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European Registry on *Helicobacter pylori* management: Single-capsule bismuth quadruple therapy is effective in real-world clinical practice

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Abstract

Background: There has been resurgence in the use of bismuth quadruple therapy (proton pump inhibitor, bismuth, tetracycline and metronidazole) for treating *Helicobacter pylori* infection thanks to a three-in-one single-capsule formulation.

Objective: To evaluate the effectiveness and safety of the single-capsule bismuth quadruple therapy.

Methods: Data were collected in a multicentre, prospective registry of the clinical practice of gastroenterologists on the management of *H. pylori* infection, where patients were registered at the Asociación Española de Gastroenterologia REDCap database on an electronic case report form until January 2020. Effectiveness by modified intention-to-treat and per-protocol as well as multivariable analysis were performed. Independent factors evaluated were: age, gender, indication, compliance, proton pump inhibitor dose and treatment line.

Results: Finally, 2100 patients were prescribed single-capsule bismuth quadruple therapy following the technical sheet (i.e., three capsules every 6 h for 10 days). The majority of these patients were naive (64%), with an average age of 50 years, 64% women and 16% with peptic ulcer. An overall modified intention-to-treat effectiveness of 92% was achieved. Eradication was over 90% in first-line treatment (95% modified intention-to-treat, $n = 1166$), and this was maintained as a rescue therapy, both in second (89% modified intention-to-treat, $n = 375$) and subsequent lines of therapy (third to sixth line: 92% modified intention-to-treat, $n = 236$). Compliance was the factor most closely associated with treatment effectiveness. Adverse events were generally mild to moderate, and 3% of patients reported a severe adverse event, leading to discontinuation of treatment in 1.7% of cases.

Conclusions: Single-capsule bismuth quadruple therapy achieved *H. pylori* eradication in approximately 90% of patients in real-world clinical practice, both as a first-line and rescue treatment, with good compliance and a favourable safety profile.

KEYWORDS
bismuth, eradication, *Helicobacter pylori*, Pylera, quadruple

Key Summary

- The development of a three-in-one single-capsule formulation has led to a resurgence in the use of bismuth quadruple therapy (BQT) to treat *Helicobacter pylori* infection.
- In the largest study carried out to date, the effectiveness of single-capsule BQT was optimal both as a firstline and as a rescue therapy.
- Compliance was the factor most closely associated with treatment effectiveness.
- Single-capsule BQT eradicates *H. pylori* in approximately 90% of patients in real-world clinical practice, with a favourable safety profile.

INTRODUCTION

Helicobacter pylori infection is known to be at the root of several of important gastrointestinal diseases, ranging in severity from gastritis, gastroduodenal ulcer disease and preneoplastic lesions, to gastric cancer.[1] In all of these conditions, eradication of this bacterium is considered the best course of action.[2] In addition, *H. pylori* has been detected in more than half the population worldwide, making it a global health burden.[3] However, we are still in a situation where no therapy is available that achieves a 100% cure rate. Hence, treatment of *H. pylori* infection remains an important clinical challenge and the current consensus is that suitable therapies should achieve a cure rate of at least 90%.[4,5] Nevertheless, the success rate of standard therapies tends to decline due to the increased resistance to antibiotics around the globe.[6–8]

All therapies to treat *H. pylori* are based on a combination of antibiotics and other adjuvants, ranging from triple therapies involving a proton pump inhibitor (PPI) plus two antibiotics, to quadruple therapies that include bismuth-free (sequential, concomitant, hybrid regimens) or bismuth-based therapies.[9] The triple therapy traditionally recommended to eradicate *H. pylori*, combining the use of a PPI with clarithromycin and amoxicillin or metronidazole, yet appears to fail in over 20% of patients, mainly due to the increasing resistance to these antibiotics worldwide.[7] When considering *H. pylori* therapies, it is important to differentiate between first-line therapies and rescue regimens, as the latter are usually compromised by selection or the acquisition of secondary bacterial resistance following previous failed attempts at eradication.[10–13]

Bismuth quadruple therapy (BQT) classically involves a combination of PPI, bismuth, and the antibiotics metronidazole and tetracycline. Randomised clinical trials have shown that BQT eradicates *H. pylori* better than standard triple therapies and, indeed, the use of BQT may be particularly recommended in areas of high clarithromycin resistance.[9] However, the limited availability of bismuth salts and tetracycline in some countries has restricted the use of BQT. Interest in this therapy resurged with the appearance of the three-in-one single-capsule BQT (marketed as Pylera), containing bismuth, metronidazole and tetracycline, and used as both a first-line and rescue therapy, as recently reported in a meta-analysis.[14] Indeed, as a first-line therapy, 10 days omeprazole and the three-in-one single-capsule BQT was more effective than a 7 days clarithromycin-based triple therapy in a European phase III trial,[15] confirming the effectiveness of 10 days single-capsule BQT initially reported.[16]

Other factors may also influence the effectiveness of both first-line and rescue therapies, making it necessary to obtain more information regarding the effectiveness of distinct treatments. For this reason, a European Registry on *H. pylori* Management (Hp-EuReg) was set up to collate data regarding the diagnosis, treatment and management of adult patients from over 300 centres in 28 countries.[17] In the current paper, we present an analysis of the data extracted from this registry regarding the patients who were prescribed the three-in-one single-capsule BQT as part of the strategy to manage their *H. pylori* infection. Accordingly, we analysed the data on the effectiveness and tolerance of this therapy in a real-world clinical setting as different lines of use. Moreover, we performed a multivariable analysis in an attempt to identify the factors that most strongly influence the success of this therapy with a view to further improving its effectiveness.

METHODS

European Registry on *H. pylori* management (Hp-EuReg)

The Hp-EuReg is an international, multicentre, prospective, non-interventional registry that has been recording information on the management of *H. pylori* infection since 2013. The Hp-EuReg scientific committee is currently made up of: Javier P. Gisbert (principal investigator), Francis Megraud, Colm A. O'Morain, Ignasi Puig and Olga P. Nyssen (the two latter are also scientific directors). The Hp-EuReg protocol[17] establishes national coordinators in the 28 countries selected, where gastroenterologists have been recruited at some 300 centres to provide input to the registry. These specialists introduced a series of variables and outcomes into the registry's database using an electronic case report form. The variables included: the patient's demographic information; any previous attempts at eradication and the treatments employed; the outcomes of any treatment, recording details such as the compliance, the cure rate, the follow-up, and so on; and any adverse event (AE) reported. The REDCap database[18] is managed and hosted by the Asociación Española de Gastroenterologia (www.aegastro.es), a nonprofit scientific and medical society that focuses on gastroenterology research. The study was approved by the ethics committee of La Princesa University Hospital (Madrid, Spain) and was prospectively registered at ClinicalTrials.gov (NCT02328131).

Data analysis

Data were extracted in January 2020, and a quality control check was performed on at least 10% of the records included for each country and centre. The dose of the PPI used for *H. pylori* eradication treatment was grouped into three categories as reported by Graham et al.[19] and Kirchheiner et al.[20]: low dose, if the potency of acid inhibition was between 4.5 and 27 mg omepra-zole equivalents when given twice daily; standard dose, between 32 and 40 mg omeprazole equivalents when given twice daily; and high dose, between 54 and 128 mg omeprazole equivalents when given twice daily.

Effectiveness analysis

The aim of the present analysis was to evaluate the effectiveness and safety of the three-in-one single-capsule BQT when used as any line

of treatment (first-line and any rescue therapy). *H. pylori* eradication was confirmed with at least one of the following diagnostic methods: urea breath test, stool antigen test and/or histology; at least 1 month after completing eradication treatment.

The main outcome used was the eradication rate achieved with the treatment and it was studied in three subgroups of patients: (a) the intention-to-treat (ITT) analysis included all patients that had been registered up to January 2020 and that had at least a 6 month follow-up, in which lost to follow-up cases were deemed treatment failures; (b) a per-protocol (PP) analysis which included all cases that had a complete follow-up and that had achieved at least 90% compliance with the drug treatment, as defined in the protocol; and (c) a modified ITT (mITT) that aimed to reflect the closest result to that obtained in clinical practice, whereby the mITT included all cases that had completed the follow-up (i.e., they had undertaken a confirmatory test—success or failure—after the eradication treatment), regardless of compliance but excluding those with an incomplete follow-up. The effectiveness analyses were performed jointly for patients treated empirically or when treatment was based on the testing of bacterial resistance (as performed in routine clinical practice in each centre). Additional effectiveness analyses were performed separately when the results of an antibiogram were available.

Statistical analyses

Continuous variables were summarised as the mean and standard deviation, while qualitative variables were presented as the absolute and relative frequencies, displayed as percentages (%). A multivariable analysis was performed to study the relation between the single-capsule BQT eradication rate in the mITT population and several variables: age, sex (female [ref] vs. male), indication (dyspepsia and others [ref] vs. ulcer disease), compliance (no [ref] vs. yes, as taking >90% of the drug intake), PPI dose (low [ref] vs. standard, and low vs. high); treatment line (first-line [ref] vs. second-line vs. all remaining rescue therapies, i.e., third-line treatment or greater).

RESULTS

Overview and baseline characteristics

From its initiation in May 2013 until January 2020, 34,460 cases from 28 countries were registered in the Hp-EuReg. Of these, 3439 cases were treated with single-capsule BQT, and 2100 (6.1%) were prescribed this treatment according to the regimen indicated in the technical sheet (three capsules q.i.d. for 10 days). These latter cases were those considered to be valid for current analysis, excluding the remaining cases. The average age of the cohort analysed was 50.4 (±18.0) years, of whom 64% were women.

The two main medical conditions (81%) for which the single-capsule BQT was prescribed were dyspepsia (66%) and peptic ulcer (16%). Although 28 countries participated in the Hp-EuReg, patients only received BQT with the single capsule in 10 of these countries (Table 1). In the five principal countries in which the single-capsule BQT was used, it was employed as a first-line treatment in between 46% and 68% of the cases. All the cases studied were treated between 2015 and 2019.

Treatment use

In the cohort analysed, treatment with the single-capsule BQT was used in different circumstances, mostly in naive patients (64%) or as a second-line rescue therapy (22%). In the remaining cases (14%), the treatment was used as a rescue treatment after different numbers of precious *H. pylori* eradication attempts: third-line (10%); fourth-line (2.8%); and fifth-line and beyond (1.4%). Also, the PPI doses used in combination with the single-capsule BQT varied, with the largest proportion receiving a low PPI dose (54%), the remainder receiving a standard (21%) or a high PPI dose (25%).

Effectiveness of single-capsule BQT treatment in different lines of therapy

The effectiveness of the single-capsule BQT was evaluated using three different measures (ITT, PP and mITT), although we focused on the mITT, as previously mentioned in Section 2. This singlecapsule BQT achieved a 95% eradication rate when used as a first-line therapy and its success rate as a rescue therapy was also over 90% eradication This success was evident when used both as a second-line treatment (89% eradication, $n = 375$) and as a subsequent treatment line, from a third to a sixth line of therapy (92% eradication, $n = 236$; Table 2). Also, overall mITT eradication significantly improved ($p < 0.05$) when either standard (recommended) or high PPI doses were used (94% both) as compared to low doses (90%). Finally, a sensitivity analysis was performed excluding patients from Spain: overall mITT effectiveness for non-Spanish countries was 91%, which did not statistically differ with that of Spain (92.1%).

Antibiotic resistance

The influence of bacterial antibiotic resistance on the effectiveness of single-capsule BQT was evaluated, in particular resistance to clarithromycin, metronidazole or both. The therapy achieved 100% eradication in bacterial antibiotic resistant strains when used as a first or second-line treatment, both single clarithromycin and metronidazole-resistant infections, and those resistant to both antibiotics (Table 3). However, this effectiveness decreased when single-capsule BQT was used as a third-line treatment for clarithromycin

TABLE 1 Patients' basal characteristics

Characteristics at baseline	*N* (%)
Single-capsule prescriptions (3 capsules q.i.d. for 10 days)	2100 (6.1)[a]
Female	1337 (63.8)
Age, mean (SD)	50.4 (18.0)
Age 18–30 years	151 (7.3)
Age 31–50 years	745 (36.1)
Age 51-highest years	1167 (56.6)
Ethnic background (*N*, %)	
Caucasian	1994 (95.0)
Black	13 (0.6)
Asian	28 (1.3)
Other	33 (1.6)
Concurrent medication	944 (45.0)
Proton pump inhibitors (daily or on demand)	675 (71.6)
Acetylsalicylic acid	138 (14.6)
NSAIDs	244 (25.9)
Statins	313 (33.2)
Penicillin allergy	670 (3.1)
Indication (*N*, %)	
Dyspepsia	1367 (65.6)
Ulcer disease	332 (15.8)
No culture performed	2052 (97.7)
Culture (with a result of the antibiotic resistance test)	48 (2.3)
No resistance	3 (6.2)
Clarithromycin resistance	33 (68.7)
Metronidazole resistance	29 (60.4)
Dual clarithromycin + metronidazole resistance	22 (45)
PPI dose	
Low	1121 (53.5)
Standard	445 (21.2)
High	529 (25.3)
Compliance	
No (<90% drug intake)	66 (3.3)
Yes (≥90% drug intake)	1916 (96.7)
Country	
Spain	1677 (79.9)
Italy	274 (13.0)
Portugal	88 (4.2)
Germany	35 (1.7)
Slovenia	17 (0.8)
Russia	3 (0.1)
France	2 (0.1)
Czech Republic	2 (0.1)
Greece	1 (0.0005)
Lithuania	1 (0.0005)

Note: (low dose 4.5–27 mg omeprazole equivalents, b.i.d; standard dose 32–40 mg omeprazole equivalents, b.i.d.; high dose 54–128 mg omeprazole equivalents, b.i.d.).

Abbreviations: *N*, number of cases; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor; SD, standard deviation.

[a]%, Percentage relative to the total number of patients in the registry (n = 34,460).

(67% eradication, n = 9) and metronidazole-resistant (73% eradication, n = 11) infections, and for those infections resistant to both these antibiotics (62%, n = 8; Table 3).

Safety

At least one AE was reported by 29% of the patients. The most common AEs reported were nausea (9.5%), diarrhoea (8%), fatigue (6.5%), metallic taste (dysgeu-sia, 5%), dyspepsia (5%) abdominal pain (5%) and vomiting (3%; see Table 4 for a full list of AEs). These AEs had a mean duration of from 4.8 (±2.9) to 8.4 (±2.3) days. While the AEs were generally mild (99%) and transient, 17% of the patients who experienced fatigue considered it to be severe, as did 14% of those who had anorexia and 10% of those who reported having heartburn (Table 4). Nevertheless, the AEs as a whole had only a limited effect on compliance (3.3% of cases) and provoked a cessation of the treatment in 36 cases (1.7%). Less than 1% of the cases experienced serious AEs that required hospitalisation during the treatment: two patients due to infection by *Clostridium difficile*; one patient with high blood pressure; one patient due to previous aggravated hypocalcaemia; and one last patient with a range of AEs that included nausea, vomiting and abdominal pain. In this latter patient, the AEs were directly related to the single-capsule BQT as no other underlying cause could be identified. In all five of these patients the AEs resolved after treatment, leaving no sequelae.

Univariate analysis

As shown in Table S1, the following variables were significantly associated with higher mITT eradication rates: compliant as opposed to noncompliant patients (93% vs. 44%); when standard or high (both

TABLE 2 Single-capsule bismuth quadruple therapy effectiveness by line of treatment

	ITT		PP		mITT	
	N (%)	95% CI	*N* (%)	95% CI	*N* (%)	95% CI
Overall	1724 (85.2)	(83.6–86.7)	1761 (92.8)	(91.6–94.0)	1777 (91.9)	(90.6–93.1)
First-line	1135 (88.1)	(86.3–89.9)	1158 (95.5)	(94.2–96.6)	1166 (94.6)	(93.2–95.8)
Second-line	361 (81.5)	(77.7–85.2)	370 (90.2)	(87.2–93.2)	375 (89.3)	(86.2–92.3)
Rescue treatment from third-line to sixth-line	228 (85.2)	(73.2–82.9)	233 (85.0)	(80.6–89.4)	236 (91.9)	(79.5–88.4)

Note: The χ^2 test showed statistical significant differences in effectiveness for the different treatment lines as measured by ITT, PP and mITT ($p < 0.001$).
Abbreviations: CI, confidence interval; ITT, intention-to-treat; mITT, modified intention-to-treat; PP, per protocol.

TABLE 3 Effectiveness (by treatment line) of single-capsule bismuth quadruple therapy in patients with antibiotic bacterial resistance

	Overall	First-line	Second-line	Third-line	Fourth-line	Fifth-line
Clarithromycin resistant						
E	26	2	7	6	7	4
N	30	2	7	9	7	5
%*E*	86.7	100	100	66.7	100	80
95% CI	(69–96)	(16–100)	(59–100)	(30–92)	(59–100)	(28–99)
Clarithromycin susceptible						
E	14	2	5	4	0	1
N	17	2	5	4	2	1
%*E*	82.4	100	100	100	0	100
95% CI	(56–96)	(16–100)	(48–100)	(40–100)	NA	(1.2–99)
Metronidazole resistant						
E	21	2	4	8	4	3
N	27	2	4	11	6	4
%*E*	77.8	100	100	72.7	66.6	75
95% CI	(58–91)	(16–100)	(40–100)	(39–94)	(22–95)	(19–99)
Metronidazole susceptible						
E	19	2	8	2	3	2
N	20	2	8	2	3	2
%*E*	95	100	100	100	100	100
95% CI	(75–99)	(16–100)	(63–100)	(16–100)	(29–100)	(16–100)
Dual resistant						
E	16	1	3	5	4	3
N	20	1	3	8	4	4
%*E*	80.0	100	100	62.5	100	75
95% CI	(56–94)	(1.2–99)	(29–100)	(24–91)	(40–100)	(19–99)
Dual susceptible						
E	24	3	9	5	3	2
N	27	3	9	5	5	2
%*E*	88.9	100	100	100	60	100
95% CI	(71–97)	(29–100)	(66–100)	(48–100)	(14–94)	(16–100)

Abbreviations: % *E*, percentage eradication in the per-protocol analysis; CI, confidence interval; *E*, number of patients eradicated; *N*, total number of patients treated; NA, not applicable.

TABLE 4 Frequency, intensity and duration of adverse events

	Frequency of AEs			Intensity of AEs									Length of AEs
	N	%	95% CI	Mild (*N*)	%	95% CI	Moderate (*N*)	%	95% CI	Severe (*N*)	%	95% CI	Mean days (SD)
Nausea	199	9.5	(8.2–10.7)	116	58.3	(51–65)	75	38.0	(31–44)	8	4.0	(1.0–7.0)	6.6 (3.2)
Diarrhoea	174	8.3	(7.1–9.5)	81	46.6	(39–54)	89	51.1	(43–59)	4	2.3	(0.6-5.7)	6.5 (3.9)
Fatigue	136	6.5	(5.4–7.5)	48	35.3	(27–44)	65	47.8	(39–56)	23	16.9	(10.2–23.6)	8.3 (3.2)
Metallic taste	108	5.1	(4.2–6.1)	62	57.4	(48–67)	45	41.7	(32–51)	1	0.9	(0.02–5.0)	7.7 (3.7)
Dyspepsia	105	5.0	(4.0–5.9)	40	38.1	(28–48)	60	57.1	(47–67)	5	4.8	(1.6–10.8)	7.8 (3.4)
Abdominal pain	103	4.9	(3.9–5.58)	46	44.7	(35–55)	51	49.5	(39–60)	6	5.8	(0.8–10.8)	7.3 (5.0)
Anorexia	79	3.8	(2.9–4.6)	13	16.5	(7.6–25)	55	69.6	(59–80)	11	13.9	(5.6–22.2)	8.4 (2.3)
Vomiting	63	3.0	(2.2–3.7)	30	47.6	(34–61)	29	46.0	(33–59)	4	6.3	(1.7–15.5)	4.8 (2.9)
Heartburn	40	1.9	(1.3–2.5)	8	20.0	(6.3–34)	28	70.0	(54–85)	4	10.0	(2.8–23.6)	6.8 (2.3)
Total	570	28.8[a]	(27–31)	444	22.0[a]	(21–24)	497	25.0[a]	(23–27)	66	3.3[a]	(2.5–4.2)	7.2 (3.3)
Serious AEs	5	0.9	(0.3–2.0)										
Compliance	1916	96.7	(96–97)										
Ceased	36	1.7	(1.1–2.4)										
Medications													
Due to AEs													

Abbreviations: AEs, adverse events; CI, confidence interval; *N*, number of reports; SD, standard deviation.

[a]Percentage relative to the total of patients reporting information on the intensity of the adverse event ($n = 1976$).

94%) PPI doses were used as opposed to low doses (90%); and when the treatment was administered as first-line (95%), or second-line (89%) therapy.

Multivariable analysis

Stepwise multivariable logistic regression analysis was performed in an attempt to define the variables that most strongly influenced the mITT eradication rate. We used a backward modelling strategy, and models were compared using the log-likelihood ratio. This analysis showed that of all the factors analysed, compliance (odds ratio [OR]: 16.0, 95% confidence interval [CI]: 7.85–32.5) and a high PPI dose (OR: 1.80, 95% CI: 1.14–2.78) were significantly associated with higher therapy success; however, second-line treatment (OR: 0.50, 95% CI: 0.33–0.75) or third-line or greater treatment (OR: 0.30, 95% CI: 0.20–0.45) were associated with lesser effectiveness.

DISCUSSION

In this study we have taken advantage of the Hp-EuReg, which has collected comprehensive information from patients diagnosed with *H. pylori* infection in several countries, to analyse the effectiveness of single-capsule BQT and the main factors that influence its effectiveness. The use of this registry, containing 2100 patients infected by *H. pylori* and treated with single-capsule BQT, makes this the largest study of its kind to date. The information extracted from the registry highlights the effectiveness of single-capsule BQT in eradicating *H. pylori* in patients when used as a therapy in different treatment lines and in conjunction with different doses of PPIs. This therapy appears to be safe and successful, both as a first-line and as a rescue therapy, even against antibiotic-resistant bacteria.

In terms of effectiveness, a 90% eradication rate has been accepted as the arbitrary threshold for an optimal *H. pylori* treatment.[4] In the current study, we found that in real-world use, single-capsule BQT achieved an eradication rate above 90% when prescribed as a first-line therapy. Moreover, a similar eradication rate was observed when this therapy was used as a rescue therapy, from a second-line to sixth-line treatment, as reported previously.[21–24] This is higher than the rates of eradication achieved by treatment regimens established previously using triple therapies.[16] In general, the loss of effectiveness of these precious therapies has been associated with bacterial resistance to antibiotics, mainly to clarithromycin or metronizadole.[14]

Although information regarding bacterial antibiotic resistance was scarce in this study, the analysis showed that single-capsule BQT was effective (≥90%) in eradicating infection in those patients with bacteria resistant to either clarithromycin or metronidazole, or both. This was also confirmed when the treatment was used as either a first-line or second-line therapy, as reported previously in an earlier meta-analysis.[14] However, in our study, it did not appear to be as effective against *H. pylori* infections that were resistant to one of these antibiotics when used as a third-line therapy.

Nevertheless, this response should be confirmed in larger samples, highlighting the utility of performing susceptibility testing on patient samples in order to control better the rates of antibiotic resistance and the potential of specific treatments to overcome this hurdle.[11]

In addition, we evaluated further factors that might influence the effectiveness of single-capsule BQT in eradicating *H. pylori* infection. While the different PPI doses appeared to have some effect on the effectiveness of the treatment, the overall effectiveness of the therapy was maintained at the threshold consensus value of 90%, even at the lowest PPI dose. As indicated above, the line of treatment influenced the effectiveness in eradicating infection, maintaining the optimal effectiveness in first-line and rescue therapy. However, the most significant factor influencing the effectiveness of single-capsule BQT was compliance. There is evidence that bacterial resistance[2,7,25] and compliance[26] represent the most important factors influencing the success of *H. pylori* eradication strategies. In our study, data regarding antibiotic bacterial resistance were only available from 6% of the cases, such that resistance was unlikely to have a strong impact on the rate of eradication. Indeed, the high success rates of the single-capsule BQT when used as a rescue therapy suggest that bacterial resistance may have a weaker negative effect on this treatment than on other alternative regimens.

In contrast to the information on bacterial resistance, compliance data were available from nearly 95% of the cases, offering a better picture of how it might influence the rate of eradication. In the registry, compliance was excellent in 97% of cases and even though three-in-one single-capsule BQT involves taking three capsules four times daily plus a PPI twice daily, it is still less complex than the classic bismuth-containing quadruple therapy published previously.[16]

Finally, it should be noted that the AEs described are consistent with those identified in previous studies[14] and in the drug's technical data sheet. Moreover, the AEs experienced did not have a significant effect on compliance or on the effectiveness of the treatment. The treatment's safety profile was similar to that of an eradication therapy using three antibiotics, as reported in previous systematic reviews.[14,27]

There are several limitations that should be borne in mind in relation to our study. In terms of the information extracted from the registry, certain features were particularly notable. At the time of sampling, single-capsule BQT was only used to treat a small percentage of the cases in the registry (6%), derived principally from three main countries (97% in Spain, Italy and Portugal). This geographical bias most likely reflected the commercialisation strategy and implementation of this treatment as well as the year this therapy was launched in these countries, and it might question the generalisability of the results obtained to a pan-European level. Nevertheless, the size of the cohort analysed (2100 patients), the largest of its type studied to date, suggests that the data obtained for patients with this profile are reliable. While this reflects the situation in Europe, it may perhaps be a limitation when considering extrapolating the data to a more global population. Hence, it will be important to carry out similar studies on other populations around the world.

In summary, we have carried out a comprehensive study on the effectiveness of single-capsule BQT in real-world cases of *H. pylori* infection collected from the Hp-EuReg, the largest cohort analysed to date. Accordingly, this therapy appears to be an effective and safe treatment to eradicate *H. pylori* infection, both as a first-line and rescue therapy overcoming those antibiotic-resistant strains. The success of this therapy is strongly influenced by the compliance with therapy. While these data seem to support the use of this single-capsule BQT to combat *H. pylori* infection, this should be further confirmed in other regions.

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CONFLICT OF INTERESTS

Javier P. Gisbert served as a speaker, a consultant and advisory member for, or has received research funding from Mayoly, Allergan and Diasorin. Olga P. Nyssen received research funding from Allergan and Mayoly. Manuel Castro-Fernandez received retribution from Allergan for training activities. Angeles Perez-Aisa received retribution from Allergan and Mylan for training activities. The remaining authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

Olga P. Nyssen: *scientific director, member of the project's scientific committee, coordinated the study, designed and programmed the electronic case report form, reviewed, analysed and interpreted the data, drafted the manuscript and approved the submitted manuscript*. Angeles Perez-Aisa, Manuel Castro-Fernandez, Rinaldo Pellicano, Jose M. Huguet, Luis Rodrigo, Juan Ortuño, Blas J. Gomez-Rodriguez, Miguel Areia, Monica Perona, Oscar Nuñez, Marco Romano, Liliana Pozzati, Miguel Fernandez-Bermejo, Peter Malfertheiner, Luis Fernanadez-Salazar, Dino Vaira: *collected and helped interpret the data, critically reviewed the manuscript and approved the submitted manuscript*. Antonio Gasbarrini, Ricardo M. Pinto, Marino Venerito: *acted as national coordinators and as recruiters. They selected national recruiters, collected and helped interpret the data, critically reviewed the manuscript and approved the submitted manuscript*. Ignasi Puig: *scientific director and member of the project's scientific committee, critically reviewed the manuscript draft and approved the submitted manuscript*. Francis Megraud: *member of the project's scientific committee, designed the protocol, planned the study, critically reviewed the manuscript and approved the submitted manuscript*. Colm O'Morain: *member of the project's scientific committee, designed the protocol, planned the study, critically reviewed the*

manuscript and approved the submitted manuscript. Javier P. Gisbert: *directed the project and the project's scientific committee, obtained funding, designed the protocol and planned the study, acted as the national Spanish coordinator, recruited the patients, analysed and interpreted the data, critically reviewed the manuscript and approved the submitted manuscript.*

ETHICS APPROVAL

The study was approved by the ethics committee of La Princesa University Hospital (Madrid, Spain) and was pro-spectively registered at ClinicalTrials.gov (NCT02328131). Written informed consent was obtained from each patient included in the study.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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