Fourteen-Day Sequential Therapy Containing Rabeprazole Versus 10 And 14-Day Concomitant Therapy in The First Line Treatment of Helicobacter Pylori Infection: A Randomized, Open-Label Clinical Trial

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Abstract

Aims:

To compare an optimized sequential therapy to 10 and 14-day non-Bismuth quadruple therapies currently recommended, in terms of efficacy, incidence of adverse effects and cost.

Patients and methods:

This open-label prospective study randomized patients with confirmed *Helicobacter pylori* (*H.Pylori*) infection to 3 groups (1:1:1): The first group received quadruple therapy of twice-daily (bid) Omeprazole 20mg, Amoxicillin 1g, Clarithromycin 500mg and Metronidazole 500mg for 10days (QT-10), the second group received a 14 day quadruple therapy following the same regimen (QT-14), and the third received an optimized sequential therapy consisting on a bid Rabeprazole 20 mg plus amoxicillin 1g for 7 days, followed by bid Rabeprazole 20 mg, clarithromycin 500 mg and metronidazole 500mg for the next 7 days (OST-14). Adverse events (AEs) were recorded throughout the study, and the *H.Pylori* eradication rate was determined 4 to 6 weeks after treatment using the ¹³C urea breath test.

Results:

In intention to treat analysis, eradication rate was 85,5%, 91,8% and 95,4% respectively in QT-10, QT-14 and OST-14 groups ($p=0,03$). In the per protocol analysis, the eradication rate was significantly higher in the OST- 14 group compared to the QT-14 and QT-10 groups (98,1%, 94,4% and 89,5% respectively, $p=0,02$).

The overall incidence of AEs was significantly lower in the OST-14 group ($p=0,01$). Furthermore, the OST-14 was the most cost-effective among the three groups.

Conclusion:

14-day optimized sequential therapy is a safe and effective alternative that allows a higher eradication rate compared to 10 and 14-days quadruple therapies while causing less adverse effects and allowing a gain in term of cost.

Introduction:

Helicobacter Pylori (*H.Pylori*) cure remains a problem of global concern¹. This bacterium is a well-known cause of peptic ulcer, gastritis, gastric mucosa-associated lymphoid tissue (MALT) lymphoma and gastric malignancies²⁻⁴. *Helicobacter Pylori* eradication is thus an effective strategy in preventing gastric malignancies^{5,6}.

Despite the *H.Pylori* infection management is evolving, no regimen can currently achieve a cure rate of 100%, the last Maastricht V consensus recommend non-Bismuth quadruple therapies (Amoxicillin 1g bid,

Clarithromycin 500mg bid, Metronidazole 500 mg bid and pump inhibitor (PPI) bid) for 10 to 14 days or Bismuth therapy for 10 days to achieve cure rate of at least 90% despite a significant rate of adverse effects⁷. However, it's observed that the prevalence of antimicrobial resistance is widely rising which become a problem of great interest worldwide⁸; In Morocco, a previous study showed a Clarithromycin resistance of more than 15%⁹. Therefore, the best strategy to increase the eradication rate of *H.Pylori* would be a personalized treatment according to antibiotics susceptibility¹⁰.

However, this strategy is not possible in many developing countries. Therefore, many studies have focused on optimizing the recommended regimens¹¹. It can be either an optimization by extending the length of the protocol¹², using higher dose and/or second-generation PPIs substances, or switch to Vonoprazan^{13,14}, modifying antibiotic therapy used and their posology, or supplementation with other molecules such as probiotics¹⁵.

Optimizing sequential therapy seems to be the most attractive strategy in terms of efficacy, tolerability and cost. The most common sequential therapy consists of a dual therapy (PPI and Amoxicillin) for the first period (5 to 7 days), followed by a triple therapy for the second period (PPI, Clarithromycin and Metronidazole). PPIs play a key role in maintaining a gastric PH allowing an optimal efficacy of antibiotics¹⁶, hence the idea of the use of new generation molecules.

The primary aim of this study was to compare the efficacy of 14-day sequential therapy optimized by using a second-generation PPI to the standard non-bismuth quadruple therapies of 10 and 14 days. The secondary aims were to compare the tolerability and adverse effects occurrence among the groups, as well as their cost- effectiveness.

Patients And Methods:

Study design and patient selection:

This was a single center, prospective, open-label, randomized study, conducted between January 2018 and March 2020, at the Gastroenterology II Department, Mohamed V Military Teaching Hospital of Rabat, Morocco. we included adult patients with *Helicobacter Pylori* infection confirmed by histological analysis of gastric biopsies performed during upper endoscopy. Five gastric biopsy samples were taken systematically according to the recommended Sydney system (antrum, incisura, greater and lesser curvature) [17], and then studied for the presence of *H.Pylori* using Hematoxylin and eosin staining at the pathology laboratory of our hospital. Patients who received eradication therapy previously, PPI, H₂-blockers, NSAIDs or Bismuth containing compounds 4 weeks prior to the study, and/or who were allergic to prescribed antibiotics were excluded from the study. Additionally, pregnant and breastfeeding females as well as patients with history of gastric surgery, kidney or liver failure, or severe psychiatric conditions were also excluded. All included patients provided a written informed consent to participate in the study. The protocol followed Helsinki Declaration guidelines and was approved by our local scientific committee

at Mohamed V Military Teaching Hospital of Rabat. Our clinical trial was registered in the Pan African Clinical Trial Registry (www.pactr.org) on 12/07/2021 / registration number: PACTR202112632957229.

Randomization and treatment:

Patients were randomly assigned in 1:1:1 ratio using a computer-generated table into three groups: QT-14, QT-10 and OST-14. Allocations were concealed in a sealed opaque envelope which was to be opened on the consultation day. The QT-14 and QT-10 groups received Omeprazole 20mg, Amoxicillin 1g, Clarithromycin 500mg and Metronidazole 500mg, all twice daily for 14 and 10 days, respectively. The OST-14 group received an optimized sequential therapy consisting on twice daily Rabeprazole 20mg and Amoxicillin 1g during 7days, followed by Rabeprazole 20mg, Clarithromycin 500mg and Metronidazole 500mg, all twice daily for the remaining 7days.

PPI was administered 30 minutes before breakfast and supper, whereas antibiotics were administered every 12 hours after meals.

Follow-up and outcomes:

The *H. Pylori* eradication was determined, at least 4 weeks after the last day of the treatment, using the ¹³C-urea Breath test (UBT), which was performed blindly at the same laboratory for all patients. The cut-off value for the UBT was 2,5 per thousand. The patients didn't undergo additional therapy with PPI, after completion of eradication therapy.

All patients were evaluated two weeks after the start of the treatment and at its end to assess adverse effects and compliance. Drugs compliance was defined by taking at least 90% of the prescribed protocol drugs and was assessed at the end of the protocol. Adverse effects (AEs) were assessed by using a pre-established structured questionnaire. The questionnaire consisted of dichotomous questions about the occurrence and intensity of AEs including diarrhea, nausea and/or vomiting, gastralgia, metallic taste, dysgeusia, symptoms related to allergic reaction, headache, dizziness, asthenia, or any other AE.

The cost-effectiveness analysis was assessed by comparing the overall cost of each protocol. The cost of every drug was calculated using a national website: www.medicament.ma. The cost-effectiveness ratio for each regimen was calculated by dividing the total cost of 100 patients treated by the percent of patients treated.

Statistical analysis:

The eradication rate of QT-10 was assumed to be 83,3% from a previous meta-analysis¹⁸. We assumed that other groups would show non-inferiority with a margin of 15%, an expected level for the primary

outcome of 85% with a strength of 0,8 and bilateral significance level of 0,05. With a presumed drop-out rate of 20% in each group, at least 120 patients were required in each group.

The primary endpoint of the study was the eradication rate of *H.Pylori*, which was assessed by intention to treat (ITT) and per-protocol (PP) analyses. The safety population included all randomized patients who received at least one treatment dose during the study, ITT population included all patients who received at least one treatment dose during the study and who were examined during the first visit, while the PP population included only patients who completed the study. Therapeutic failure was recorded as outcome for patients with missing data due to incomplete treatment. The secondary outcomes were the incidence of AEs, therapeutic compliance and cost-effectiveness of the protocols.

Descriptive and inferential statistical analyses were performed using Software Package Social Science SPSS® for mac OS version 22.0 (IBM Corp, Armonk, NY, USA). For all statistical analyses, *p value* less than 0,05 was considered statistically significant. Qualitative variables were compared using Chi-square test and Fisher's exact. Continuous variables were compared between the three groups using one-way ANOVA test. A logistic binary regression was performed to assess factors influencing *H.Pylori* cure rate.

Results:

Population characteristics

A total of 360 patients met the inclusion criteria and were enrolled in safety population.

Thirty-two patients refused to participate to the study. We therefore included 328 patients in the ITT analysis who were randomly assigned to the 3 groups. After eliminating the dropped-out patients from the study, the PP analysis included 317 patients. The flow chart of patients of different groups is resumed on figure 1. Demographic and clinical characteristics of different groups are shown in Table 1 and were not significantly different between the groups.

Table 1
Basic overall population and groups characteristics

	Overall (n=317)	QT-14 (n=107)	QT-10 (n=105)	OST-14 (n=105)	<i>p</i> value
Age, years (mean +/- SD)	44,13+/-15,30	43,37+/-14,40	43,36+/-15,9	45,67+/-15,53	0,46
Sex ratio Male/Female	0,98	1,03	1	0,92	0,91
Smoking habit	49(14,9)	18(16,4)	14(12,7)	17(15,7)	0,62
Gastroduodenal ulcer	47(14,3)	22(20)	13(11,8)	12(11,1)	0,16
Gastric atrophy	51(15,5)	14(12,7)	18(16,4)	19(17,6)	0,58
Gastric metaplasia	18(5,5)	7(6,4)	8(7,3)	3(2,8)	0,26
HP antral density:					0,30
+	114(34,9)	37(33,9)	37(33,6)	40(37)	
++	170(52)	58(53,2)	56(50,9)	56(51,9)	
+++	35(10,7)	11(10,1)	12(10,9)	12(11,1)	
HP fundic density:					0,74
+	147(44,8)	54(49,1)	46(41,8)	47(43,5)	
++	62(18,9)	20(18,2)	22(20)	20(18,5)	
+++	7(2,1)	1(0,9)	2(1,8)	4(3,7)	

All values are expressed as n (%) unless otherwise stated. +, sparse; ++, moderate; +++, marked SD: standard deviation HP: Helicobacter Pylori

Eradication rates:

In the ITT analysis, the *H.Pylori* eradication was achieved in 85,5% in the QT-10 group, 91,8% in the QT-14 group and 95,4% of the OST-14 group ($p=0,03$). In the PP analysis, the results were as follow: 89,5% (94/105), 94,4% (101/107) and 98,1% (103/105) in the QT-10, QT-14 and OST-14 groups, respectively ($p=0,02$). The results are shown in figure 2.

Safety

The treatment tolerance was better in the OST-14 group, with an incidence of AEs of 24,7% compared to 42,7% and 39% in the QT-14 and QT-10 respectively ($p=0,03$). (Table 2)

However, the treatment was globally well tolerated among the three groups, and adverse effects were mild to moderate in all patients.

The drugs compliance was excellent among the three groups: 97%, 95% and 98,9% in the QT-10, QT-14 and OST-14 respectively ($p=0,48$).

Table 2
Incidence of Adverse effects among the study groups

	QT-10	QT-14	OST-14	<i>p value</i>
ITT analysis	39%	42,7%	24,7%	0,03
PP analysis	45,1%	49,5%	31,3%	0,01

Cost-effectiveness

The overall cost was lower in the OST-14 group (427,10dhs), comparing to QT-14 and QT-10 groups (691,90dhs and 587,10dhs respectively). Considering the effectiveness of different regimens, the cost-effectiveness ratio was lower in the OST-14 group as shown in Table 3.

Table 3
Cost-effectiveness ratio in the three protocols Costs are expressed in Moroccan dirhams

Therapeutic protocol	Overall cost of 100 patients	Effectiveness	Cost-effectiveness Ratio
QT-10	58710	89,5%	655
QT-14	69190	94,4%	732
OST-14	42710	98,1%	435

Predictive factors of therapeutic success

In the multivariate logistic regression analysis, the use of sequential therapy versus concomitant therapy ($OR=8,21$; 95% IC(1,01-66,66); $p=0,04$) and the absence of drugs adverse effects ($OR=2,84$; 95%IC(1,09-7,38); $p=0,03$) were associated to *Helicobacter Pylori* successful eradication in the PP analysis. Age, sex, smoking, gastroduodenal ulcer, gastric atrophy, gastric metaplasia, 10days vs 14days regimens were included in the multivariate analysis but were not associated to successful eradication. (Table 4)

Table 4

univariate and multivariate analyses of predictive factors of *Helicobacter Pylori* successful eradication.

	Univariate analysis			Multivariate analysis		
	OR	p	95% CI	OR	p	95%CI
Age	1	0,60	0,82-1,03			
Sex	0,59	0,20	0,27-1,31			
Smoking	2,66	0,19	0,61-11,61			
Gastroduodenal ulcer	1,68	0,29	0,64-4,42			
Gastric atrophy	2,44	0,23	0,55-10,68			
Gastric metaplasia	1,83	0,56	0,23-14,37			
Adverse effects	3,49	0,008	1,39-8,74	2,48	0,03	1,09-7,38
14 vs 10days regimens	1,89	0,10	0,87-4,11			
Sequential vs concomitant therapy	6,86	0,01	1,59-29,54	8,21	0,04	1,01-66,66

OR: Odds-Ratio; CI: confidence interval

Discussion:

According to the Maastricht V consensus, the most recommended regimens for *Helicobacter Pylori* infection are non-Bismuth quadruple concomitant therapy and Bismuth quadruple therapy⁷. However, eradication rates vary widely by geographic area, due to varying antimicrobial resistance, especially to Clarithromycin and Metronidazole¹⁹. Therefore, several regimens have been tested to improve the management of *Helicobacter Pylori* infection^{20,21}. One of them is the modified sequential therapy^{12,22}. In the present study, we aimed to compare the results of the standard 10- and 14-day non-bismuth quadruple therapies to a modified sequential therapy by using a second-generation PPI.

Overall, we found that the 14-day optimized sequential regimen using Rabeprazole achieves a higher cure rate compared to the standard non-bismuth quadruple therapy for 10 or 14 days (95,4%, 85,5% and 91,8% in the OST- 14, QT-10 and QT-14 respectively, $p=0,03$). The OST-14 allowed a great tolerance with a lower adverse effects rate compared to quadruple therapies ($p=0,01$), and there was no difference in term of drugs compliance between the three groups. Furthermore, the cost-effectiveness ratio was lower in the OST-14 group.

The sequential therapy was introduced for the first time in 2000 in Italy by Zullo²³. We personally demonstrated its superiority compared to the standard triple therapy in a previous study²⁴.

A recent metanalysis by Youhua wang et al showed that there is no difference in term of eradication rate between 14-day sequential and 14-day concomitant therapy²⁵. Another study showed that 14-day

sequential therapy is equivalent to 10-day bismuth quadruple therapy in terms of eradication rate (91,3% and 91,6%) but with more adverse effects with the second regimen²⁶. The same team demonstrated in a meta-analysis that 14-day sequential therapy is more effective than 14-day triple therapy²⁷.

In the present study, the gain in terms of eradication rate can be explained by the use of a second-generation PPI (Rabeprazole 20mg bid) in the OST-14 group. In fact, the last Maastricht consensus states that switching Omeprazole 20mg twice daily to Rabeprazole 20mg bid or Esomeprazole 40mg bid may increase eradication rate by 8-12%⁷. The advantage of PPIs lies in the fact that the majority of proposed regimens are PH dependent and become less effective when the intragastric PH is low²⁸, hence the use of higher doses of PPIs and second-generation substances. A possible explanation for the superiority of second-generation PPIs (Rabeprazole and Esomeprazole) can be their metabolism, which is less dependent on CYP2C19 genetic variables and their higher acid inhibition power²⁹. A further meta-analysis by McNichol et al confirmed that both Esomeprazole and Rabeprazole lead to higher eradication rates compared to first-generation PPIs (Omeprazole, Lansoprazole and Pantoprazole)³⁰.

All therapeutic regimens currently recommended are associated with gastrointestinal adverse effects³¹. Herein, the OST-14 allowed a gain in terms of adverse effects incidence compared to quadruple concomitant therapies. These findings confirm those of previous studies³²⁻³⁴.

The 14-day sequential therapy consists of the same antibiotics as the 14-day concomitant regimen but for a shorter duration. It should therefore be responsible for less adverse effects. This was the case in our study with a benefit of 18% in terms of AEs occurrence (31,3% vs 49,5%; $p=0,03$). Moreover, the absence of drug adverse effects was a predictive factor of successful treatment (OR=2,48; 95%IC=1,09-7,38; $p=0,03$).

Because the treatment cost is a determining factor especially in developing countries, we carried out a cost-effectiveness analysis and showed that the OST-14 is the most cost-effective among the study three groups. The same result was reported by Nagwan S et al previously who found that 14-day sequential therapy is cheaper than

14 triple therapy³³, Kate V et al. confirmed in a meta-analysis that sequential therapies are cheaper than standard therapies³⁵. Other cost-analysis studies have shown the same results and found that sequential therapy is the most economically attractive option^{36,37}.

This benefit can be explained by the fact that clarithromycin is the most expensive drug used in different protocols, and will be used for a shorter duration in the sequential therapy.

One of the limitations of this study is that we didn't perform *Helicobacter Pylori* cultures and didn't have data about antibiotic susceptibility. However, a previous recent study showed that the local primary resistance to Clarithromycin was 29% in Morocco, 40% to Metronidazole and 0% to Amoxicillin⁹.

Another potential limitation is that second line treatments were not included, which makes hard to interpret the cost effectiveness analysis. Additionally, it's difficult to generalize our results to other areas as the study was conducted in a single center. Nonetheless, the sample size was reasonable allowing correct statistical analysis. Though our results have to be completed by further studies in different geographic areas to have them validated. In conclusion, the results of the present study showed that 14-day sequential therapy using Rabeprazole is an optimal therapy leading to an excellent cure rate, and demonstrate its superiority to the standard non-bismuth quadruple therapies particularly in terms of tolerance and adverse effects occurrence.

Declarations

Data Availability:

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Author contributions: H.S. was responsible for study concept and planning and supervised the statistical analysis and redaction of the manuscript. H.B. was involved in performing the statistical analysis and writing the manuscript, with input from all authors. S.B., R.B., I. E., S.M., K.L., A.B., A.S., T.A., S.S. and A.B., were involved in patient enrollment and data collection and were involved in the preparation of the manuscript. Milutin Bulajic was involved in reviewing the manuscript. All authors reviewed the manuscript.

Additional information

- **Competing interests**

The author(s) declare no competing interests.

- **Funding sources.**

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Figures

Figure 1

Flow-chart of patients in the study

Figure 2

Helicobacter pylori eradication rates with Intention to Treat and Per-Protocol analyses among the three groups