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Bismuth-based Quadruple Therapy Following *H. pylori* Eradication Failures: a Multicenter Study in Clinical Practice

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ABSTRACT

Background & Aims: *Helicobacter pylori* (*H. pylori*) eradication in patients who failed one or more therapeutic attempts remains challenging. This study aimed to assess the efficacy of three-in-one capsules bismuth-based quadruple therapy (Pylera®) in these patients managed in clinical practice.
Methods: This was a prospective, open-label, multicenter study enrolling consecutive, adult patients with persistent *H. pylori* infection following at least one standard therapy. All patients received a rescue quadruple therapy with Pylera (3 capsules four times daily) and esomeprazole 20 mg (1 tablet twice daily) for 10 days. *H. pylori* eradication was assessed by using Urea Breath Test 4-6 weeks following therapy ending. *H. pylori* eradication rates, compliance, and side-effects were calculated.
Results: A total of 208 patients in the 9 participating centres were enrolled. Overall, 180 patients were successfully cured from the infection, accounting for 86.5% (95% CI 81.9-91.2) and 92.3% (95% CI 88.6-96.1) eradication rates at intention-to-treat analysis and at per protocol analysis, respectively. Cure rates were similar across patients who failed one to three previous therapy attempts, but the success rate fell to 67% after 4 or more therapy failures. Compliance to therapy was good in 198 (95.2%) patients, whilst in 7 (5.3%) cases the therapy was interrupted within 5 days due to side effects. A total of 97 (46.6%) patients complained of at least one side effect; nausea, diarrhea and vomiting were the most frequently reported.
Conclusions: Our study found that this bismuth-based quadruple therapy is highly effective as second-line and rescue therapy for *H. pylori* eradication in clinical practice.

Key words: *Helicobacter pylori* – quadruple therapy – rescue therapy – bismuth.

Abbreviations: CI: confidence intervals; ITT: intention-to-treat; PP: per protocol; UBT: urea breath test.

INTRODUCTION

Helicobacter pylori (*H. pylori*) eradication is recommended in patients with different gastro-duodenal and extra-intestinal diseases [1, 2]. However, it remains challenging since no first-line therapy achieves a 100% cure rate [3]. Conversely, the success rate following standard therapies is declining [4, 5], mainly due to the increased resistance towards both clarithromycin and metronidazole worldwide [6], a trend seen in Italy as well [7]. Similarly, the efficacy of levofloxacin-amoxicillin triple therapy, generally used as a second-line treatment [8], has decreased so that the therapeutic options for curing *H. pylori* infection in clinical practice are quite limited [9, 10]. The interest towards the bismuth-based quadruple therapy has recently been renewed by the marketing of a novel, three-in-one capsule, containing bismuth, tetracycline, and metronidazole (Pylera®), firstly introduced in 2001 [11]. The bismuth-based quadruple therapy is advised as first-line or rescue therapy by different guidelines, including the updated Italian guidelines [1, 12, 13]. A high efficacy of such therapy is expected in those geographic areas where a low prevalence of primary tetracycline in *H. pylori* isolates is low. Unfortunately, despite the three-in-one capsule formulation, as many as 3 tablets four times daily for 10 days plus 2 proton pump inhibitor tablets (equaling 14 tablets per day) must be taken. Therefore, patients' compliance with this therapy could be a matter for concern in the real-life, especially in elderly patients or those already taking drugs for other chronic diseases. Therefore, we assessed the efficacy of bismuth-based quadruple regimen in patients who failed at least one standard

eradication therapy, consecutively observed in clinical practice in different centers.

PATIENTS AND METHODS

Patients

This was a prospective, open-label study enrolling consecutive, adult patients with persistent *H. pylori* infection following at least one standard therapy, observed in clinical practice in out-patient Gastrointestinal Clinics. Patients with major liver or kidney diseases, those with known allergy to the prescribed drugs, and pregnant or breast feeding women were excluded from the study. Persistent infection was documented by either ^{13}C-urea breath test (UBT) or upper endoscopy with histological assessment. The UBT was done after an overnight fast. A baseline breath sample was obtained, and a 100 mg of ^{13}C-urea with citric acid (1.5 mg) was administered as an aqueous solution, and another breath sample was collected following 30 minutes. The results of the test were considered positive if the difference between the baseline sample and the 30-minute sample exceeded 4.5 parts per 1000 of $^{13}CO_2$, according to the manufacturer's instructions. For each consenting patient, the main clinical data and the previous therapeutic attempts were collected. The study was performed according to guidelines for Good Clinical Practice [12] and the Declaration of Helsinki (1996 version, amended October 2000) [13].

Therapy regimen

A rescue quadruple therapy with the three-in-one capsules plus the proton pump inhibitor was prescribed, as suggested in the current European and Italian guidelines [14, 15],

In detail, esomeprazole 20 twice ½ hour before breakfast and dinner, and three Pylera capsules four times daily (following breakfast, lunch, dinner and at bedtime, after eating a snack) were administered for 10 days, according to the manufacturer's suggestions. After the initial visit, patients were fully explained about the need for such regimen and strongly encouraged to comply fully, in order to minimize the rate of drop-outs. A self-explanatory page with the therapeutic scheme was given. The use of alcohol was discouraged during the therapy. The patients were instructed about the possibility that dark stools and the metallic taste could appear during therapy, and that such events were clinically irrelevant. The drugs for other diseases were continued without changing during the eradication therapy. At the end of antibiotic treatment, the patients were interviewed again to assess the compliance to the therapy and the incidence of side-effects. Compliance was considered good when ≥90% of prescribed drugs were taken, acceptable when between >50% and 89%, whilst those patients who consumed ≤50% of prescribed drugs were considered as drop-outs. Side-effects were scored on a semi-quantitative scale as mild (present, but easily tolerable), moderate (fastidious, but not requiring therapy interruption), and severe (intolerable, requiring the interruption of therapy). *H. pylori* eradication was assessed by using UBT, 4-6 weeks following therapy ending. At least 10 consecutive patients had to be enrolled in each participating centers.

Statistical analysis

The cure rates were calculated as a percentage with their 95% confidence intervals, at both 'intention-to-treat' (ITT) and 'per protocol' (PP) analyses. The ITT included all patients who took at least one drug dose, but failed to complete therapy or when they did not complete follow-up for any reason. The PP analysis considered patients with good compliance to the therapy and underwent the scheduled UBT control. Before pooling the estimates, the chi-squared test or Fisher's exact test were applied to investigate the heterogeneity among centers. The SPSS (version 16.0) was used for all statistical computations.

RESULTS

A total of 9 centres participated in this study, distributed throughout northern (2 centres), central (3 centres) and southern (4 centres) Italy. The main demographic and clinical characteristics of the 208 enrolled patients are listed in Table I. Overall, 13 patients were considered drop-outs due to either therapy compliance less than 5 days (5 cases) or those who failed to undergo the scheduled UBT control (8 cases). Therefore, there were 208 and 195 patients included at ITT and PP analyses, respectively. A total of 180 patients were successfully cured from the infection, accounting for an 86.5% (95% CI 81.9-91.2) eradication rate at ITT analysis and a 92.3% (95% CI 88.6-96.1) at PP analysis. The eradication rates according to the number of previous failed therapy attempts were provided in Table II. Cure rates were similar across one to three therapy attempts, but the success rate fell to 67% after 4 or more therapy failures. In detail, eradication rates remained comparable across the second-line or rescue therapy (74/87, 85.1% vs. 106/121, 87.6%; P = 0.6). Similarly, no difference

Table I. Demographic and clinical characteristics of the patients.

Variable	Number
Patients	208
Age (mean±SD); years	53.8 ± 13.2
Males:Females	86:122
Smoking habit; (Yes/No/Not available)	50/99/59
Disease	64/9
Non-ulcer dyspepsia	163
Peptic ulcer/erosions	45
No. of previous eradication therapies	
1	87
2	88
3	24
≥ 4	9
No. of other concomitant therapies	
None	73
1	39
2	18
3	7
4	5
5	5
Not available	59

Table II. Eradication rate at ITT analysis according to the previous failed therapies

No. of previous therapies	Cured/Total	Eradication rate %; (95% CI)
1	74/87	85.1 (77.6-92.5)
2	79/88	89.9% (83.4-96.1)
3	21/24	87.5% (74.3-100)
≥4 (from 4 to 7)	6/9	66.7% (35.8-97.4)

was noted when comparing the cure rates between males and females (87.2% vs. 86.1%; P = 0.8), smokers and no smokers (82% vs. 84.8%; P = 0.6), patients with peptic ulcer/erosions or non-ulcer dyspepsia (88.9% vs. 85.9%; P = 0.4), and patients assuming ≤1 or >2 co-therapies (84.8% vs. 81.1%; P = 0.6).

Compliance to therapy was good in 198 (95.2%) patients, and acceptable in further 5 patients (8 days in 3 patients, and 6 days in other 2), whilst in 5 cases the therapy was interrupted within 5 days. Among the 5 patients with acceptable compliance, 3 were cured, 1 failed eradication, and the last one was a drop-out.

By excluding dysgeusia and stool darkening, at least one side-effect was complained by 97 (46.6%) patients, and the most frequently observed are listed in Table III. Moreover, there were 2 cases of monilial vaginitis, 1 of oral candidiasis, 1 case of cystitis and 1 patient who developed onychomycosis. Side-effects were mild in the majority of cases, but in 11 (5.3%) patients therapy was discontinued earlier due to vomiting in 4 cases (Days: 6, 4, 4, and 3), nausea in 3 (Days: 9, 9, and 8), diarrhea in 2 (Days: 8, and 4), oral candidiasis (Days: 8), and urticaria (Days: 6).

Table III. List of most frequent side-effects

Side-effects	Number (%)
Nausea	35 (16.8)
Mild	26
Moderate	6
Severe	3
Diarrhoea	18 (8.6%)
Mild	16
Moderate	-
Severe	2
Vomiting	10 (4.8%)
Mild	2
Moderate	4
Severe	4
Abdominal pain	8 (3.8)
Mild	8
Moderate	-
Severe	-
Urticaria/pruritus	6 (2.9)
Mild	4
Moderate	1
Severe	1
Headache	5 (2.4)
Mild	5
Moderate	-
Severe	-
Muscular cramps	4 (1.9)
Mild	4
Moderate	-
Severe	-

More than 1 symptom may be present in a single patient.

DISCUSSION

Curing *H. pylori* infection following first-line therapy failure is notoriously difficult [16]. Different guidelines advise the use of a levofloxacin-amoxicillin based triple therapy as second-line regimen [1, 14, 15]. However, the success rate following this therapy seems to be declining in several countries, including Italy, most likely due to an increased prevalence of levofloxacin-resistant *H. pylori* strains [17]. In previous Italian, multicenter studies, a 76.4% and 76% eradication rates were achieved when such a therapy regimen was administered as a second- or third-line treatment, respectively [16, 18]. Regrettably, no novel molecules active towards *H. pylori* strains have been introduced, so that clinicians are left with 5-6 antibiotics to use in combination. Moreover, some delivery problems emerged with bismuth salts and tetracycline in different countries, including Italy, so that the use of bismuth-based quadruple therapy has been largely limited in the last decade in several countries [19]. Starting March 2016, Pylera® has become available in Italy. Therefore, we assessed the efficacy of such a bismuth-based quadruple therapy for curing *H. pylori* in patients with persistent infection despite one or more therapeutic attempts.

Overall, our data showed an eradication rate as high as 86.5%, which is particularly impressive when considering that the enrolled patients already had failed different eradication therapies. Of note, we observed that the success rate of such a therapy did not significantly decrease when administered as a second-line until to the fourth-line regimen. Moreover, the efficacy is not affected by any of the considered factors, including sex, smoking habit, and gastroduodenal disease. However, the success rate decreased to 67% after 4 or more therapy failures. Our data are in agreement with results of other studies recently performed in Spain and Italy, showing an 82.4% cure rate on 14 patients treated from second- to fourth-line [20] and 55.6%-80.2% as third-line therapy [21, 22]. We also observed that patients' compliance to therapy was good (≥90% of prescribed drugs) in 95.2% of patients, despite the large number of tablets needed daily. Likewise, such a good result depends on a high motivation of the enrolled patients, who already have experienced previous therapy failures. In this respect, the importance of a strong patient-doctor interaction should be stressed. Indeed, the majority of patients continued therapy despite the fact that nearly half of the cases complained of one or more mild side-effects. Luckily, side-effects required an earlier therapy interruption in only 5.3% of patients. Our data are similar with the 47%-67.3% incidence of side-effects and 3%-8.7% interruption rate observed in other studies [22-25].

Our results may also depend on a very low prevalence of primary tetracycline in *H. pylori* isolates in Italy [26], as in other European countries. Unfortunately, tetracycline resistance is already as high as 8.8% in Korea, 26.8% in Chile, and 43.9% in Cameroon [24].

Our study has some strengths. Patients were enrolled in different centers throughout Italy, so that the results are representative of different areas. The study involved a large number of patients (more than 200) who had failed at least one eradication therapy. Half of these patients received this quadruple therapy as second-, third-, and even fourth-line therapy. We performed the study in a clinical practice, where patients were receiving co-therapies (≥3 drugs in our series) potentially affecting compliance to this eradication therapy. Therefore, our data provide relevant information for the immediate application into the clinical practice in a setting of difficult to treat patients.

CONCLUSION

Our study found that this bismuth-based quadruple therapy is highly effective as second-line and rescue therapy for *H. pylori* eradication in clinical practice, most likely due to very low level of tetracycline resistance in Italy. Since the tetracycline resistance is expected to increase in different areas with the implementation of such a therapy, it could be wise to avoid its use as first-line therapy, at least in those areas where acceptable effective therapies are still available.

Conflicts of interest: None to declare.

Author contributions: Z.A. conceived and designed the study. Z.A., D.F.V. and P.P. wrote the manuscript. All authors enrolled patients and approved the final version of the manuscript.

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