ORIGINAL PAPER

DOI: http://dx.doi.org/10.15403/jgld-6238

Prospective Randomised Study of a 14 day Clarithromycin Triple Regimen and a 14 Day Bismuth based Quadruple Regimen for *Helicobacter Pylori* Eradication

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Received: 01.04.2025
Accepted: 03.07.2025

ABSTRACT

Background & Aims: *Helicobacter pylori (H. pylori)* is a grade I carcinogen, responsible for the development of 89% of non-cardia gastric cancers. All infected patients have an indication for treatment. The ideal first line therapy has not been defined yet. The objective of this study was to evaluate the effectiveness and safety of 14 day bismuth based quadriple and 14 day triple regimens in treatment naive *H. pylori* infected patients.
Methods: Computer based random allocation of patients was used to assign to either a 14 day triple regimen (group 1, esomeprazole 40 mg BID, amoxicillin 1000 mg BID and clarythromycin 500 mg BID) or a 14 day bismuth based quadruple regimen (group 2, esomeprazole 40 mg BID, amoxicillin 500 mg QID, metronidazole 400 mg QID and bismuth oxide 120 mg QID).
Results: Altogether 201 patients were included, 101 to group 1 and 100 to group 2. Average age of patients were 75 years of age (± 18 years). Twenty five patients were lost to follow up (12.4%), 176 were available for analysis (91 patients from group 1 and 85 from group 2). Eradication rate was 94.5% in the first group and 97,6% in the second group (NS). Side effects were reported in 22.8% in the first treatment group and in 24% in the second treatment group (NS). The majority of side effects were mild and did not resulted in any discontinuation of treatment.
Conclusions: Clarithromycin based triple regimen can still be the first line *H. pylori* regimen in Slovenia. Bismuth based quadruple regimen is to be used in future *H. pylori* screen and treat programs as the methodology of primary gastric cancer prevention.

Key words: GERD – gastroesophageal reflux disease – *Helicobacter pylori* – first line treatment – 14 day clarithromycin triple regimen – 14 day bismuth based quadruple regimen.

Abbreviations: *H. pylori: Helicobacter pylori*; mITT: modified intention to treat; OLGIM: operative link for for gastric intestinal metaplasia; RUT: rapid urease test; UBT: urea breath test.

INTRODUCTION

Infection with Gram-negative bacterium *Helicobacter pylori (H. pylori)* is the most common chronic bacterial infection in the world affecting 43% of the world population [1]. Approximately 20% of infected patients will develop *H. pylori* infection related diseases: peptic ulcer disease, *H. pylori* related dyspepsia, iron deficient anaemia, idiopathic thrombocytopenic purpura, mucosa associated lymphoid tissue lymphoma or gastric cancer [2]. WHO's International Agency for Research on Cancer classified *H. pylori* as a definite (group 1) carcinogen responsible for 89% of non-cardia gastric cancer [3, 4]. Several international and national guidelines have recommended *H. pylori* eradication in all *H. pylori*-infected individuals to prevent the spread of infection and reduce the future burden of *H. pylori*-induced diseases, especially gastric cancer [5-7]. The Kyoto consensus on *H. pylori* gastritis recommends treating all *H. pylori* infected patients independent of whether clinical manifestations are present or not [8]. Expert recommendations have established that any acceptable therapy should achieve a minimal cure rate of 90% [9].

The ideal first line therapy has not been defined yet. Most guidelines advise abandoning triple therapies that include two antibiotics (clarithromycin plus either amoxicillin or metronidazole) and introducing quadruple regimens (either bismuth or non-bismuth based [6, 7, 9].

The objective of the study was to evaluate the effectiveness and safety of a 14 day triple regimen and a 14 day bismuth based quadruple regimen in treatment naive *H. pylori* infected patients.

METHODS

From our previously published data 14 a day clarithromycin triple regimen has an eradication rate of 93% in Slovenia [10]. Preliminary results of our previous unpublished data as well as EUROHELICAN and TOGAS projects data [11, 12] showed that a 14 day bismuth based quadruple regimen had an eradication rate between 97 % and 100%. When we calculated a sample size to show a significant difference between these two therapies, 200 patients would be enough if a 14 day bismuth based quadruple therapy eradication success rate would be 99.5% (power of the study 80% and beta error 0.5).

Registration and Ethics

The study was registrated at EU level (EUDRA CT: 2019-01914-41) and ClinicalTrials.gov NCT04359966. The study received approval from the National Medical Ethics Committee of the Republic of Slovenia.

Patients who fulfilled the following criteria were included: older than 18 years of age, confirmed and previously untreated *H. pylori* infection, willingness to participate in the study and signed informed consent.

Exlusion criteria were: younger than 18 years of age, advanced chronic disease that would not allow the patient to complete follow-up or attend visits, allergies to any of the study drugs, previous gastric surgery, pregnancy or breastfeeding, alcohol or drug abuse, previous *H. pylori* eradication treatment, use of any antimicrobials or bismuth salt within the 4 weeks or PPI treatment within the last 2 weeks before inclusion in the study. Female participants with child-bearing potential were required to use medically accepted contraception for the duration of the study.

Patients were defined as being *H. pylori* positive if culture was positive or both histology and rapid urease test (RUT) during upper endoscopy were positive.

We used computer based random allocation to either a 14 day clarithromycin triple eradication regimen (group 1, esomeprazole 40 mg BID, amoxicillin 1000 mg BID and clarithromycin 500 mg BID) or a 14 day bismuth based quadruple regimen (group 2, esomeprazole 40 mg BID, amoxicillin 500 mg QID, metronidazole 400 mg QID and bismuth oxide 120 mg QID).

Two diagnostic centers with several study sites that cover whole country conducted the study. Treatment of naive patients were included after signed informed consent was obtained upper endoscopy. During the endoscopy two biopsies taken from corpus and antrum for RUT, two biopsies from antrum and corpus for culture and antibiotic susceptibility testing and four biopsies from antrum and corpus for hystology and OLGIM staging. Gastric biopsies for culture were collected and transported in Portagerm pylori (bioMerieiux, France) transport medium. After homogenization in 1 mL PBS, 0.1 mL aliquots were inoculated for gram stain and culture. Two selective and one non-selective media were used. Plates were incubated at 37°C in a microaerophilic atmosphere for 9 days and inspected for growth every 72 h. An enriched atmosphere was created using Anoxomat (Mart Microbiology). Typical colonies were identified with a typical gram stain and positive urease, catalase and oxidase reactions. Eradication success was confirmed one month post treatment with standard urea breath test (UBT).

Statistical Analyses

The eradication rate was the main outcome assessed in two sets of patients. As defined in the approved protocol, the analysis included all patients that finished follow-up and took at least 90% of the treatment drugs [modified intention to treat (mITT) group].

Averages (expected values) of proportional variables in independent groups were tested with an unpaired t-test, and stochastic ordering ("median location") of non-proportional numerical variables in independent groups was tested with the Wilcoxon-Mann-Whitney test. The structures of the proportions of dichotomous and categorical variables in independent groups were tested with Fisher's test, the proportion of differences in "favorable" outcomes in independent groups was estimated with Wang's confidence interval for the difference in proportions. Test results were considered statistically significant at $p<0.05$. All hypothesis tests or the corresponding confidence intervals were two-sided with exception of the last, eighth section, where it was a one-sided hypothesis or a one-sided confidence interval.

RESULTS

All together 201 patients were included, 101 to treatment group 1 and 100 to treatment group 2. The average age of patients was 75 years of age (Standard deviation ± 18 years) with no difference between treatment groups. Patients who took > 91% of drugs were included in the analysis as mITT. We had 176 patients in this group, 25 were lost to follow up (12.4%).

Ninety-one patients were analysed from group 1 and 85 were analysed from group 2.

The three most frequent endoscopic diagnosis were H pylori gastritis, gastroesophageal reflux disease (GERD) and duodenal ulcer (Table I).

Table I. Endoscopic diagnosis at inclusion

Endoscopic Diagnosis	Group 1, n (%)	Group 2, n (%)
GERD	27 (29.7)	21 (24.7)
Gastric ulcer	2 (2.2)	1 (1.2)
Duodenal ulcer	24 (26.4)	29 (34.1)
Gastritis	38 (41.7)	34 (40)
Total	91 (100)	85 (100)

GERD: gastroesophageal reflux disease.

Operative link for for gastric intestinal metaplasia (OLGIM) 1-3 stage were reported in 29.5% of patients. There were no statistical significant differences in endoscopic diagnosis at inclusion or in OLGIM stage between treatment groups (Table II).

Culture of *H. pylori* was successful in 90.9% of patients (Table III). *Helicobacter pylori* was resistant to amoxicilin in 1.1% [group 1: 1 patient (1.1%), group 2: 1 patient (1.2%)], to

Table II. OLGIM stages at inclusion

	OLGIM stage, n (%)			
	Stage 0	Stage 1	Stage 2	Stage 3
Group 1	62 (68.1)	23 (25.3)	5 (5.5)	1 (1.1)
Group 2	62 (72.9)	15 (17.6)	6 (7.1)	2 (2.4)
Total	124 (70.5)	38 (21.6)	11 (6.3)	3 (1.7)

OLGIM: operative link for for gastric intestinal metaplasia.

Table III. Results of Helicobacter pylori culture

	Helicobacter pylori culture, n (%)		
	Positive	Negative	Not successful
Group 1	83 (91.2)	0 (0)	8 (8.8)
Group 2	77 (90.6)	2 (2.4)	6 (7.1)
Total	160 (90.9)	2 (1.1)	14 (8)

clarithromycin in 14.8% [group 1: 15 patients (16.5%), group 2: 11 patients (12.9%)], to metronidazole in 25,6% [group 1: 23 patients (25.3%), group 2: 22 patients (25.9%), to levofloxacine in 8% [group 1: 9 patients (9.9%), group 2: 5 patients (5.9%)], to tetracycline in 1.1% [group 1: 2 patients (2.2%), group 2: 0 patient]. There were no statistical differences in resistance to antibiotics between the groups.

Eradication rate for clarithomycin triple regimen was 94.5% and for bismuth based quadruple regimen 97.6% (Table IV). There were no statistical significant difference in the eradication rate between groups.

Table IV. Eradication rate between groups

	Urea breath test (end of the study), n (%)	
	Negative	Positive
Group 1	86 (94.5)	5 (5.5)
Group 2	83 (97.6)	2 (2.4)
Total	169 (96)	7 (4)

Side effects were reported in 22% of the first treamnent group and in 23.5% in the second treatment group. The majority of side effects were mild and did not caused any discontinuation of treatment. There were no statistical differences in side effects between treatment grops and no side effects were serious enough to result in the prematurely halt of treatment. Compliance with the treatment was 99.9 % in both treatment groups (Tables V and VI).

Table V. Treatment related side effects

	Side effects, n (%)	
	No	Yes
Group 1	71 (78)	20 (22)
Group 2	65 (76.5)	20 (23.5)
Total	136 (77.3)	40 (22.7)

DISCUSSION

All patients were included after upper endoscopy and the three most frequent diagnosis were GERD, duodenal ulcer

Table VI. Side effects severity rate

	Side effect severity, n (%)			
	0	1	2	3
Group 1	71 (78)	16 (17.6)	3 (3.3)	1 (1.1)
Group 2	65 (76.5)	15 (17.6)	5 (5.9)	0 (0)
Total	136 (77.3)	31 (17.6)	8 (4.5)	1 (0.6)

1: the patient reports them without asking the doctor; 2: it is difficult for the patient to complete the regimen for 14 days; 3: medical intervention is required or discontinuation of treatment due to side effects.

or *H pylori* gastritis, with no difference between the groups. Since average age was 75 years it is not surprising that 31.9% of patients in the treatment group 1 and 27.1% of the patients in the treatment group 2 had OLGIM stage 1-3.

After the third recomendations/position statement of the Slovenian Association for Gastroenterology and Hepatology on the management of patients infected with *H. pylori* was published in 2018, a 14 day high dose esomeprazole triple regimen (clarithromycin 500 mg and amoxicillin 100 mg BID) was proposed as the first line treatment of choice in Slovenia [7]. In our last analysis this regiments had 93% eradication rate and resistance to clarithromycin was < 15% [10]. In the study presented, the resistance rate to clarithromycin was 16.5% in study group 1, but the eradication rate was still 94%. This is a bit surprising because Maastricht/ Florence VI recomendations speak against clarithromycin based triple regiments in regions with *H. pylori* resistance to clarithromycin > 15% [6]. Regular *H. pylor*i antibiotic susceptibility studies are required in order to change the treatment recomendations for the first line therapy if clarithromycin based triple regimen eradication rate falls under 90%. Hp-EuReg data can serve as a surrogate marker for the monitoring *of H. pylori* antibiotic resistance rate in the country. If the *H. pylori* resistance rate to clarithromycin is <15%, eradication rate should be > 90% [13].

Bismuth based high PPI 14 day regimen is recommended in regions with *H. pylori* resistance to clarithromycin > 15% [6] and is the first line therapy in 39% of regimens registrated at Hp-EuReg in 2021 [14]. Eradication rate of this regimen in our study was 97.6%, an excellent result. The difference in eradication between both treatment groups was not statistically significant. There are two resons that could explain this result. Eradication rate of clarithromycin triple regimen was surprisingly high and if a substantial number of patients drop out it reduces the power of the study. With eradication rates achiewed for both treatment regimens we would need 230 patients in both group to demonstrate statistically significant higher eradication rate of bismuth based quadruple regiment.

We can assume that with the increase in *H. pylori* resistance to clarithromycin, the bismuth based quadruple regimen will become the first line regiment in many more countries. Bismuth use offers a strong bacteriostatic effect that is not altered by resistances, beneficial synergy when combined with several antibiotics and a good tolerability and safety profile [15]. The other advantage of this regimen is also its use in future *H. pylori* screen and treat programs as the way forward for primary gastric cancer prevention programs. We use it in two ongoing studies, EUROHELICAN and TOGAS [11, 12] because antibiotics used frequently for

other indications should not be used for national screen and treat programs. A good option for screen and treat antibiotic regimens would be to replace amoxicillin with tetracycline, but tetracyclin is unavailable in many countries, also in Slovenia [6, 14, 16, 17].

In clarythromycin based triple regiments patients reported side effects in 22% and in the bismuth based quadruple regimen in 23.5%. There were no difference betwen treatment groups in grade of severity and no patients prematurely stoped the treatment due to side effects. It has been shown long time ago that decreased compliance is significantly associated with side effects [18].

According to Hp-EuReh data out of 22,492 patients side effects were recorded in 23% of the cases. The bismuth-based quadruple therapy has caused side effects in 37% of patients. Taste disturbance was reported in 7%, diarrhea in 7%, nausea in 6%, and abdominal pain in 3%. The majority of side effects were mild (57%), 6% were severe, and only 0.08% were serious, with an average duration of 7 days. The treatment compliance rate was 97%. Only 1.3% of the patients discontinued treatment due to side effects. Longer treatment durations were significantly associated with a higher incidence of side effects [19]. Discontinuation was low even in other reported series due to serious side effects (1-5 %) [20-22].

This study was the first random comparison between a 14 day high PPI clarithromycin regimen and a 14 day high PPI bismuth based regimen in Slovenia. Our results show that clarithromycin based triple regimen can still be used as the first line treatment. The weakness of this study is the low number of included patients, partially due to 12.4% of patients drop out. Since 2018 general practitioners can test young patients without alarming symptoms and start eradication regimens [6]. Because of that it is not so easy to find enough treatment naive patients in outpatient endoscopic departments to conduct such comparative study.

It is important to raise the public awarennes of *H. pylori* related diseases and the importance of patients'compliance with treatment regimens. Careful explanation of possible side effects before treatment can increase the treatment compliance.

CONCLUSIONS

Based on results, a clarithromycin based triple regimen can still be the first line *H. pylori* eradication regimen in Slovenia. A bismuth based quadruple regimen might be used in future *H. pylori* screen and treat programs as the way forward to primary gastric cancer prevention.

Conflicts of interest: B.T. has served as a speaker/consultant or has received research funding from KRKA, Ewopharma, SWIX pharma. M.S. has received funding from KRKA, SWIX pharma and FujiFilm. The remaining authors declare no conflicts of interest.

Authors' contribution: B.T. coordinated the current study, analysed, synthetized and interpreted the data. B.T. wrote the first draft and approved the submitted manuscript. M.S. D.U. and K.T collected data, critically reviewed the manuscript's drafts, and approved the manuscript.

Acknoledgements: This project was funded by KRKA pharmaceuticals and Slovenian Association for Gastroenterology and Hepathology.

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