

Low- versus high-dose azithromycin triple therapy for *Helicobacter pylori* infection

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Accepted for publication 17 July 1998

SUMMARY

Background: We report a clinical trial which evaluated the effectiveness of triple therapy containing low- and high-dose azithromycin to treat *Helicobacter pylori* infection.

Methods: From March 1997 to March 1998, patients infected with *H. pylori* were assigned to receive either: Treatment 1: ranitidine bismuth citrate (RBC) (400 mg b.d.) and amoxicillin (1 g b.d.) for 10 days with azithromycin 500 mg o.m. for 3 days; or Treatment 2: RBC and amoxicillin for 10 days with azithromycin 1 g o.m. for 3 days. *H. pylori* eradication was established by a urea breath test at least 4 weeks after

therapy. Side-effects and compliance were assessed using a diary.

Results: Sixty-eight patients were enrolled. Fifty-seven per cent of patients were treated for active peptic ulcer disease or a history of peptic ulcer disease. Treatment 1 cured *H. pylori* in 44% and 44% by per protocol and intention-to-treat analysis, respectively. The corresponding eradication rates for Treatment 2 were 79% and 75%. Two patients taking Treatment 2 dropped out of the study because of side-effects.

Conclusions: With RBC and amoxicillin for 10 days, azithromycin at a dose of 1 g/day for 3 days was significantly better at curing *H. pylori* infection than azithromycin 500 mg/day for 3 days.

INTRODUCTION

Helicobacter pylori is an important cause of peptic ulcer disease and has been linked to the pathogenesis of gastric malignancy.¹ In the USA the currently FDA-approved regimens for *H. pylori* infection consist of two to four drugs given for 2–4 weeks. Eradication rates given in the medical literature for these therapies have varied considerably but it is apparent that regimens containing two antibiotics are more effective than those containing only one.² Although European studies suggest otherwise,^{3, 4} it appears that treatment should be given for more than 7 days in the USA.^{1, 5} With

these thoughts in mind, the search for simple, well-tolerated therapies for *H. pylori* continues.

Currently, the macrolide antibiotic clarithromycin provides the backbone for several therapeutic regimens for *H. pylori*. The azilide antibiotic, azithromycin, is a potentially attractive therapeutic agent for *H. pylori* given its excellent mean inhibitory concentration for this organism⁶ and long biological half-life.⁷ However, results from the available published trials utilizing azithromycin have yielded conflicting results.^{8–13}

We evaluated two regimens containing low- and high-dose azithromycin given for 3 days in combination with ranitidine bismuth citrate (RBC) and amoxicillin for 10 days to eradicate *H. pylori* infection. We also assessed the frequency and severity of side-effects associated with each regimen.

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MATERIALS AND METHODS

Patient population

Patients with documented *H. pylori* infection were recruited from the outpatient gastroenterology clinics and Medical Procedures Unit of the University of Michigan Medical Center between 1 March 1997 and 31 March 1998. The study goal was to enter 50 patients into each treatment arm to yield confidence intervals of 20% for each therapy. It was believed that the treatments could be considered clinically different only if this magnitude of efficacy difference was obtained by the regimens. The study was approved by the University of Michigan Institutional Review Board for human investigation.

Study design

Patients were eligible for enrolment if *H. pylori* infection was confirmed by histology (haematoxylin and eosin staining in all cases, with silver stains reserved to resolve cases where chronic gastritis but no organisms were identified), rapid urease test (CLO-test, Tri-Med Specialties or Pyloritek, Serim Research) or ¹⁴C-urea breath test (UBT) (PyTest, Tri-Med Specialties). With the exception of two patients found to be infected on the basis of UBT alone, *H. pylori* infection was confirmed in all cases with either rapid urease test and/or histology. The patient's personal physician determined the appropriateness of *H. pylori* therapy. To be eligible for this study, patients had either active peptic ulcer disease (PUD), a history of PUD, or non-ulcer dyspepsia. Asymptomatic infected patients were not eligible. In addition, patients who had received previous therapy for *H. pylori* were not eligible for enrolment.

Eight gastroenterologists from the University of Michigan participated in the study. Four of the physicians were assigned to treat *H. pylori* with RBC (Tritec, GlaxoWellcome) 400 mg b.d., amoxicillin (Biocraft Laboratories) 1 g b.d. with food for 10 days and azithromycin (Zithromax, Pfizer Labs) 500 mg before breakfast for 3 days (Treatment 1). The other four physicians were assigned to use RBC 400 mg b.d., amoxicillin 1000 mg b.d. with food for 10 days and azithromycin 1000 mg before breakfast for 3 days (Treatment 2). After 6 months, physicians changed over to treat patients with the alternative regimen.

Compliance and the frequency of side-effects were assessed using a diary which the patient completed during treatment. For purposes of the per protocol analysis, medical compliance was defined as the patient taking all of the study medications. Side-effects were rated using a scale of 0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = intolerable. Side-effects present for more than 3 out of 7 days and rated as at least moderate in severity were considered significant.

H. pylori eradication was assessed no earlier than 4 weeks after the completion of therapy using the ¹⁴C-urea breath test.

Statistical analysis

Differences in age, sex distribution and indication for *H. pylori* therapy between the two treatment groups were compared using the Student's *t*-test. A *P*-value of less than 0.05 was considered significant.

We calculated the per protocol and intention-to-treat eradication rates and 95% confidence intervals for Treatments 1 and 2. For the per protocol analysis, only patients who took all of their medications for the prescribed duration of therapy were evaluated. For the intention-to-treat analysis, all patients, including those non-compliant or those who did not complete the full course of therapy, were included.

A statistically significant difference between the effectiveness of the two treatment strategies was defined as no overlap between their respective 95% confidence intervals. We compared eradication rates yielded by the two treatment regimens using the chi-squared test. A statistically significant difference between therapies was defined as a *P*-value of less than 0.05.

RESULTS

Although the study goal was to enter 50 patients into each treatment arm to yield confidence intervals of 20% for each therapy, we performed an interim analysis after 13 months because of the striking difference in eradication rates yielded by the two therapies. When this interim analysis revealed a statistically significant difference between the therapies, we felt compelled to discontinue the trial for ethical reasons. A total of 68 patients (32 on Treatment 1 and 36 on Treatment 2) were enrolled into the study. The two treatment groups were similar in age, percentage of those who smoked, and indication for *H. pylori* therapy (Table 1).

Table 1. Treatment group demographics: age, sex and indication for *H. pylori* therapy were not significantly different between treatment groups ($P > 0.05$)

	Treatment 1	Treatment 2
Number	32	36
Mean age (range)	58 ± 3 (23–84)	56 ± 3 (31–85)
% females	59%	50%
Indications for therapy (%)		
PUD	59%	56%
NUD	41%	44%

Mean age is expressed in years ± standard error.

PUD, active or a documented history of peptic ulcer disease; NUD, non-ulcer dyspepsia.

Twenty-seven patients who received Treatment 1 were compliant with the protocol. Five patients in this group did not take all of the assigned medications. For Treatment 2, 29 patients took all of the assigned medications and five were not fully compliant with therapy. Two patients taking Treatment 2 had to drop out of the protocol due to intolerable side-effects. Neither of these patients turned in a diary or underwent a follow-up urea breath test. These patients were considered treatment failures in the intention-to-treat analysis for Treatment 2.

H. pylori eradication

Treatment 1, which utilized low dose azithromycin, eradicated *H. pylori* infection in 12/27 (44%) patients by per protocol analysis. By an intention-to-treat analysis, Treatment 1 eradicated *H. pylori* infection in 14/32 (44%) patients (Table 2).

Using a per protocol analysis, Treatment 2, which utilized high dose azithromycin, eradicated *H. pylori*

Table 2. Per protocol (PP) and intention-to-treat (ITT) eradication rates (% and 95% confidence intervals) for Treatment 1 (RBC 400 mg b.d. and amoxicillin 1000 mg b.d. × 10 days with azithromycin 500 mg × 3 days) and Treatment 2 (RBC 400 mg b.d. and amoxicillin 1000 mg b.d. × 10 days with azithromycin 1000 mg × 3 days)

	PP	ITT
Treatment 1	12/27 (44%) (25–63%)	14/32 (44%) (27–61%)
Treatment 2	23/29 (79%) (64–93%)	27/36 (75%) (61–89%)
Significance	< 0.05	< 0.02

infection in 23/29 patients (79%). On an intention-to-treat basis, Treatment 2 led to *H. pylori* eradication in 27/36 (75%) patients (Table 2).

Using the chi-squared test, we found that the per protocol ($P < 0.05$) and intention-to-treat ($P < 0.02$) eradication rates achieved with Treatment 2 proved superior to Treatment 1.

Side-effects

Twenty-five out of 32 (78%) patients who completed Treatment 1 and 26/34 (76%) patients who completed Treatment 2 returned their diaries. Those who did not return their diary as instructed at enrolment completed a diary at the follow-up urea breath test. Two patients enrolled in Treatment 2 were not able to complete the study because of intolerable side-effects (diarrhoea in one and abdominal pain in the other). Minor, transient side-effects were common with both therapies: 84% taking Treatment 1 and 88% taking Treatment 2 reported at least one side-effect.

We considered side-effects present for > 3 out of 10 days and rated as at least moderate in severity to be significant. Thirty-six per cent of those receiving Treatment 1 reported at least one significant side-effect. The most common significant side-effects observed with Treatment 1 were black stool (24%) and loose stools (16%). With Treatment 2, 50% of patients experienced at least one significant side-effect. The most common significant side-effects associated with Treatment 2 were black stool (27%) and loose stools (23%).

DISCUSSION

Triple therapy, consisting of a proton pump inhibitor and two antibiotics, is currently felt to provide the most effective means of eradicating *H. pylori* infection.^{1–3} The antibiotics most commonly used in triple therapy include clarithromycin, amoxicillin and metronidazole.^{1–3} Recently, it has been shown that RBC can be substituted for a proton pump inhibitor without a loss in effectiveness.¹⁴ It also appears that at least 10 days of therapy are necessary to achieve eradication rates of greater than 90% in the USA.^{5, 15}

The azilide antibiotic, azithromycin, is acid stable and has very good *in vitro* activity against *H. pylori* with a mean inhibitory concentration (MIC) of 0.25 mg/L and a mean bactericidal concentration (MBC) of 0.5 mg/L.⁶ Absorption of the drug after oral administration is greatly reduced when given with food. In addition,

following oral administration, azithromycin is widely distributed throughout the body and achieves greater concentrations in the tissue than in plasma.^{6, 7} This accounts for the long biological half-life of azithromycin, which is measured in days rather than hours.^{6, 7} In theory, the long half-life of this drug could allow shorter dosing duration, which in turn could improve patient compliance and reduce the overall cost of therapy.

The role of azithromycin in the treatment of patients infected with *H. pylori* has not been clearly defined. At the time of this manuscript's preparation, a literature search uncovered six full manuscripts which reported the effectiveness of therapies containing azithromycin for *H. pylori* infection.⁸⁻¹³ All of the available studies have utilized different treatment regimens and reported eradication rates have varied considerably. Five of the six trials were from Europe⁸⁻¹² and four were from Italy.⁹⁻¹² There has been only one published trial from the USA.¹³ The dosing schedule for

azithromycin in these studies was 500 mg/day for 3-14 days. One study did evaluate azithromycin at a dosage of 750 mg/day for 14 days in a small number of patients.¹³ This study found that the regimen containing 750 mg/day for 14 days was superior to that containing azithromycin 500 mg/day for 14 days. Side-effects were more frequent with the higher dosage of azithromycin. A summary of the available literature is given in Table 3.

The main finding of our study is that azithromycin given at a dose of 1 g/day for 3 days combined with RBC and amoxicillin for 10 days was associated with a significantly greater rate of *H. pylori* eradication than with a dose of 500 mg/day. Both therapies were relatively well tolerated. There did appear to be a trend toward more frequent side-effects in the group which received high-dose azithromycin, although this did not achieve statistical significance. Two patients in the high-dose azithromycin treatment arm did experience side-effects

Table 3. Published trials evaluating therapies containing azithromycin for *H. pylori* infection

Study	Regimen	# points	ITT (%)	PP (%)	Country
Vcev <i>et al.</i> ⁸	O 20 mg × 28 days Az 500 mg × 5 days M 1500 mg × 5 days	25	NA	18 (72%)	Serbo-Croatia
	O 20 mg × 28 days Az 500 mg × 5 days	25	NA	16 (64%)	
Caselli <i>et al.</i> ⁹	L 30 mg × 7 days Az 500 mg × 3 days M 500 mg × 3 days	60	NA	56 (93.3%)	Italy
	L 30 mg × 7 days A 2000 mg × 7 days Az 500 mg × 3 days	33	NA	20 (61%)	
Bertoni <i>et al.</i> ¹¹	O 400 mg × 14 days A 2000 mg × 14 days Az 500 mg × 3 days	51	44 (86.3%)	48 (91.6%)	Italy
	O 40 mg × 14 days M 1000 mg × 7 days Az 500 mg × 3 days	69	47 (68%)	47/65 (72%)	
Di Mario <i>et al.</i> ¹²	BS 960 × 14 days M 1000 mg × 7 days Az 500 mg × 3 days	63	33 (52%)	33/56 (59%)	Italy
	T 2000 mg × 14 days BS 960 mg × 14 days Az 500 mg × 14 days	18	5 (28%)	NA	
al-Assi <i>et al.</i> ¹³	T 2000 mg × 14 days BS 960 mg × 14 days Az 500 mg × 14 days	12	10 (83%)	NA	USA
	T 2000 mg × 14 days BS 960 mg × 14 days Az 750 mg × 14 days				

A, amoxicillin; Az, azithromycin; BS, bismuth subsalicylate; L, lansoprazole; M, metronidazole; O, omeprazole; T, tetracycline.

severe enough to prevent successful completion of the protocol.

A recent study by Harrison *et al.*¹⁴ may provide at least a partial explanation for our findings. In this study, 27 patients received a single 500 mg dose of azithromycin prior to surgical intervention for gastric cancer. Azithromycin was found in much greater concentrations in gastric tissue than in either gastric mucus or gastric juice. In fact, the drug achieved gastric tissue concentrations far in excess of the MIC or MBC for *H. pylori* for several days. However, the mean azithromycin concentration in gastric juice was well below the MIC and MBC for *H. pylori*. The mean azithromycin concentration in the gastric mucus, where *H. pylori* typically resides, was 0.44–0.52 g/mL 24–120 h after drug administration. It is noteworthy that the range of azithromycin concentration in the gastric mucus was 0–1.6 g/mL. As such, an unclear number of patients did not achieve an adequate concentration of azithromycin in the gastric mucus to affect *H. pylori*. Despite the results of this small study, we were surprised by the eradication rate of only 44% with Treatment 1 which contained low dose azithromycin. On the basis of European studies, we were hopeful that this dosage of azithromycin would be effective when administered with two other drugs with well established activity against *H. pylori*. Our study suggests that the effectiveness of this triple therapy can be enhanced by using a larger dose of azithromycin. It is reasonable to speculate that the 1 g/day dose may result in a relative increase in gastric mucus concentration of azithromycin and improved cure of *H. pylori* infection. Whether a further increase in *H. pylori* eradication can be achieved by increasing the duration of therapy with azithromycin deserves consideration. The most obvious disadvantages to prolonging the duration of azithromycin therapy would be the resulting increase in the overall cost of therapy and the potential for significant side-effects.

In conclusion, when combined with RBC and amoxicillin, the dosage of azithromycin utilized had a significant effect on the effectiveness of therapy. Further studies evaluating triple therapies containing high-dose azithromycin for more prolonged periods are warranted. However, at the current time, azithromycin cannot be recommended for the routine treatment of *H. pylori*.

ACKNOWLEDGEMENTS

This work was supported by a grant from Pfizer Labs.

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