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ORIGINAL ARTICLE

WILEY Helicobacter

Limited effectiveness with a 10-day bismuth-containing quadruple therapy (Pylera®) in third-line recue treatment for *Helicobacter pylori* infection. A real-life multicenter study

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Abstract

Background: *Helicobacter pylori* antibiotic resistance is an increasing problem worldwide. Pylera® may be an option as salvage therapy.

Aim: To assess the effectiveness, safety, and tolerance of Pylera® as a third-line in clinical practice.

Materials and Methods: This was a multicenter, observational, prospective database study in four Spanish hospitals. Consecutive *H. pylori*-infected individuals treated with Pylera® and a proton-pump inhibitor (PPI) were invited to participate if they had failed to respond to PPI-clarithromycin-amoxicillin as first-line and to levofloxacin-amoxicillin-PPI as second-line therapy. Eradication was tested 4-8 weeks after Pylera® using a C^{13}-urea breath test. Treatment-related adverse effects (TRAEs) were assessed through a questionnaire and by reviewing databases. A questionnaire on patient satisfaction was completed in the last visit.

Results: Of 103 subjects fulfilling the selection criteria, 101 were included in the intention-to-treat (ITT) analysis and 97 in the per-protocol (PP) analysis. A 10 day course was prescribed in all patients. Esomeprazole 40 mg b.i.d. was the most used PPI regimen (ITT=94.1%). Ninety-seven individuals (ITT=96.04%) completed more than 90% of the treatment. Overall eradication rates were ITT=80.2% (95% confidence interval [CI]: 72.3%-88.1%) and PP=84.4% (95% CI: 76.8%-91.8%). One or more TRAEs were experienced by 67.3% (95% CI: 57.7%-75.7%), all mild or moderate. TRAEs and the number of pills were the main complaints.

Conclusion: In an area of high antibiotic resistance to *H. pylori*, 10-day Pylera® plus double-dose PPI emerged as an alternative as third-line therapy, although not achieving optimal eradication rates. TRAEs were common but were neither severe nor did they condition compliance.

Rodríguez de Santiago and Martín de Argila de Prados share co-first authorship.

KEYWORDS
bismuth, helicobacter, Pylera, quadruple therapy, rescue, third-line

1 | INTRODUCTION

Helicobacter pylori infection is a global health problem affecting more than a half of the world population.[1,2] It is a well-established cause of chronic gastritis, peptic ulcer disease, MALT lymphoma, and gastric adenocarcinoma, and its eradication cures or prevents most of these diseases.[3] During the late twentieth and early twenty-first centuries, clarithromycin-based triple therapy and levofloxacin regimens achieved high eradication rates in most countries. However, in parallel with the situation for other bacterial infections, antibiotic resistance has steadily increased and has become a significant challenge for national health systems and attending physicians.[4,5] Specific point mutations in the DNA of *H. pylori* caused by antibiotic misuse are the main molecular mechanism of drug resistance.[6] Currently, clarithromycin resistance is highly prevalent in Western nations, and recent clinical practice guidelines no longer recommend the classic triple therapy as a first-line option (amoxicillin, clarithromycin, and a proton-pump inhibitor [PPI], [PPI-AC]), rather they favor the concomitant regimen (PPI-AC plus metronidazole).[3,7,8] Levofloxacin-containing second-line rescue therapy has traditionally been one of the most used alternatives and was supported by the Maastricht IV/Florence consensus report published in 2012 and by our national guidelines.[9,10] Nonetheless, *H. pylori*'s resistance to levofloxacin is on the rise due to fluoroquinolone overuse, and rates have been estimated at 22%-33.9% in Europe, 4.9%-34.5% in Asia, and 31.9% in the United States accordingly to a recent study among male US Veterans.[4,11] Thus, in the subgroup of patients refractory to first- and second-line treatment, bismuth-quadruple therapy (bismuth, metronidazole, tetracycline, and a PPI) is lately recommended, although available evidence supporting this approach is limited.[3,7] This combination has several advantages: First, tetracycline resistance is rare (<1%) or even absent in some regions[4]; second, its effectiveness despite in vitro metronidazole resistance has been reported[12,13]; and third, it has been shown that bismuth tends to aggregate within and on the surface of *H. pylori* exerting an antibacterial effect.[14] However, on the downside, tetracycline availability is highly variable in many countries, side effects are common, and adherence to this bismuth-quadruple therapy is usually suboptimal.

In 2016, Pylera® (three-in-one capsules containing metronidazole 125 mg, bismuth subcitrate potassium 140 mg, and tetracycline 125 mg) was marketed in many countries of southern Europe to facilitate posology, overcome shortage of tetracycline, and eventually improve eradication rates. However, the effectiveness of this specific formulation as third-line treatment in clinical practice is largely unknown.

The objective of this multicenter study was to ascertain the usefulness in a real-world scenario of quadruple therapy with this three-in-one formulation (Pylera®). Additionally, we determined the safety, compliance, and patient perception of Pylera®.

2 | METHODS

This was a prospective database, single-arm, observational study conducted at four Spanish hospitals.

The study protocol adhered to the principles of the Declaration of Helsinki and was approved by the ethics committees for clinical research of the participating centers and by the Spanish Agency of Medicinal Products and Medical Devices. Signed informed consent was required for participation in the study.

2.1 | Study population and procedures

Patients over 18 years of age with *H. pylori* infection who were treated with Pylera® three capsules q.i.d and a PPI as third-line treatment were consecutively enrolled. In all patients, first-line treatment with PPI-AC and second-line treatment with levofloxacin, amoxicillin plus a PPI had failed. The inclusion period was March 2016 to December 2016.

For inclusion, *H. pylori* infection had to have been documented by a C^{13}-labeled urea breath test (UBT) in the year prior to treatment with Pylera®. Before the inclusion, *H. pylori* infection was reassessed with a new UBT in those patients with antibiotic usage after second-line therapy. Eradication was assessed through a UBT four to eight weeks after Pylera® administration. Consumption of antibiotics or PPIs 20 days before this test was an exclusion criterion.

In two centers (Hospital Universitario Ramón y Cajal de Madrid and Hospital Universitario de Salamanca), a patient satisfaction survey was performed in the last visit. All participants were followed from Pylera® prescription until the visit in which they were informed about eradication status and in which treatment-related adverse events (TRAEs) were assessed.

2.2 | Study endpoints

The primary endpoint was *H. pylori* eradication, defined as one negative^{13}C-labeled UBT between 4 and 8 weeks after treatment. Secondary endpoints were safety, tolerance, compliance, predictors of eradication, and patient opinion in real clinical practice. Optimal compliance was defined as taking at least 90% of the prescribed medications.

Treatment-related adverse events were classified as follows: mild when easily tolerated by the patient, did not require specific therapy or medication, and did not lead to treatment suspension; moderate when they limited routine activities or required specific therapy or medication; and severe when they required hospitalization, caused death, or were disabling for usual activities and required specific therapy or medication. TRAEs were assessed in the last visit through a detailed questionnaire specifically designed for this study and by reviewing hospital and primary care electronic databases.

TABLE 1 Baseline demographic and clinical characteristics (n=101)

Age	57.9 (14.1) years (mean, SD)
Female sex	75 (74.3%)
Body mass index	25.5 (3.6) kg/m^2 (mean, SD)
Comorbidities	
Hypertension	28 (27.7%)
Diabetes mellitus	10 (9.9%)
Depression	15 (14.85%)
Ischemic cardiomyopathy	7 (6.9%)
Cirrhosis	1 (1%)
Previous gastrectomy	0
Active smoker	20 (19.8%)
Alcohol abuse	3 (2.9%)
Treatment indication	
Nonulcerous dyspepsia	65 (64.4%)
Peptic ulcer disease	14 (13.9%)
Preneoplastic lesion	13 (12.9%)
First-degree relative(s) with gastric adenocarcinoma	6 (5.9%)
Iron deficiency anemia	3 (3%)

Compliance was routinely assessed in the last visit during clinical interview by means of a specific questionnaire and recovery of empty medication envelopes of both Pylera® and PPI. In case of discordance, the lowest compliance was assumed. In cases where patients did not provide the blisters, results from the questionnaire were used.

2.3 | Statistical analysis

Data were analyzed separately for the intention-to-treat (ITT) analysis, which included all subjects prescribed Pylera®, and for the per-protocol (PP) population, which included all ITT subjects who completed the study without any events that could potentially bias the study outcome. 95% confidence intervals (CI) for eradication rates and TRAEs were calculated based on the Wilson method. The number of medical visits needed for treatment, including primary care visits, was registered. The UBT visit for eradication assessment was not included in this variable.

Mean, standard deviation, median, and range were calculated for continuous variables and frequency counts and percentages for categorical data. The Mann-Whitney *U* test was used to compare continuous data. Chi-squared and Fisher's exact tests were used for categorical data. All analyses were two-tailed, and *P*-values less than .05 were considered significant. Analyses were performed at the promoting institution (Hospital Universitario Ramón y Cajal, Madrid, Spain) using STATA software version 14.1 (Stata corp. Texas, CA, USA).

3 | RESULTS

One hundred and three patients met the inclusion criteria and none of the exclusion criteria, two individuals refused to participate, and three were lost to follow-up after Pylera® prescription. Thus, 101 patients were included in the ITT analysis and 97 in the PP analysis. Baseline demographic characteristics and indications for *H. pylori* treatment are summarized in Table 1. In all patients, treatment duration was 10 days. Esomeprazole 40 mg b.i.d was prescribed in 95 subjects (ITT=94.1%) and omeprazole 40 mg b.i.d. in six (ITT=5.9%). Compliance was optimal in 97 patients (ITT=96.04%) and only 60% in one patient. The overall eradication rate for the ITT population was 80.2% (95% CI: 72.3% - 88.1%) and 84.4% (95% CI: 76.8% - 91.8%) for the PP participants; participating institutions did not show significant differences in this factor (Table 2). Neither were significant differences in eradication rates detected between those treated because of nonulcer dyspepsia (65 of 101, eradication rate ITT=83.1%, 95% CI: 72.2% - 90.3%) versus other indication (36 of 101 eradication rate ITT=75%, 95% CI: 58.9% - 86.2%, *P*=.13); patients who were prescribed omeprazole (eradication rate ITT=83.3%, 95% CI: 43.6% - 97%) vs esomeprazole (eradication rate ITT=80%, 95% CI: 70.9% - 86.8%, *P*=1.0); or patients who were active smokers versus nonsmokers (*P*=.33). No predictors of eradication were found. Of 195 TRAEs recorded, 165 were mild (84.6%, 95% CI: 78.9% - 89%), 30 moderate, and none of them severe. Sixty-eight patients (67.3%, 95% CI: 57.7% - 75.7%) reported one or more TRAEs; dyspepsia and asthenia were the most common (Table 3). Ten patients were seen at the emergency department or by a general practitioner because of a TRAE. Headache was the final diagnosis in four patients, dyspepsia in three, mucosal candidiasis in two, and hypertensive crisis in one without complications who did not require hospitalization or treatment suspension. Patients were followed for a median of 116 days after Pylera® prescription (range: 1-192 days). A median of two medical visits (range 2-5) was recorded between prescription and the visit in which the patient was informed about Pylera® success, both appointments inclusive. No clinically significant changes in vital signs or physical examination findings were documented.

The results of the patient's opinion questionnaire about Pylera® completed by 78 participants are provided in Table 4.

TABLE 2 Eradication rates

	HRyC (n=45)	HUSA (n=37)	HUCA (n=10)	HC (n=9)
ITT analysis	75.6%	86.5%	80%	77.7%
PP analysis	77.3%	86.5%	100%	88.8%

HRyC, Hospital Universitario Ramón y Cajal; HUSA, Hospital Universitario de Salamanca; HUCA, Hospital Universitario Central de Asturias; HC, Hospital de Cabueñes; ITT, Intention to treat; PP, Per-protocol.

TABLE 3 Treatment-related adverse events (n=98)

Dyspepsia	43 (43.9%)
Asthenia	35 (35.7%)
Dysgeusia	34 (34.7%)
Nausea	26 (26.5%)
Abdominal pain	25 (25.5%)
Abdominal bloating	20 (20.4%)
Hyporexia	19 (19.4%)
Diarrhea	14 (14.3%)
Headache	13 (13.3%)
Myalgia	13
Heartburn	7 (7.1%)
Flatulence	8 (8.1%)
Hives/eczema	5 (5.1%)
Paresthesia	4 (4.1%)
Arthralgia	4
Drowsiness	3 (3.1%)
Cough	3
Depression	3
Oral aphthous ulcers	2 (2.7%)
Itching	2
Mucosal candidiasis	2
Insomnia	1 (1.4%)
Constipation	1
Hypertensive crisis	1

TABLE 4 Patient questionnaire results (n=78)

Main drawbacks of treatment were as follows	
Side effects	44 (56.4%)
Number of pills	17 (21.8%)
Price	7 (9%)
Other	4 (5.1%)
None	6 (15.2%)
Adherence to treatment was as follows	
Easy	23 (29.5%)
Difficult	20 (25.7%)
Manageable	43 (55.1%)
Compared to previous treatments, compliance was as follows	
More difficult	25 (25.4%)
Easier	18 (23.1%)
Similar	35 (44.9%)
Compared to previous treatments, tolerance was as follows	
Worse	35 (44.9%)
Equal	23 (29.5%)
Better	20 (25.6%)

4 | DISCUSSION

Helicobacter pylori treatment failure is an ever-increasing reality worldwide. The development of effective, safe, and accessible rescue therapies is probably one of the major concerns with respect to this infection. In this multicenter real-life observational study, Pylera® gave rise to a limited overall eradication rate as third-line therapy in a common, well-defined refractory population (ITT=80.2%, PP=84.4%). According to recent guidelines, *H. pylori* eradication rates should be above 90%; consequently, these results should be categorized as poor. This arbitrary threshold is hardly achievable in real-world rescue therapies; in fact, the recent Maastricht V consensus recommends third-line regimens with <80% of success.[3] We consider that this study shows that Pylera®, although not obtaining ideal eradication rates, emerged as an alternative as a third-line regimen in an ever-increasing antibiotic resistance scenario.

To the best of our knowledge, this is the first study to specifically address its effectiveness after failure to respond to PPI-AC and a levofloxacin-amoxicillin regimen. Our findings are also the first data for Pylera® from Spain. In two phase III randomized clinical trials, one conducted in Europe and another in USA, improved ITT eradication rates over PPI-AC therapy were observed in naïve patients of 80% vs 55% and 87.7% vs 83.2%, respectively.[13,15] In 2014, Delchier et al. performed an open-label, phase 3b, uncontrolled study in 49 patients who had failed to respond to ≥1 course of PPI-AC therapy with or without up to three supplementary treatments. Pylera® plus omeprazole eradication rates were 93.2% to 93.8% in the ITT analysis and 94.7% to 95% in the PP population.[16] These better outcomes than in our participants could be explained by the interventional design of the trial including stricter selection criteria, a smaller sample size, and the inclusion of patients with only one failed regimen. Muller et al.[12] (2016) conducted a prospective open-label study in 103 heterogeneous subjects infected with a *H. pylori* strain resistant to clarithromycin, metronidazole, and levofloxacin or individuals in whom multiple lines of treatment using these three antibiotics had failed. Their results resemble our findings: an ITT eradication rate=83% (95% CI: 75%-89%) and a PP eradication rate=87% (95% CI: 80%-94%). Recently, Tursi et al.[17] (2017) described an initial encouraging Italian experience with Pylera® in a multicenter study in 131 patients, 76 having undergone previous eradication therapy. Eradication was recorded in 73 of these 76 patients (96.0%, 95% CI: 89%-98.6%). However, it is important to remark that only 17 had been refractory to more than one regimen and more specific data were not available for this subgroup.

Other reports exist of bismuth-based quadruple therapy out of a three-in-one formulation as a third-line salvage regimen, and the results of the most relevant researches in the last decade are summarized in Table 5. The most representative in our area was a prospective, multicenter investigation with similar selection criteria to our study. ITT eradication was achieved in 65% (95% CI, 58%-72%), and PP eradication was 67% (95% CI, 60%-74%). Although compliance (PP=97%) was comparable to that observed here, treatment duration, PPI, doses of antibiotics, and bismuth were highly heterogeneous. This variability, besides geographic differences and the different composition of Pylera®-bismuth salt, could explain the lower eradication rates.[18]

TABLE 5 Bismuth-quadruple therapy as a rescue treatment

Author	Number of patients	Line	Regimen	Duration (days)	ITT
Tursi, 2017[17]	76	2nd-3rd	Pylera® Omeprazole 20 mg b.i.d. Esomeprazole 40 mg b.i.d.	10	96%
Muller, 2016[12]	103	2nd-5th	Pylera® Omeprazole 20 mg b.i.d.	10	83%
Cao, 2015[29]	143	2nd	Lansoprazole 30 mg b.i.d B: 240 mg b.i.d. M: 400 mg q.i.d. T: 500 mg q.i.d.	14	88.1%
Gisbert, 2014[18]	200	3rd	PPI: standard dose b.i.d. B: 120 mg q.i.d. or 240 mg b.i.d. T: 250 mg t.i.d. to 500 mg q.i.d. M: 250 mg t.i.d. to 500 mg q.i.d.	7-14	65%
Delchier, 2014[16]	49	2nd-4th	Pylera® Omeprazole 20 mg b.i.d.	10	93.2%
Yoon, 2012[30]	169	2nd	Pantoprazole 40 mg b.i.d. B: 300 mg q.i.d. M: 500 mg t.i.d. T: 500 mg q.i.d.	7 14	83.5% 87.5%
Chung, 2011[31]	199	2nd	Pantoprazole 40 mg b.i.d. B: 300 mg q.i.d. M: 500 mg t.i.d. T: 500 mg q.i.d.	7 14	81.6% 85.1%
Wu, 2011[32]	62	2nd	Esomeprazole 40 mg b.i.d. B: 120 mg q.i.d. T: 500 mg q.i.d. M: 250 mg q.i.d.	7	81%
Lee, 2011[33]	45	3rd	Omeprazole or Esomeprazole 20 mg b.i.d. B: 600 mg b.i.d. M: 500 mg b.i.d. T: 1 g b.i.d.	14	66.7%
Lee, 2010[34]	112	2nd	Esomeprazole 20 mg b.i.d B: 300 mg q.i.d. M 500 mg t.i.d. T 500 mg q.i.d.	7 14	64.3% 82.6%
Usta, 2008[35]	89		Omeprazole 20 mg s.i.d. B: 8 mg/kg/day M: 30 mg/kg/d D: 2 mg/kg/d	Omeprazole: 14 B, M, D: 7	66.7%
Chung, 2007[36]	87	2nd	PPI b.i.d. B: 300 mg q.i.d. M: 500 mg t.i.d. T: 500 mg q.i.d.	7	84%

PPI, Proton-pump inhibitor; B, Bismuth; M, Metronidazole; T, Tetracycline; D, Doxycycline; ITT, Intention to treat.

As third-line treatment, rifabutin-containing regimens could be an alternative. In a systematic review, an overall eradication rate of 66% was provided for this option (95% CI, 55%-77%).[19] However, this antibiotic has major limitations of a potential risk of serious myelotoxicity, high cost, and concerns that its widespread use could lead to a rise in multidrug-resistant strains of *M. tuberculosis*.[20]

In our study, the PPI preferred by most clinicians was esomeprazole 40 mg b.i.d over omeprazole 40 mg b.i.d. Esomeprazole is not included in the Pylera® European Medicines Agency data sheet, and recent guidelines do not unanimously support the benefits of last-generation or double-dose PPIs in all scenarios.[3,7,8,21] This decision, although controversial and not supported by head-to-head comparisons, could be explained by some data pointing to better overall eradication rates for triple therapies including new-generation PPIs.[22,23] An important finding of this study is that overall eradication rates remained suboptimal despite high-dose esomeprazole.

Optimal duration of therapy is another key question that remains unanswered. All our patients were treated for 10 days as Pylera® is licensed in this format. This could be seen as an important limitation of this formulation as this duration is longer than necessary for metronidazole-susceptible and insufficient for metronidazole-resistant strains,[7] what could partially explain our low eradication rates. The benefits of empirically prolonging Pylera® to up to 14 days are not as well established as for PPI-AC combination therapy. Some studies have detected a higher eradication rate with classic bismuth-quadruple therapy when treatment is continued for at least two weeks.[24] In contrast, a noninferiority clinical trial found no significant differences between 10- and 14-day regimens despite increased costs.[25] The results of a pilot study by Salazar et al.[26] in 47 patients indicate that 14 days of Pylera® (PP eradication=97.1%, 95% CI: 86.3%-99.9%) is more effective than a <10-day course (PP eradication=44.4%, 95% CI: 16%-76%) when metronidazole resistance is suspected. Nonetheless, more rigorous data are needed to determine the real efficiency of this approach.

Consistent with the available literature on Pylera©, TRAEs were frequent (67.3% showed ≥1) though in all cases transient and mild to moderate, also in line with literature data.[12-17] The most frequent side effects were dyspepsia, asthenia, and dysgeusia. Ten patients sought medical attention due to TRAEs. Nonetheless, compliance (96.04%) was not hampered, and only one patient had to stop taking Pylera® after 7 days of treatment because of severe paresthesia, dysgeusia, and headache. The high adherence to treatment rate observed here could be attributable to patients under third-line being well-aware of *H. pylori* infection yet first-line interventional studies have also reported good compliance rates.[13-15] Although this study was observational and resembling clinical practice, prospective designs may be at risk of Hawthorne bias; hence, a slight increase in adherence is possible.

Among the strengths of our study are that data were obtained from real-life practice and we also provide patient satisfaction data (Table 4). TRAEs and the number of pills were the main complaints. This is not surprising considering that the whole treatment course consists of 130-140 capsules. Sporadic reports of severe TRAEs associated with prolonged treatments have classically burdened bismuth-quadruple therapies.[27] From our perspective, the present data lend support to an acceptable safety profile, suggesting the use of this medication should not be restricted for this concern.

This study has some limitations that should be acknowledged. (1) Its uncontrolled design prevents direct comparisons with other options, and although multicentric and involving different geographic areas, it was conducted in a single country. Spain has elevated clarithromycin (18%-34%), levofloxacin (15%-20%), and metronidazole (41%) resistance rates[7] such that we would predict similar results in populations with comparable antibiotic resistance profiles. (2) The study was underpowered to detect predictors of eradication. (3) Our lack of antibiotic testing could be viewed as a weakness. However, microbiologic culture is not available in many centers and is rarely undertaken in clinical practice. Additionally, a recent review revealed no clear benefit of third-line susceptibility-guided treatment.[28] Collectively, these findings question the utility of culture in this context.[8]

In conclusion, our results provide evidence for Pylera® as a rescue regimen after PPI-AC and levofloxacin-amoxicillin triple therapy failure. Although common and unpleasant for patients, TRAEs were not severe and had no impact on compliance. In future studies, the benefits should be explored of a 14-day Pylera® course and alternative posology to help compliance and reduce TRAEs (eg, t.i.d instead of q.i.d or concomitant use of probiotics). Also, this formulation needs to be compared with other second- and third-line regimens, and the most efficient PPI regimen needs to be established.

CONFLICT OF INTEREST

Carlos Martín de Argila de Prados declares scientific counseling: Casen recordati. Educational activities: Casen recordati, Allergan, Norgine.

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