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Brief report: *Lactobacillus bulgaricus* GLB44 (Proviotic™) plus esomeprazole for *Helicobacter pylori* eradication: A pilot study

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Abstract

Background: Recent studies of *Lactobacillus delbrueckii* subsp. *bulgaricus* GLB44 plus a proton-pump inhibitor (PPI) reported cures of more than 90% of patients with active *Helicobacter pylori* infections.

Aim: To confirm the high *H. pylori* cure rates reported previously.

Method: A pilot study was done in healthy *H. pylori*-infected volunteers using 3-gram sachet (3 billion cells) of *L. delbrueckii* GLB44 plus 22.3 mg of esomeprazole b.i.d., for 14 days. The result was determined by urea breath testing 4 weeks after therapy. Stopping rules required for ending enrollment if less than 3 of the first 10 subjects were cured.

Results: Nine subjects were entered and because all failed to achieve negative urea breath test, the stopping rule required the study to end.

Conclusion: We were unable to confirm reports of achieving a high *H. pylori* cure rate with *L. delbrueckii* GLB44 plus a PPI.

Keywords

clinical trial; *Helicobacter pylori*; *Lactobacillus bulgaricus*; probiotic; therapy

1 | INTRODUCTION

Probiotics are defined as microorganisms that may provide health benefits when consumed. Probiotics can be consumed as drugs or contained in natural, usually fermented, foods. The use of fermented milk products dates back at least to the early Egyptians. Fermented milk products have been regularly consumed as buttermilks, yogurts, or kumis (fermented mare's milk) for thousands of years.¹ The fermentation products often include lactic acid, which is responsible for the sour taste. Pasteur studied fermentation and showed that it was due to the presence of microbes. The health benefits of fermented milk were highlighted in the late 19th century by Metchnikoff who linked the use of yogurt, a fermented product produced by

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DISCLOSURES

The other authors have nothing to declare.

Lactobacilli, with unusual longevity of Bulgarians.¹ Metchnikoff believed that senility was related to ingestion of bacterial products in food and proposed the diet contain fermented milk in which high lactic acid could theoretically prevent growth of harmful bacteria (http://nobelprize.org/nobel_prizes/medicine/laureates/1908/mechnikov-bio.html). His observations result in a keen interest in medicinal foods.¹ In the late 19th and early 20th centuries, gastroenterologists and microbiologists became interested the identification of lactic acid-producing bacteria (eg, Boas bacillus) in the stomachs and stools of patients the diagnosis of gastric cancer.²⁻⁴ Lactic acid in the human stomach and previously been identified in the human stomach during early investigations regarding the chemical nature of gastric acidity (reviewed in⁵).

Recently, two studies of a new formulation of *Lactobacillus delbrueckii* subsp. *bulgaricus* GLB44 plus a proton-pump inhibitor (PPI) reported cures of more than 90% of patients with active *Helicobacter pylori* infections. The first⁶ included 24 subjects and gave GLB44 tablets or capsules equal to 15×10^9 organisms alone with rabeprazole 20 mg (36 mg omeprazole equivalent) or pantoprazole 20 mg (4.5 mg omeprazole equivalent) twice a day for 7 days followed by GLB44 alone for 3 days.^{7,8} Fecal antigen testing was done after at least 43 days. The cure rate was 91.7% (95% CI = 73%–99%). The second study⁹ involved 52 subjects and involved the same dosing schedule of GLB44 along with 20 mg b.i.d. of rabeprazole, pantoprazole, esomeprazole (32 mg omeprazole equivalent), or omeprazole. The cure rate was 92.3% (95% CI = 81%–97%). Both studies were done in Europe (Bulgaria). This study was a pilot study designed to confirm the effect of GLB44 and a PPI on *H. pylori* infections.

2 | METHODS

This was a pilot study with the sample size predicated on the ability to confirm the results of the two prior studies. Success was defined as achieving at least an 85% cure rate with the combination of GLB44 and a PPI. Inclusion criteria included otherwise healthy men or women with normal general laboratory screening tests (complete blood count, metabolic profile, serum creatinine, and serum transaminases) and a positive urea breath test. The probiotic, *L. delbrueckii* subsp. *bulgaricus* GLB44 is available in the United States as Proiotic™ and was supplied pro bono as fresh sachets containing 3 grams of powder containing 1 billion cells/gram. Stock sachets of GLB44 were refrigerated until use.

Each UBT-positive subject had a confirmatory positive UBT followed by GLB44 therapy consisting of one 3 gram sachet (3 billion cells) of GLB44 probiotic mixed with 60 mL juice, milk, or water for a total daily dose of 2 sachets per day (total dose 6 million cells/d). The schedule was one dose before the morning meal and one dose 1 hour after the evening meal along with 22.3 mg of esomeprazole given with the morning and evening meals for 14 days. The subject refrained from alcohol and soft drinks during the 14 days but ate a normal diet. Subjects were asked to keep a simple record of any symptoms. Subjects returned empty packets. The UBT was repeated 4 or more weeks after therapy. Success was defined as the positive UBT becoming negative (a DOB of <2.4 four or more weeks after stopping therapy).

2.1 | Planned analyses

The pilot study design allowed inclusion of up to 25 subjects and included a stopping rule requiring the study to be halted if it became apparent that it would be impossible to achieve a cure rate of at least 80%. For example, if 0 of the first 10 subjects became UBT negative, the study would be declared a failure (95% C.I. for 0 of 10 = 0% to 21%) and would exclude a successful response of 80% or greater. If there were at least 3 subjects of the first 10 subjected tested negative by UBT (20% success) the study would continue until 25 subjects had completed.

The study was approved by the local Institutional review committee at Baylor College of Medicine and all subjects signed informed consent before entering.

3 | RESULTS

Nine *H. pylori* treatment naïve subjects with mild dyspepsia without any alarm features were entered (3 women, 6 men; average age 30 years, range 26 to 34). All UBTs remained positive, and the study was stopped as it was judged to be impossible to achieve the minimum number of treatment successes required to continue (eg, 3 successes in the first 10 subjects). The cure rate was 0% (95% CI 0%–29%). Even if the remaining projected subjects were successful (ie, 16 additional subjects), the cure rate would have been <85% (ie, 64%). All subjects failing the final UBT were referred to their family doctors for appropriate anti-*H. pylori* therapy.

Side effects include several loose stool and bloating for days attributed to the milk (vehicle) in one. Another subject experienced 2 days of mild nausea without vomiting and noted that family members had similar viral-like symptoms

4 | DISCUSSION

Clinical studies of probiotics as the primary treatment of *H. pylori* infections have generally produced variable, but overall disappointing, results.^{10,11} The study was based on the reported success of previous clinical studies with *L. delbrueckii* subsp. *bulgaricus* suggesting 1) high cure rates,^{6,9} 2) the presence of bacteriocin-like inhibitory activities active against many but not all *H. pylori* strains,¹² and 3) studies using agar-well diffusion methods showing growth inhibition of between 40% and 86.7% of *H. pylori* strains at low pH and 16.7% to 66.7% at neutral pH with the activity being strain-specific.¹³ However, we were unable to confirm the prior excellent experience reported by two other groups of investigators.^{6,9} There were some differences between our study and theirs included 1) we used a lower dose of *L. delbrueckii* subsp. *bulgaricus* GLB44 (ie, 6 billion vs 15 billion cell/d, 2) we used a powder formulation, whereas they used tablets and capsules. 3) we used a longer duration (14 days) than had been used previously (ie, 10 days), and 4) we used one type of PPI (rabeprazole), whereas prior studies has used a variety of PPIs.

Overall, our results are not inconsistent with studies in which probiotics have been shown to only slightly improve the cure rates with antimicrobial therapies in populations in which

antimicrobial resistance had resulted in a decrease in cure rate.¹¹ On average, the increase in cure rates with triple therapy has been in the range of 10% to 14%.^{14–20}

The approach using noninvasive and rapid reliable methods of testing *H. pylori* status with the UBT or stool antigen testing allows efficient and inexpensive evaluation of different test strategies. Studies with probiotics used as adjuvant therapy to antibiotics have not shown that any one is superior to others and none has yet proven to be an effective monotherapy.^{15–17} Pilot studies examining different dosing schedules, number of doses, dosing in relation to meals, etc. in a systematic fashion will be required to identify if one probiotic is more effective than others.

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Dr. Graham is a consultant for RedHill Biopharma regarding novel *H. pylori* therapies and has received research support for culture of *H. pylori* and is the PI of an international study of the use of antimycobacterial therapy for Crohn's disease. He is also a consultant for BioGaia and Takeda in relation to probiotic therapy for *H. pylori* infection and for Takeda.

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