Bismuth-based quadruple therapy versus standard triple therapy for the eradication of Helicobacter pylori in Belgium: a multicentre, non-blinded randomized, prospective study

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Abstract

Background: **Helicobacter pylori (Hp) infection predisposes to malignant and non-malignant diseases warranting eradication. In Belgium, resistance rates for clarithromycin demonstrate regional variations making the use of standard triple therapy (STT) borderline acceptable. According to a recent Belgian survey, STT and bismuth-based quadruple therapy (BQT), are equally frequent prescribed as first line treatment for treatment naïve Hp positive patients. This study aims to evaluate the eradication rates (ER) of BQT versus STT.**

Methods: **Multicentre, non-blinded randomized, prospective study comparing ER in treatment-naïve Hp positive patients. ER were compared by intention to treat (ITT) and per protocol (PP) analysis.**

Results: **Overall 250 patients were included (STT 126, BQT 124). Seventeen patients were lost to follow-up (6,8%). No significant difference in ER between BQT and STT was observed in ITT (73% vs 68%, p= 0,54) neither in PP analysis (81% vs 75%, p= 0,33). Side effects and endoscopic findings were comparable between groups. Post-hoc analysis showed no differences according to gender or site allocation.**

Conclusion: **The numerical advantage of BQT did not translate in a significant improvement of ER when compared with STT. These results question the cost-effectiveness of BQT, while confirming the suboptimal eradication rates on STT. A nationwide monitoring of resistance patterns, maximal investments in treatment adherence as well as a detailed follow-up of the changing treatment landscape are mandatory to continuously optimise Hp ER in Belgium.** (Acta gastroenterol. belg., **2024,** 87, **235-240**).

Keywords: Helicobacter pylori, Belgium, standard triple therapy, bismuth-based quadritherapy, eradication.

Introduction

Helicobacter pylori (Hp) selectively infects the human stomach, being the most prevalent chronic infection worldwide. Its prevalence in Europe fluctuates between 20% and 40%, with a lower prevalence in the northern and western regions compared to the southern and eastern regions (1). In Belgium, no studies on prevalence are available in adults since the 1990s, when it was estimated at about 32% (2). On the other hand, a prospective study from 2010 established a very low prevalence in children of Belgian origin (3,2%), contrasting with a high prevalence in children with a personal or familial migration background (30-60 %) (3).

Hp represents the major cause of relevant malignant and non-malignant diseases like peptic ulcer, atrophic gastritis and gastric cancer, thus warranting eradication. This gram-negative bacterium was defined as a carcinogen type 1 in 1994 by the World Health Organisation (4). With over 1 000 000 new cases and an estimated 733 000 deaths in 2018, gastric cancer represents the fifth most frequently diagnosed cancer and the third leading cause of cancer deaths in both sexes worldwide (5). There is evidence that the eradication of Hp and surveillance of patients with high-risk gastric lesions such as advanced gastric atrophy and incomplete intestinal metaplasia, are the best strategies for gastric cancer prevention (6).

Although there is no doubt about the importance of eradication of Hp, worldwide eradication rates with conventional therapies have dropped to unacceptable levels due to increasing antibiotic resistance. Table 1 provides an overview of the evolution of the resistance pattern observed in the Belgian population according to different studies during the last decade (7-10). In summary, clarithromycin resistance increased until 2014 after which there was a decline in resistance dropping just below the 15% limit in 2020. Metronidazole resistance was stable but high during the observed period as well as levofloxacin resistance. Amoxicillin and tetracycline resistance remained low to absent over the years.

Notwithstanding the Maastricht/Florence recommendations favouring bismuth-based therapy (11), a recent survey on eradication regimen preferences in Belgium showed that the same number of Belgian gastroenterologists prescribe STT compared to BQT as first line empiric treatment for Hp gastritis (unpublished data, Ntounda R.) As the reported clarithromycin resistance on the verge of 15% in Belgium mandates a switch to bismuth-based regimens, we conducted a study

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Table 1. — **Overview of primary resistance rate of Hp in Belgium the last decade**[7-10]

Antibiotics (% resistance)	2013 n=606	2014 n=741	2015 n=850	2016 n=438	2018 n= 99	2020 n=270
Amoxicillin	1,3	1,2	1,2	0	2,7	0
Clarithromycin	27,6	29,5	26,5	18	13,5	14,4
Metronidazole	36,3	40,1	36,5	40	29,7	49,6
Levofloxacin	28,5	29,1	26,5	22,8	29,7	22,2
Tetracyclin	0,5	0,1	0		0	0,4

evaluating the actual eradication rates (ER) obtained by BQT vs. STT in Hp-treatment naïve patients in Belgium.

Methods

Between 2017 and 2021, 4 second or third-line centres (UZ Brussel, CHU Saint-Pierre, CHU Charleroi and UZ Antwerpen) conducted a multicentre non-blinded randomized prospective study comparing eradication rate (ER) in treatment-naive Hp positive patients treated with 14 days of STT consisting of pantoprazole 40mg, clarithromycin 500mg and amoxicillin 1000mg bis in die (bid) versus 10 days of BQT consisting of bismuthsubcitrate 140mg, tetracycline 125mg and metronidazole 125mg quater in die (qid) combined with pantoprazole 40mg bid. All consecutive patients with histology-proven Hp gastritis were eligible for participation. Immunochemistry was used for histological diagnosis. Exclusion criteria consisted of a history of previous eradication, antibiotic use during the past 8 weeks, no possible follow-up by phone calls or e-mail, known allergy to one of the treatment drugs, age < 18 years , substantial organ impairment, prior major surgery of the upper gastrointestinal tract, pregnancy or lactation. Approval was obtained from the local ethics committee in each participating centre and registered in the European Union Drug Regulating Authorities Clinical Trials (EudraCT) database (2016-000228-24). All participating patients provided written informed consent.

Randomization by a system of envelops ensured equal distribution among treatment arms. Ethnicity of each participant was recorded. Antibiotic treatment was provided during the consultation according to the randomization regimen. Standard triple therapy comprised of clarithromycin 500 mg and amoxicillin 1 g, both administered twice daily, for fourteen days. Bismuth quadruple therapy consisted of 3 pills of the triple combination 140 mg bismuth subcitrate potassium, 125 mg metronidazole and 125 mg tetracycline hydrochloride, taken 4 times daily for ten days. Participants received a prescription for pantoprazole 40 mg, to order from their pharmacist, and were instructed to take it twice daily for the duration of the eradication regimen.

Assessment of adherence to treatment and side effects took place on the second and sixth day after the start of the treatment as well as at the end of treatment, by phone calls or e-mails, as per preference of the patient chosen at the study start-up. Each investigator site had a responsible study nurse to complete these liaison checks. Telephone contacts were repeated until the patient replied the call. For those patients who were followed up by mail, a response was required within 24h. If no answer was obtained, the patient was contacted by phone. If one of the contact moments fell at the weekend, it was postponed to the following Monday.

An 13C urea breath test (UBT) performed at least 6 weeks after eradication, with cessation of PPI and antibiotics for a minimum of 14 days, established eradication success.

All statistical analysis was performed by SPSS (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0.0.0 Armonk, NY: IBM Corp). Assuming an eradication rate of 75% for standard therapy vs. 90% for BQT and 10% loss during follow-up, demonstration of a statistical significance by Chi-square at the .05 level with 80% power required a total of 125 patients in each group. Comparison of treatment response was performed according to intention to treat and per protocol. A p-value < 0,05 was considered significant. In post-hoc analysis, logistic regression with conditional backward elimination was performed with treatment response in the intention to treat analysis as dependent variable and gender, site allocation, ethnicity and presence of structural abnormalities on gastroscopy as predictors. We additionally performed a Chi-square comparing eradication rates in ITT between different ethnic groups and different sites.

Results

Patient characteristics

Two hundred fifty patients were included between August 2017 and October 2021 (figure 1). As a result of the hampered patient recruitment during COVID-19 pandemic, the initial recruitment period was extended to 15/12/2021. Patients characteristics are provided in table 2. Gender and age was equally distributed among treatment arms. Endoscopic findings were available for 192 (77%) participants and were categorised as normal, gastritis, bulbitis, combination of both, ulcer disease or atrophy. Seventeen patients (6,8%)were lost to follow-up (9 and 8 in STT and BQT respectively).

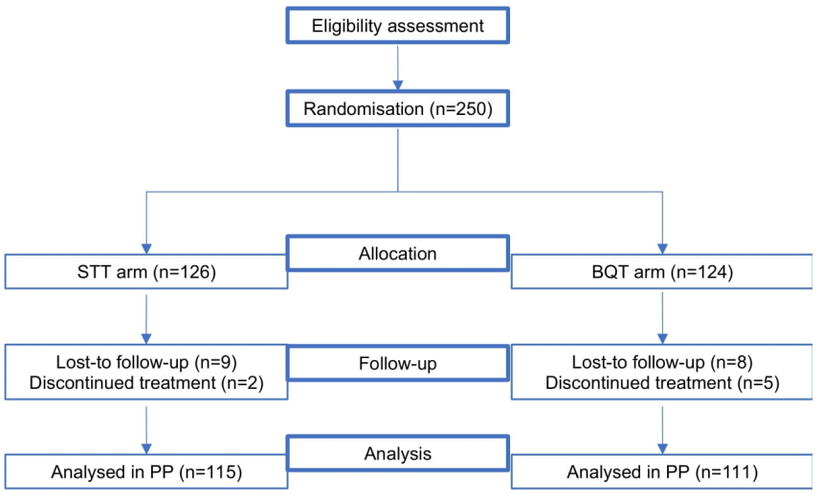

Figure 1. — Flowchart trial.

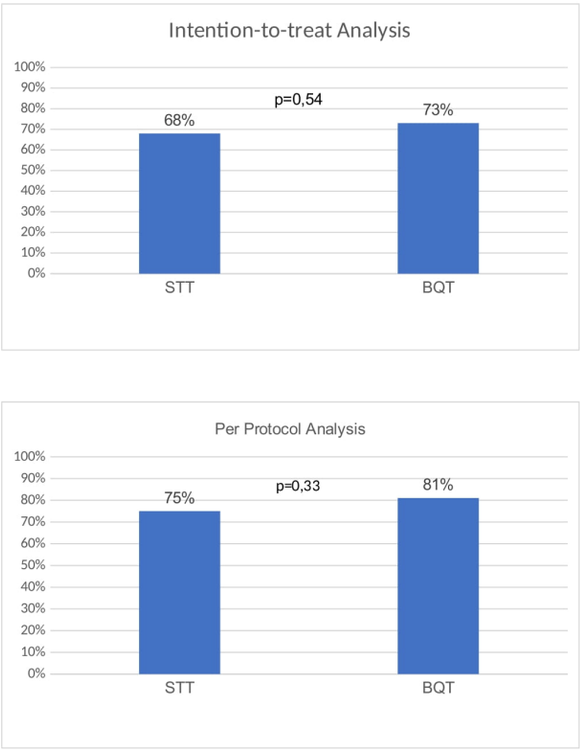

Figure 2. — Eradication rates according to
A. intention-to-treat analysis. B per protocol analysis.

Eradication rate

ER did not differ significantly between STT and BQT, neither by intention-to-treat analysis (68% vs. 73%, p= 0,54) or per-protocol analysis (75% vs. 81%, p= 0,33), as shown in figure 2. Post-hoc logistic regression found that only site allocation and ethnicity contributed significantly to treatment response (resp. p=0,015 and p=0,033). Ethnicity remained the only contributing variable when solely including subjects from the centre with the largest recruitment (p=0,038). However, eradication rates in ITT were comparable among the different ethnic groups (Caucasian 59/76, Asian 6/8, North African 70/112, Black African 26/36 and unknown 15/18, p=0,144) and different centres (UZ Brussel 124/185, St-Pierre 28/34, Charleroi 16/20, UZ Antwerpen 8/11, p=0,235).

Side effects

Distribution of side effects is illustrated in table 2. During follow-up, 78 patients (62%) in the standard triple therapy vs. 62 patients (50%) in the BQT group reported side effects (p=0,058). Seven patients (2 in STT and 5 in BQT), discontinued the treatment.

Adherence

An acceptable treatment adherence was obtained, as shown in figure 1. No more than 2 patients in the STT arm (2%) and 5 patients (4%) in BQT group reported discontinuing treatment (p=0,253). This cessation was attributed to intolerance of side effects.

Discussion

This multicentric non-blinded randomised study failed to demonstrate a difference in eradication rate by bismuth-based quadruple therapy over standard tri-therapy in treatment-naïve Hp-positive patients in Belgium in intention-to-treat as well as per protocol analysis. In post-hoc logistic regression, ethnicity emerged as a possible confounding factor, although its role appears limited. The unexpected failure of BQT over STT in this study questions the Maastricht guidelines favouring bismuth-based quadruple therapies in areas with high clarithromycin resistance. Resistance profile, treatment duration, patients characteristics, acid-suppression, and compliance all need consideration when assessing factors potentially affecting eradiation outcome.

Table 2. — **Patient characteristics**

	Standard Triple Therapy n (%)	Bismuth-based Quadruple therapy n (%)
Gender Male	57 (45)	61 (49)
Female	69 (55)	63 (51)
Age		
16-30y	40 (32)	25 (20)
31-50y	44 (35)	68 (55)
51-65y	19 (15)	24 (19)
65+	9 (7)	5 (4)
Unknown	14 (11)	2 (2)
Site Allocation		
UZ Brussel	92 (73)	93 (75)
St Pierre	20 (16)	14 (11)
UZ Antwerpen	8 (6)	12 (10)
CHU Charleroi	6 (5)	5 (4)
Ethnicity		
Caucasian	29 (23)	47 (38)
Asian	4 (3)	4 (3)
North-African	59 (47)	53 (43)
Black-African	18 (14)	18 (15)
Unknown	16 (13)	2 (2)
Endoscopic findings		
Normal	68 (49)	72 (49)
Gastritis	45 (33)	47 (32)
Bulbitis	4 (3)	2 (2)
Gastritis+bulbitis	3 (2)	3 (2)
Ulcer disease	10 (7)	14 (9)
Atrophy	8 (6)	10 (7)
Side effects		
Anorexia	1 (1)	1 (1)
Diarrhoea	24 (19)	16 (13)
Nausea	12 (10)	9 (7)
Abdominal pain/ bloating	4 (3)	7 (6)
Headache	7 (6)	10 (8)
Halithosis	27 (21)	14 (11)
Constipation	2 (2)	3 (2)
Asthenia	1 (1)	2 (2)

Studies on resistance pattern in Belgium indicated high regional variation in clarithromycin resistance, repeatedly reporting the highest resistance rates in the Brussels' region (8,9). As the majority of our patients were recruited from this area, the poor ER in the STT arm was not unexpected. Regarding metronidazole, different studies reported on the even higher resistance in the Belgian population (7-10). In the past, based on observed high eradication rates even in spite of metronidazole resistance, it was hypothesized that BQT overcomes metronidazole resistance by dose escalation or extended treatment duration (12). Contrasting with this assumption, a recent Korean study defined a high level of metronidazole resistance (minimum inhibitory concentration (MIC) >32µg/mL) as the only independent risk factor for eradication failure of rescue bismuth quadruple therapy among multiple parameters (13). The eradication rate for cases with 'low' metronidazole resistance was 92,8% as opposed to 60% in cases with high MIC. The latter is in line with the ER obtained in this study. Additionally, others reported on the deleterious influence of previous exposure to metronidazole on eradication success (14). A pilot study in US Hispanics in 2012 confirmed the superiority of a 14-day course over a 10-day course of bismuth-based quadruple therapy in metronidazole resistant Hp (15). Undoubtedly, information on prior antibiotic use, antibiotic resistance in general and metronidazole in particular would help understand the disappointing results from the BQT arm. Additionally, given the overall lower ER as expected in both groups, further research investigating the cost/ benefit efficiency of AST prior to first-line treatment should be investigated in Belgium. Moreover, the most recent European guideline recommend clarithromycin susceptibility testing if available prior to STT (11).

Treatment duration differed between both treatment arms in our study, with a 14-days course for STT vs. 10 days for BQT. Different studies demonstrated the impact of treatment duration on ER. For fluoroquinolone-amoxicillin-based regimen, a 10-day eradication course provided 90,9% success as opposed to only 63.6% of a 7-day course (16). Further prolonging treatment from 10 to 14 days revealed higher eradication rates for quadruple bismuth-based treatment with antofloxacin-amoxicillin (17). In a double-blind randomised trial in Thailand, eradication by amoxicillin-clarithromycin non-bismuth based tritherapy increased from 67,6% to 86,8% when treatment was provided for 14 days vs. 10 days only (18). In contrast, a study in Greece, where high levels of clarithromycin resistance is observed, eradication rates obtained by non-bismuth quadruple therapy were about 90% irrespective of the 10- or 14-day regimen (19). Findings from the European registry on Helicobacter management confirmed the higher eradication rates with prolonged treatment (20). This registry pointed out that only 10-day bismuth quadruple or 14-day concomitant treatments provided over 90% eradication. As all these studies indicate eradication success of about 90% or more with a regimen of at least 10 days, it seems unlikely that prolonging BQT up to 14 days would improve our eradication rates.

Gender- and age-distribution remained balanced between both treatment arms. In contrast, the BQT arm included more Caucasian, while ethnicity was more frequently unknown in the STT group. Interestingly, ethnicity appears as the best predictor of treatment response according to post-hoc analysis. However, the study was not powered to further study differences among different ethnic groups. Literature provides only limited data on the role of ethnicity on eradication rates. It might reflect differences in access to healthcare and locoregional patterns of antibiotic use, although genetic and cultural influences may also come into play (21). However, a study on antibiotic resistance in the population of Brussels Belgium, identified ethnicity as an independent risk factor, as well as female gender, age 40-64 years and prior eradication attempts (7). Unfortunately, while patients were treatment-naïve as far as Hp is concerned, our study protocol did not assess for prior exposure to antibiotics, neither did it include antibiotic resistance testing.

The choice of proton-pump inhibitor can be debated. Indeed, esomeprazole and rabeprazole are less influenced by extensive or ultra-rapid metabolism and are more potent than other PPIs (22), warranting further evaluation of their impact on eradication rates. In a retrospective study of 7896 subjects, esomeprazole proved superior to omeprazole (85,0% vs 77,5%), while a trend to superior response in subjects receiving quadruple therapy was observed for esomeprazole vs. omeprazole (90,0% vs. 82,0%) (23). The concept that more acid-suppression results in better eradication rates is further supported by the promising results obtained with vonoprazan, a potassium-competitive acid secretion inhibitor that provides more profound acid suppression than traditional PPIs. A meta-analysis of five Japanese studies including 1599 patients reported that while eradication rates for vonoprazan-based and conventional PPI-based therapies did not significantly differ among those infected with clarithromycin-susceptible Hp, (95% vs 93%), vonoprazan-based therapies were significantly more effective for clarithromycin-resistant strains (82% vs 40%) (24,25). Although pantoprazole was used in our study, we cannot exclude that a more potent PPI would result in better eradication rates in one or both treatment arms.

Data from the European Registry demonstrated that compliance constitutes the most significant factor influencing the effectiveness of single-capsule BQT (20). In our study, follow-up by phone call or email was provided on day 2, 6 after the start as well as at the end of the treatment in both groups. Side effects could impair compliance. However, we observed no differences in the prevalence of side effects between study arms. Future studies should aim to evaluate compliance and side effects more objectively by pill counting or a validated questionnaire respectively. As a comparable number of subjects were lost to follow-up, it seems unlikely that treatment adherence played a role in the low eradication rates in both arms.

Some limitations of the study need mentioning. First, cost-effectiveness wasn't studied. In Belgium, treatment with BQT (Tryplera®) costs around €75 for the patient compared to €24 for standard triple therapy. Furthermore, in contrast to STT, healthcare insurance do not cover costs of BQT, making it an expensive choice for the patient. Therefore, the comparable ER between both treatments regimens largely favour STT over BQT from the economic point of view of the patient. Second, in contrast to antibiotic therapy, PPI was not provided to the patient. Although non-compliance to this aspect of eradication cannot be fully excluded, the intensive follow-up provided during treatment mitigates this possibility.

Conclusion

This randomised trial failed to demonstrate a statistical difference in eradication rates between amoxicillin-clarithromycin-based triple therapy and bismuth-based metronidazole-tetracycline quadruple therapy. Noticeable is the lower ER in both treatment arms and in the BQT arm especially. While the study design and data from previous studies do not incriminate adherence and treatment duration for the bad figures, high resistance toward clarithromycin and metronidazole, the choice of acid-suppressive treatment and an unbalanced distribution of ethnicity between treatment arms could come into play. Further research including antibiotic susceptibility testing and exclusion of ethnicity as confounding bias is indispensable to continue improving Hp eradication in Belgium.

Conflict of interest statement

The authors declare no competing interests.

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