Rescue therapy using a rifabutin-based regimen is effective for cure of *Helicobacter pylori* infection

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OBJECTIVE: To evaluate the efficacy of rescue therapy using rifabutin, amoxicillin and a proton pump inhibitor (PPI) in the eradication of *Helicobacter pylori* in patients who have failed at least one course of PPI-based triple therapy.

METHODS: The present study was a single-centre case series of 16 consecutive patients who had received at least one course of standard eradication therapy. Pretreatment evaluation included endoscopy with biopsies for histology and culture for *H pylori* infection. Treatment consisted of a one-week regimen containing a PPI twice daily, amoxicillin (A) 1 g twice daily and rifabutin (R) 300 mg once daily (PPI-AR). Post-treatment evaluation consisted of a repeat endoscopy with biopsy for histology and culture, or a validated urea breath test at least four weeks after treatment was completed. Pretreatment antibiotic susceptibility to metronidazole, clarithromycin and A was evaluated using a validated epsilometer test.

RESULTS: Of the 16 patients, four had previously received one course of triple therapy, 10 had received two courses and two had received more than two courses. The overall success rate of PPI-AR was 63% (10 of 16). Resistance to A was 0% (0 of 13), metronidazole 77% (10 of 13), clarithromycin 70% (seven of 10), and both metronidazole and clarithromycin 60% (six of 10). There was no correlation between resistance patterns and cure rate.

CONCLUSIONS: An R-containing regimen such as PPI-AR is a viable option as rescue therapy for *H pylori* infection.

Key Words: *Amoxicillin; Antibiotic resistance; Clarithromycin; Eradication rate;* Helicobacter pylori*; Metronidazole; Proton pump inhibitor; Rifabutin; Treatment*

Une thérapie de rattrapage au moyen d'un régime posologique à base de rifabutine est efficace pour guérir une infection à *Helicobacter pylori*

OBJECTIF : Évaluer l'efficacité d'une thérapie de rattrapage faisant appel à de la rifabutine, de l'amoxicilline et un inhibiteur de la pompe à protons (IPP) pour éradiquer l'*Helicobacter pylori* chez des patients qui n'ont pas réagi à au moins une cure de trithérapie à base d'IPP.

MÉTHODOLOGIE : La présente étude était une série de cas monocentrique auprès de 16 patients consécutifs qui avaient reçu au moins une cure de traitement d'éradication standard. L'évaluation avant le traitement incluait une endoscopie et des biopsies afin de procéder à l'histologie et à la culture de l'infection à *H pylori*. Le traitement se composait d'un régime d'une semaine contenant un IPP deux fois par jour, 1 g d'amoxicilline (A) deux fois par jour et 300 g de rifabutine (R) une fois par jour (IPP-AR). L'évaluation après le traitement était constituée d'une reprise de l'endoscopie et d'une biopsie afin de procéder à l'histologie et à la culture ou d'un test respiratoire à l'urée validé, effectué au moins quatre semaines après la fin du traitement. La susceptibilité au métronidazole, à la clarithromycine et à l'A avant le traitement ont été évaluées au moyen d'un test d'epsilomètre validé.

RÉSULTATS : Des 16 patients, quatre avaient déjà reçu une cure de trithérapie, dix en avaient reçu deux et deux, plus de deux. Le taux de réussite global de l'IPP-AR s'élevait à 63 % (dix cas sur 16). La résistance à l'A correspondait à 0 % (zéro cas sur 13), au métronidazole, de 77 % (dix cas sur 13), à la clarithromycine, de 70 % (sept cas sur dix), et à la fois au métronidazole et à la clarithromycine, de 60 % (six cas sur dix). Il n'y avait pas de corrélation entre les profils de résistance et le taux de guérison.

CONCLUSIONS : Un régime posologique contenant de la R comme l'IPP-AR est un option viable en guise de thérapie de rattrapage de l'infection à *H pylori*.

In North America, the efficacy of current recommended treatment to cure *Helicobacter pylori* infection, which consists of a proton pump inhibitor (PPI), clarithromycin (C), and either amoxicillin (A) or metronidazole (M) given for seven to 10 days, is 76% to 88% (1). A meta-analysis (2) reported a success rate of 84% for PPI-CA and 82% for PPI-CM in Canada. The selection of second-line therapy for patients who failed eradication is based on the initial choice of treatment and may consist of switching the combination of antibiotics (PPI-CA to PPI-CM or vice versa) or using quadruple therapy (PPI, bismuth, M and tetracycline). Second-line quadruple therapy is superior to switching to an alternative PPI-CA or PPI-CM regimen, which has also been shown in Canada (3,4). It would help if the subsequent choice of therapy was guided by antibiotic susceptibility testing of the organism; however, this is not routinely available in most centres. Certainly with multiple treatment failures, there is an increased likelihood of resistance, particularly to M and C (5).

Rifabutin is a rifamycin-S derivative, which is commonly used to treat *Mycobacterium avium* complex in HIV-infected patients (6). Rifabutin has potential utility against *H pylori* because the in vitro sensitivity is high and it does not share resistance to either C or A (7,8). Over the past few years, several studies examining the efficacy of rifabutin with PPI-A to

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cure *H pylori* infection have been published (9-18). To date, no studies on the use of a rifabutin-based regimen in Canada have been reported. Our aim was to describe the Halifax (Nova Scotia) experience with this regimen in terms of eradication rates and to evaluate the potential influence of resistance to antibiotics.

METHODS

The present study was a single-centre case series of 16 consecutive patients seen at the Queen Elizabeth II Health Sciences Centre in Halifax. All patients had undergone at least one course of *H pylori* eradication therapy. All patients were initially evaluated in a clinic visit. The diagnosis of *H pylori* infection was based on the results of endoscopically obtained biopsies. In each patient, three biopsies each were taken from both the antrum and body of the stomach: two for histology and one for culture. Histological specimens were stained with hematoxylin and eosin, and were reviewed by one gastrointestinal pathologist (DM). When the diagnosis of *H pylori* was in doubt, a modified Steiner stain was performed. Each patient was treated with a seven-day course of PPI twice daily, A 1g twice daily and rifabutin 300 mg once daily. Cultures for *H pylori* were performed as previously described (19).

H pylori status was also evaluated with gastric biopsies or a validated urea breath test (20,21) at four and eight weeks after treatment. None of the patients were on other antibiotics or antisecretory drugs for four weeks before post-treatment testing.

Cultures obtained from patients before initiation of rifabutin therapy were assessed for antibiotic resistance to C, M and A using the National Committee for Clinical Laboratory Standards by epsilometer test (E test, AB Biodisk, Sweden) methods (19). Strains were grown on Mueller Hinton blood agar without antibiotics for no more than three subcultures. Each *H pylori* strain was suspended at a density equivalent to MacFarlands #2 in sterile saline. For E testing, an antibiotic-free plate was inoculated with the suspension equivalent to MacFarlands #2 and an E test strip was added to the plate. The plates were incubated under microaerobic conditions using an anaerobic incubator set to 5% oxygen, 10% carbon dioxide and 85% nitrogen at 35°C. Minimum inhibitory concentrations (MICs) were recorded at 72 h. The E test MIC was defined as the point at which the growth intersected the strip. M resistance was defined by growth above 8 µg/mL, C resistance was defined by growth above 1 µg/mL and A resistance was defined by growth above 8 µg/mL. A haze of growth that could not be distinguished from the inoculum was discounted. No systematic antibiotic testing was performed after rifabutin treatment.

Compliance was established during the patient interview at follow-up. A patient was considered to be compliant if more than 90% of their medication was taken. Patients were asked about medication side effects at the follow-up visit; however, responses were not systematically recorded using a checklist.

RESULTS

Data regarding the 16 patients is shown in Table 1. There were 12 women and four men, with a mean age of 46 years (range 29 to 65 years). Four (25%) patients had received one previous course of anti-*H pylori* therapy, 10 (62%) had received two courses, and two (13%) had received three courses. The PPI used in the rifabutin therapy was omeprazole 20 mg twice daily in 12 (75%) patients, lansoprazole 30 mg twice daily in three (19%) patients and pantoprazole 40 mg twice daily in one (6%) patient. One patient was lost to follow-up. In 13 patients, gastroscopy with gastric biopsies was performed and two patients underwent a urea breath test. All patients self-reported that they had been compliant with treatment and took all the medications. This high adherence of 100% was likely related to the fact that all patients were highly motivated to be treated – they received detailed instructions regarding the importance of compliance. There were no serious side effects or discontinuation of treatment.

The overall success rate was 63% (10 of 16). With the exclusion of the patient who was lost to follow-up, the cure rate would have been 67% (10 of 15). Before rifabutin treatment, all patients had received a C-containing regimen, 13 of the 16 patients (81%) had received a previous A-containing regimen, while nine (56%) had received previous therapy that contained M. Cure rates were 67% (eight of 12) for those previously treated with A and 56% (five of nine) for those previously treated with M-containing regimens. Before the start of the rifabutin treatment, *H pylori* culture results were available for 13 patients; in three patients, cultures failed to grow *H pylori* and, consequently, no resistance data were available. Resistance to M was present in 77% (10 of 13) of patients, to C in 70% (seven of 10; in three patients in whom M resistance was documented, C resistance results were not available), combined resistance to both M and C was 60% (six of 10) and none (zero of 13) to A. For A, the MIC range of the 10 isolates tested was between 0.016 µg/mL and 0.064 µg/mL. There were no consistent correlations between the presence of resistance and cure rates; however, the sample sizes used for these comparisons were small. The eradication rate according to pretreatment resistance was as follows: M resistant 50% (five of 10), M sensitive 67% (two of three), C resistant 50% (three of six; one patient with C resistance was lost to follow-up), C sensitive 33% (one of three) and dual resistance to M and C 80% (four of five; one patient with C resistance was lost to follow-up).

DISCUSSION

Several studies (9-18) examining the eradication rate with rifabutin-containing second-line regimens have demonstrated varying eradication rates of between 44% and 91%, with most studies (except the 44% reported by Navarro-Jarabo et al [17]) reporting success rates greater than 70%. The reason for this wide variation in reported cure rates is unknown, including whether it makes a difference to give rifabutin 300 mg once a day or 150 mg twice a day. Compared with other rifabutin studies, the eradication rates in our case series (63%) are somewhat lower. This may be due, in part, to the small sample size. Another contributing factor may be because 75% (12 of 16) of our patients had failed at least two courses of eradication therapy and, therefore, may have harboured *H pylori* strains that were more difficult to eradicate. A recent study (22) documented a cure rate of 72% with the use of rifabutin-based therapy in patients who had undergone between one and nine previous attempts at eradication; however, success rates were lower with increasing numbers of previous therapies.

The in vitro MIC of rifabutin against *H pylori* was 0.008 µg/mL (6,7). This was significantly lower than the values for C, A and

M, which were 0.25 µg/mL, 0.031 µg/mL and 4 µg/mL, respectively (6). Rifabutin is highly lipid soluble, is well absorbed via the oral route and has high penetrance into neutrophils, lymphocytes, macrophages and the central nervous system (6,7). In one in vivo study performed in rats (23), the concentrations of rifabutin in gastric juice were 10 to 17 times higher than in blood, indicating extensive secretion into the stomach. In vitro, rifabutin had an additive bactericidal effect when combined with A or M (6). It is stable over a wide pH range (2 to 8) and is not degraded by gastric acid (6,7). Given the low frequency of its use in the general population, the likelihood of *H pylori* resistance is low.

The reasons for failure with initial or repeated treatment against *H pylori* may include primary or secondary resistance to antibiotics, poor compliance and virulence factors. However, in up to 50% of patients, the reason for treatment failure is unknown (24). The eradication rates in patients who have failed at least one course of therapy have varied between 50% and 80% (3,15,18,25-28).

One report (29) documented the possibility of resistance to rifabutin; however, resistance was largely explained by previous exposure to rifabutin.

There are limitations to rifabutin use, especially given the possibility of myelotoxicity. In one study (30), a case of severe pancytopenia developed on day 6 of treatment that resolved 15 days after rifabutin was discontinued. In another study (31), an increased risk of severe neutropenia was reported in nine of 39 healthy volunteers who participated in a randomized trial addressing possible drug interactions between rifabutin and either C or azithromycin. We did not systematically follow patients for myelotoxicity because we were unaware of these reports. However, no patients in the present study experienced significant side effects.

The value of rifabutin-based triple therapy to treat *H pylori* infection will likely be realized in patients who have failed at least two courses of eradication therapy, including a course of quadruple therapy. However, myelotoxicity is an area of concern. Recently, other rescue therapies have been tested, especially the combination of a PPI, A and levofloxacin (32). The reported success rate for this combination therapy was 80%; however, it should be noted that most studies were conducted in Italy – it is uncertain whether similar results can be obtained elsewhere. In a study comparing rifabutin with levofloxacin PPI-A triple therapy (33), the levofloxacin regimen was superior (81% versus 45%). Five of 20 rifabutin-treated patients developed leukopenia. One study of 103 patients (34) using the combination of esomeprazole, moxifloxacin and rifabutin for seven days achieved a cure rate of 77%. Furthermore, a new form of quadruple therapy, so-called sequential therapy consisting of a PPI twice daily plus A 1 g twice daily given for five days followed by PPI twice daily, C 500 mg twice daily and M 500 mg twice daily, also for five days, has shown a slightly higher success rate than standard PPI-based triple therapy, and has been advocated by some as the new first-line therapy (35,36).

What is the likelihood of curing an antibiotic-resistant patient of *H pylori* infection? Two studies (37,38) have investigated the cumulative success rates of giving patients three or four different treatments. The reported success rates were 99.5% and 98.1%, respectively, but for the latter study (38), the intention to treat result was 89.6%.

TABLE 1
Summary of 16 treated patients

Patient	Age, years	Sex	Endoscopic diagnosis*	Previous treatment†	*Helicobacter pylori* status after treatment
1	49	Female	1	OCA, OCM	Negative
2	43	Female	1, 2, 3	OCA, OCM, OCA	Negative
3	48	Female	4	OCA, LCA	Negative
4	41	Female	4	LAC	Negative
5	51	Male	1	RBC + C	Negative
6	59	Female	4	OCA	Negative
7	49	Female	4	OCM, OBMT	Negative
8	35	Female	2, 3	OCA	Negative
9	58	Female	5	OCM, OBMA	Negative
10	65	Male	2	OCM, OCA	Negative
11	29	Female	2	OCA, PCA	Positive
12	41	Male	4	PCA, LBMT	Positive
13	37	Female	4	BMT, OA, OAC	Positive
14	46	Male	1	LCM, BMT	Positive
15	46	Female	1, 2	OCM, LCA	Positive
16	43	Female	1	RBC+ C, LCA	Unknown

**1 Esophagitis; 2 Gastritis; 3 Duodenitis; 4 Nonulcer dyspepsia. †Amoxicillin (A) 1 g twice daily; Bismuth 525 mg four times a day + metronidazole 250 mg four times a day + tetracycline 500 mg four times a day (BMT); Clarithromycin (C) 500 mg twice daily; Lansoprazole (L) 30 mg twice daily; M 500 mg twice daily; Omeprazole (O) 20 mg twice daily; Pantoprazole (P) 40 mg twice daily; Ranitidine bismuth citrate (RBC) 400 mg twice daily*

CONCLUSION

We have shown that for patients who failed previous anti-*H pylori* treatments, the success rate for a seven-day course of PPI-A-rifabutin was 63%. Whether rifabutin remains a viable option to treat *H pylori* in the future will depend on further studies that must include head-to-head comparison of the various treatment options.

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