION

Eradication of *Helicobacter pylori* infection is a primary goal in the management of peptic ulcer disease and other *H. pylori*-related complications.[1] Optimal eradication is usually evaluated by analysis of outcomes of two or more consecutive therapies, which include a proton-pump inhibitor (PPI) and two antimicrobial agents. Current recommended treatment regimens using a combination of PPI or ranitidine bismuth citrate (RBC), clarithromycin and either amoxicillin or nitroimidazole achieved eradication rates ranging from 81% to 100%.[2-4] This means up to 20% of patients will fail to eradicate the bacteria and remain *H. pylori*-positive[5] and this value could be higher in clinical practice.[6] As a consequence, patients failing to respond to primary treatment may harbour *H. pylori* strains resistant to key antibiotics used in the first treatment.[7, 8] These patients constitute a significant medical problem which needs an effective 'salvage therapy' to eradicate the infection. However, the choice of a 'salvage therapy' largely depends upon the antibiotics used initially. Therefore, if a clarithromycin-based regimen was used first then a metronidazole-based regimen should follow and vice versa. As clarithromycin-based therapy is used predominantly, this treatment strategy becomes problematical because of a steady rise in resistance to clarithromycin in most countries,[9-11] including Australia.[12] About 20–68% of patients who are not cured with the consecutive treatments will carry antibiotic-resistant bacteria including those resistant to both metronidazole and clarithromycin[6, 7, 13] for which no effective treatment remains. Recently, *H. pylori* has been shown to be highly sensitive *in vitro* to rifabutin, a derivative of rifamycin.[14-16] To date, no resistant *H. pylori* strain has been isolated from patients who have been untreated or treated for *H. pylori* infection.[17] Recent studies including randomized-controlled trials have shown that it is an effective component in a 1 week salvage triple therapy combining rifabutin 300 mg once daily, 20 mg rabeprazole or 20 mg omeprazole or 30 mg lansoprazole or 40 mg pantoprazole b.d. and amoxicillin 1 g b.d. or levofloxacin 500 mg once daily with overall mean eradication rate of 71% in patients who failed at least twice standard eradication therapy.[13, 14, 18, 19] In addition to the high clinical efficacy, the regimen was well tolerated compared with quadruple therapy.[13, 20] Nevertheless, potential adverse reactions characterized by fever and myelotoxicity can occur when higher dose of rifabutin is used, especially combined with macrolides.[18] Attempts to minimize the side-effects by reducing the rifabutin dose from 300 to 150 mg however, resulted in a significant drop in eradication rate from 87% to 67%.[20] Thus, modification of the dosing regimen may be necessary in order to minimize complications and yet to improve efficacy. The aims of this study were: (i) to evaluate the efficacy of a 12-day treatment regimen consisting of halving the dose of rifabutin to 150 mg daily but increasing the dose of amoxicillin to 1 g t.d.s or 1.5 g t.d.s and pantoprazole 80 mg t.d.s in patients who have failed one or more treatment eradications and (ii) to assess the influence of antibiotic resistance on treatment outcome.

METHODS

Patient population

We studied prospectively 130 consecutive patients with 'eradication failure' referred by general practitioners to the Centre for Digestive Diseases (Five Dock, NSW, Australia). Patients were still *H. pylori*-positive on ^{14}C-urea breath test (UBT) after receiving one or more clarithromycin-based eradication treatments. Patients included in the study had not been taking H_2-receptor blockers, bismuth or PPIs in the preceding 4 weeks. Exclusion criteria were as follows: inclusion in current clinical trials, previous gastric surgery, known allergy to study drugs, cardiorespiratory, liver or renal diseases, malignancy, pregnancy or lactation. Post-treatment *H. pylori* status was assessed by ^{14}C-UBT at 4 weeks and eradication was considered successful in the case of a negative test. A full white blood cell count and other clinical laboratory tests were conducted at baseline and then every 4 days following commencement of rifabutin-based treatment. All patients were treated with rifabutin (150 mg once daily), pantoprazole (80 mg t.d.s) and amoxicillin (either 1.0 g t.d.s or 1.5 g t.d.s) for 12 days. Drug tolerability, compliance and clinical laboratory tests were documented by the investigators during and after treatment.

Upper endoscopy and biopsy

During endoscopy, four biopsy specimens were taken from the antrum and one each from the distal body, the proximal body and the fundus of the stomach. Four biopsy specimens (one each from the antrum, the

distal body, the proximal body and the fundus) were used for *H. pylori* culture and the remaining were used for histology, and rapid urease CLO test. Antral and body biopsy tissues were collected into Amies transport medium plus Charcoal (Amyl Media, Sydney, Australia) and transported on ice to the Australian National *Helicobacter pylori* Reference Laboratory for culture within 24 h. Biopsy tissues for histological examination were fixed in 10% phosphate-buffered formalin solution and processed routinely. Paraffin sections (4 μm thick) were stained with haematoxylin and eosin, and with May Grunwald-Giemsa stain. All sections were examined for bacteria and gastritis by pathologists who were blind to all clinical information. *H. pylori* infection was defined as two of the three positive tests (rapid urease test, histology and culture).

Culture and antibiotic sensitivity test

The susceptibility pattern of each isolate was determined using the E-test (AB Biodisc, Solna, Sweden) for metronidazole, clarithromycin, amoxicillin, tetracycline and rifabutin. An inoculum from the bacteria suspension was spread onto the dry surface of Iosensitest agar (Oxoid, Sydney, Australia) supplemented with 5% horse blood using a cotton swab. E-test strips for each of metronidazole, clarithromycin, amoxicillin, tetracycline and rifabutin were applied to individual plates. All plates were then incubated at 37 °C for 3 days under microaerobic conditions. The minimal inhibitory concentration (MIC) was defined as the lowest concentration of antimicrobial agent that completely inhibited any visible growth. Resistance breakpoints were set at >8 mg/L for metronidazole, ≥1 mg/L for clarithromycin, >4 mg/L for amoxicillin, ≥1 mg/L for tetracycline and ≥0.002 mg/L for rifabutin. *H. pylori* ATCC 43504, *H. pylori* ATCC 43579 and *Bacteroides fragilis* ATCC 25285 organisms were used a quality control for the E-test strips. The sensitivity and specificity of the E-test were 100% and 89.1%, respectively.

^{14}C-urea breath test

Patients who had not taken antibiotics or antisecretory drugs, were fasted for 6 h before performing the UBT test (Pytest, Tri Med, Western Australia). The gelatine capsule containing ^{14}C-urea was swallowed whole with water by the patient in order to avoid contamination with oral bacteria. Breath samples were taken 10 min after ingestion. The ^{14}C-isotope enriched in the breath was measured in a liquid scintillation counter (Ballard Medical Products, Draper UT, USA). The result was considered positive if the ^{14}C-UBT count was >200 dpm. The sensitivity and specificity of UBT, evaluated using histology as the gold standard, were 98% and 94%, respectively.

Statistical analysis

For analysis of eradication rate, an intention-to-treat (ITT) analysis was performed to include all patients entered in the study regardless of compliance with the study protocol (patients with non-evaluable data were considered to fail eradication) and on a 'per-protocol' basis (excluded patients who defaulted). The variables shown were mean and standard deviation, percentage and 95% confidence interval. Categorical variables were compared using the Fisher's exact test.

RESULTS

Clinical and patient characteristics

A total of 130 patients have been included in the study (mean age, 51.7 years; range: 20–80; Table 1). There were 62 males (mean age, 51.8 years; range: 20–80) and 68 females (mean age, 51.7 years; range: 23–76). Of the total number of patients, 63 (48.5%; 35 males, 28 females) patients had previously failed to respond to one course of clarithromycin-based eradication treatment and 67 (51.5%; 27 males and 40 females) patients had failed to respond to two or more courses (mean 3.2). There were significantly more females than males with multiple eradication failures ($P < 0.03$; 95% CI: 0.024–0.36). The majority of patients had non-ulcer dyspepsia (74 of 130, 56.1%). Fifty-two patients (40%) had reflux oesophagitis and four (3%) had duodenal ulcer. One patient was lost to follow-up after therapy due to pregnancy and was included in the ITT analysis. There was no difference in age between the different disease categories and the number of failed eradications and gender.

Antibiotic resistance in patients with failed eradication

Helicobacter pylori was cultured from 115 patients (88.5%) previously treated with standard clarithromycin-

Table 1. Clinical and demographic variables of patients failing to eradicate *H. pylori* infection

Number of patients (intention-to-treat)	Gender (M/F)	Age (M/F; years)	Diagnosis	Previous failed eradication (mean)
63	35/28	50.3 ± 13.9/50.6 ± 13.2	38 NUD; 25 oesophagitis	1
67	27/40	52.2 ± 15.4/53.9 ± 11.7	4 DU; 36 NUD; 27 oesophagitis	3.2
130 (total)	62/68	51.8 ± 14.8/51.7 ± 12.5	4 DU; 74 NUD; 52 oesophagitis	2.3

NUD, non-ulcer dyspepsia; DU, duodenal ulcer.

Table 2. Antibiotic sensitivity and *H. pylori* eradication rates

Previous failed eradication treatment (mean)	MetS ClaS, *n* (%)	MetR ClaS, *n* (%)	MetS ClaR, *n* (%)	MetR ClaR, *n* (%)	Total ITT eradication rate, *n* (%)
1.0 ($n = 63$, positive culture = 52)	5/52 (9.6)	8/52 (15.3)	11/52 (21.2)	28/52 (53.8)	58/63 (92.1)
3.2 (range: 2–6; $n = 67$, positive culture = 63)	2/63 (3.2)	14/63 (22.2)*	12/63 (19.4)	35/63 (55.6)	60/67 (89.6)
2.3 (range 1–6; total: $n = 130$, positive culture = 115)	7/97 (7.2)	22/115 (19.1)	23/115 (20)	63/115 (54.8)	118/130 (90.8)

* One patient lost to follow-up.
MetS, metronidazole-sensitive; MetR, metronidazole-resistant; ClaS, clarithormcyin-sensitive; ClaR, clarithromycin-resistant.

based triple therapy (Table 2). In the remaining 15 patients, *H. pylori* primary cultures for antibiotic sensitivity testing were unsuccessful. For patients who had failed one course of clarithromycin-based therapy, resistance to metronidazole was found in eight patients (15.3%) and resistance to clarithromycin in 11 patients (21.1%). Double resistance to metronidazole and clarithromycin was found in 28 patients (53.8%). In patients with multiple eradication failures (2–6, mean: 3.2), the metronidazole resistance rate was 22.1% and the clarithromycin resistance rate was 19.4%. The double resistance rate to metronidazole and clarithromycin was 55.6%. No difference in resistance to metronidazole or/and clarithromycin between patients failing initial eradication and those with multiple eradication failures was found. The overall resistance rates for metronidazole and clarithromycin were 19.1% and 20%, respectively and the double resistance rate was 54.8%. No resistant strains to amoxicillin, tetracycline or rifabutin were found.

By ITT analysis at 4 weeks, *H. pylori* eradication rates for patients who failed one eradication treatment and those with multiple failures were 92.1% and 89.6%. The overall per-protocol and ITT eradication rates for the study population were similar, being 90.8% (118 of 130; 95% CI: 85.9–95.7).

Impact of antibiotic resistance on eradication of H. pylori infection

Table 3 shows the ITT analysis of rifabutin-based therapy with respect to metronidazole and clarithromycin sensitivity data in 106 (92.2%) patients who failed one or more clarithormycin-based eradication treatments. A high *H. pylori* eradication rate was achieved despite the presence of metronidazole and clarithromycin resistance. The overall eradication rate was 92.3% for patients who failed initial eradication treatment and 92.1% for patients who failed two or more eradication treatments (mean: 3.2). For patients harbouring double resistant strains to metronidazole and clarithromycin, the eradication rate for the once failed eradication group was 92.3% and 95.7% for the multiple failed eradication group.

Table 3. Impact of antibiotic sensitivity on intention-to-treat *H. pylori* eradication rates

	Eradication rate, *n* (%)					
	One previous failed eradication treatment			Multiple previous failed eradication treatments		
	MetS	MetR	Total	MetS	MetR	Total
ClaS	5/5 (100)	7/8 (87.5)	12/13 (92.3)	2/2 (100)	11/14 (78.6)*	13/16 (81.3)
ClaR	10/11 (90.9)	26/28 (92.9)	36/39 (92.3)	12/12 (100)	33/35 (94.3)	45/47 (95.7)
Total	15/16 (93.8)	33/36 (91.7)	48/52 (92.3)	14/14 (100)	44/49 (89.8)	58/63 (92.1)

* One patient lost to follow-up.
MetS, metronidazole-sensitive; MetR, metronidazole-resistant; ClaS, Clarithromycin-sensitive; ClaR, clarithromycin-resistant.

Table 4. Effect of increased dose of amoxicillin on eradication rate

Isolate (phenotype)	*RPA_3 Included	*RPA_3 Eradicated, *n* (%)	*$RPA_{4.5}$ Included	*$RPA_{4.5}$ Eradicated, *n* (%)
MetS ClaS	2	2/2 (100)	4	4/4 (100)
MetR ClaS	11	11/11 (100)	11	11/11 (100)
MetS ClaR	11	11/11 (100)	12	12/12 (100)
MetR ClaR	30	25/30 (83.3)	33	31/33 (93.9)
95% CI ITT analysis	54	90.7 (82–98.6)†	60	96.6 (92–101)†

* Rifabutin-based regimen containing 1 g or 1.5 g amoxicillin.
† 95% CI; not significant ($P < 0.25$).
RPA_3, rifabutin therapy with 1.0 g amoxicillin (t.d.s); $RPA_{4.5}$, rifabutin therapy with 1.5 g amoxicillin (t.d.s); MetS, metronidazole-sensitive; MetR, metronidazole resistance; ClaR, clarithromycin resistance; ClaS, clarithromycin-sensitive.

Effect of amoxicillin on *H. pylori* eradication rate

Of the 129 patients treated with rifabutin triple therapy and for whom cultures were available for analysis, 54 (41.8%) received a treatment regimen with amoxicillin 1 g thrice daily (RPA_3 group) and 60 (46.5%) received a regimen with amoxicillin 1.5 g thrice daily ($RPA_{4.5}$ group) for 12 days. The ITT *H. pylori* eradication rate was 90.7% in the RPA_3 group and 96.6% in the $RPA_{4.5}$ group (Table 4). Although both treatment regimens achieved a high eradication rate, the $RPA_{4.5}$ regimen was more effective than the RPA_3 regimen in eradicating metronidazole- and clarithromycin-resistant strains but the difference, however, was not significant ($P = 0.25$).

Side-effects

Adverse events were noted in 52 patients (40%) with one lost to follow-up because of pregnancy in the multiple failed eradication group (Table 5). None of the patients developed neutropenia or thrombocytopenia within the 12 days of treatment or stopped therapy due to side-effects.

DISCUSSION

The current first-line standard triple therapy combining clarithromycin and amoxicillin fails in a significant proportion of patients, with a mean eradication rate of about 71% in clinical trials.[21–23] In patients who failed initial treatment, a high proportion of *H. pylori* strains

Table 5. Side-effects

	Number of patients reporting (%)
Nausea	5 (3.8)
Abdominal pain	5 (3.8)
Diarrhoea	8 (6.2)
Flu-like symptoms	4 (3.1)
Skin rash	4 (3.1)
Thrush (oral, vaginal)	5 (3.8)
Dizziness	4 (3.1)
Headaches	5 (3.8)
Lethargy	5 (3.8)
Others	7 (5.4)
Total patients (%)	52 (40)

developed resistance to metronidazole and/or clarithromycin.[6, 7] Re-treatment with a second-line therapy in patients receiving clarithromycin has limited effect on clarithromycin-resistant strains, especially those with double resistance.[24] Several salvage therapies have been recommended including a quadruple combination of PPI, bismuth, tetracycline and metronidazole but they still fail to eradicate the bacterium in 5–43% of the cases,[25–30] not to mention the complicated dosing schedule and poor compliance due to side-effects in the majority of cases. Consequently, patients who do not eradicate the infection harbour antibiotic-resistant strains that are ineradicable after several courses of treatments.[16] In the present study, a novel rifabutin-based triple therapy was found to be highly effective and reliable as an alternative 'rescue therapy' for the treatment of *H. pylori* infection after one or more failed eradication treatments. The overall *H. pylori* eradication rate was 90.9% by ITT analysis. Furthermore, the treatment regimen was highly effective against metronidazole- and clarithromycin-resistant *H. pylori* strains, especially those with double resistance in patients who failed one (eradication rate of 92.3%) or more eradication treatments (eradication rate of 94.3%).

Several studies have shown that rifabutin, 300 mg daily, in combination with PPI and amoxicillin for 1 week achieves an ITT eradication rate ranging from 38% to 71% after failure of standard triple therapy.[15, 16, 31] In a recent study in Hong Kong, a combination of rifabutin 300 mg once daily with levofloxacin achieved an ITT eradication rate of 91%.[13] In a randomized-controlled trial of rifabutin-based therapy, reducing the dosage of rifabutin from 300 to 150 mg once daily for 10 days resulted in an ITT eradication rate falling from 87% to 67%,[20] indicating that the success rate of the rifabutin-based triple therapy is determined by the dosage of rifabutin used. Our present open single centre study showed for the first time that, 12 days of half the dose of rifabutin (150 mg daily) in combination with increasing frequency of dosing with amoxicillin (1 g thrice daily) and pantoprazole (80 mg thrice daily) achieved an ITT eradication rate of 90.7% in patients after failure of one or more courses of previous standard *H. pylori* eradication therapy. By increasing the dosage of amoxicillin to 1.5 g thrice daily for 12 days, an excellent overall eradication rate of 96.6% can be achieved. Furthermore, the regimen was highly effective for patients carrying double resistance. In the randomized-controlled study, the regimen combining half the dose of rifabutin (150 mg daily) plus pantoprazole (40 mg twice daily) and amoxicillin (1 g twice daily) was less effective in the presence of metronidazole- and clarithromycin-resistant strains as well as sensitive strains.[20] Thus, our data suggest that frequent dosing of a high-dose amoxicillin (1–1.5 g thrice daily) and a double dose PPI (80 mg thrice daily) in the presence of low-dose rifabutin (150 mg daily) are critical in driving the efficacy of rifabutin-based triple therapy. Furthermore, an excellent eradication rate (>90%) was achieved without performing culture after failure of eradication treatment, suggesting that the treatment regimen is considered highly effective as a rescue therapy when compared with high-dose (300 mg) rifabutin triple therapies and quadruple therapy.[13, 20]

In the present study, there were significantly more females than males who have failed more than one previous clarithromycin-based eradication treatments (59.7% vs. 40.4%, $P < 0.03$). This may be due to the fact that females are likely to have had previous exposure to antibiotics for urological and gynaecological problems. The proportion of patients with side-effects was 40% but in general the rifabutin-based treatment regimen was well tolerated and no side-effects were considered serious. Unlike regimes which use higher doses of rifabutin, no patients developed drug-related neutropenia or thrombocytopenia after treatment. Nevertheless, the widespread use of rifabutin may still be a major concern due to the possible development of antibiotic resistance. The treatment regimen in this study using a reduced dose of rifabutin combined with higher doses of amoxicillin and PPI for 12 days

resulted in excellent eradication rates and would minimize the development of rifabutin resistance. This novel 'rescue therapy' is highly effective especially for increasing number of patients carrying clarithromycin resistance and failing primary *H. pylori* eradication therapy.

ACKNOWLEDGEMENT

This study was funded by a grant from The Centre for Digestive Diseases.

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