

Title:

Compliance, adverse effects and effectiveness of first line bismuth-containing quadruple treatment (Pylera®) to eradicate *Helicobacter pylori* infection in 200 patients

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Compliance, adverse effects and effectiveness of first line bismuth-containing quadruple treatment (Pylera®) to eradicate *Helicobacter pylori* infection in 200 patients

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CONFLICT OF INTERESTS

Manuel Castro-Fernández participated in the preparation of the II-III and IV Spanish Conferences of the Consensus of *H. pylori*. He also participated as a lecturer for a training course on *H. pylori* (2016), organized by the SEPD and sponsored by Allergan. Furthermore, he has attended scientific meetings (2016-2018) financed by Abbie, Janssen, Tillotts, Faes, Ferring, Allergan and Takeda.

ABSTRACT

Introduction and objectives: quadruple therapy with bismuth is recommended as a first line treatment for *Helicobacter pylori* (*H. pylori*) infection. The aim of this study was to evaluate the compliance, adverse effects and effectiveness of this treatment with the new galenic three-in-one capsule formulation containing bismuth subcitrate, metronidazole and tetracycline (Pylera®).

Methods: a prospective, non-controlled, single center observational study was performed in a cohort of 200 consecutive patients with an untreated *H. pylori* infection; 58% were female. The subjects were treated for ten days with Pylera® of three capsules four times daily with meals and a proton pump inhibitor taken before breakfast and dinner. The Pylera® capsule contains 140 mg of bismuth subcitrate, 125 mg of metronidazole and 125 mg of tetracycline. The compliance and adverse effects of the treatment were evaluated via telephone contact and via an interview during the clinical revision. Eradication of infection was controlled for at least four weeks after treatment termination via the urea breath test, the stool antigen test with monoclonal antibodies or by histology.

Results: treatment compliance was observed in 96% (192/200) of the patients. Only 28.5% (57/200) of the patients experienced adverse effects, which led to abandoning the treatment in only seven subjects. Severe adverse effects developed in only one case due to *Clostridium difficile* infection. The effectiveness based on intention to treat was 91.5% (183/200, 95% CI: 87.1-96.8) and per protocol was 95.2% (182/191, 95% CI: 90.9-98.9).

Conclusions: in our experience, Pylera® is an effective and safe treatment that should be considered as a first line therapeutic option for the eradication of *H. pylori* infection

Key words: Helicobacter pylori. Pylera®.

INTRODUCTION

Helicobacter pylori infection (*H. pylori*) is very prevalent and affects approximately 50% of the population in Spain and worldwide. Furthermore, it represents the main known cause of chronic gastritis, duodenal-gastro ulcers and gastric neoplasms (1-3). In fact, eradication of *H. pylori* infection is the main strategy to prevent gastric cancer according to the World Health Organization (WHO), with favorable supporting data (4-6). The recommended treatment to eradicate *H. pylori* has changed over the past 20 years, as reflected in successive consensus documents (7-14). These changes are always motivated by the aim to achieve the best possible effectiveness, in association

with a high rate of compliance and tolerable adverse effects (AEs). The current goals are to reach effectiveness rates above 90% and the treatments that achieve this goal are therefore recommended. These include the quadruple therapy without bismuth administered over 14 days, using clarithromycin, amoxicillin and metronidazole in association with a proton pump inhibitor (PPI), as well as the bismuth containing quadruple therapy administered over ten days, which is the focus of this study and combines a PPI with tetracycline, metronidazole and bismuth subcitrate in a single capsule (13,14). This second treatment has been marketed in Spain under the name of Pylera® since 2016 (Allergan Pharmaceuticals International Ltd., Dublin, Ireland). Nevertheless, the effectiveness of treatments for the eradication of *H. pylori* infection may differ in different countries and geographic areas. Therefore, their effectiveness should first be evaluated in the region of interest prior to implementing any eradication treatment.

The main objective of the present study was to evaluate the compliance, AEs and effectiveness of Pylera® therapy when used as a first line treatment in the clinical setting to combat *H. pylori* infection in our healthcare area. Effectiveness was evaluated according to intention to treat (ITT) and per protocol (PP).

METHODS

An observational, prospective, non-controlled, single center study was performed in 200 consecutive patients with *H. pylori* infection recruited between 2016 and 2018. The patients had not received any prior eradication treatment and accepted to undergo eradication treatment with Pylera®. The mean age of the cohort was 54 years of age (range 18-81) and 58% were female. The clinical diagnoses of the cohort included undefined dyspepsia (52.5%), functional dyspepsia (21.5%), gastroduodenal ulcer (15%) and other diagnoses (11%), such as iron-deficiency anemia, family history of gastric cancer, abdominal pain or vitamin B12 deficiency. The diagnosis of *H. pylori* infection was determined via the 13C labelled urea breath test (UBT, 38%), a monoclonal ELISA-based stool antigen test (SAT, 38%) and histology (24%).

All patients were treated with Pylera® of three capsules at breakfast, lunch, afternoon tea and dinner. A PPI was also taken before breakfast and dinner of omeprazole 40 mg

(50%), omeprazole 20 mg (18%) or esomeprazole 40 mg (32%). The Pylera[®] capsule contained 140 mg of bismuth subcitrate potassium, 125 mg of metronidazole and 125 mg of tetracycline hydrochloride. This regime was not associated with the intake of probiotics in any cases. In order to improve compliance with the treatment, the patients were advised of the possible AEs indicated in the Pylera[®] Package Leaflet (information for the user) and were given a document that explained in detail the posology of the treatment. This recommended that the drug should be taken after meals. A clinical check-up was scheduled at our out-patient clinic 4-8 weeks after the end of the treatment in order to evaluate its effectiveness in infection eradication using the UBT (79.5%), SAT (16%) or histology (2%). Control of eradication was not performed in five patients. Compliance and the AEs associated with the treatment were evaluated via telephone contact with the patients, with prior oral authorization. This was performed 7-10 days after the programmed end of the treatment and during the scheduled check-ups at the out-patient clinic. Specifically, the patients were asked about their compliance with the treatment and the occurrence of AEs that were not evident at the outset of treatment and affected their general health and well-being. The causes of the AEs were determined.

The treatment was considered to have been effective when a negative result was obtained at the eradication control check-up to, ensuring that the antibiotic or PPI had not been used two or four weeks prior to the test, respectively. The effectiveness was evaluated by PP, including patients that complied with at least 90% of the doses during treatment and also performed the eradication test. Effectiveness was also evaluated by ITT that included all patients that started eradication treatment, irrespective of whether they complied with the treatment regimen or underwent the scheduled final check eradication. The data were analyzed using the IBM SPSS Statistical software package.

The study was approved by the Research Ethics Committee at our institution and complied with the tenets of the Declaration of Helsinki and Good Clinical Practices.

RESULTS

In terms of compliance with the treatment, 192 patients (96%) correctly followed the treatment protocol and eight patients (4%) failed to comply with the treatment regime; six of them were female and two were male. Failure to comply with the protocol was due to AEs in seven cases and confusion regarding the treatment regime in the remaining case. The treatment of these eight patients lasted between two and seven days, with a mean of five days. The main AEs that motivated their incompletion with the full treatment protocol were nausea and vomiting in three cases and headaches, asthenia, diarrhea and abdominal pain in the other four cases.

With regard to the AEs reported by 57 patients (28.5%) that might be related to the treatment, the most frequent AEs were: abdominal pain (9.5%), diarrhea (8.5%), asthenia (6.0%), nausea and vomiting (5.0%) and headaches (2.5%). None of these symptoms were reported after terminating the treatment with Pylera®. Urticaria developed in one patient that was controlled with corticoids. Another patient was admitted to hospital due to diarrhea, which commenced on terminating the treatment and was due to *Clostridium difficile* infection. The patient responded well to treatment (Table 1).

The treatment proved to be effective in eradicating the *H. pylori* infection in 183 of 200 patients analyzed by ITT (91.5%; 95% CI: 87.1-96.8). According to the PP analysis, the treatment was effective in 182 of 191 patients that complied with the full treatment regime (95.2%; 95% CI: 90.9-98.9) (Table 2). With regard to the latter subjects, eight failed to comply with the treatment protocol and one individual did not undergo the check-up to assess eradication. This patient was considered to have been lost in the follow-up, as there was no contact with this patient for > 6 months after treatment termination.

DISCUSSION

Treatment to eradicate *H. pylori* infection is still particularly relevant, especially due to the influence of this bacteria on gastric cancer. Thus, highlighting the importance of clinical research in this area and some recently drafted consensus documents (13,14). In the latest international consensus document drawn up in Maastricht (2016), quadruple therapies, with or without concomitant bismuth treatment, were

recommended as first line treatments. This latest treatment is available in Spain marketed as PPI-Pylera[®] and it is particularly important as the rate of dual resistance to clarithromycin and metronidazole is above 15% in a given geographic area (14). For any eradication treatment to be recommended it must have an effectiveness in terms of ITT higher than 90%, as stated during the last Spanish Consensus Conference in 2016. Therefore, the quadruple therapy without bismuth (especially over 14 days) and PPI-Pylera[®] could be recommended if its effectiveness was demonstrated in the clinical practice (13). This treatment would be clearly recommended for patients with an allergy to penicillin. Earlier consensus documents had recommended other treatments, such as triple therapy with clarithromycin or metronidazole. However, despite their initial widespread acceptance, these treatments were later abandoned due to a loss of effectiveness. In fact, the classic quadruple therapy containing bismuth was initially abandoned due to its complexity and a higher rate of AEs compared to the triple therapy. In spite of the similar effectiveness, it was subsequently no longer available when tetracycline drugs were taken off the market (9-11,15-18).

PPI-Pylera[®] treatment was seen to be more effective than triple therapy in clinical trials (19,20) and demonstrated a greater efficacy than clarithromycin therapy and an equivalent efficacy to the quadruple therapy without bismuth, either sequentially or concomitantly. However, there were more AEs. Pylera[®] was first sold in Spain in 2016 and its effectiveness as a first line treatment in the clinical practice has been studied. As such, the use of Pylera[®] was associated with an effectiveness of 97.6% in terms of ITT in 41 patients in Seville (2017) (21) and an effectiveness of 90.7% per ITT was reported in another study of 75 patients in Madrid in 2018 (22). However, a further study of 107 patients in Madrid (2018) reported an effectiveness of 78.15% by ITT, which was considerably lower than that reported previously (23). Similarly, other data was published in 2017-18 regarding the effectiveness of Pylera[®] as a first line of treatment in Italy and Germany (24-27). These studies reported an effectiveness of 90.2-92.7% per ITT in the clinical practice and the effectiveness per ITT in a clinical trial was only 82.5 (28). In a German multicenter study of 266 patients, an effectiveness of 95.6% was reported in terms of ITT (29). Finally, data was presented from a European multicenter study that included 666 patients treated with Pylera[®] as a first line

treatment during a meeting of the Spanish Gastroenterology Association in Madrid in 2018. This study reported an effectiveness of 92% in terms of ITT and 95% for PP (29). A satisfactory effectiveness (> 90%) was confirmed in terms of ITT and PP in our study of a population of 200 unselected patients in the everyday clinical practice. This is consistent with the majority of studies published previously. The highly acceptable rate of compliance should be highlighted (96%), which might even be improved by patient adherence to the treatment. We consider that it is useful to provide the patient with written recommendations and a scheme of the treatment protocol. In addition, we feel that the patients should be informed of any possible AEs in order to prevent them from abandoning the treatment. As with similar studies, this study was limited by the fact that the veracity of the data provided by the patients cannot be validated with regard to compliance with the treatment protocol or the AEs experienced. In conclusion, treatment with PPI-Pylera® is currently effective and safe and should be considered as a first line therapeutic option to eradicate *H. pylori* infection.

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Table 1. Adverse effects of eradication of *H. pylori* infection with Pylera[®], in the first-line (no. of patients: 200)

<i>Adverse effect</i>	<i>No. of cases</i>	<i>(%) patients</i>
Abdominal pain	19	9.5
Diarrhea	17	8.5
Asthenia	12	6.0
Nausea-vomiting	10	5.0
Headache	05	2.5
Urticaria	01	0.5
Vertigo	01	0.5
<i>Clostridium difficile</i> infection	01	0.5
Any adverse effect (*)	57	28.5

*There was a non-compliance of treatment in seven cases.

Table 2. Effectiveness according to ITT and PP for the eradication of *H. pylori* infection with Pylera®, in the first line

Effectiveness according to ITT	183/200	91.5% (95% CI: 87.1-96.8)
Effectiveness according to PP	182/191	95.2% (95% CI: 90.9-98.9)

ITT: intention to treat; PP: per protocol.

Accepted Article