Lactobacillus reuteri versus triple therapy for the eradication of *Helicobacter pylori* in functional dyspepsia

GASTROENTEROLOGY

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Abstract

Background and aim. The eradication of *H. pylori* infection using PPI associated with different combinations of two or three antibiotics entails high risks of side effects and non- adherence. Therefore probiotics have been proposed for *H. pylori* eradication.

We tested the efficacy of *Lactobacillus reuteri* plus Pantoprazole compared to a triple regimen based on Pantoprazole plus Amoxicillin plus Clarithromycin in patients with *H. pylori* infection and functional dyspepsia.

Methods. In a prospective design, 46 patients (M: 13, F: 33, mean age 48.80 ± 13.82 years) fulfilled the following inclusion criteria: age at least 18, documented informed consent, positive *H. pylori* finding by histology, no morphological changes of the gastric mucosa at upper gastrointestinal endoscopy and complaints of functional dyspepsia according to the Rome III criteria. Exclusion criteria were: presence of any other chronic organic diseases that required drug treatment, use of antibiotics, PPIs or H2 antagonists in the previous 3 months; pregnancy or lactation. Patients were randomly divided into two equal groups (23 patients each group). One group received the standard therapy in our area: Pantoprazole 40 mg bid for 30 days associated with Amoxicillin 2x1000 mg/day and Clarithromycin 500 mg bid for 14 days. The other group received Pantoprazole 40 mg/day plus *L. reuteri* DSMZ 17648 twice a day for 8 weeks. Post-treatment eradication was tested by *H. pylori* antigen stool assay at 30 days after therapy.

Results. The group on *L. reuteri* plus Pantoprazole presented 65.22% eradication rate compared to 73.91% cure rate in the group that received the Pantoprazole and Amoxicillin and Clarithromycin therapy, with no statistically significant difference in eradication rate between the two groups (p=0.75). The total adherence was good and eradication of *H. pylori* was associated with improvement of dyspeptic symptoms for both eradication regimens.

Conclusion. *L. reuteri* is a good alternative for patients with chronic dyspepsia for the eradication of *H. pylori* infection. Its efficacy is similar to the triple therapy.

Keywords: dyspeptic symptoms, *Helicobacter pylori*, *Lactobacillus reuteri*, probiotics

Introduction

Helicobacter pylori (*H. pylori*) is a gram negative, spiral-shaped, micro-aerophilic human pathogen that colonizes the gastric mucosa of more than 50% of the global population [1,2]. *H. pylori* is able to survive the acid environment of the stomach due to its ability to adhere to the gastric mucosa, colonizing the mucosal lining of the stomach [3]. Most *H. pylori* carriers remain asymptomatic; however, it is associated with a number of gastrointestinal diseases such as peptic ulcer (10-20%), gastric cancer (1-2%) and rarely mucosa-associated lymphoid tissue lymphoma [4]. There is evidence of an association between the amount of gastric colonization by *H. pylori* and the chance of developing symptoms of disease [5]. In the National Health and Nutrition Examination Survey III, *H. pylori* was strongly positively associated to gastric cancer mortality [6]. The 5th edition of the Maastricht Consensus Report offers diagnostic guidelines and recommends always therapeutic regimes for *H. pylori* eradication [7].

H. pylori is encountered in 30% to 50% of functional dyspeptic patients, but

its pathogenic implications are not yet established [8,9]. In dyspeptic patients a test-and-treat strategy is suggested. Therapeutic options for *H. pylori* infection with the purpose of eradication include different combinations of proton pump inhibitors associated with two or three antibiotics. Unfortunately this complex approach has high risks of side effects and non-compliance [10].

Probiotics are used in the treatment of *H. pylori* infection [11]. They have proven helpful in reducing side effects of antibiotics and enhance patient compliance [12]. Strains of *Lactobacillus reuteri* (*L. reuteri*) have been shown to exert an inhibitory effect on the settlement of human gastric mucosa by *H. pylori* [13]. *L. reuteri* has the capacity to produce reuterin, a wide spectrum antibiotic active against *H. pylori* [14]. *L. reuteri* strain DSMZ 17648 was tested for antibiotic resistance and no resistance was found [5].

The aim of this study was to test the efficacy of *L. reuteri* in eradication of H. pylori in an area where data on antibiotic resistance are very scarce.

Methods
Subjects
The study population included recently diagnosed *H. pylori* positive subjects referred to a tertiary gastroenterology unit by family physicians or specialists from other medical centers, for chronic dyspeptic symptoms.

Subjects were included in this study if they had reached the age of 18, had documented informed consent, a positive *H. pylori* finding, had no morphological changes of the gastric mucosa in upper gastrointestinal endoscopy and presented of functional dyspepsia (FD) according to the Rome III criteria [15].

Patients were excluded if they had any other chronic organic diseases that required drug treatment: myocardial ischemia or infarction, congestive heart failure, diabetes mellitus, renal failure, cirrhosis, previous gastric surgery, gallstone disease, chronic pancreatitis, chronic obstructive pulmonary disease, rheumatoid arthritis or regular use of nonsteroid anti-inflammatory drugs or bisphosphonates, oral intake of antibiotics, PPIs or H2 antagonists in the precedent 3 months, pregnancy or lactation.

Protocol
Baseline *H. pylori* infection was defined as the presence of *H. pylori* on histological examination of gastric biopsies.

At baseline, patients were evaluated for symptoms, history of allergy to any of the drugs used, and absence of prior treatment for *H. pylori* infection. Demographic data including age, gender, height and weight were collected for each patient. Body mass index was also calculated. We investigated severity of five symptoms (general abdominal symptoms, satiety, fullness, bloating and epigastric pain) by using independent visual analogue scale (VAS) (0-100 mm) and the anxiety score by using Hamilton's Anxiety Scale. The measurements were made at baseline and at 30 days after therapy.

We undertook a prospective single center comparative study between *L. reuteri* plus PPI versus the standard of care consisting in triple therapy plus PPI.

Patients were randomly divided in two equal groups. One group received Pantoprazole 40 mg bid. for 30 days associated with Amoxicillin 1000 mg bid and Clarithromycin 500 mg bid (PAC) for 14 days. The other group received Pantoprazole 40mg/day plus *L. reuteri* DSMZ 17648 (Pylopass, Remedia Laboratories, Romania) twice a day (PLR) for 8 weeks.

All drugs in this study were self-administered as tablets. Adherence was checked at the end when patients were asked to bring the drug packages.

Post-treatment eradication success was defined by the negative *H. pylori* antigen stool assay at 30 days after therapy.

Statistics
Statistic assessments were performed with a commercially available package and included descriptive statistics and ANOVA comparison between groups. The significance levels between comparisons was set at 0.05.

Ethical issues
The study was approved by the local ethical committee and conducted in accordance to the Helsinki regulations on experiments on humans.

Results
A total of 46 FD patients (M: 13, F: 33); with a mean age of 48.80 ± 13.82 years fulfilled inclusion criteria. FD patients were divided into three subgroups according to the cardinal symptoms: Postprandial Distress Syndrome (PDS), Epigastric Pain Syndrome (EPS) and overlapping PDS and EPS [16,17]. They were then randomly divided into two equal groups (23 patients each group). The baseline demographic data are given in Table I.

Table I. Baseline demographic data of treated patients.

	L. reuteri	Triple therapy
No. of patients	23	23
PDS/EPS/Overlap	12/7/4	11/8/4
Male/Female	5/18	8/15
Mean age (years) ± SD	50.00 ± 1.50	47.61 ± 16.25
BMI – mean (kg/m2) ± SD	25.42 ± 3.3	26.83 ± 3.09

The first group, receiving PLR therapy, showed 65.22% (15/23) eradication rate. The second group, receiving PAC therapy, showed 73.91% (17/23) eradication rate. There wass no statistically significant difference in eradication rate between the two groups (p=0.75). There was no drop out in this study.

The therapy adherence for the entire group was 97.83%. One patient from the PLR group did not fully comply with treatment due to side effects consisting in

nausea and heartburn, which lead to a compliance rate of 95.65% in this group. The PAC group had a 100% rate of compliance. Five patients from this group reported heartburn, nausea and epigastric pain, but all this side-effects were self-limiting, did not required specific therapy and improved until the end of the treatment.

There was no correlation between BMI and eradication rate.

In both groups, the eradication of *H. pylori* was associated with improvement of dyspeptic symptoms and anxiety score. There was no difference between the two groups regarding the alleviation of symptoms (Table II).

Table II. Symptoms and anxiety score changes in both groups.

Parameter (final - initial)	*L. reuteri* (n=16)	Triple therapy (n=17)	Value of *p*
General symptoms	6.50 ± 1.21	6.82 ± 0.88	0.192
Satiety	5.31 ± 1.14	5.06 ± 0.90	0.241
Fullness	5.25 ± 0.86	4.65 ± 0.93	0.031
Bloating	5.06 ± 1.24	4.71 ± 0.69	0.155
Pain	2.75 ± 1.06	2.94 ± 0.75	0.276
Anxiety	2.50 ± 0.63	2.65 ± 0.70	0.266

Discussion

Despite the fact that the *H. pylori* infection is recognized as an etiological factor in gastrointestinal pathology including gastric cancer, only a part of the patients actually develop symptoms [18]. Eradication is recommended as the standard procedure for patients who develop acute symptoms, and it should also be performed in the infected population. Unfortunately, in the general population this desiderate may be not accomplished, especially in regions with high prevalence of *H. pylori* infection, high rate of antimicrobial resistance or poorly developed health systems [5].

There have been many attempts to develop an effective treatment protocol to eradicate *H. pylori* infection. For decades, the use of antimicrobials was the first choice of therapy. The most effective treatment regimens are quite complicated, requiring the ingestion of three or four different drugs at multiple intervals of time and for a longer time [19]. Borody et al where the first to develop a therapy with a high eradication rate in *H. pylori* infection. It involved three drugs: bismuth, metronidazole and tetracycline administrated for 10 to 14 days without a PPI [20]. Association of a PPI and increased dose of metronidazole improved eradication rates [21]. The triple therapy approach, PPI and amoxicillin and clarithromycin, provided low eradication rates in some regions, explained by the pretreatment antibiotic-resistant strains [22]. The choice of antibiotics requires the knowledge on microbial antibiotic resistance in each specific area. Unfortunately, in our country there are no data on *H. pylori* antibiotic resistance or sensitivity. Therefore, using probiotics for *H.*

pylori eradications seems to be attractive.

Indeed, in the last decades the efficacy of probiotics for *H. pylori* eradication was tested to avoid antimicrobial resistance, allergies or other antibiotic side effects. *L. reuteri* DSMZ 17648 showed a significant decrease of *H. pylori* stomach colonization in vivo study [5]. A pilot study conducted by Dore et al showed that *L. reuteri* have potential role in *H. pylori* eradication. *L. reuteri* plus pantoprazole bid was able to eradicate 13.6% of patients with *H. pylori* infection [23].

Starting from this hypothesis, we tested efficacy of *L. reuteri* plus pantoprazole compared with pantoprazole plus amoxicillin plus clarithromycin in our area (Western Romania). Our results show a good eradication rate in the *L. reuteri* plus pantoprazole group (65.22%) much higher than the one showed by Dore et al. [23]. This can be explained by the geographical differences which involve different cultural and alimentary habits.

In the pantoprazole and amoxicillin and clarithromycin group we also had a good *H. pylori* eradication rate, and this is similar to other studies involving this therapy [24].

The only drawback seems to be the long time administration period, which might lead to lack of compliance in these patients, and the relative high cost for this treatment. Our data are consistent with other data from reviews suggesting that probiotics may be considered as alternative therapy to the antibiotic therapy for *H. pylori* eradication [25,26].

Eradication of *H. pylori* was associated with improvement of dyspeptic symptoms in both groups, but we noticed an increase of these symptoms in the first days of administration of pantoprazole plus amoxicillin plus clarithromycin in some patients. We consider this finding as an explanation for lack of adherence in patients which develop this adverse effect.

Given the fact that data on the association of *H. pylori* infection and BMI are conflicting [27] and some authors found a positive association between *H. pylori* infection and an increased BMI [28], we have analyzed data in our groups which included patients with a mean BMI classified according to the World Health Organization recommendations as overweight (25-29.9 kg/m) and found no correlation between BMI and eradication rate.

Our study represents to our knowledge the first attempt in our area to test the efficacy of *L. reuteri* plus PPI in eradicating *H. pylori*.

However, this prospective trial has some limitations. The sample size is small, neverthelss the data are useful and open the hope to an alternative in patients with unknown antibiotic sensitivity, with adverse effects or reluctant to ingest antibiotics. Further trials of larger amplitude and multicentric would be useful to establish the role of the probiotics in eradicating *H. pylori*.

Conclusions

L. reuteri in association with pantoprazole eradicates *H. pylori.* It has a very good compliance and almost no side effects. It is useful in areas with ignored antibiotic resistance to antibiotics for *H. pylori.* Its non-inferiority versus the PAC triple therapy should be confirmed by further trials.

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