EFFECTIVENESS OF RIMACTAZID FOR ERADICATION OF HELICOBACTER PYLORI IN RESISTANT CASES: A RANDOMIZED CONTROLLED CLINICAL STUDY

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Abstract

Background: The global rise in antibiotic resistance to *Helicobacter pylori* has markedly reduced the efficacy of standard eradication regimens. Rifamycin-based treatments constitute optimistic recovery options owing to their low propensity for resistance. Rimactazid (a fixed-dose combination of rifampicin and isoniazid) is broadly accessible and exhibits strong intracellular antibacterial efficacy; however, its clinical application in H. pylori eradication has not been sufficiently studied. We aimed to assess the efficacy and safety of a Rimactazid-based triple therapy for eradication of *H. pylori* infection in cases with documented resistance or at least two previous eradication regimens failure.
Methods: In this prospective randomized controlled trial, individuals with refractory *H. pylori* infection were allocated to receive either Rimactazid-based triple therapy or a rifabutin-based rescue regimen. Eradication was evaluated by the ^{13}C-urea breath test 8 weeks following therapy. Intention-to-treat (ITT) and per-protocol (PP) analyses were used.
Results: Two hundred and twelve cases were randomized (106 per group). Eradication rates were significantly elevated in the Rimactazid group (ITT: 82.1%; PP: 86.7%) compared with the control group (ITT: 68.9%; PP: 73.5%). Adverse events were mild and comparable among groups.
Conclusions: Rimactazid-based triple treatment is a highly effective and well-tolerated rescue regimen for resistant *H. pylori* infections eradication.

Keywords: *Helicobacter pylori*, Antibiotic Resistance, Rifampicin, Isoniazid, Rimactazid, Rescue Therapy

Introduction:

Helicobacter pylori infection continues to be among the most widespread chronic bacterial infections globally, impacting about 4.4 billion individuals worldwide [1]. The bacterium is integral to the pathogenesis of chronic gastritis, peptic ulcer disease, mucosa-associated lymphoid tissue (MALT) lymphoma, and gastric adenocarcinoma [2]. Effective eradication of *H. pylori* significantly decreases ulcer recurrence and diminishes the long-term risk of gastric cancer [3].

For many decades, proton pump inhibitor (PPI)-based triple therapy that includes clarithromycin and either amoxicillin or metronidazole has been regarded as the standard first-line treatment. Nevertheless, eradication rates have gradually decreased, frequently dropping below 70%, primarily as a result of increasing antimicrobial resistance [4]. Current international guidelines recommend against the empirical use of clarithromycin-based regimens in areas where resistance rates surpass 15–20% [5]. Metronidazole and fluoroquinolone resistance rates often surpass 40% in numerous regions, significantly constraining second-line therapeutic options [6, 7].

As a result, an increasing number of patients encounter multiple eradication failures, leading to a growing population with refractory H. pylori infection. In these instances, rifamycin-based treatments, especially regimens containing rifabutin, have attracted interest owing to their low resistance rates (<1%) and absence of cross-resistance with frequently employed antibiotics [8, 9].

Research has shown that rifabutin-based rescue therapies achieve eradication rates between 69% and 79% following multiple treatment failures [9, 10].

Rifampicin, a further derivative of rifamycin, inhibits bacterial DNA-dependent RNA polymerase and has exhibited strong in vitro activity against *H. pylori* [11]. Nevertheless, initial clinical investigations employing rifampicin-based regimens produced variable outcomes, frequently ascribed to inadequate dosing, abbreviated treatment courses, or previous rifamycin exposure [12]. Rimactazid, a fixed-dose formulation of rifampicin and isoniazid, is extensively employed in tuberculosis therapy and provides superior tissue penetration and intracellular efficacy. Although H. pylori does not contain mycolic acids, isoniazid may produce indirect or synergistic antibacterial effects via mechanisms involving oxidative stress [13].

Considering the limited availability and increased cost of rifabutin in numerous regions, investigating alternative rifamycin-based treatment regimens is of significant clinical importance. We aimed to assess the efficacy and safety of a Rimactazid-based triple therapy as a rescue option for resistant *H. pylori* infection.

Patients and Methods:

This prospective randomized controlled clinical study carried out at DM Health care (Medcare & Aster) , Dubai and involved cases with persistent *H. pylori* infection diagnosed by positive ^13C-urea breath test.

An informed written consent was taken from the patient.

Inclusion criteria:

- Age ≥ 18 years
- Persistent *H. pylori* infection identified by positive ^{13}C-urea breath test
- Failure of at least two prior eradication regimens, including a clarithromycin-based and a fluoroquinolone-based therapy

Exclusion criteria:

- Previous rifampicin or isoniazid exposure within 12 months
- Known hypersensitivity to rifamycins or isoniazid
- Baseline ALT or AST > 3× upper limit of normal
- Severe renal impairment (eGFR < 30 mL/min/1.73 m^2)
- Lactation or Pregnancy
- Alcohol abuse or anticipated poor compliance

After randomization, cases were allocated in a 1:1 ratio to one of the following regimens:

Rimactazid Group:

Patients received esomeprazole 40 mg twice every day, amoxicillin 1 g twice every day, and Rimactazid containing rifampicin 300 mg plus isoniazid 150 mg administered twice daily. Treatment duration was 10 consecutive days. Patients were instructed to take rifampicin-containing medication on an empty stomach and were counseled regarding potential drug discoloration effects and gastrointestinal symptoms.

Control Group (Rifabutin-based therapy):

Patients received esomeprazole 40 mg twice every day, amoxicillin 1 g twice every day, and rifabutin 150 mg twice every day for 10 days, consistent with commonly used rescue regimens reported in the literature [9, 10].

Compliance was assessed by pill count and patient interview. Compliance was considered adequate if ≥85% of prescribed doses were taken.

Eradication of *H. pylori* was assessed by ^{13}C-urea breath testing done at least 8 weeks following treatment completion, with proton pump inhibitors discontinued for 2 weeks before testing. Adverse events were recorded throughout treatment and categorized as mild, moderate, or severe.

Sample Size Calculation

Based on previous rescue-therapy studies reporting eradication rates of approximately 70% with rifabutin-based regimens [9, 10], we assumed an expected eradication rate of 80% in the Rimactazid group. With $\alpha = 0.05$ and power = 80%, a minimum of 100 patients per group was required. Allowing a 5% dropout rate, the target enrollment was 212 patients.

Statistical analysis

Statistical analysis was performed by SPSS v26 (IBM Inc., Armonk, NY, USA). Shapiro-Wilks test and histograms were utilized to assess the normality of the distribution of data. Quantitative data were expressed as mean and standard deviation (SD) and were analyzed by unpaired student t-test. Qualitative data were expressed as frequency and percentage (%) and were analyzed by Chi-square test or Fisher's exact test when appropriate. A two tailed P value ≤ 0.05 was regarded statistically significant.

Results:

A total of 238 cases were screened; 212 met eligibility criteria and were randomized (106 per group). Twelve cases were excluded from PP analysis because of loss to follow-up or inadequate compliance.

No significant differences in both groups according to age, sex distribution, underlying clinical presentation (peptic ulcer disease versus non-ulcer dyspepsia), or the mean number of previous eradication failures was found **(Table 1)**.

Table 1: Baseline characteristics of the study population

	Rimactazid (n=106)	**Control (n=106)**	**P value**
Age, years (mean ± SD)	52.4 ± 11.1	52.8 ± 11.6	0.798
Male sex, n (%)	66 (62.3)	65 (61.3)	0.888
Peptic ulcer disease, n (%)	38 (35.8)	41 (38.7)	0.670
Non-ulcer dyspepsia, n (%)	68 (64.2)	65 (61.3)	
Mean previous eradication failures	2.4 ± 0.6	2.3 ± 0.5	0.189

Data presented as mean ± SD or number (%)

Rimactazid-based regimen achieved significantly increased *H. pylori* eradication rates compared with the control regimen in both ITT and PP analyses (p = 0.025 and 0.020 respectively) **(Table 2)**.

Table 2: H. pylori eradication rates

	Rimactazid (n=106)	**Control (n=106)**	**P value**
ITT	87/106 (82.1%)	73/106 (68.9%)	0.025*
PP	85/98 (86.7%)	72/98 (73.5%)	0.020*

Data presented as number (%), ITT: Intention-to-treat, PP: per-protocol, *: significant as P value ≤ 0.05

The overall frequency of adverse events was low and did not differ significantly among groups. Gastrointestinal symptoms, mainly nausea or dyspepsia, were the most commonly reported events and were generally mild. Transient elevations of liver enzymes were infrequent and similar in both groups, with no cases of clinically significant hepatotoxicity or myelosuppression. Treatment discontinuation due to adverse events was rare **(Table 3)**.

Table 3: Adverse events

	Rimactazid (n=106)	Control (n=106)	P value
Any adverse event	15 (14.2%)	14 (13.2%)	0.842
Nausea / dyspepsia	8 (7.5%)	7 (6.6%)	0.789
Transient ALT/AST elevation	4 (3.8%)	3 (2.8%)	1.000
Treatment discontinuation	2 (1.9%)	1 (0.9%)	1.000

Data presented as number (%), ALT: alanine aminotransferase, AST: aspartate aminotransferase

Discussion

The current randomised controlled trial demonstrates that a triple therapy based on Rimactazid resulted in significantly greater eradication rates of Helicobacter pylori compared to a standard rifabutin-based rescue regimen in patients with refractory infection. Both ITT (82.1%) and PP (86.7%) eradication rates surpassed the minimum 80% threshold typically regarded as acceptable for rescue therapy, thereby endorsing the clinical effectiveness of this regimen in challenging cases.

Rifabutin-based regimens are presently considered the most efficacious empirical rescue strategy following multiple eradication failures, primarily owing to the minimal prevalence of primary resistance (<1%) [9, 10]. Nevertheless, the reported eradication rates exhibit considerable variability Gisbert et al. [9] preformed a systematic review and meta-analysis encompassing more than 3,000 patients receiving rifabutin-based regimens, reporting aggregated eradication rates of 73% (ITT) and 79% (PP). Comparable results were documented in clinical case series by Navarro-Jarabo et al. [10] and Toracchio et al. [11], with eradication rates varying from 70% to 85%, depending on the duration of treatment and the specific antibiotic regimens used.

In this study, the control rifabutin group demonstrated eradication rates (ITT 68.9%, PP 73.5%) that align with previously published data, thereby confirming the representativeness of our study population. Importantly, the Rimactazid-based regimen exhibited outcomes that were both statistically and clinically superior. This indicates that, when properly dosed and administered to appropriately selected patients, rifampicin may be at least as effective as rifabutin for H. pylori rescue therapy.

Previous clinical investigations examining rifampicin-based regimens documented suboptimal eradication rates Ahuja et al. [12] Evaluated a rifampicin-based rescue therapy in cases with multiple previous eradication failures and observed eradication rates of only 32–33%, concluding that rifampicin has no significant function in refractory H. pylori infection. These findings significantly impacted subsequent guideline recommendations that advise against the use of rifampicin.

Nonetheless, several significant distinctions set that study apart from the current investigation. Initially, rifampicin was administered once daily at a dose of 450 mg, whereas rifamycins are recognised for their time-dependent antibacterial activity. Second, the duration of treatment was restricted to 10 days without any optimisation of gastric acid suppression. Third, prior exposure to rifamycin was not consistently ruled out, thereby elevating the risk of pre-existing resistance.

In contrast, the current study employed twice-daily rifampicin administration, effective acid suppression, and rigorous exclusion of patients with previous rifamycin exposure. These methodological improvements probably explain the significantly higher eradication rates observed. This interpretation is corroborated by pharmacokinetic data indicating that rifampicin attains elevated gastric mucosal concentrations and demonstrates potent intracellular activity when administered at appropriate doses [13].

Concerning the incorporation of isoniazid in the Rimactazid formulation, H. pylori does not possess mycolic acids, which are the traditional target of isoniazid in Mycobacterium tuberculosis. Nonetheless, empirical evidence indicates that isoniazid may augment oxidative stress and interfere with intracellular redox homeostasis in specific non-mycobacterial organisms [14]. Rizvanov et al. [15] proposed that isoniazid may indirectly hinder H. pylori survival by enhancing oxidative damage, especially when used in conjunction with agents that suppress transcription, such as rifampicin.

Although the intrinsic antibacterial activity of isoniazid against H. pylori appears to be limited, a synergistic or potentiating effect cannot be ruled out and may have played a role in the enhanced eradication rates observed. Additional in vitro and molecular investigations are required to elucidate this mechanism.

Alternative salvage strategies encompass levofloxacin-based, bismuth-based quadruple, and susceptibility-guided treatments. However, fluoroquinolone resistance rates now surpass 30% in numerous regions, significantly diminishing the effectiveness of regimens containing levofloxacin [6, 7]. Bismuth quadruple therapy continues to be efficacious but is linked to a high tablet burden and decreased adherence, especially among elderly patients [4].

Susceptibility-guided therapy attains the highest eradication rates (>90%) but is constrained by cost, technical intricacy, and limited availability in standard clinical practice [16]. In this context, a highly effective empirical regimen based on rifamycin continues to hold significant clinical importance.

Rifabutin-based therapies are linked to dose-dependent myelotoxicity, particularly neutropenia and leukopenia, which occur in approximately 2–5% of patients undergoing treatment [9, 10]. Conversely, rifampicin is more frequently linked to hepatotoxicity, particularly with extended use.

In this study, there were no instances of severe hepatotoxicity, myelosuppression, or adverse events that limited treatment. The brief treatment duration of 10 days, meticulous patient selection, and baseline liver function assessment probably played a role in the observed favourable safety profile. These findings are consistent with pharmacovigilance data suggesting that short-course rifampicin therapy is typically safe outside the context of tuberculosis [17].

Current international guidelines do not endorse rifampicin-based regimens for H. pylori eradication, primarily owing to concerns regarding resistance development and unfavourable early clinical outcomes [5]. However, these recommendations precede more recent pharmacokinetic insights and did not account for optimised dosing strategies.

Our results indicate that, in carefully selected patients with no prior rifamycin exposure, short-course rifampicin-based therapy can attain satisfactory eradication rates while maintaining safety. This does not endorse the indiscriminate use of rifampicin but rather emphasises its potential as a rescue option in regions where rifabutin is unavailable or prohibitively costly.

Limitations: It was conducted at a solitary centre, and culture-based susceptibility testing was not routinely implemented. Long-term monitoring for reinfection or the development of resistance was not conducted. Nonetheless, the randomised methodology, sufficient sample size, and employment of validated eradication assessment enhance the credibility of the results.

Conclusions:

Rimactazide-based triple therapy is a highly effective, safe, and accessible rescue regimen for the eradication of resistant H. pylori infections. Its effectiveness contrasts favourably with rifabutin-based regimens and may serve as a viable alternative in contexts where rifabutin accessibility is restricted.

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Conflict of Interest: Nil

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