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The effect of oral administration of Lactobacillus GG *on antibiotic-associated gastrointestinal side-effects during* Helicobacter pylori *eradication therapy*

A. ARMUZZI*§, F. CREMONINI*, F. BARTOLOZZI†, F. CANDUCCI*, M. CANDELLI*, V. OJETTI*, G. CAMMAROTA*, M. ANTI*, A. DE LORENZO§, P. POLA‡, G. GASBARRINI* & A. GASBARRINI‡
*Departments of *Internal Medicine, †Hygiene and ‡Medical Pathology, Catholic University, Rome, Italy; and §Human Nutrition, Tor Vergata University, Rome, Italy*

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SUMMARY

Background: One-week triple therapy is currently considered the golden standard against *Helicobacter pylori*. However, gastrointestinal side-effects are among the major pitfalls in such regimens. Probiotic supplementation might help to prevent or reduce such drug-related manifestations.

Aim: To determine whether adding the probiotic *Lactobacillus GG* to an anti-*H. pylori* regimen could help to prevent or minimize the gastrointestinal side-effects burden.

Methods: Sixty healthy asymptomatic subjects screened positive for *H. pylori* infection were randomized to 1 week rabeprazole (20 mg b.d.), clarithromycin (500 mg b.d.), tinidazole (500 b.d.) and the probiotic *Lactobacillus GG* for 14 days or to the same regimen with a placebo preparation. Patients completed validated questionnaires during the week of treatment and during the following 3 weeks, to determine the type and severity of side-effects and an overall judgement of tolerability.

Results: Diarrhoea, nausea and taste disturbance were significantly reduced in the *Lactobacillus GG* supplemented group (relative risk = 0.1, 95% CI: 0.1–0.9; relative risk = 0.3, 95% CI: 0.1–0.9; relative risk = 0.5, 95% CI: 0.2–0.9, respectively). An overall assessment of treatment tolerability showed a significant difference in favour of the *Lactobacillus GG* supplemented group ($P = 0.04$).

Conclusions: *Lactobacillus GG* supplementation showed a positive impact on *H. pylori* therapy-related side-effects and on overall treatment tolerability.

INTRODUCTION

The recognized association between *Helicobacter pylori* infection and a wide range of gastrointestinal illnesses has profoundly modified the management and therapeutic approach towards most of these conditions.[1] There are several treatment options to cure *H. pylori* infection and many are still under investigation.[2] Currently, a 1-week therapy, which combines acid suppression with two antibiotics, is regarded as the reference standard of anti-*H. pylori* schemes, representing the best value for efficacy, tolerability, simplicity of administration, compliance and cost.[1, 3–5] However, inadequate prescriptions, bacterial resistance, and poor patient compliance, are among the factors which make *H. pylori* eradication difficult.[6] Antibiotic-associated gastrointestinal side-effects may represent a serious drawback of triple therapies, even though they are mild in most cases.[7] The high prevalence of side-effects might cause even motivated and dyspeptic patients to discon-

Correspondence to: Dr A. Gasbarrini, Department of Medical Pathology, Catholic University, Policlinico Gemelli, Largo Gemelli 8, 00168 Rome, Italy.
E-mail: angiologia@rm.unicatt.it

tinue therapy, with the risk of treatment failure or possible development of antibiotic resistant strains.

Gastrointestinal side-effects most often associated with antibiotic treatments may include diarrhoea, nausea, vomiting, bloating and abdominal pain.[8] These manifestations have been related to quantitative and qualitative changes in the intestinal microflora due to unabsorbed or secreted antibiotics in the intestinal content, with a resulting reduction in normal saprophytic flora and overgrowth and the persistence of potentially pathogenic antibiotic-resistant indigenous strains.[9, 10]

Probiotics are regarded as effective tools for controlling the overgrowth of potentially pathogen micro-organisms and may help to prevent or lower the incidence of antibiotic-associated side-effects.[11] *Lactobacillus casei* sps. rhamnosus (*Lactobacillus GG*), a probiotic of human origin, reportedly exerts a beneficial effect in the prevention and treatment of several intestinal conditions.[12]

In a recent open trial, the addition of *Lactobacillus GG* to an anti-*H. pylori* standard triple therapy has been demonstrated to exert some help in preventing and/or minimizing the occurrence of gastrointestinal side-effects.[13] That study was biased because it did not have a placebo-controlled design. The outcomes, all based on subjective parameters, could have been, in part, affected by such an issue.

We examined, through a double-blind placebo-controlled study, the effect on antibiotic-associated side-effects and treatment tolerability, of adding a *Lactobacillus GG* preparation, during and after a standard triple *H. pylori* eradication therapy.

METHODS

Patients

The study was a single centre, double-blind, prospective, randomized, placebo-controlled trial, carried out on 60 *H. pylori*-positive healthy asymptomatic volounteers (male/female: 25/35; mean age 40 ± 12 years). The volunteers were all personnel of the *Gemelli Hospital* (Catholic University Teaching Hospital in Rome) working as physicians, biologists, nurses or administrators, from September 1st 1999 to January 31st 2000. The enrolled subjects were attending a screening programme for the assessment of prevalence and risk factors for *H. pylori* infection among healthcare workers.[14] Both ^{13}C-urea breath test and enzyme-linked immunosorbent assay for *H. pylori* IgG antibodies measurements were performed in each participant. *H. pylori*-positive asymptomatic subjects who wished to be eradicated were included in the study, which was approved by the Ethics Committee of the Catholic University. Subjects were defined as asymptomatic in the absence of dyspeptic symptoms. Only asymptomatic subjects were admitted, in order to prevent interference between baseline symptoms and newly occurring gastrointestinal manifestations.

Six weeks after completion of the therapy, the ^{13}C-urea breath test was repeated to check whether eradication had been achieved.

Treatment

Subjects were randomly assigned to a 7-day triple therapy consisting of rabeprazole 20 mg b.d. (before breakfast and dinner), clarithromycin 500 mg b.d. (half an hour after breakfast and dinner), tinidazole 500 mg b.d. (half an hour after breakfast and dinner) plus a probiotic preparation (freeze-dried powder) containing *Lactobacillus GG* (6×10^9 of viable bacteria, Giflorex, Errekappa Euroterapici S.p.A, Milan, Italy) b.d. (2 h after breakfast and dinner, mixed with water) for 14 days, during and the week after eradication therapy (group 1). Alternatively, they were assigned to the same proton pump inhibitor and antibiotic regimen plus probiotic-matched placebo (group 2). Boxes containing placebo had the same shape, dimension, trade mark indication and contained the same amount of sachets of boxes containing the viable *Lactobacillus GG* and were provided by the probiotic producer. Patients were informed by a blind investigator that such a supplementation could have been of some help in avoiding side-effects related to antibiotics (but information on the precise type and timing of such symptoms was not given to patients). The method of 'closed envelopes' was used for drug administration.

Side-effects and treatment tolerability evaluation

For each subject, a side-effects profile and treatment tolerability were assessed using a slightly modified version of the questionnaire proposed by de Boer *et al.*[15] In order to obtain the highest compliance in registering any possible treatment-related side-effect, subjects received careful instruction and training on filling-in questionnaires (verbal explanations and printed instructions were both given). In particular, each subject had

to report on the presence of symptoms (taste disturbance, loss of appetite, nausea, vomiting, stomach pain, bloating, diarrhoea, constipation, skin rash) and was asked to judge each side-effect according to severity: mild (effect observed, but could be disregarded); moderate (effect sometimes interfered with daily activities); or severe (effect continuously interfered with daily activities). The side-effects questionnaire was filled in four times (during the week of the eradication regimen and the first, second and third week thereafter). Moreover, in order to evaluate the impact of side-effects on treatment compliance, subjects provided an overall judgement of tolerability based on a five point scale (1: no side-effects; 2: slight discomfort, not interfering with daily activities; 3: moderate discomfort, sometimes interfering with daily activities; 4: severe discomfort, subject could finish the treatment but work was not possible; 5: severe discomfort, subject forced to discontinue treatment).[15] Finally, protocol adherence was verified through a tablet count in medication containers returned by subjects the day after finishing therapy and by directly asking the subject about therapy completion.

Statistical analysis

For each symptom, the relative risk and 95% confidence interval (CI) in the *Lactobacillus GG* supplemented group (group 1) with respect to the placebo group (group 2) were calculated. When the relative risk and CI values were less than 1, *Lactobacillus GG* supplementation was considered a significant protective factor for that single side-effect.

The symptom severity score was analysed by means of Fisher's exact test, whilst the two-sample Wilcoxon rank-sum test was used for an overall judgement of tolerablity score. Differences in *H. pylori* eradication between the groups were compared by means of the Mann–Whitney *U*-test. A *P*-value less than 0.05 was considered statistically significant. Calculations were made using the STATA 6.0 program (STATA Corporation, College Station, TX).

RESULTS

Side-effect profile

The frequencies of side-effects experienced by the two groups, during both the eradication week and follow-up, are reported in Table 1. Nausea (group 1: 10% vs.

Table 1. Frequencies of side-effects reported by the two groups during the eradication week and follow-up

	Triple therapy week				1st week				2nd week				3rd week			
Symptoms	Group 1 (%)	Group 2 (%)	RR	95% CI	Group 1 (%)	Group 2 (%)	RR	95% CI	Group 1 (%)	Group 2 (%)	RR	95% CI	Group 1 (%)	Group 2 (%)	RR	95% CI
Taste disturbance	23.3	50	0.5	0.2–0.9*	6.6	23.3	0.3	0.1–1.2	3.3	6.6	0.5	0.1–5.2	—	—	—	—
Loss of appetite	6.6	13.3	0.5	0.1–2.5	6.6	6.6	1	0.1–6.6	3.3	3.3	1	0.1–15.2	—	—	—	—
Nausea	10	36.6	0.3	0.1–0.9*	10	26.6	0.37	0.1–1.2	0	6.6	—	—	3.3	3.3	1	0.1–15.2
Vomiting	3.3	6.6	0.5	0.1–5.2	—	—	—	—	—	—	—	—	—	—	—	—
Epigastric pain	33.3	30	1.1	0.5–2.3	3.3	6.6	0.5	0.1–5.2	3.3	6.6	0.5	0.1–5.2	3.3	3.3	1	0.1–15.2
Bloating	36.6	56.6	0.6	0.3–1.1	30	26.6	1.1	0.5–2.5	10	13.3	0.7	0.1–3.1	6.6	13.3	0.5	0.1–2.5
Diarrhoea	3.3	26.6	0.1	0.1–0.9*	3.3	10	0.3	0.1–3.0	3.3	6.6	0.5	0.1–5.2	—	—	—	—
Constipation	20	16.6	1.2	0.4–3.5	16.6	16.6	1	0.3–3.1	6.6	3.3	2	0.2–20.8	—	—	—	—
Skin rash	3.3	6.6	0.5	0.1–5.2	—	3.3	—	—	—	—	—	—	—	—	—	—

* Significant.
RR, relative risk.

group 2: 36.6%; relative risk = 0.3, 95% CI: 0.1–0.9; $P = 0.01$), taste disturbance (group 1: 23.3% vs. group 2: 50%; relative risk = 0.5, 95% CI: 0.2–0.9; $P = 0.03$), and diarrhoea (group 1: 3.3% vs. group 2: 26.6%; relative risk = 0.1, 95% CI: 0.1–0.9; $P = 0.01$) were significantly lower in the *Lactobacillus GG* supplemented group with respect to the placebo group. In particular, in both groups, side-effects progressively decreased during follow-up (Table 1). However, no significant difference between groups remained after the eradication week, although a trend towards significance was present for those symptoms listed above. At the end of the study, symptoms, when present, did not significantly differ between study groups (Table 1).

The severity of side-effects was judged mild (especially) to moderate and severe (sometimes) during the eradication week (Table 2), whilst only mild side-effects were reported in the following weeks by both groups. Significant differences between the groups were observed only for diarrhoea ($P = 0.026$).

Treatment tolerability

Based on the five point scale, the overall judgement of tolerability adopted in the *Lactobacillus GG* supplemented group (group 1) was as follows: 18 out of 30 subjects reported no side-effects, nine out of 30 subjects experienced slight discomfort, one out of 30 subjects reported moderate discomfort, and two out of 30 subjects reported severe discomfort. In the placebo group (group 2), 10 out of 30 subjects reported no side-effects, 14 out of 30 subjects reported slight discomfort, four out of 30 subjects reported moderate discomfort, and two out of 30 subjects reported severe discomfort. Severe discomfort forcing treatment discontinuation was not reported in either group. The two-sample Wilcoxon rank-sum test between groups showed significant differences ($P = 0.04$).

Based on a tablet count after returning medication containers, all subjects were 100% compliant with their respective protocols.

H. pylori *eradication*

No significant differences were observed between the groups with respect to the success of *H. pylori* eradication. Treatment was successful in 25 out of 30 patients in group 1 (83.3%) and in 24 out of 30 patients in group 2 (80%).

DISCUSSION

This study describes the effects of the oral administration of probiotics (*Lactobacillus GG*) on antibiotic-associated gastrointestinal side-effects related to an anti-*H. pylori* standard scheme. Probiotic supplementation showed a significant improvement in treatment tolerability.

In the treatment of *H. pylori*-associated gastrointestinal diseases, various antibiotic regimens are used in current clinical practice. One-week triple regimens, in which two antibiotics are administered with an acid suppressing agent, are preferred to dual prescriptions, given the combinate efficacy of the antimicrobial drugs.[1] The frequency and duration of drug administration and the occurrence of side-effects, which may influence patients' compliance, should be borne in mind at the time of choosing a particular drug.[16] However, the use of

Table 2. Comparison of side-effects severity between study groups during eradication week

	None		Mild		Moderate		Severe		
Symptoms	Group 1 (%)	Group 2 (%)	Group 1 (%)	Group 2 (%)	Group 1 (%)	Group 2 (%)	Group 1 (%)	Group 2 (%)	*P*-value
Taste disturbance	76.6	50	6.6	23.3	13.3	20	3.3	6.6	N.S.
Loss of appetite	93.3	86.6	6.6	13.3	—	—	—	—	N.S.
Nausea	90	63.3	3.3	13.3	3.3	10	3.3	10	N.S.
Vomiting	96.6	93.3	3.3	6.6	—	—	—	—	N.S.
Stomach pain	66.6	70	16.6	10	10	13.3	6.6	6.6	N.S.
Bloating	63.3	43.3	23.3	16.6	6.6	26.6	6.6	13.3	N.S.
Diarrhoea	96.6	73.3	3.3	26.6	—	—	—	—	0.026
Constipation	80	83.3	20	16.6	—	—	—	—	N.S.
Skin rash	96.6	93.3	3.3	6.6	—	—	—	—	N.S.

various scoring systems, the difficulty in defining a symptom as a 'side-effect', or physician-to-physician differences in evaluating such complaints, make it extremely difficult to compare side-effect profiles among different anti-*H. pylori* drug combinations.[7] Additionally, because of such discrepancies, the frequencies of side-effects in many triple therapy studies have a broad range, but the severity of manifestations is described as 'mild' to 'moderate'.[2, 7] Overall treatment tolerability, (i.e. the real impact of side-effects on a patient's compliance) should remain of key clinical interest.[7] Data from *H. pylori* eradication trials concerning side-effects-influenced compliance are puzzling, although there is little evidence indicating a strong influence of therapy-related side-effects on eradication rates.[3] These observations, however, may not apply to the whole community setting.

A 'perfect' approach to the issue of *H. pylori* eradication will probably never exist. However, issues of effectiveness, simplicity, safety, absence of side-effects and costs all have room for improvement. In patients complaining of dyspeptic symptoms, any further discomfort should be avoided. In addition, patients are often unwilling to start or to comply with any antibiotic therapy, when they have previously experienced some of the associated gastrointestinal complaints. An attempt to safely and simply avoid this problem could be by probiotic administration.

A probiotic is defined as a 'live microbial organism which, when ingested, beneficially affects human health, including amelioration or prevention of a specific disease state'.[17] Many studies have documented the effectiveness of prophylactic probiotics taken with antibiotics in preventing or lowering the antibiotic-related gastrointestinal side-effect burden.[11] *Lactobacillus GG* is a probiotic strain of human origin, which shares most of the general characteristic (survival in gastric and bile secretions, adherence, colonization, antimicrobial production, immune stimulation, antigenotoxic activity, prevention of pathogens) with the proposed model of an 'ideal' probiotic.[12] In particular, *Lactobacillus GG* supplementation has been shown to be useful in several illnesses, reducing both the duration and severity of Rotavirus diarrhoea, lowering the incidence of traveller's diarrhoea, preventing and treating relapses of *Clostridium difficile* colitis, and preventing or improving antibiotic-associated diarrhoea.[18–23] *Lactobacillus GG* is able to resist a number of widely used antibiotics and its colonization, even in the course of antibiotic treatments, could reasonably allow antibiotic-probiotic combinations.[21, 24, 25]

We observed a relevant incidence of gastrointestinal side-effects during the *H. pylori* eradication week. The side-effect scoring system we used is, in our opinion, one of the most accurate proposed, because it has been planned as a mix of previously adopted questionnaires.[15, 26–28] Moreover, the characteristics of the selected study population (asymptomatic subjects were taken in order to avoid confusion with pre-treatment symptoms), which was well informed about compliance with the treatment schedule, educated to strictly register each side-effect and who worked in the same institution (an easy-to-manage population), may explain the results. In the *Lactobacillus GG* supplemented group, a significant reduction in the percentage of subjects who experienced at least one side-effect was observed. Interestingly, as far as each side-effect is concerned, the incidence of nausea, taste disturbance and diarrhoea during the eradication week was significantly lower in the probiotic supplemented group. Diarrhoea was also significantly lower in severity within the same group.

Recent studies have shown that qualitative/quantitative alterations in intestinal flora were related to 7 days anti-*H. pylori* schemes, combining a proton pump inhibitor, clarithromycin or amoxicillin and metronidazole; disturbances were even more severe with the use of clarithromycin.[10] A mechanism of microbiological disruption may be involved in the development of antibiotic-associated gastrointestinal side-effects, such as those reported in our study. Supplementation with *Lactobacillus GG* may partially restore physiological micro-ecology in the intestine. An additive mechanism, by which *Lactobacillus GG* is able to prevent diarrhoea, could be the postulated inhibition of macrolides' prokinetic action.[11, 29, 30] These effects could help to prevent or significantly decrease some antibiotic-associated manifestations.

Finally, for treatment tolerability, the five point scale overall judgement which we utilized showed a significant difference between study groups, with improved treatment tolerance documented in the *Lactobacillus GG* supplemented group.[15] Moreover, follow-up for side-effects, which included a repeated questionnaire administration, documented a progressive decrease in both groups for all the symptoms assessed in the questionnaire.

The reported effect attributable to *Lactobacillus GG* supplemented subjects could be considered helpful for patients in which eradication fails. If a side-effect lowering agent is added, the acceptance or compliance of a patient to a further eradication attempt may be higher. The addition of *Lactobacillus GG* to an anti-*H. pylori* scheme did not seem to affect the eradication rate at all, even if other probiotic species have shown certain suppressing effects on *H. pylori* activity.[31]

In conclusion, this study showed that probiotic supplementation, during and after a standard triple *H. pylori* eradication therapy, may positively influence therapy-related symptoms and overall treatment tolerance. However, these preliminary data deserve further investigation with a larger population to include patients' microflora microbiological assessment, which could lead to the confirmation or modification of these results.

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