

Bovine antibody-based oral immunotherapy for reduction of intragastric *Helicobacter pylori* colonization: A randomized clinical trial

CM den Hoed MD^{1,2}, AC de Vries MD PhD^{1,2}, PBF Mensink MD PhD^{1,2}, CM Dierikx MSC PhD^{1,2},
H Suzuki MD PhD³, L Capelle MD PhD¹, H van Dekken MD PhD⁴, R Ouwendijk MD PhD⁵, EJ Kuipers MD Prof^{1,2,6}

CM den Hoed, AC de Vries, PBF Mensink, et al. Bovine antibody-based oral immunotherapy for reduction of intragastric *Helicobacter pylori* colonization: A randomized clinical trial. *Can J Gastroenterol* 2011;25(4):207-213.

BACKGROUND: Antibiotic-based regimens are frequently used for the treatment of *Helicobacter pylori* infection. These regimens fail to eradicate *H pylori* in 15% to 40% of patients, primarily due to antimicrobial resistance and insufficient patient compliance. Effective prevention and eradication of *H pylori* by passive immunization with orally administered bovine antibodies has been demonstrated in animal studies, and may serve as an alternative therapy in humans.

OBJECTIVE: To study the efficacy and safety of orally administered bovine anti-*H pylori* antibodies for the reduction of intragastric bacterial load and eradication of *H pylori* in humans.

METHODS: Dairy cows were immunized against *H pylori*. After confirmation of the presence of anti-*H pylori* antibodies in the milk, the milk was subsequently processed into a whey protein concentrate (WPC). In a prospective, double-blind, placebo-controlled randomized clinical trial, *H pylori*-infected subjects were randomly assigned to treatment with the WPC preparation or placebo. Study medication was continued for 28 days; subjects were followed-up for 56 days.

RESULTS: Of the 30 subjects included, 27 completed the protocol. Of these 27 evaluable subjects, 14 were treated with WPC and 13 with placebo. There was no significant difference in urea breath test decrease between the WPC- and placebo-treated group ($P=0.75$). *H pylori*-associated gastritis and density were not significantly reduced in either group after treatment ($P>0.05$ for all).

CONCLUSION: Bovine antibody-based oral immunotherapy appears to be safe, but does not significantly reduce intragastric *H pylori* density in humans. Further studies are needed to determine whether WPC treatment has additional value to conventional antibiotic treatment for *H pylori*.

Key Words: *H pylori*; Eradication treatment; Immunotherapy; Gastritis

Helicobacter pylori infection causes chronic active gastritis in virtually all infected patients and is associated with an increased risk of peptic ulcer disease, mucosa-associated lymphoid tissue lymphoma and gastric cancer (1-3). Therefore, *H pylori* eradication therapy is frequently prescribed in patients in whom the presence of *H pylori* colonization has been confirmed. The current European guidelines state that a positive *H pylori* test is an indication for eradication treatment (4). Such treatment regularly consists of the combination of two to three antimicrobial drugs in combination with a proton pump inhibitor (PPI). However, treatment failure occurs in up to 40% of patients, primarily due to bacterial resistance and insufficient patient compliance, among others, and as a result of gastrointestinal side effects (Table 1) (5,6). Consequently, new therapeutic strategies with

Une immunothérapie orale à base d'anticorps bovin pour réduire la colonisation intragastrique de *Helicobacter pylori* : un essai clinique aléatoire

HISTORIQUE : On utilise souvent des antibiotiques pour traiter les infections à *Helicobacter pylori*. Chez 15 % à 40 % des patients, ces antibiotiques n'éradiquent pas le *H pylori*, surtout en raison d'une antibiorésistance et d'une observance insuffisante de la part des patients. Des études auprès d'animaux ont démontré une prévention et une éradication efficaces du *H pylori* par immunisation passive au moyen d'anticorps bovins administrés par voie orale, ce qui pourrait constituer une autre thérapie chez les humains.

OBJECTIF : Étudier l'efficacité et l'innocuité de l'administration d'anticorps anti-*H pylori* pour réduire la charge bactérienne intragastrique et l'éradication du *H pylori* chez les humains.

MÉTHODOLOGIE : Des vaches laitières ont été immunisées contre le *H pylori*. Après confirmation de la présence d'anticorps anti-*H pylori* dans leur lait, ce lait a été transformé en concentré de protéine de lactosérum (CPL). Dans un essai clinique à double insu aléatoire et contrôlé contre placebo, des personnes infectées par le *H pylori* ont été réparties au hasard entre le traitement à l'aide de la préparation de CPL et un placebo. L'étude du médicament s'est poursuivie pendant 28 jours, et les sujets ont été suivis pendant 56 jours.

RÉSULTATS : Des 30 sujets participants, 27 ont terminé le protocole. De ces 27 sujets évalués, 14 ont été traités par CPL, et 13, par placebo. On n'a constaté aucune différence significative de diminution du test respiratoire à l'urée au sein du groupe traité par CPL et de celui traité par placebo ($P=0,75$). La gastrite et la densité associées au *H pylori* n'avaient pas diminué de manière significative dans les deux groupes après le traitement ($P>0,05$ dans tous les cas).

CONCLUSION : Une immunothérapie orale à l'anticorps bovin semble être sécuritaire, mais elle ne réduit pas la densité intragastrique de *H pylori* de manière significative chez les humains. D'autres études s'imposent pour déterminer si un traitement au CPL a une valeur supplémentaire par rapport à l'antibiothérapie classique du *H pylori*.

broader approaches to treating, suppressing or possibly preventing *H pylori* infections to circumvent problems with drug resistance and side effects are required.

Passive immunization with orally administered antibodies against *H pylori* may constitute one of these alternatives. This approach has been shown to be effective in the prevention and treatment of a variety of pathogens such as *Candida albicans*, rotavirus, *Clostridium difficile* and *Campylobacter jejuni* (7-11). Animal studies have shown that bovine antibodies against *H pylori* reduce bacterial load and that *H pylori* infection can thereby be prevented and even eradicated (12,13). In humans, breastfeeding seems to protect infants from early acquisition of *H pylori*, also suggesting that passive delivery of immunoglobulin (Ig) A antibodies affect *H pylori* colonization (14).

Departments of ¹Gastroenterology; ²Hepatology, Erasmus University Medical Center, Rotterdam, The Netherlands; ³Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan; ⁴Department of Pathology, Erasmus University Medical Center; ⁵Department of Gastroenterology and Hepatology, Ikazja Hospital, Ziekenhuis; ⁶Department of Internal Medicine, Erasmus University Medical Center, Rotterdam, The Netherlands

Correspondence: Dr CM den Hoed, Department of Gastroenterology and Hepatology, Erasmus MC, Room Ca 409, PO Box 2040,

3000 CA Rotterdam, The Netherlands. Telephone 0031-10-7033042, fax 0031-10-7032908, e-mail c.denhoed@erasmusmc.nl

Received for publication January 12, 2010. Accepted October 6, 2010

TABLE 1
Eradication rates, and first-, second-, third- and fourth-line treatments for *Helicobacter pylori* infection

Author (reference), year	Country	Study type	Treatment	Eradication rate, %
Rokkas et al (41), 2009	Greece	Prospective (n=540)	First line: Omeprazole + amoxicillin + clarithromycin	76
			Second line: Omeprazole + bismuth + metronidazole + tetracycline	73
			Third line: Omeprazole + amoxicillin + levofloxacin	70
Hojo et al (42), 2001	Japan	Meta-analysis	Second-line treatment:	
			Proton pump inhibitor + 1 antimicrobial agent	45.8
			Proton pump inhibitor + 2 antimicrobial agents	69.8
			Ranitidine-bismuth + 2 antimicrobial agents	80.2
Seppälä et al (43), 2000	Finland	Prospective (n=644)	Proton pump inhibitor + bismuth + 2 antimicrobial agents	75.8
			First-line treatment of choice of treating physician:	81
			Second line: Bismuth + metronidazole + amoxicillin/tetracycline or omeprazole + bismuth + metronidazole + amoxicillin/tetracycline or triple therapy* based on susceptibility test	58
			Third line: One of the treatments mentioned under second line	76
Pontone et al (44), 2010	Italy	RCT (n=84)	Fourth line: Another one of the treatments mentioned under second line	100
			Sequential therapy: Lansoprazole + amoxicillin for 5 days and lansoprazole + clarithromycin + metronidazole for an additional 5 days	83
			Rescue therapy: Lansoprazole + levofloxacin + amoxicillin	100
Kearny and Brousal (45), 2000	United States	RCT (n=224)	Bismuth + metronidazole + tetracycline	81
			Lansoprazole + metronidazole + clarithromycin	90
			Proton pump inhibitor + bismuth + metronidazole + tetracycline	87
Vaira et al (46), 2007	Italy	RCT (n=300)	Proton pump inhibitor + amoxicillin (5 days) and proton pump inhibitor + clarithromycin + tinidazole (5 days)	89
			OR Proton pump inhibitor + clarithromycin + amoxicillin (10 days)	77

*Triple therapy: Proton pump inhibitor plus two different antibiotics. RCT Randomized controlled trial

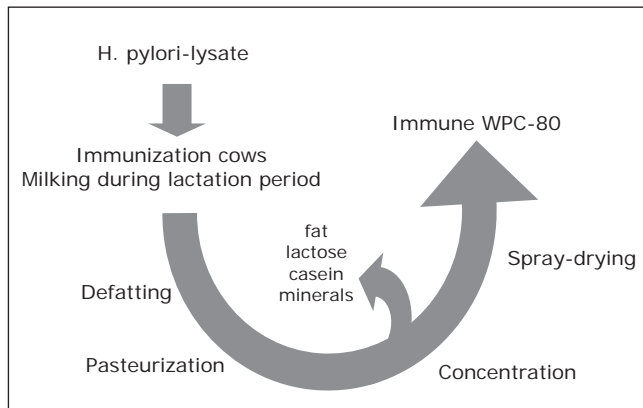


Figure 1 Whey protein concentrate (WPC) preparation. *H. pylori* *Helicobacter pylori*

The primary underlying mechanism is probably based on inhibition of adherence of *H pylori* to the gastric mucosa by specific antibodies to the main *H pylori* surface-binding antigens (15). However, results of clinical studies on the effect of specific anti-*H pylori* antibodies are scarce. The studies that are available have reported conflicting results (16-20). While two studies did not demonstrate any effect of treatment with bovine antibodies (16,18), three others reported that treatment with bovine antibodies could eradicate *H pylori* infection in all patients (19,20) or decrease *H pylori* colonization density and the extent of gastritis (17). None of these studies were, however, placebo controlled. Therefore, we performed a randomized, placebo-controlled clinical study to evaluate the efficacy and safety of specific anti-*H pylori* polyclonal bovine IgA antibodies for the reduction of intragastric bacterial load and gastritis activity in humans.

METHODS

Study medication: Immune whey protein concentrate preparation

A polyclonal antibody-enriched immune whey protein concentrate (WPC-80 [80% protein]) was prepared from milk collected from cows immunized with whole antigen lysates of eight clinical *H pylori* isolates.

The immunization of six dairy cows comprised repeated nasal (mucosal every two weeks) and supramammary lymph node administration (percutaneous once every month). After immunization, the presence of polyclonal secretory component (sIgA) anti-*H pylori* antibodies in the milk was confirmed by ELISA. Immune WPC-80 was prepared using standard milk industry techniques (Figure 1). The whey fraction was pasteurized, concentrated by ultra filtration and spray-dried to yield the final whey powder. One gram of the final enriched WPC preparation contained approximately 80% protein, of which approximately 20% consisted of Ig, and was completely free of lactose. Inhibition of the adherence of *H pylori* to gastric tissue by specific antibodies in the WPC-80 preparation was demonstrated in vitro using fluorescently labelled *H pylori*. The adherence of *H pylori* in the presence of phosphate-buffered saline/bovine serum albumin and nonspecific antibodies was used as the control.

Study design

The present study was designed to be a double-blind, placebo-controlled trial (Figure 2). Adult *H pylori*-positive subjects (18 years of age and older), as demonstrated by both a positive ¹³C-urea breath test and histopathology confirming *H pylori* gastritis were eligible for inclusion (Figure 3). Thirty *H pylori*-positive subjects were randomly assigned to either immune WPC treatment (15 subjects) or placebo (15 subjects). Randomization occurred within blocks containing four subjects each, according to a randomization table designed by Department of Statistics at the University of California, Los Angeles (USA). Consecutive eligible patients were included after informed consent, and a coded study number was assigned to each patient.

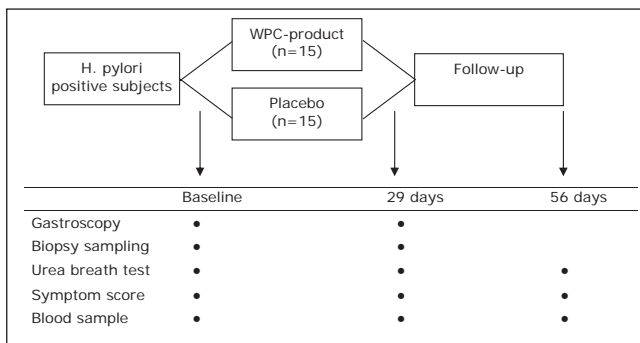


Figure 2) Study design. *H. pylori* Helicobacter pylori; WPC Whey protein concentrate

Treatment with H₂-blockers or PPIs was allowed, provided that the doses were stable at least two weeks before the start of the study medication, including the time of the ¹³C-urea breath test and sampling of gastric biopsies, and remained stable during the study period. Subjects who underwent previous treatment for *H pylori* infection with standard therapy were also included. Exclusion criteria were as follows: lactose intolerance, pregnancy or lactation, active peptic ulcer disease, malignancy, significant systemic comorbidity and use of antibiotics within four weeks before the start of the study.

All subjects received 2.5 g of immune WPC or placebo, to be taken three times daily during meals for 28 days. The medications had identical appearances. Adherence to study medication was monitored by recording the number of empty medication sachets and conducting interviews. The follow-up period was 56 days.

Gastroscopy with biopsy sampling was performed at baseline and at the end of treatment (at 29 days). During gastroscopy, two antral and two corpus biopsies were obtained for histological assessment. In addition, one antral and one corpus biopsy were obtained for *H pylori* culture. ¹³C-urea breath tests and serological tests were performed at the start of the study, after completion of study medication and at the end of follow-up. Serological evaluation comprised hematological and biochemical markers, and serum levels of gastrin, pepsinogen I, pepsinogen II and *H pylori*-specific IgG. In addition, serum anticytotoxin gene A (CagA) protein IgG antibodies were evaluated at the start of the study.

Dyspeptic symptoms including heartburn, acid regurgitation and epigastric discomfort were evaluated using a validated questionnaire. All items were rated according to seven criteria of the Gastrointestinal Symptom Rating Scale (21,22). The questionnaires were completed before treatment, each week during treatment, just after completion of treatment and at 56 days. In addition, all adverse events during follow-up were recorded.

The Institutional Review Board of the Erasmus University Medical Centre (Rotterdam, The Netherlands) approved the study protocol. All subjects provided informed written consent before enrollment.

Histological and culture methods

Gastric biopsy specimens were fixed in buffered formalin and embedded in paraffin. Hematoxylin-eosin stained sections were used for standard histological evaluation. A single, expert gastrointestinal pathologist performed all histological assessments. The pathologist was blinded to the timing of biopsies, treatment assignment, and clinical and endoscopic data. The samples were assessed according to the updated Sydney classification. The sections were graded for *H pylori* density, polymorphonuclear neutrophil activity, mononuclear cells, gastric glandular atrophy and intestinal metaplasia. All parameters were scored using the following four-point scale: absent = 0, mild = 1, moderate = 2 and severe = 3. Culture of *H pylori* was performed under microaerophilic conditions (5% oxygen, 10% carbon dioxide and 85% nitrogen) using blood agar plates (Dent-plates, Biotrading, The Netherlands).

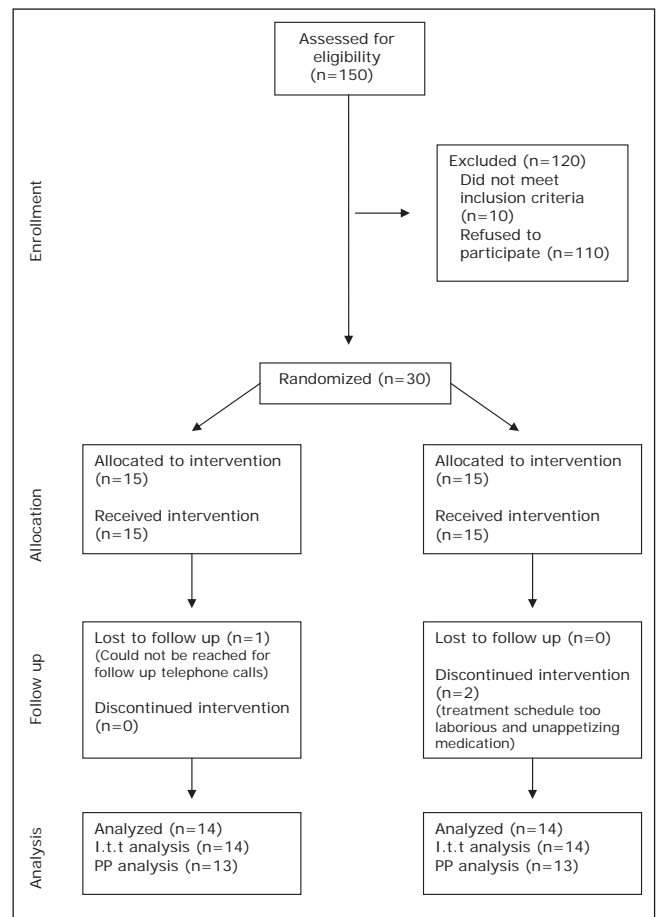


Figure 3) Consort diagram. I.t.t Intention to treat; PP Per protocol

Data analysis

The efficacy of the WPC preparation to reduce intragastric *H pylori* bacterial load was evaluated according to the reduction in intragastric urease activity measured by ¹³C-urea breath tests and reduction of bacterial colonization, as well as acute gastritis quantified by histological assessments according to the updated Sydney system. The number of patients was sufficient to demonstrate a 30% difference in the above mentioned parameters, with a predictive power of 90%. An intention to treat and per-protocol analysis were performed comparing the immune WPC-80 treatment group and placebo group. Statistical analysis was performed using Wilcoxon's rank sum test for changes from baseline to end of treatment for histological severity grades of gastritis. A subgroup analysis of patients receiving acid-suppressive drugs was performed. A two-sided P<0.05 was considered to be statistically significant. Power was not calculated due to the explorative nature of the study.

RESULTS

Participants

In total, 30 subjects were included and randomly assigned to the placebo- or WPC-treated group. One patient in the WPC group was lost to follow-up immediately after randomization before the start of the study medication. Two patients in the placebo group discontinued the study medication within two weeks – one due to the intensity of the treatment regimen, the other due to the unappetizing flavour of the placebo; therefore, follow-up data on these patients were not available.

TABLE 2
Baseline epidemiological, histological, serological and ¹³C urea breath test results of both treatment groups

	Treatment group		P
	WPC (n=14)	Placebo (n=15)	
Sex, n (male/female)	5/9	9/6	0.27
Age, years (mean ± SD)	44.7±14.0	51.3±14.4	0.22
Range	25–67	25–75	
Acid-suppressant use, n			
Proton pump inhibitor	4	5	1.0
H ₂ -blocker	3	2	
Previous eradication treatment, n	6	6	1.0
Country of birth, n			
The Netherlands	8	6	0.81
Turkey	3	5	
Morocco	1	1	
Other	2	3	
Histological findings			
Antrum			
<i>H. pylori</i> colonization	1.86 (1.03)	1.67 (1.05)	0.63
Activity	1.14 (0.77)	1.47 (0.92)	0.31
Inflammation	2.28 (0.47)	2.07 (0.80)	0.37
Corpus			
<i>H. pylori</i> colonization	1.0 (0.82)	1.33 (0.82)	0.29
Activity	0.92 (0.76)	0.80 (0.68)	0.66
Inflammation	1.54 (0.66)	1.73 (0.59)	0.42
Premalignant gastric lesions, n (%)	1 (7.1)	4 (26.7)	0.33
Urea breath test, mean delta value ± SD	24.2±17.4	23.8±16.3	0.95
<i>H. pylori</i> IgG, mg/mL (mean ± SD)	202±178	152±127	0.40
CagA positive, n (%)	9 (64)	11 (73)	0.43
Gastrin, ng/L (mean ± SD)	20.7±24	24±25	0.73
Pepsinogen I, ng/mL (mean ± SD)	163±90.0	147±61	0.58
Pepsinogen II	14.2±3.7	15.9±4.3	0.85
Pepsinogen ratio I/II, mean ± SD	16.5±4.9	17.0±8.8	0.86

CagA Cytotoxin-associated gene A; *H. pylori* Helicobacter pylori; Ig Immunoglobulin; WPC Whey protein concentrate

Baseline characteristics

Following randomization, 14 patients were treated with the WPC-80 preparation and 15 patients with placebo. The groups were similar with respect to several baseline characteristics (Table 2). At baseline, 14 (48%) patients used acid-suppressive drugs; these patients were equally distributed between both treatment arms (P=1.00). Infection with CagA-positive *H. pylori* strains was present in nine (64%) patients

TABLE 3
Urea breath test and serology results in both treatment groups at day 29 and day 56

	Day 29			Day 56		
	WPC treatment group (n=14)	Placebo group (n=13)	P	WPC treatment group (n=14)	Placebo group (n=14)	P
Urea breath test						
Mean delta value	24.3±24.2	22.9±14.4	0.85	25.5±25.5	24.0±15.8	0.85
Mean reduction	-0.15±13.4	2.3±14.4	0.66	-1.2±14.0	0.15±11.8	0.78
Serology						
Gastrin, ng/L	4.5±3.6	6.4±4.8	0.25	7.9±5.2	8.4±6.3	0.84
Pepsinogen I, ng/mL	1524±727	1825±829	0.33	1716±923	1829±753	0.72
Pepsinogen II, ng/mL	102±74	121±82	0.55	109±74.5	125±78	0.57
Pepsinogen ratio I/II	17.4±5.5	18.1±8.0	0.79	18.0±6.7	17.0±6.6	0.66

Data presented as mean ± SD unless otherwise indicated. WPC Whey protein concentrate

included in the WPC-80 group, compared with 11 (73%) patients in the placebo group (P=0.43). Premalignant gastric lesions, atrophic gastritis and intestinal metaplasia were found in one patient in the WPC group and in four patients in the placebo group (P=0.33).

H. pylori bacterial load

In the intention to treat analysis, no significant differences between groups were found in urea breath test results at baseline or follow-up and, similarly, in the effect of treatment on urea breath test results (P>0.05 for all) (Table 3). Moreover, no significant differences were observed between subgroups within treatment arms (P=0.57), or in patients with or without simultaneous use of acid-suppressive drugs (P=0.35).

Histological assessment did not demonstrate an effect of active or placebo treatment on acute gastritis and the *H. pylori* colonization scores in the antrum (Figures 4 and 5). The *H. pylori* colonization scores in the corpus even seemed to increase after treatment with WPC-80 (P=0.03) (Figure 5). In addition, no significant differences in outcome were observed between treatment groups. Subgroup analysis of patients with or without simultaneous use of acid-suppressive drugs showed no significant differences (P>0.05 for all). In one patient, *H. pylori* eradication was achieved after concomitant use of the WPC preparation and a one-day course of metronidazole; this patient was not included in the per-protocol analysis. Twenty-six patients were considered in the per-protocol analysis, which did not demonstrate an effect of the WPC-80 or placebo treatment. No differences were obtained using the per-protocol analysis versus the intention to treat analysis (P>0.05 for all).

Serology

Comparison of anti-*H. pylori* IgG antibody levels did not demonstrate any differences between the WPC-80 group and the placebo group at day 29 (P=0.63) nor at day 56 (P=0.33) (Table 2). No significant differences with respect to the mean reduction in serum *H. pylori* antigen concentration at day 0 (P=0.33) and day 56 (P=0.54) in the WPC-80 group and the placebo group, respectively, were found.

No differences were demonstrated between the WPC-80 group and the placebo group when the mean values of gastrin, pepsinogen I and pepsinogen II levels, and the pepsinogen ratio at baseline at day 29 or day 56 were compared. The levels of these parameters did not change significantly within either group during follow-up, nor were there significant changes between groups in this respect (Table 3).

Safety

Twenty-seven subjects completed the study – 14 in the WPC group and 13 in the placebo group. None of the patients experienced adverse effects due to WPC-80 treatment, and the preparation was well tolerated. No significant differences were identified in the quality of life scores of the WPC-80 group compared with the placebo group on days 7, 14, 21, 28 and 56 (P>0.05 for all). Quality of life scores remained stable during the course of the study in both groups.

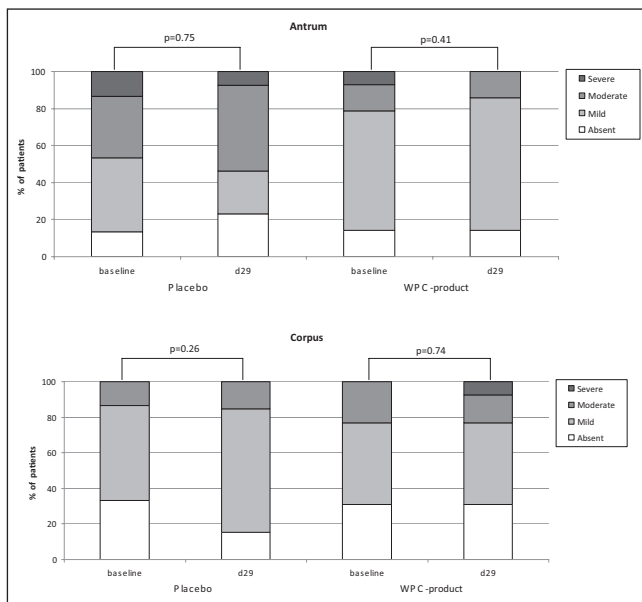


Figure 4) Histological grade of active gastritis in antrum and corpus in patients randomly assigned to placebo or whey protein concentrate (WPC) preparation. d Day

Analysis of general blood test parameters revealed no significant changes in either treatment group, nor were there changes in serum liver enzymes or additional serological parameters (eg, hemoglobin, leukocytes, etc) ($P > 0.05$ for all).

DISCUSSION

The present clinical study did not demonstrate a positive effect on *H pylori*-associated gastritis or colonization density following administration of a polyclonal antibody-enriched (sIgA) WPC-80 preparation in humans. No significant reduction was demonstrated in urea breath test levels determined on days 0, 29 and 56. Treatment in either arm had no effects on serum *H pylori* IgG antibody titres, gastrin, pepsinogen I and II levels, or on the pepsinogen I/II ratio. Correcting for the use of PPIs did not influence differences in the outcomes. However, we demonstrated that WPC-80 was well tolerated and did not cause any adverse effects or a decrease in quality of life scores.

H pylori infection is widespread in humans. Although it can be cured by antimicrobial therapy, large-scale use of antibiotics has led to the increasing emergence of antibiotic-resistant strains. Furthermore, side effects of current eradication treatments, although partially preventable by the coadministration of probiotics, limit their efficacy by induction of early treatment withdrawal (23). This has prompted investigators to focus on several alternatives. These alternatives must be effective; however, considerations such as costs, side effects and ease of administration should also be taken into account.

Because previous studies have shown protection against early acquisition of *H pylori* through breastfeeding in breastfed infants (14), the concept of passive immunization (ie, mimicking mechanisms of natural protection) as a logical approach has emerged. An in vitro study conducted in 2001 confirmed the possible effectiveness of antibodies by showing a complement-dependent bactericidal effect of WPC with *H pylori*-specific antibodies. The WPC prevented adherence of *H pylori* to the gastric mucosa (24,25). In addition, an early clinical study in 1991 (19) demonstrated *H pylori* eradication in 20 patients receiving an *H pylori*-specific bovine Ig. The outcomes of more recent studies with *H pylori*-infected patients (16-18,20) have shown modest, albeit encouraging, results. However, one of these studies was open labelled (18) and used a treatment period of only two days, while two others included children only (16,17). Furthermore, the methodology of the other studies were unclear (16-18,20).

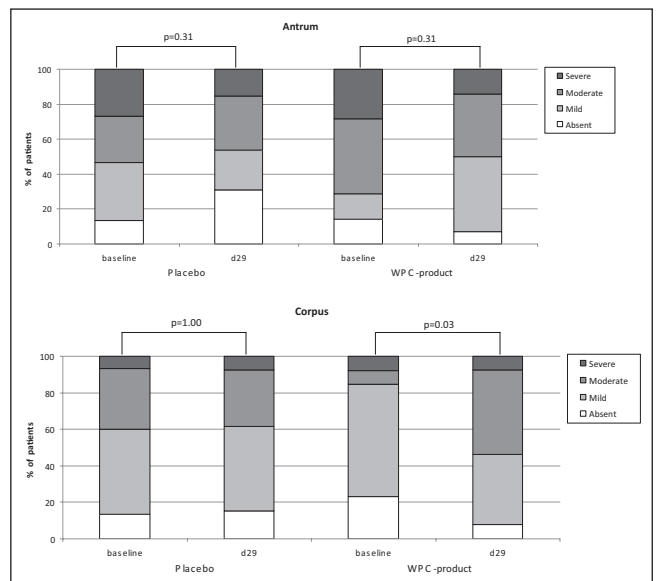


Figure 5) Histological grade of Helicobacter pylori colonization in antrum and corpus in patients randomly assigned to placebo or whey protein concentrate (WPC) preparation. d Day

A possible limitation of the present analysis was the size of the study population, which may have been too small to demonstrate significant reductions in intragastric bacterial load or gastritis activity by treatment with bovine antibody-based oral immunotherapy. Furthermore, because the optimal length of treatment remains unknown, our study may have been limited by the relatively short duration of WPC-80 treatment. Previously conducted studies (15) used a duration of between two days and four weeks. However, given the total absence of any effect after four weeks in the population studied, we consider it unlikely that an increase in the study population or prolongation of treatment with the same dose would have led to measurable changes.

We cannot exclude the possibility that an increase in dose and/or dosing frequency would have led to an effect on *H pylori* colonization. The dose and administration frequency used in the present study were chosen on the basis of previous experience with similar products, particularly those against *C difficile* (11). Finally, our study may have been limited by the fact that intragastric antibody availability has yet to be clarified (25). Therefore, future research in human subjects is necessary to obtain additional information regarding the optimal antibody dose, frequency of administration and ratio.

The strengths of the present study were the strictly defined outcome parameters, the double-blinded design with repeated follow-up assessments and the exclusion of a possible concomitant antibiotic effect. Except for one subject, all patients completed the four-week treatment course and no adverse effects linked to treatment were identified.

Current research has focused on several alternatives to replace antibiotic eradication therapy. In contrast to our study of bovine-derived IgA antibodies, Japanese researchers have described positive effects of egg yolk-derived IgY, demonstrating a decrease in urea breath test parameters in patients treated with IgY (26,27). Similar studies examining the natural antimicrobial properties of colostrum and egg yolk have focused on the possible use of lactoferrin and lysozyme, which are also components of the humoral immune reaction. Positive effects of bovine antibodies were demonstrated in vitro and in animal models, but conflicting results were obtained in human studies (28). Some studies described a suppressive effect of lactoferrin and lysozyme on *H pylori* colonization (28,29), while others even described an increase in *H pylori* growth and gastric inflammation (30). However, supplementing current eradication therapy with lactoferrin appears to increase eradication rates and could be helpful in patients who fail

eradication therapy. Furthermore, addition of lactoferrin may also have a positive impact on *H pylori* therapy-related side effects (31).

Several studies examining the effects of probiotics, especially in combination with current therapies, have been conducted (23,32-35), and have demonstrated positive effects and trends. A combination of antibiotics and probiotics seems to improve eradication rates primarily by decreasing side effects, resulting in increased adherence.

Another possible alternative to current therapy are DNA vaccines. DNA vaccines are constructed by inserting DNA encoding a pathogen's antigen into a bacterial plasmid, thus inducing both humoral and cell-mediated immunity (36). A recent study by Sun et al (37) has shown a protective effect of DNA vaccines on *H pylori* infection in mice. In addition, vaccination to both prevent and treat infection appears to be a very cost-effective alternative in *H pylori* treatment (38).

Monotherapy with bovine antibodies may not be the optimal alternative to current eradication therapies. Recent studies have described positive effects of combination therapy, for example, the addition of *Lactobacillus* to the current standard treatment. Such a positive effect could also be expected from adding WPC-80 to current eradication therapies. This adjunct to antibiotic therapy requires further investigation while the search for alternatives continues. The prevention of *H pylori* infection is a subject of interest, particularly in the developing world and could be another focus of research, especially because this effect has been described in vitro (15).

Due to increases in the current failure rates of antibiotic-based eradication therapy, the goal of future immunotherapy should focus on replacing antibiotic-based treatment entirely, instead of searching for adjunctive therapies. Presently, the most hopeful alternatives are preventive or therapeutic vaccination therapy. A recent study (39) demonstrated the cost-effectiveness of preventive vaccination in children.

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A recent review article (40) reported that *H pylori* vaccination prevents, reduces and eliminates *H pylori* infection in animal models, and that vaccines based on multiple virulence factors cure and prevent infection. A phase I study with a vaccine based on virulence factors in healthy volunteers (39) demonstrated a strong antibody response and was well tolerated, and currently appears to be the most promising alternative for *H pylori* treatment. Unfortunately, significantly more funding and research is needed before this particular alternative treatment is fully developed.

CONCLUSION

Monotherapy with bovine antibody-based oral immunotherapy does not reduce intragastric *H pylori* bacterial load, nor does it have an effect on *H pylori*-associated gastritis. However, WPC-80 is well tolerated and does not cause any adverse effects, nor does it have a negative influence on quality of life scores. Further research into the possible use of WPC-80 as a supplement to current eradication regimens is necessary.

ACKNOWLEDGEMENTS: This study was designed and conducted to meet internationally accepted ethical standards and complies with the CONSORT statement. The authors acknowledge Muco Vax BV, Leiden, the Netherlands and DMV International, Veghel, The Netherlands, for the development of the platform technique and the production of the immune WPC-80 preparation and the placebo.

DISCLOSURE: This study was funded, in part, by Muco Vax BV, Leiden, The Netherlands.

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