Original research

# Bismuth quadruple three-in-one single capsule three times a day increases effectiveness compared with the usual four times a day schedule: results from the European Registry on *Helicobacter pylori* Management (Hp-EuReg)

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## ABSTRACT

**Background** The recommended schedule for single capsule bismuth quadruple therapy (scBQT, Pylera) includes a proton pump inhibitor (PPI) two times a day and three scBQT capsules four times a day. Four times a day treatments are inconvenient and reduce adherence. In contrast, adherence improves with three times a day schedules. In clinical practice, many gastroenterologists use four capsule scBQT three times a day. However, the effectiveness and safety of this latter approach remain uncertain.

**Aim** To assess the effectiveness and safety of scBQT administered three times a day in the patients included in the European Registry on *Helicobacter pylori* Management (Hp-EuReg).

**Methods** All Spanish adult patients registered in the Asociación Española de Gastroenterología Research Electronic Data Capture (REDCap) database from June 2013 to March 2021 receiving 10-day scBQT were analysed. Modified intention-to-treat effectiveness, adherence and the safety of scBQT given three times a day were calculated and compared with the four times a day schedule. A multivariate analysis was performed to determine independent factors predicting cure of the infection.

**Results** Of the 3712 cases, 2516 (68%) were four times a day and 1196 (32%) three times a day. Mean age was 51 years, 63% were women and 15% had a peptic ulcer. The three times a day schedule showed significantly better overall cure rates than four times a day (1047/1112, 94%; 95% CI 92.7 to 95.6 vs 2207/2423, 91%; 95% CI 89.9 to 92.2, respectively, p=0.002). Adherence and safety data were similar for both regimens. In the multivariate analysis, three times

**WHAT IS ALREADY KNOWN ON THIS TOPIC**

⇒ Single capsule bismuth quadruple therapy (scBQT) is one of the most effective treatments for *Helicobacter pylori* infection. ScBQT currently recommended prescription schedule includes three capsules four times a day plus concomitant omeprazole 20 mg two times a day.

**WHAT THIS STUDY ADDS**

⇒ Giving scBQT four capsules, three times a day increases cure rates as compared with the currently recommended schedule; the concomitant use of higher omeprazole doses (40 mg two times a day) further increases the effectiveness of scBQT.

**HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY**

⇒ The study strongly suggests that prescribing information in technical sheet should recommend four capsules three times a day scBQT schedule concomitantly with higher omeprazole doses (40 mg two times a day).

a day dosage, first-line therapy, use of standard or high-dose PPIs and adherence over 90% were significantly associated with cure of the infection.

**Conclusions** ScBQT prescribed three times a day was more effective than the traditional four times a day schedule. No differences were observed in treatment adherence or safety.

## INTRODUCTION

*Helicobacter pylori* infection is related to several major gastrointestinal diseases, ranging in terms of severity from dyspepsia to gastroduodenal peptic ulcer disease, or gastric cancer.[1] *H. pylori* infects more than half of the world's population and is a global health problem.[2 3]

Consensus conferences on the eradication of *H. pylori* infection recommend using treatments that achieve a minimal cure rate of 90%, as none of the currently available therapies reaches a level of 100% effectiveness. The worldwide increase in bacterial resistance to antibiotics makes even this 90% optimal threshold challenging for many therapies and settings.[4–8]

Currently, *H. pylori* treatment requires a combination of drugs, including a proton pump inhibitor (PPI), antibiotics and, in some schedules, adjuvant therapies such as bismuth, probiotics or prebiotics. The most common regimens are triple therapies that include a PPI plus two antibiotics, non-bismuth quadruple therapies, including a PPI and three antibiotics, or bismuth-based quadruple therapies with a PPI, two antibiotics and bismuth.[9–11] Recent studies and consensus guidelines have advised against triple therapies because cure rates were reported to be suboptimal. This has generally been attributed to the increase in *H. pylori* resistance to clarithromycin.[10–12]

Randomised clinical trials have shown that classical bismuth quadruple therapies (BQT) combining bismuth with a PPI, metronidazole and tetracycline are more effective than triple therapies.[9 13] Its use, however, has been limited because the treatment complexity and/or because bismuth or tetracycline salts are unavailable in many countries. For example, in Spain, tetracycline is currently not marketed, and bismuth salts are often unavailable because of shortage.

Interest in this therapy resurfaced with the commercialisation of a three-in-one single capsule (marketed as Pylera), which contains bismuth, metronidazole and tetracycline. The combination of a PPI with Pylera (henceforth, single capsule BQT, scBQT) has markedly simplified the BQT prescription and schedule. ScBQT has shown excellent effectiveness in clinical trials, clinical practice series and metanalyses both in first-line treatment and in rescue therapy.[13–17]

One of the key factors that determines the effectiveness of *H. pylori* eradication treatment is adherence. Previous reviews have shown that the number of daily doses was strongly related to treatment adherence.[18] The three-in-one scBQT strategy appears to make treatment far easier than the administration of four separated drugs used in quadruple therapies. However, the recommended dosage according to the scBQT technical datasheet is three capsules every 6 hours. It has been described that four times a day schedules are inconvenient and may reduce adherence. Furthermore, lowering the number of daily doses from 4 to 3 increases treatment adherence from 10% to 15%.[18 19] In clinical practice, gastroenterologists often prescribe scBQT in a four capsules three times a day scheme in order to adapt the treatment to the meal times and, thus, potentially facilitate adherence.[20] However, the efficacy and safety of this approach are yet to be evaluated in detail.

The European Registry on *H. pylori* Management (Hp-EuReg) compiles data on the diagnosis, treatment and outcomes of *H. pylori*-infected adult patients. This allows real-time auditing of clinical practices, comparing real-life results to the current guidelines and allowing the design of therapeutic strategies to improve the management of the infection[21]

This substudy of the Hp-EuReg focuses on patients who received a 10-day course of scBQT, following either the four capsules three times a day or the three capsules every 6 hours schedule. The objective was to assess and compare the cure rates, adherence rates and the adverse events (AEs) in the two scBQT schedules.

## METHODS

### European Registry on *H. pylori* Management

The Hp-EuReg is an international, multicentre, prospective, non-interventional registry that has been collecting information on the management of *H. pylori* infection since 2013. The Hp-EuReg protocol[21] establishes national coordinators in each of the 29 currently participating countries, where gastroenterologists from some 300 centres have been selected. Data are recorded on the Asociación Española de Gastroenterología (Spanish Gastroenterology Association, AEG) Research Electronic Database Capture (REDCap) platform,[22] managed and hosted by the AEG (www.aegastro.es), a non-profit scientific and medical society that focuses on gastroenterology research.

Variables and outcomes are collected using an electronic case report form and include patients' demographics, previous eradication attempts, treatments used and eradication outcomes. Further information on the variables is available in the published protocol.[21]

The study was prospectively registered at ClinicalTrials.gov (NCT02328131). Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

### Data management and analysis

Data were extracted in March 2021 and a quality control check was performed on 10% of the records included at each centre.

The prescribed treatment consisted of the administration of a PPI two times a day and the three-in-one scBQT, including bismuth subcitrate potassium 140 mg, metronidazole 125 mg and tetracycline hydrochloride 125 mg for 10 days according to one of the two administration schedules: either the technical datasheet schedule, three capsules every six hours, or the four capsules three times a day scheme.

The PPI dose used for *H. pylori* eradication treatment was grouped into three categories according to the degree of acid inhibition of the different PPI schedules, as reported by Graham *et al* and Kirchheiner *et al*.[23 24] PPI dose was calculated in omeprazole equivalents by multiplying the PPI dose by a correction factor related to its relative power for inhibiting acid secretion in human studies. This factor was 0.23 for pantoprazole, 0.9 for lansoprazole, 1.6 for esomeprazole and 1.82 for rabeprazole. Thus, 40 mg of pantoprazole was considered equivalent to 9 mg of omeprazole, 30 mg of lansoprazole equivalent to 27 mg of omeprazole, 20 mg of rabeprazole equivalent to 36 mg of omeprazole and 40 mg of esomeprazole equivalent to 64 mg of omeprazole. PPI daily doses were classified as low (4.5–27 mg of omeprazole equivalents given two times a day), standard (32–40 mg of omeprazole equivalents given two times a day) or high (64–72 mg of omeprazole equivalents given two times a day).

The incidence rate of AEs, compliance and effectiveness were compared according to the different lines of therapy and to the treatment schedule (four capsules three times a day or three capsules every 6 hours).

### Effectiveness analysis

The main outcome variable was the cure rate (eradication) of the infection achieved with the treatment. *H. pylori* eradication was evaluated at least 1 month after completing the treatment by at least one of the following diagnostic methods: urea breath test, stool antigen test or histology.

Effectiveness was analysed using three different approaches: (1) a modified intention-to-treat (mITT), which aimed to reflect the closest result to those obtained in clinical practice, including all cases that had completed follow-up (ie, with a confirmatory test result—success or failure—after the eradication treatment), regardless of adherence; (2) a per-protocol (PP) analysis, which included all cases that had completed follow-up and had achieved at least 90% compliance and (3) the ITT analysis included all patients registered up to March 2021 considering the cases lost to follow-up as treatment failures.

### Safety and adherence analysis

The adherence and AE rates were evaluated using a patient questionnaire which included both open-ended and closed format questions. Adherence was defined as adequate if the patient had taken at least 90% of the prescribed drugs.

AEs were classified depending on the intensity of symptoms as evaluated by the physician: mild (not interfering with daily routine), moderate (affecting daily routine), intense/severe (prohibiting normal daily routine) and serious (causing death, hospitalisation, disability, congenital anomaly and/or requiring intervention to prevent permanent damage).

### Statistical analyses

Continuous variables were shown as means and SD, while qualitative variables were reported as absolute frequencies and percentages with their respective 95% CI.

The sociodemographic and clinical characteristics of patients allocated to either treatment schedule (three capsules every six hours or four capsules three times a day) were compared using the $\chi^2$ test for qualitative variables and the Student's t-test for quantitative variables. Likewise, the differences in the mITT effectiveness of scBQT were compared both overall and according to line of treatment using the $\chi^2$ test.

A multivariate logistic regression model was performed using mITT effectiveness as the dependent variable and the following independent variables: sex, age, scBQT schedule (three capsules every 6 hours (reference value) vs four capsules three times a day), line of therapy (first line (reference value), second line and rescue therapy from third line to sixth line), indication (dyspepsia (reference value) and peptic ulcer disease), PPI dose (low (reference value), standard and high) and adherence (no (<90% drug intake) (reference value), yes≥90%). These variables were entered by means of the backward step strategy (entry criterion: $p<0.05$ and exit criterion: $p>0.1$). The OR with respective 95% CIs were reported. To assess variance, the Hosmer-Lemeshow goodness of fit test and Nagelkerke's $R^2$ were calculated.

In all the analyses performed, a p value below 0.05 was considered statistically significant.

## RESULTS

### Baseline characteristics and prescriptions

During the study period, 3712 Spanish patients treated with an scBQT were identified. Of those, 2516 (68%) cases received the three capsules every 6 hours schedule and 1196 (32%) cases received the four capsules three times a day schedule. Regarding concomitant treatment, the most frequently used PPI were omeprazole 20 mg (n=1556, 39%), omeprazole 40 mg (n=916, 23%) and esomeprazole 40 mg (n=1332, 33%). In all, 2350 (63%) patients were women; mean age was 51 (SD: 14) years; 1716 (46%) were on concurrent medication, including PPIs (66%), acetylsalicylic acid (12%), non-steroidal anti-inflammatory drugs (NSAIDs) (29%) and statins (32%). Dyspepsia was the most frequent (67%) indication for *H. pylori* treatment. *H. pylori* eradication was confirmed by urea breath test (83.2%), stool antigen test (7.3%) and/or histology (2.5%).

A few statistically significant (though numerically small) differences in the demographic characteristics of patients were observed between the two treatment groups: in the group receiving four capsules three times a day, patients were an average of 2 years older, patients were less often receiving treatment with PPIs or NSAIDs and the indication was less frequently dyspepsia (5.8% less). Furthermore, there was a significant difference between groups in the dose of PPIs co-administered with the scBQT: the four capsules three times a day group received high-dose PPI in 51% of cases versus 24% in the three capsules every six hours group (table 1).

### Effectiveness of three-in-one scBQT

The mITT scBQT overall cure rate was significantly higher in the four capsules three times a day group (94%; 95% CI 93% to 96%) than in the three capsules every six hours group (91%; 95% CI 90% to 92%; p=0.002).

In the analysis by treatment line, the highest overall scBQT effectiveness was reported in patients naïve to treatment (94%; 95% CI 93% to 95%) when compared with second line or rescue therapy (table 2). Again, in naïve patients, cure rates were significantly higher in the four capsules three times a day group (96%) than in the three capsules every 6 hours group (93%) with significant differences between prescriptions (p=0.004).

The mITT effectiveness fell in second-line therapy. Cure rates were numerically higher in the four capsules three times a day group (90%) than in the three capsules every six hours group (88%) although the differences were not statistically significant (p=0.69).

When patients prescribed with a rescue therapy (encompassing from third line to sixth line) were analysed, cure rates

**Table 1** Characteristics of the patients

| ScBQT* | Total, N (%) (n: 3712) | Three capsules every six hours, N (%) (n: 2516) | Four capsules three times a day, N (%) (n: 1196) | P value |
|---|---|---|---|---|
| Sex, % female | 2350 (63) | 1596 (63.5) | 754 (63) | 0.823 |
| Age, mean (SD) (years) | 51 (14) | 50 (14) | 52 (14) | <0.001 |
| Concurrent medication | 1716 (46) | 1197 (48) | 519 (43) | 0.019 |
| PPIs | 1137 (66) | 853 (71) | 284 (55) | <0.001 |
| Acetylsalicylic acid | 208 (12) | 156 (13) | 52 (10) | 0.092 |
| NSAIDs | 496 (29) | 385 (32) | 111 (21) | <0.001 |
| Statins | 555 (32) | 398 (33) | 157 (30) | 0.23 |
| Penicillin allergy | 281 (8) | 203 (8) | 78 (6.5) | 0.11 |
| Indication | | | | |
| Dyspepsia | 2492 (67) | 1736 (69) | 756 (63) | <0.001 |
| Peptic ulcer disease | 544 (15) | 443 (18) | 101 (8) | <0.001 |
| PPI dose† | | | | |
| Low | 1609 (44) | 1324 (53) | 285 (24) | <0.001 |
| Standard | 910 (25) | 612 (24) | 298 (25) | |
| High | 1175 (32) | 568 (23) | 607 (51) | |
| Confirmation test | | | | |
| Urea Breath Test | 3146 (85) | 2187 (87) | 958 (80) | 0.59 |
| Stool antigen | 307 (8) | 187 (7) | 120 (10) | 0.04 |
| Histology | 96 (3) | 58 (2) | 38 (3) | 0.15 |
| Treatment line | | | | |
| Naive | 2760 (74) | 1789 (71) | 971 (81) | >0.001 |
| Second line | 646 (17) | 493 (20) | 153 (13) | |
| Rescue | 306 (8) | 231 (9) | 75 (6) | |

*ScBQT as per recommended doses: three capsules every 6 hours, or the tailored schedule of four capsules every 8 hours.
†PPI dose: low dose, between 4.5 mg and 27 mg omeprazole equivalents twice a day; standard dose, between 32 mg and 40 mg omeprazole equivalents twice a day; high dose, between 64 mg and 72 mg omeprazole equivalents twice a day.
NSAIDs, non-steroidal anti-inflammatory drugs; PPIs, proton pump inhibitors; ScBQT, single capsule bismuth quadruple therapy.

were 85.5% in the four capsules three times a day and 86% in the three capsules every six hours schedules. There were no significant differences between treatment groups (table 2). PP and ITT analysis are also given in table 2. Results of both PP and ITT analysis were virtually identical to those observed in the mITT analysis.

## Safety

In all, 995 (27%) patients presented with at least one AE. The most frequent AEs were nausea (10%), diarrhoea (9.5%) and fatigue (8%). No statistically significant differences were found between the treatment schedules: a sligthly higher overall incidence of AEs was reported in the three capsules every six hours

**Table 2** Effectiveness (by mITT, PP and ITT) according to line of treatment

| | Total (n: 3536) | | Three capsules every 6 hours* (n: 2420) | | Four capsules every 8 hours† (n: 1116) | | |
|---|---|---|---|---|---|---|---|
| **mITT** | **Cured (%)** | **95% CI** | **Cured (%)** | **95% CI** | **Cured (%)** | **95% CI** | **P value** |
| Overall | 3255 (92) | 91% to 93% | 2204 (91) | 90% to 92% | 1051 (94) | 93% to 96% | 0.001 |
| First line | 2468 (94) | 93% to 95% | 1602 (93) | 91% to 94% | 866 (96) | 94% to 97% | 0.002 |
| Second line | 537 (88) | 86% to 91% | 407 (88) | 85% to 91% | 130 (90) | 84% to 95% | 0.66 |
| Rescue therapy‡ | 250 (86) | 81% to 90% | 195 (86) | 81% to 91% | 55 (85) | 75% to 94% | 0.84 |
| | **Total (n: 3470)** | | **Three capsules every 6 hours* (n: 2376)** | | **Four capsules every 8 hours† (n: 1094)** | | **P value** |
| **PP** | **Cured (%)** | **95% CI** | **Cured (%)** | **95% CI** | **Cured (%)** | **95% CI** | |
| Overall | 3214 (93) | 92% to 93% | 2179 (92) | 91% to 93% | 1035 (95) | 93% to 96% | 0.002 |
| First line | 2442 (94) | 93% to 95% | 1587 (93) | 92% to 94% | 855 (96) | 95% to 97% | 0.003 |
| Second line | 527 (89) | 86% to 91% | 400 (89) | 85% to 91% | 127 (89) | 83% to 94% | 0.88 |
| Rescue therapy‡ | 245 (87) | 82% to 90% | 192 (87) | 81% to 91% | 53 (86) | 73% to 93% | 0.83 |
| | **Total (n: 3529)** | | **Three capsules every 6 hours* (n: 2418)** | | **Four capsules every 8 hours† (n: 1111)** | | **P value** |
| **ITT** | **Cured (%)** | **95% CI** | **Cured (%)** | **95% CI** | **Cured (%)** | **95% CI** | |
| Overall | 3247 (92) | 91% to 93% | 2201 (91) | 90% to 92% | 1046 (94) | 93% to 95% | 0.001 |
| First line | 2461 (94) | 93% to 95% | 1599 (93) | 91% to 94% | 862 (96) | 94% to 97% | 0.002 |
| Second line | 536 (88) | 85% to 91% | 407 (88) | 85% to 91% | 129 (90) | 83% to 93% | 0.88 |
| Rescue therapy‡ | 250 (86) | 81% to 90% | 195 (86) | 81% to 90% | 55 (86) | 74% to 93% | 1 |

*Three capsules every 6 hours.
†Four capsules three times a day.
‡From third line to sixth line.
BQT, bismuth quadruple therapy; ITT, Intention to treat; mITT, modified intention-to-treat; PP, per protocol.

**Table 3** Incidence of at least one AE

| | Total (n: 3614) | Three capsules every 6 hours* (n: 2461) | Four capsules three times a day† (n: 1153) | P value |
|---|---|---|---|---|
| Total | 995 (27) | 661 (27) | 334 (29) | 0.199 |
| Nausea | 383 (10) | 290 (11) | 93 (8) | 0.001 |
| Diarrhoea | 353 (9) | 248 (10) | 105 (9) | 0.324 |
| Fatigue | 296 (8) | 238 (9) | 58 (5) | <0.001 |
| Metallic taste | 258 (7) | 158 (6) | 100 (8) | 0.024 |
| Dyspepsia | 163 (4) | 130 (5) | 33 (3) | 0.001 |
| Abdominal pain | 238 (6) | 143 (6) | 95 (8) | 0.011 |
| Anorexia | 175 (5) | 167 (7) | 8[1] | <0.001 |
| Vomiting | 164 (4) | 105 (4) | 59 (5) | 0.333 |
| Heartburn | 77 (2) | 70 (3) | 7[1] | <0.001 |
| Serious AEs | 5 (0.1) | 5 (0.1) | 0 (0) | 0.174 |
| Interruption of treatment due to AEs | 54 (1.4) | 37 (1.5) | 17 (1.4) | 0.556 |

*BQT as per the schedule included on the technical datasheet: three capsules every 6 hours.
†BQT as per the tailored schedule of four capsules every 8 hours.
.AEs, adverse events; BQT, bismuth quadruple therapy.

**Table 4** Multivariate logistic regression final model; dependent variable was effectiveness (by mITT)

| | | 95% CI | | |
|---|---|---|---|---|
| | OR | Lower | Upper | P value |
| Pylera dose (reference: three capsules every 6 hours) | | | | |
| Four capsules three times a day | 1.58 | 1.07 | 2.33 | 0.022 |
| Line (reference: first line) | | | | |
| Second line | 0.67 | 0.47 | 0.96 | 0.002 |
| Rescue treatment from third line to sixth line | 0.51 | 0.33 | 0.78 | |
| PPI dose (reference: low dose) | | | | |
| Standard | 2.08 | 1.37 | 3.14 | 0.001 |
| High | 1.46 | 1.03 | 2.06 | |
| Adherence (reference: no (<90% drug intake)) | | | | |
| Yes (≥90% drug intake) | 10.3 | 5.62 | 18.8 | <0.001 |

mITT, modified intention-to-treat; PPI, proton pump inhibitor.

group (29%) than in the four capsules three times a day group (27%). The differences in the types of AE according to treatment group were as follows: nausea (11.5% in the three capsules every 6 hours group vs 7.8% in the four capsules three times a day group), fatigue (9.5% vs 4.8%), dyspepsia (5.2% vs 2.8%), anorexia (6.6% vs 0.7%), heartburn (2.8% vs 0.6%), metallic taste (6.3% vs 8.4%) and abdominal pain (5.7% vs 7.9%); all the differences were statistically significant.

Five (0.5%) serious AEs required hospitalisation, all in the three capsules every 6 hours group. One patient had mild hypertension, two had *Clostridioides difficile* infection causing diarrhoea, one had treatment-related nausea and abdominal pain and one had a stroke on the 4th day of treatment, which had to be interrupted (table 3).

### Adherence

Overall adherence to treatment was 97.1%, with no statistically significant differences between groups: 96.8% in the three capsules every 6 hours group versus 97.3% in the four capsules three times a day.

### Multivariate analysis

The multivariate logistic regression analysis showed that administering scBQT in the four capsules three times a day schedule (OR: 1.58; 95% CI 1.07 to 2.33), using standard (OR 2.08, 95% CI 1.37 to 3.14) or high-dose PPIs (OR: 1.5, 95% CI 1.03 to 2.06) and adequate adherence (OR: 10.3, 95% CI: 5.62 to 18.8) were independent predictive factors for cure of the infection.

In addition, previous treatment failure was significantly associated with a decrease in the probability of cure in second line (OR: 0.67, 95% CI 0.47 to 0.96) and successive (OR: 0.51, 95% CI: 0.33 to 0.78) lines of treatment (table 4).

The model had an adequate goodness of fit (Hosmer-Lemeshow test: 0.241) and a Nagelkerke $R^2$ of 7.7%.

## DISCUSSION

Our study suggests that giving scBQT three times a day instead of the currently recommended four times a day schedule significantly increases cure rates, especially in treatment-naïve patients (96% vs 93%, respectively), and slightly reduces the incidence of AEs. Furthermore, the multivariate analysis confirmed that using the scBQT three times a day scheme was an independent predictor of cure, supporting the conclusions of the study. Other independent predictors of the cure of the infection were the use of standard or high dose of PPI, the treatment line and adherence as captured by the register. Regarding PPI, it should be noted that the omeprazole 20 mg two times a day dose account for more than 90% of the schedules included in the low-dose PPI group. This is important, as the scBQT technical datasheet recommends this dose of PPI; however, our data strongly suggest that cure rates increased when omeprazole 40 mg (representing the great majority of the treatments in the standard PPI dose group) or esomeprazole 40 mg (the high PPI dose group) two times a day was prescribed as concomitant treatment.

Although the increase in cure rates was numerically small, it may be clinically significant as it brings treatment effectiveness closer to the desired hundred per cent cure rate. This improvement may have an impact on decision-making in some of the current management therapeutic strategies.

At present, there are no other reports in the literature comparing the effectiveness, compliance and safety of the three times a day and four times a day schedules. Data on the effectiveness of the three times a day schedule, however, have been reported as small series and conference proceedings, generally finding better adherence and cure rates when compared with four times a day schedules.[20]

As regards previous reports, pivotal scBQT studies using four times a day schedules had shown PP cure rates above 90%.[14 15] Furthermore, in clinical practice, a Hp-EuReg study evaluating the four times a day treatment in a large cohort of 1196 patients also confirmed cure rates above 90% with scBQT, being one of the most effective treatments currently available[14]; a metanalysis also presented similar results.[25]

Several aspects of the present study merit comment. First, it is no coincidence that a three times a day treatment schedule was developed in Spain. The late eating habits of the Spanish are well known; meals have been progressively delayed to match solar time.[26] In consequence, the European approach to four times a day schedules—one intake in each meal plus one before going to bed—is difficult to apply in Spain as dinner is usually taken late and dinner and bedtime are often very close. In this context, using three times a day with meals was believed to improve adherence.

In connection, a surprising result of our study is that adherence was not better in the three times a day schedule although, according to the literature, a notable increase in adherence would have been expected.[18 19] In our study, global adherence to

treatment was excellent (97.1%) in line with previous data from the Hp-EuReg.[14] Unexpectedly, three times a day and four times a day schedules showed very similar adherence rates (97.1% vs 96.8%). There may be some alternative explanations for this finding. First, the use of handouts clarifying the treatment schedule may have raised adherence in both groups. Although its use is infrequent in our setting, the register did not collect data on this topic, so we cannot rule out the possibility that its use would explain the exceedingly high degree of adherence. Alternatively, the particularly high interest of the co-investigators in *H. pylori* may have had a positive effect on adherence. Finally, the lack of differences between the groups might raise the issue of whether the methods to determine non-adherence in the Hp-EuReg were sufficiently sensitive, as differences in adherence constituted the most probable explanation of the differences in effectiveness between treatment groups. Regarding safety, all AEs described are consistent with those identified in previous studies. In our cohort, 27% of patients presented AEs, which were slightly more frequent in the four times a day group. Only 0.5% of adverse reactions were serious, all of them in the four times a day group. However, presenting an AE did not have a significant effect on adherence to treatment or its effectiveness.

A major limitation of the present study is that data did not come from a randomised controlled trial (RCT). RCTs are difficult to run and are expensive; furthermore, they are not free of biases and cannot cover every aspect of care. Relying exclusively on RCTs may notably slow down improvements in medicine and, in fact, observational studies may also help to identify and disseminate best practices. An additional point to make is that, as treatments become more effective, the sample size needed to find significant differences increases exponentially, raising costs and lengthening recruitment time. For this reason, it is unlikely that an RCT will ever be performed on the particular topic covered by the present study.

However, although the registry is recorded prospectively, the comparison of data is not as reliable as it would have been in an RCT. In fact, the cohorts compared showed several baseline differences that may, in part, explain the differences observed in outcomes, the most remarkable being that the group receiving a three times a day schedule also received more often a standard or high PPI dose. Multivariate analysis showed, however, that both scBQT schedule and PPI dose were independent predictors of cure. This suggests that both the three times a day treatment and standard/high-dose PPI had an independent effect on improving *H. pylori* eradication rates. Furthermore, as shown in table 2, three times a day schedules performed numerically better in all treatment lines, although the differences were only significant for the whole group and for first-line therapy. In rescue therapy, the reduced number of patients and the lower cure rates probably ruled out the possibility of reaching statistical significance.

In addition, as in previous studies of the Hp-EuReg,[10–12] data on *H. pylori* resistance to antibiotics were available in less than 10% of our cases; in consequence, the presence of resistances potentially affecting scBQT effectiveness could not be analysed. However, it is well known that *H. pylori* antibiotic resistances were very high in our area. Thus, the reported primary resistances to clarithromycin, metronidazole and quinolones were 28%, 31% and 24%, respectively. In contrast, resistance to tetracycline was extremely rare (0.1%).[27] Antibiotic stewardship, with the selection of antibiotics with a very low rate of resistance (like tetracycline in our case), is essential. Metronidazole, however, is an exception to this rule as it has been repeatedly shown that using 10-day or 14-day schedules may overcome 'in vitro' resistances.[25] In this regard, our article identified mITT cure rates clearly above 90% with both scBQT schedules, despite very high local rates of metronidazole resistances. We can, therefore, reliably conclude that antibiotic resistances had (at most) a minimal effect on the eradication rates in our study.

Regarding the strengths of the study, the Hp-EuReg is currently the largest sample of *H. pylori* treated patients worldwide, which allows us to collect data from series of patients in a real-world clinical setting and to detect differences and compare treatments in a way that would not be possible in a randomised clinical trial.

Our data suggest that three times a day schedules are not only equivalent but even slightly safer and more effective than the currently recommended four times a day schedule. Following the same line, our results may raise the question of whether scBQT may be further simplified using two times a day schedules. This possibility should be evaluated in future studies.

Finally, the article adds strong evidence to the previous data suggesting that scBQT—at both schedules analysed—is currently one of the most effective and safest *H. pylori* treatments. Efforts to make this treatment available in countries where it is currently still inaccessible are now warranted.

In conclusion, three in one scBQT administered as four capsules three times a day for 10 days appears to be more effective than the 10-day four times a day schedule recommended in the technical datasheet. This treatment schedule was strongly effective both as a first-line therapy and rescue therapy. The results of this study support the use of scBQT in a four capsules three times a day schedule to eradicate *H. pylori* infection. Nevertheless, these findings should be confirmed in other geographical regions and clinical settings.

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