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ORIGINAL ARTICLE

A Lyophilized Form of *Saccharomyces Boulardii* Enhances the *Helicobacter pylori* Eradication Rates of Omeprazole-Triple Therapy in Patients With Peptic Ulcer Disease or Functional Dyspepsia

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KEY WORDS: *Saccharomyces boulardii; Helicobater pylori infection; classic triple therapy; omeprazole; clarithromycin; amoxicillin.*

ABBREVIATIONS
ARR = absolute risk reduction
CLO = campylobacter-like organism test
CTT = classic triple therapy
GERD = gastro-esophageal reflux disease
ITT = intention-to-treat
MALT = mucosa-associated lymphoid tissue
NNT = number needed to treat
NSAID = non-steroidal anti-inflammatory drugs
OAC = omeprazole, amoxicillin, clarithromycin
PP = per protocol
PPI = proton-pump inhibitor
RR = relative risk

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ABSTRACT

BACKGROUND: *Saccharomyces boulardii* prevents antibiotic-induced diarrhea and exerts anti-*H.pylori* effects *in vitro* and *in vivo*.

AIM: To assess whether *S. boulardii* enhances the efficacy of classic triple therapy in eradicating *H. pylori*.

METHODS: Seventy patients with peptic ulcer or functional dyspepsia according to Rome III criteria and *H. pylori* infection were treated with omeprazole 20 mg bid, clarithromycin 500 mg bid and amoxicillin 1 g bid for 14 days. A total of 36 out of 70 (51%) patients were randomized to *S. boulardii* [Ultralevure®, two capsules tid for 14 days (group A) and 34 (49%) on no intervention (group B). *H. pylori* eradication was assessed by a ^{13}C-Urea Breath Test.

RESULTS: At baseline there were no significant differences between the two groups in any patient or disease characteristics. *H. pylori* was eradicated in 30/36 (83.4%) patients in group A vs 20/34 (58.8%) in group B (P=0.034, 95% CI 4.4% to 43.6%). Seven patients in group B (20.6%) and 1 patient in group A stopped treatment because of diarrhea (95% CI 3.3% to 32.7%, P=0.026). Multi-factorial analysis did not reveal any patient or disease related parameter linked to treatment outcome except for the use of the probiotic.

CONCLUSION: *S. boulardii* enhanced the effect of classic triple therapy mainly by preventing antibiotic- and/or proton pump inhibitor-induced diarrhea.

INTRODUCTION

Helicobacter pylori (*H. pylori*) infection affects 70-90% of the population in developing countries and 25–50% in developed countries.[1] In the majority of the cases *H.*

Conflict of Interest: none declared

pylori induces a life-long mild chronic superficial antral gastritis which may be asymptomatic and causes no harm to the affected individuals. Less often, however, the infection may initiate a sequence of events leading onto the development of peptic ulcer disease, gastric adenocarcinoma, mucosa-associated lymphoid tissue (MALT) B-cell lymphoma and/or extra-gastric diseases.[2-5] Since we lack data on risk factors for predicting unequivocally who of the infected individuals will develop *H. pylori*-related diseases, it has been recommended that the infection be cured in all patients.[2,3]

A proton-pump inhibitor (PPI) with amoxicillin and clarithromycin (classic triple therapy, CTT) is still the treatment of choice for eradication of *H. pylori* infection and is now recommended for 10-14 days.[2] However, the efficacy of CTT is compromised by increasing resistance to clarithromycin and poor adherence.[6] The latter is largely due to the number of consumed tablets, duration of treatment, and treatment-related adverse events, predominantly gastrointestinal, such as nausea, bloating, epigastric pain, vomiting, and diarrhea.[7] Discontinuation of treatment reduces eradication rates of *H pylori* and increases further resistance to antibiotics. Thus, CTT cannot usually achieve eradication rates greater than 80%, a figure that is considerably lower for patients who harbor clarithromycin-resistant *H. pylori* strains.

The most worrisome adverse event, diarrhea, is related to both antibiotics and PPIs and is usually due to quantitative and qualitative alterations in the gut microbiota including the development of *Clostridium difficile* infection.[8] Thus, at least in theory, some probiotics could enhance the efficacy of CTT by a dual mechanism, improving adherence (by preventing diarrhea) and exerting a synergistic effect to antibiotics (by a direct *anti-H. pylori* action). Probiotics are 'live microorganisms which when administered in adequate amounts confer a health benefit on the host.[9] Various probiotics have been documented to exert anti-*H. pylori* effects both *in vitro*[10,11] and *in vivo*.[12-21] *Saccharomyces boulardii* probiotics have shown efficacy in several types of acute diarrhea[22] and may also induce morphologic changes in *H. pylori* cell lines consistent with cellular damage[23] and reduce by 12% *H. pylori* colonization of infected children.[24] Thus, the aim of this study was to investigate the efficacy of a widely available, single strain of *S. boulardii* preparation as an adjunct to CTT.

PATIENTS AND METHODS

PATIENTS

This was a prospective, randomized, controlled, single-center study conducted in the first Department of Gastroenterology, at Evagelismos Hospital, Athens, Greece, which recruited consecutive patients aged 18-75 years with *H. pylori*-related peptic ulcer disease or functional dyspepsia according to Rome III criteria during a 3-year period (January 1, 2005 – December 31, 2007). Rome III criteria include one or more of the following symptoms of at least 3-month duration, with onset at least 6 months previously: bothersome postprandial fullness, early satiation, epigastric pain, epigastric burning and no evidence of structural disease (including upper endoscopy) that is likely to explain the symptoms. Exclusion criteria were age under 18 years, prior treatment with clarithromycin, treatment with other antibiotics and/or PPIs in the last 3 months prior to inclusion, chronic treatment with aspirin and/or non-steroidal anti-inflammatory drugs (NSAID), gastro-esophageal reflux disease (GERD), cholelithiasis, current or intended pregnancy, chronic heart, pulmonary, hepatic, or renal failure, malignancy, and inability to comply with the terms of the study protocol.

STUDY PROTOCOL

Consecutive dyspeptic patients who consented to participate in this study underwent detailed physical examination, laboratory tests (full blood count, erythrocyte sedimentation rate, C-reacting protein, routine liver function tests, blood-urea nitrogen, blood glucose, serum creatinine, and urinalysis), abdominal ultrasound, and esophago-gastro-duodenoscopy. The presence of *H. pylori* was sought by a rapid urease test (CLO-test, Delta West Ltd, Bentley, Australia) on fresh biopsy specimens from the antrum and by histology (modified Giemsa staining) on 10% formalin fixed paraffin embedded mucosal biopsies obtained from uninvolved areas of the gastric antrum and the body. Gastritis activity and severity were scored according to the Houston updated Sidney classification.[25] Patients were considered infected when both the CLO-test and histology confirmed the presence of *H. pylori*.

H. pylori infected patients were randomized to two treatment groups as follows: Group A included patients who received omeprazole (20 mg twice daily, one hour before meals), clarithromycin (500 mg twice daily with meals), and amoxicillin (1 g, twice daily with meals) for 14 days (OAC-14) plus a *S. boulardii* preparation [Ultra Levure® capsules, two capsules three times a day; 1 capsule contains 50mg (x10^6 live microorganisms) *S. boulardii* strains in lyophilized form]. Group B patients received OAC-14 only. Group B did not include a *S. boulardii placebo* preparation. In addition, patients in each group were unaware that there was another treatment arm in the study employing a different therapeutic regimen.

Cure of *H. pylori* infection was considered when a commercially available ^{13}C-Urea Breath Test [^{13}C-UBT, INFAI-test (Institut Fór biomedizinische Analytik & NMR-Imaging), Bochum, Germany] at 6 weeks post treatment was negative in patients who had discontinued PPIs, probiotics and/or antibiotics.

A single non-blinded physician (AR) randomized patients, allocated prescriptions, reviewed patients notes and arranged the appointments for the ^{13}C-UBT tests. Patients used note books to record proper intake of prescribed medication and any adverse event that developed during the course of treat-

ment. In order to ascertain the highest possible adherence to treatment, all enrolled patients were given oral and written instructions concerning proper intake of treatment and free-access to mobile telephone of the physician who was responsible for the randomization (AR). All other study personnel were unaware of patient data and treatment category.

STATISTICAL ANALYSIS

In calculating the sample size it was estimated that 34 patients per group should be studied to detect a 20% difference in eradication rates with 80% probability (two-sided test; a=0.01) assuming a 65% eradication rate after OAC-14 therapy which is the median successful eradication rate in our department using the classical triple therapy for 14 days. The primary end-point of this study was the eradication of *H. pylori*. Secondary end-points were the influence of patient clinical and demographic parameters on eradication rates of *H. pylori* and the rate of adverse events overall and diarrhea in particular. Results were analyzed both by the intention-to-treat (ITT) and per protocol (PP) methods. All patients that received at least one of the study medications were included in the ITT analysis; patients who for whatever reason did not complete the 14-day therapy or did not return for re-evaluation after treatment were considered as treatment failures. Only patients who completed the treatment and underwent successfully UB testing 6 weeks post treatment were included in the PP analysis. Comparisons between the two treatment groups were performed using the Mann-Whitney U-test and the Fisher's exact test where appropriate. Exact binomial 95% confidence intervals (95% CI) were calculated for *H. pylori* eradication and adverse events to treatment. *P* values lower than 0.05 were considered significant. Multiple logistic regression analysis was performed to evaluate the potential risk factors for the outcome of treatment, including age, gender, smoking (yes/no), peptic ulcer disease (yes/no) functional dyspepsia (yes/no), gastritis score (severity and activity) in the antrum and the corpus of the stomach, social drinking (yes/no), body mass index (normal/abnormal), and treatment (combined OAC-14 with *S. boulardii* versus OAC-14). The study was approved by the Institution Review Board of the Evagelismos Hospital. All patients gave written informed consent.

RESULTS

Between January 1, 2005 and December 31, 2007, 125 *H. pylori* infected patients were evaluated for inclusion in this study but finally only seventy patients who fulfilled the inclusion criteria and consented to participate were enrolled. Patient demographic and clinical data are given in Table 1. Notably, patients with peptic ulcer disease and/or functional dyspepsia were more or less equally distributed in the two treatment groups (*P*=0.47). A flow-chart of the study protocol is outlined in Figure 1.

Overall, 33 of 36 (91.7%) patients completed the study in group A versus 27 of 34 (79.4%) patients in group B (*P*=0.182) (Figure 1). Considering patients who did not complete the study as 'treatment failures', *H. pylori* infection was eradicated in 30 of

TABLE 1. Patient demographic and clinical characteristics

Patients	OAC-14 plus *S. boulardii* (Group A)	OAC-14 alone (Group B)	P
n	36	34	n.s.
Gender (male/female)	19/17	19/15	n.s.
Age (years) median (range)	47 (18-72)	45 (19-70)	n.s.
Disease duration (years) Median (range)	12 (0.2-27)	14 (0.2-29)	n.s.
Smokers (n, %)	20 (56%)	21 (62%)	n.s.
Social drinkers (n, %)	12 (33%)	12 (35%)	n.s.
Body mass Index (BMI) median (range)	29 (25-33)	30 (23-32)	n.s.
Cause of dyspepsia			
Peptic ulcer disease (n, %)	15 (42%)	11 (32%)	n.s.
Functional (n, %)	21 (58%)	23 (68%)	n.s.

OAC-14, classical anti-*Helicobacter pylori* triple therapy consisting of Omeprazole, Amoxicillin, and Clarithromycin for 14 days. n.s.: not significant.

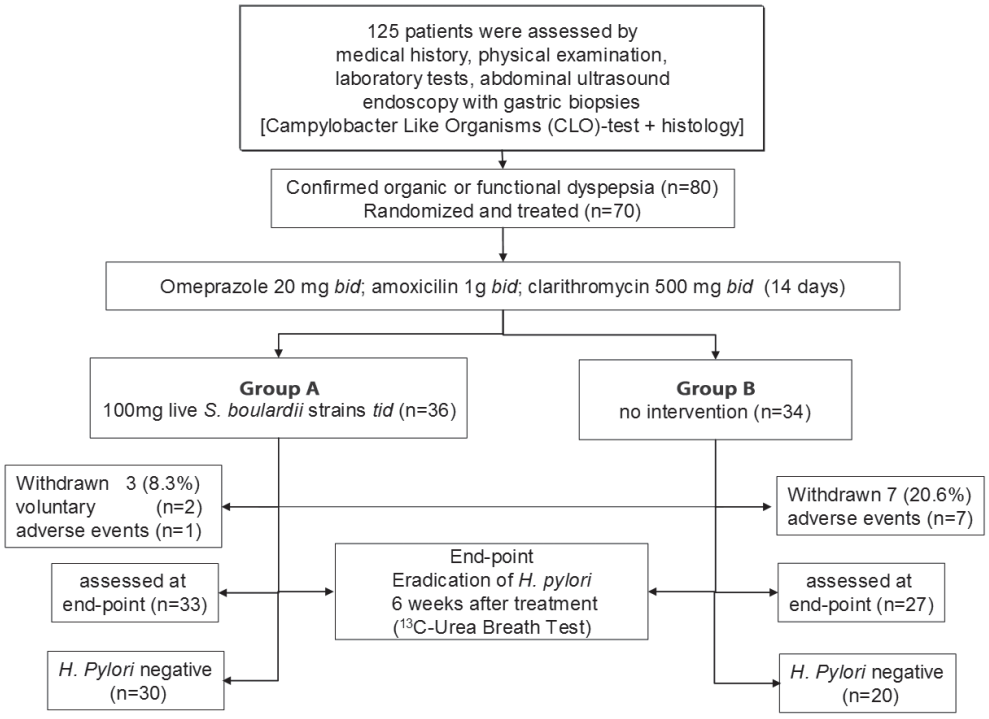

FIGURE 1. Flow chart of patients, reasons for treatment discontinuation and outcome of treatment.

36 (83.4%) patients in group A and in 20 of 34 (58.8%) in group B (ITT analysis, $P=0.034$, 95% CI 4.4% to 43.6%) (Table 2). The absolute gain in eradication rates by the combined OAC-14 and *S. boulardii* therapy over OAC-14 alone was 24.6%. By PP analysis, eradication rates were 90.9% in group A and 74% in group B, respectively (95% CI -43.76% to 77.76%, $P=0.097$) (Figure 1) (Table 2). Multi-factorial analysis did not reveal any other patient demographic, clinical, endoscopic and/or histologic parameter related to the effectiveness of treatment except for the use of *S. boulardii*.

Treatment was better tolerated in group A: two patients with peptic ulcer disease were withdrawn voluntarily after they had completed 10 days of treatment because they felt well and only one patent (2.8%) was withdrawn for adverse events (diarrhea) (Table 2). In contrast, seven patients were withdrawn in group B (20.6%), all because of protracted treatment-related

TABLE 2. Cumulative results of the study

Patients	OAC-14 plus *S. boulardii* (Group A)	OAC-14 alone (Group B)	P
n	36	34	n.s.
Completed treatment, n (%)	33 (91.7%)	27 (79.4%)	0.182
Withdrawals, n (%)	3 (8.3%)	7 (20.6%)	n.s.
voluntary	2 (5.6%)	0	
diarrhea	1 (2.8%)	7 (20.6%)	0.026
Eradication of H. pylori [n, (%) ITT analysis]	30/36 (83.4%)	20/34 (58.8%)	0.034
Eradication of H. pylori [n, (%), PP analysis]	30/33 (90.9%)	20/27 (74.1%)	0.097

OAC-14: Omeprazole, Amoxicillin, and Clarithromycin anti-*H. pylori* classical triple therapy for 14 days, ITT: Intention-To-Treat analysis, PP: Per Protocol analysis, n.s.: not significant

diarrhea. *C. difficile* toxin A was isolated in the stools of two of 7 patients in group B who were withdrawn for diarrhea and were treated accordingly (Table 2). Thus, although by ITT analysis there was no significant difference between groups A and B in the proportion of patients completing the study (91.7% vs 79.4% for groups A and B, respectively, $P=0.182$, 95% CI 6.7% to 39.25%) withdrawals for treatment-related diarrhea were significantly fewer in patients receiving adjunctive probiotic therapy [1 of 36 (2.8%) cases (group A) vs 7 of 34 (20.6%) cases (group B), respectively, 95% CI 3.3% to 32.7%, $P=0.026$] (Table 2). The absolute risk reduction for diarrhea in patients receiving the combination therapy of OAC-14 and *S. boulardii* therapy over patients treated with OAC-14 alone was 17.8%.

There were no significant differences in eradication rates between patients with peptic ulcer disease or functional dyspepsia both within and between treatment groups (data not shown). None of the patients developed systemic *S. boulardii* infection.

DISCUSSION

Classic triple therapy (CTT) consisting of the combination of a PPI and two antibiotics, clarithromycin and amoxililin, is still considered the treatment of choice for eradication of *H. pylori* infection. However, resistance to clarithromycin and poor adherence may undermine the efficacy of treatment. Antibiotic- and PPI-related related diarrhea is the predominant cause for premature cessation of treatment that results in failure to eradicate *H. pylori* and development of *H. pylori* strains resistant to antibiotics. Preventing adverse events, and especially diarrhea, is not only an attractive but also a very cost-effective strategy to enhance adherence resulting in completeness of treatment and higher eradication rates.

Various lactobacilli can inhibit or even eliminate *H. pylori in vitro*[10,11] and *in vivo* either directly or by secreted metabolic products, especially lactic acid, and may also increase the efficacy of antibiotics.[12-21] *S. boulardii* induces morphologic changes that are consistent with cellular damage in *H. pylori* cell lines[23] and reduces *H. pylori* colonization of infected children.[24] *S. boulardii* has also been tested with varied degrees of clinical efficacy in several types of acute diarrhea including antibiotic-associated diarrhea, *C. difficile* infection, acute adult diarrhea, enteral nutrition-related diarrhea, and traveler's diarrhea.[22] In theory, therefore, *S. boulardii* probiotics could prevent and/or counterbalance the untoward effects of antibiotics and/or PPIs on the intestinal microflora allowing patients to complete a 14-day CTT but may also exert synergistic affects with antibiotics by their potential direct anti-*H. pylori* action. Indeed, there are five studies in the literature in adults and pediatric population that have suggested that *S. boulardii* increases the eradication rates of *H. pylori* and prevents adverse events related to the CTT.[24, 26-29] A meta-analysis of 5 randomized controlled studies with various end-points involving 1307 subjects (1217 adults and 90 children) who were treated with CTT and *S. boulardii* vs placebo or no intervention has been published recently. Eradication rates of H. pylori infection was assessed in 4 of 5 trials involving 915 patients (the end-point of the 5th trial was only prevention of diarrhea and eradication rates were not reported); the combination of S. *boulardii* and CTT increased significantly the eradication rates of *H. pylori* compared to placebo or no intervention [relative risk (RR) 1.13, 95% CI 1.05-1.21, with an absolute gain in eradication rates of 9% and a number needed to treat (NNT) of 11]. Occurrence of diarrhea was an end-point in 4 of 5 trials in the meta-analysis involving 1215 patients; the combined treatment reduced significantly the risk for developing diarrhea (RR 0.47, 95% CI 0.32-0.69, with an absolute risk reduction (ARR) of 6.6% and a NNT of 16). Finally, the RR for developing any adverse event was tested in all 5 trials involving 1305/1307 patients (two patients who did not complete the anti-*H. pylori* treatment were excluded). The incidence of diarrhea was reduced significantly by the combined treatment (RR 0.46, 95% CI 0.3-0.7, with an ARR of 11.4% and a NNT of 11) but when adverse events other than diarrhea were analyzed there was no statistical difference between patients on *S. boulardii* vs. no intervention/placebo.[30] These results support the important role of *S. boulardii* as an adjunct to CCT to prevent diarrhea and increase compliance of patients with anti-*H. pylori* regimens.

Our study is in accordance with the results of this meta-analysis[30] and some previous reports depending on the population studied, type and duration of therapy, and whether analysis of results was performed on an intention-to-treat or per protocol.[24,26-29] For instance, Song et a[26] found significantly higher reported eradication rates for the *S. boulardii* group compared with a control group (80% vs. 71,6%, respectively, ITT analysis, $P=0,03$). Chindoruk et al[27] treated 124 patients with H. pylori infection with a 14-day triple therapy (clarithromycin 500 mg b.i.d., amoxicillin 1000 mg b.i.d., and lansoprazole 30 mg b.i.d.) plus *S. boulardii* or placebo. Although *H. pylori* eradication rates were numerically but not statistically higher in the treatment group [44/62 (71%) vs. 37/62 (59.7%), PP analysis] the incidence of diarrhea was statistically lower in the *S. boulardii group* [9 (14.5%) vs.19 (30.6%), respectively, $P<0.05$]. Cremonini et al[28] using a 7-day rabeprazole, tinidazole and amoxycilin *H. pylori* eradication regimen in association with 3 different probiotic strains or placebo showed a trend towards better eradication rate with the probiotics (81% vs 76%, PP analysis) but a significantly higher reduction in the incidence of diarrhea. Also, in the study of Hurduc et al[29] in infected children, the *H. pylori* eradication rate in controls was 80.9% vs. 93.3% in the *S. boulardii* group (PP analysis, $P=0.750$). However, the incidence of side effects was reduced in the *S. boulardii group* (8.3% vs. 30.9% in the control, $P=0.047$) leading to the conclusion that the addition

of *S. boulardii* to the standard eradication treatment conferred a 12% non non significant enhanced therapeutic benefit on *H. pylori* eradication and reduced significantly the incidence of side effects. In our study, eradication rates were significant on ITT analysis but felt marginal significance in the PP analysis; however, the incidence of diarrhea was significantly reduced irrespective of the analysis used. As in all these studies the concomitant administration of *S. boulardii* with CTT against *H. pylori* led to statistically or numerically higher eradication rates and to statistical reduction of diarrhea it is not surprising that the results of the Szajewska et al[30] meta-analysis justified the use of *S. boulardii* as adjunctive therapy of CTT for better tolerance of therapy resulting in increased eradication rates of the infection.

Although a direct effect of *S. boulardii* on anti-*H. pylori* cannot be excluded, this study was not adequately powered to reveal any synergistic effect(s) of *S. boulardii* and CTT. It is, therefore, likely that prevention of treatment-related diarrhea was the leading mechanism underlying the higher efficacy of the combined treatment. Indeed, the combined treatment was tolerated very well by all except one patient. The other two patients with peptic ulcer disease stopped prematurely the combined treatment not because they developed adverse events but because they felt very well after 10 days of treatment (Figure 1, Table 2). In fact, both patients were tested negative by a ^{13}C-UBT outside the context of this clinical trial 6 and 8 months later, respectively, after the cessation of treatment.

A limitation of our study was the lack of a placebo controlled arm that would ensure an entirely blind study for all investigators and the rather small number of patients to assess any long-term effects of combination therapy vs. OAC-14. However, this is at least in part counterbalanced by the heavy involvement of a single unblinded investigator who was responsible for many activities in the trial that could lead to potential violation of the results. None of the other study personnel was aware of any treatment intervention. In addition, although this study was not double-blind, patients were unaware that there was another study arm employing a different treatment. Therefore, there was no ground for potential bias in subjects of stratum B reporting diarrhea or any other symptoms as a result of knowledge that another patient group were receiving *S. boulardii* preparations

In conclusion, this study adds evidence to recommend the concomitant use of *S. boulardii* with OAC-14, a CTT, for eradicating *H. pylori* in order to reduce treatment-related diarrhea and enhance compliance with treatment which may lead to higher rates of eradication of this pathogen.

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