ORIGINAL ARITCLE

Effects of selective COX-2 inhibitor and *Helicobacter pylori* eradication on precancerous gastric lesions

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ABSTRACT

Objective *Helicobacter pylori* infection and overexpression of cyclo-oxygenase-2 (COX-2) are associated with gastric cancer and its precursors. To evaluate the effect of a selective COX-2 inhibitor alone and combined with *H pylori* eradication on the evolution of precancerous gastric lesions, a randomised, placebo-controlled trial was conducted in Linqu County, Shandong Province, China.

Methods A total of 1024 participants aged 35—64 years with *H pylori* infection and advanced gastric lesions were randomly assigned in a factorial design to two interventions or placebo: anti-*H pylori* treatment for 7 days, and a COX-2 inhibitor (celecoxib) for 24 months. The effects of the interventions were evaluated by the regression or progression of advanced gastric lesions.

Results Of the 1024 participants who received anti-*H pylori* treatment or placebo, 919 completed a subsequent 24-month treatment with celecoxib or placebo. The *H pylori* eradication rate by per-protocol analysis was 78.2%. Compared with placebo, the proportions of regression of gastric lesions significantly increased in the celecoxib treatment (52.8% vs 41.2%) and anti-*H pylori* treatment (59.3% vs 41.2%) group, and OR by per-protocol analysis was 1.72 (95% CI 1.07 to 2.76) for celecoxib and 2.19 (95% CI 1.32 to 3.64) for *H pylori* eradication. No statistically significant effect was found for *H pylori* eradication followed by celecoxib on the regression of advanced gastric lesions (OR 1.48, 95% CI 0.91 to 2.40).

Conclusion This population-based intervention trial revealed that celecoxib treatment or *H pylori* eradication alone had beneficial effects on the regression of advanced gastric lesions. No favourable effects were seen for *H pylori* eradication followed by celecoxib treatment.

Trial registration HARECCTR0500053 in accordance with WHO ICTRP requirements.

Significance of this study

What is already known about this subject?

- Gastric cancer is an end result of a continuous stepwise evolution of precancerous gastric lesions.
- *Helicobacter pylori* infection may play an important role in the development of gastric cancer.
- Overexpression of COX-2 is involved in *H pylori*-associated gastric carcinogenesis.
- Effects of a selective COX-2 inhibitor (such as celecoxib) alone and combined with *H pylori* eradication on precancerous gastric lesions are still unknown.

What are the new findings?

- *H pylori* eradication or celecoxib treatment may enhance the regression of advanced gastric lesions.
- No favourable effect was found for *H pylori* eradication followed by celecoxib on the regression of advanced gastric lesions.

How might it impact on clinical practice in the foreseeable future?

- This study suggests that a single anti-*H pylori* treatment or long-term use of celecoxib has a favourable effect on the regression of *H pylori*-associated advanced gastric lesions, but *H pylori* eradication followed by celecoxib is not recommended.

INTRODUCTION

Gastric cancer (GC) is the second leading cause of cancer deaths worldwide, including in China.[1 2] Accumulated evidence has revealed that GC, particularly of the intestinal type, is an end result of a continuous stepwise evolution of premalignant gastric lesions.[3 4] Our 4.5-year gastroscopy-based cohort study in Linqu County, a high-risk GC area in Shandong Province, China,[4] and a cohort study in the Netherlands strongly support the idea that the risk of GC is markedly increased by baseline histopathological severity.[5]

Infection with *Helicobacter pylori* causes chronic atrophic gastritis (CAG) and is considered a risk factor in the development of GC.[6–8] Several randomised trials, including our two intervention trials, indicate that *H pylori* eradication may significantly reduce the risk of precancerous gastric lesions and have a favourable effect on GC.[9–13] A meta-analysis has also shown that *H pylori* eradication can reduce GC risk,[14] suggesting that anti-*H pylori* treatment may be an effective strategy for preventing GC.

Cyclo-oxygenase-2 (COX-2), an enzyme that catalyses the conversion of arachidonic acid into prostaglandins, has been found to be involved in *H pylori*-associated gastric carcinogenesis.[15] *H pylori*

can induce COX-2 overexpression, and higher levels of COX-2 expression have been found in gastric carcinoma and premalignant lesions.[16 17] It is therefore expected that intervention with a COX-2 inhibitor will inhibit or reverse the process of *H pylori*-related carcinogenesis.

A few cohort studies have reported that use of non-steroidal anti-inflammatory drugs (NSAIDs) was associated with a reduced risk of gastrointestinal cancers, including GC.[18–20] Other studies have shown that celecoxib, a selective COX-2 inhibitor, can significantly reduce the risk of colon, lung, breast and prostate cancers.[21] However, no population-based study of the effect of celecoxib on GC prevention or its precursors has yet been reported.

On the basis of this evidence, we conducted a randomised placebo-controlled trial to assess whether celecoxib alone or combined with anti-*H pylori* treatment can independently or jointly prevent the progression, or enhance the regression, of advanced gastric lesions in a high-risk GC population in Linqu.

METHODS

This randomised, double-blind, placebo-controlled trial was conducted in Linqu County, a high-risk GC area in Shandong Province, China. The project was approved by the institutional review board of Peking University School of Oncology (PUSO) and University of Hong Kong (EC-1721-01), and implemented with the full knowledge and consent of the participants. In brief, after the names of all of the residents had been transcribed from village population rosters, field staff visited each person, explained the study design—including information on placebo, duration of the trial and follow-up, the benefits and risks—and invited them to participate in this intervention trial. Written informed consent was obtained from each subject. The project was registered as HARECCTR0500053 in accordance with WHO ICTRP requirements.

Participants and gastric pathology

A total of 2813 (89.0%) subjects out of 3161 residents from 12 randomly selected villages in Linqu agreed to participate in the initial screening programme in 2002. The programme consisted of an interview, carbon-13 urea breath test (^{13}C-UBT), physical examination, upper endoscopy, and pathological diagnosis. Trained field staff from PUSO interviewed all the participants using a standard structured questionnaire including age, gender, cigarette smoking history, alcohol consumption, occupation, previous history of peptic ulcers, use of antibiotics and NSAIDs, and any allergic reactions to antibiotics.

Upper endoscopy examination was conducted by four experienced gastroenterologists using fibre-optic or video endoscopes (Olympus). The gastric mucosa was examined, and five biopsy samples were taken from standard sites in the stomach according to the Updated Sydney System[22]: lesser curvature of the antrum, greater curvature of the antrum, angulus, lesser curvature of the body and greater curvature of the body. A diagnosis was made from each biopsy specimen, and each participant was assigned a global diagnosis based on the most severe diagnosis among the biopsy specimens.

Each slide was reviewed by a panel of three senior pathologists at the Department of Pathology of PUSO. Pathological diagnoses followed the criteria of the Updated Sydney System[22] and Padovo International Classification.[23] We graded intestinal metaplasia (IM) as superficial—involving the surface epithelium and pits—or deep—involving the deeper part, or even whole layer, of mucosa. Indefinite dysplasia (Ind DYS) was divided into two subtypes, foveolar hyperproliferation and hyperproliferative IM. In such atypical cases, tortuous glandular structures are lined by mucus-depleted epithelial cells with large, hyperchromatic nuclei with thickened nuclear membrane and prominent nucleoli. Mitosis may be prominent, and some glands show elongated and pseudostratified nuclei. In both subtypes of this category, the structural and cellular alterations tend to decrease from the bottom to the most superficial mucosal layers.

A total of 196 quality-control slides with IM, Ind DYS or DYS were randomly selected including 98 slides from 2002 and 98 from 2006, and blindly reviewed by Dr Xiang-hong Li (professor and chief pathologist at the General Hospital of the People's Liberation Army). Consensus was reached on 95.9% (188) of the 196 slides.

All participants underwent the ^{13}C-UBT to determine *H pylori* status at baseline and 45 days after the *H pylori* treatment. Details of the ^{13}C-UBT are given in previous publications.[24 25] The sensitivity and specificity of the ^{13}C-UBT were 93.1% and 95.5%, respectively.[26]

Selection criteria for the trial included participants aged 35–64 years with *H* pylori ^{13}C-UBT positive and baseline histology of severe CAG, IM, Ind DYS or DYS. Exclusion criteria before randomisation included refusal to provide informed consent, a prior negative *H pylori* test, non-atrophic gastritis (NAG), mild or moderate CAG, heart failure, emphysema, renal or liver disease, bleeding diathesis and/or requiring anticoagulant therapy, hypertension (diastolic blood pressure >95 mm Hg, systolic blood pressure >165 mm Hg), history of stroke or transient ischaemic attack within the last 2 years, history of neoplastic disease within the previous 10 years, or allergy to antibiotics.

In March 2004, 1024 eligible people were invited to participate in this intervention trial. Another upper endoscopy examination and histological diagnosis in a double-blind fashion were conducted in all participants at the end of the trial in April 2006 using the same procedures as at baseline, and histological diagnoses were made by the same pathologists who conducted the 2002 survey. The incident GCs were identified during the trial from 2004 to 2006 and follow-up period from 2007 to 2009.

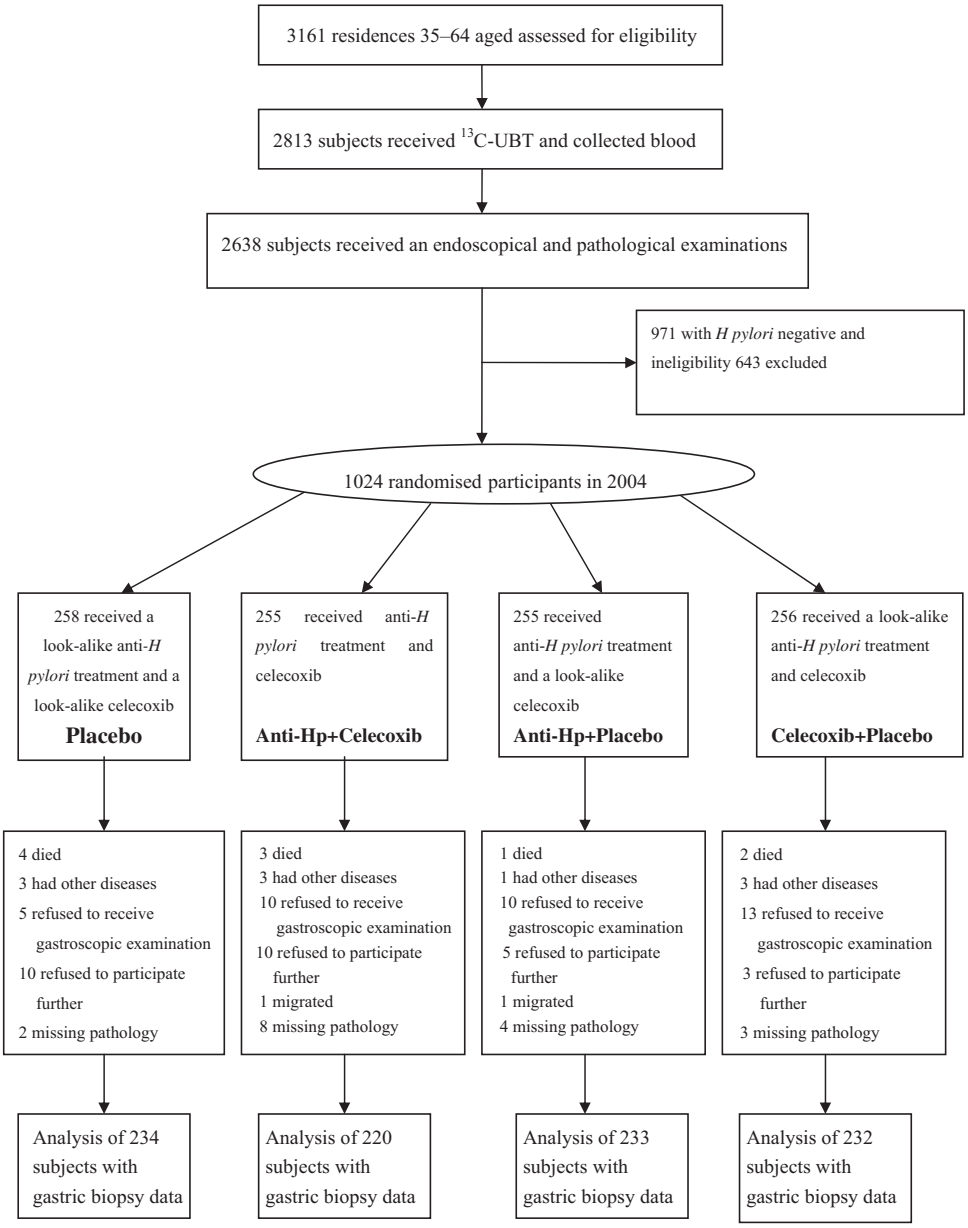
Study design and treatment

Trial participants were randomly assigned to two interventions (anti-*H pylori* treatment and/or COX-2 inhibitor) or placebo in a 2×2 factorial design (figure 1 and table 1). The participants were divided into four groups: (1) to receive placebo of anti-*H pylori* treatment in the first week, followed by placebo of celecoxib for 24 months; (2) to receive anti-*H pylori* treatment (omeprazole 20 mg, amoxicillin 1 g and clarithromycin 500 mg, twice daily) for 7 days, followed by celecoxib (200 mg; Pfizer, New York, NY, USA) twice daily for 24 months; (3) to receive anti-*H pylori* treatment in the first week, followed by placebo for 24 months; (4) to receive placebo in the first week, followed by celecoxib for 24 months. All placebos were identical in number, size and colour to the original medications. Both participants and investigators were blinded to treatment assignments. Randomised treatment assignments were generated blindly by Westat Inc, (Rockville, MD, USA) after eligibility was determined.

Compliance and adverse events

During the 24-month celecoxib (or placebo) treatment, the PUSO field staff distributed the medications in a labelled bottle to each participant and collected the bottle of the previous month at the participant's home every month. The staff

Figure 1 Participant flow diagram.



counted and recorded the number of pills remaining in each bottle before the new bottle was distributed. A participant was considered to be compliant if all pills were taken and the bottle was empty at the end of that month. The PUSO field staff visited the participant's home to monitor compliance and adverse reactions every 2 weeks. In each village, at least one doctor was assigned in the clinic and responsible for monitoring and recording participants' adverse events in the 24-month trial period. If the presenting symptoms were considered to be related to celecoxib, doctors in each village would be asked to report to township hospital doctors and PUSO physicians. An independent Data and Safety Monitoring Board received regular reports about the conduct and progress of the study, as well as the safety data.

End points and statistical analysis

The hypothesis tested in this study was that celecoxib alone or combined with anti-*H pylori* treatment could prevent the progression or enhance the regression of the advanced gastric lesions. The end point was the regression or progression of advanced gastric lesions after interventions. To estimate the treatment effects of the interventions, each subject was assigned a global severity score at baseline (A) and end point (B) according to the global diagnosis: 0 for NAG; 1 for mild or moderate CAG; 2 for severe CAG; 3 for superficial IM; 4 for deep IM; 5 for Ind DYS; 6 for low-grade DYS; 7 for high-grade DYS; 8 for GC. We used B−A to determine the evolution status of gastric lesions for each subject. If B−A was >0, =0 or <0, then the subject was classified into the progression group, no-change group or regression group, respectively.

For the intention-to-treat analysis, we compared placebo and treatment group on the basis of the initial randomisation. For the per-eradication-protocol analysis, we compared the proportion of participants who remained *H pylori* positive in the placebo group with treatment participants who had *H pylori* eradicated (negative by ^{13}C-UBT after 45 days). ORs and 95% CIs for the main effects of the interventions were computed by logistic regression analysis, with adjustment for age, gender, smoking and drinking status at baseline. Stratified analysis was used to evaluate the effect of interventions by histopathology

Table 1 Baseline characteristics of the study participants

Characteristic	Placebo (n=258)	Anti-Hp+ celecoxib (n=255)	Anti-Hp +placebo (n=255)	Celecoxib +placebo (n=256)	p Value
Age (years)	52.9±6.5	53.0±6.5	53.0±6.5	52.9±6.5	0.999
Sex					0.998
Men	120 (46.5)	118 (46.3)	118 (46.3)	117 (45.7)	
Women	138 (53.5)	137 (53.7)	137 (53.7)	139 (54.3)	
Daily smoking					0.944
Yes	166 (68.6)	168 (70.9)	169 (70.7)	168 (69.7)	
No	76 (31.4)	69 (29.1)	70 (29.3)	73 (30.3)	
Alcohol use					0.581
Yes	148 (61.2)	156 (65.8)	158 (66.1)	150 (62.2)	
No	94 (38.8)	81 (34.2)	81 (33.9)	91 (37.3)	
Baseline histology					0.287
CAG	65 (25.2)	53 (20.8)	59 (23.1)	50 (19.5)	
IM	63 (24.4)	64 (25.1)	59 (23.1)	54 (21.1)	
Ind DYS	113 (43.8)	108 (42.4)	115 (45.1)	133 (52.0)	
DYS	17 (6.6)	30 (11.7)	22 (8.7)	19 (7.4)	

Anti-Hp, anti-*H pylori* treatment; CAG, chronic atrophic gastritis; DYS, dysplasia; IM, intestinal metaplasia; Ind DYS, indefinite dysplasia.

category, such as severe CAG, IM, Ind DYS and DYS, and by site, such as antrum, angulus or body of the stomach.

According to our previous gastroscopy-based cohort study without intervention in Linqu, the rates of regression and progression of premalignant gastric lesions were 28.2% and 27.3%, respectively.[4] Thus, the sample size was set at 250 for each arm in the present study, which could achieve a statistical power ≧0.90 at a 5% level of significance to detect a 15% difference in rate of regression or progression between any of the treatment arms and placebos. All p values were two-sided, and $p<0.05$ was considered significant. All statistical calculations were performed with SAS statistical software, version 8.2.

RESULTS

A total of 1024 subjects (473 male and 551 female) enrolled in the trial including 227 (22.2%) with CAG, 240 (23.4%) with IM, 469 (45.8%) with Ind DYS and 88 (8.6%) with DYS. The number of subjects with baseline gastric pathology was balanced in each treatment group (table 1). No significant difference in age, sex, smoking or alcohol consumption was found between treatment and placebo groups at baseline (all $p>0.05$).

Compliance and *H pylori* eradication

A total of 105 participants withdrew from the trial because of 10 deaths (lung cancer, 3; oesophageal cancer, 1; brain cancer, 1; cerebral haemorrhage, 2; traffic accident or suicide, 3), 10 unrelated medical illnesses, 66 refusals to continue, 2 emigrations and 17 with missing pathological diagnosis. The remaining 919 subjects (89.7%) completed the repeat upper endoscopy and histology examinations, including 234 in the placebo group, 220 in the anti-*H pylori* combined with COX-2 inhibitor group, 233 in the anti-*H pylori* group, and 232 in the COX-2 inhibitor group. Compliance with celecoxib treatment over 2 years was more than 90% in all four treatment arms. The rate of *H pylori* eradication in subjects who had received anti-*H pylori* treatment was 71.3% by intention-to-treat analysis and 78.2% by per-eradication-protocol analysis. Table 2 shows the *H pylori* eradication rate in each active *H pylori* treatment arm; no significant difference was found between anti-*H pylori* alone and anti-*H pylori* followed by celecoxib by intention-to-treat or per-eradication-protocol analysis ($p>0.05$).

Effects on precancerous gastric lesions

We analysed the proportions of transitions of precancerous gastric lesions among 919 participants during the trial period (table 3). From baseline in 2002 to 2006, more than half of participants (56.5%) with severe CAG at baseline persisted in this state or reverted to a lesser lesion. In contrast, subjects with superficial IM at baseline were more likely to have progressed to deep IM. A large fraction of subjects with Ind DYS at baseline reverted to lesser lesions in 2006. The distributions of gastric histopathology in 2002 and 2006 by treatment are presented in online supplementary table 1.

To assess the treatment effects of the interventions on the advanced gastric lesions, the participants were classified into three categories: regression, no change and progression. Table 4 shows the proportions of regression and progression by different treatment arms. There were no significant differences in the

Table 2 *Helicobacter pylori* eradication rate in different treatment groups

	Placebo (n=234)	Anti-Hp +celecoxib (n=220)	Anti-Hp +placebo (n=233)	Celecoxib +placebo (n=232)
H pylori status by ^{13}C-UBT after 45 days (n)				
H pylori positive	199	46	44	193
H pylori negative	18	161	162	23
Not available	17	13	27	16
H pylori eradication rate (%)				
Intention-to-treat analysis	–	73.2	69.5	–
Per-eradication-protocol analysis	–	77.8	78.6	–

Anti-Hp, anti-*H pylori* treatment; ^{13}C-UBT, carbon-13 urea breath test.

Table 3 Distribution of gastric histopathology by year

2002 baseline pathology	2006 pathology n	≦CAG n=219 (%)	Superficial IM n=18 (%)	Deep IM n=448 (%)	Ind DYS n=208 (%)	Low-grade DYS n=18 (%)	High-grade DYS n=1 (%)	Cancer n=7 (%)
Severe CAG	207	117 (56.5)	5 (2.4)	66 (31.9)	18 (8.7)	1 (0.5)	0 (0.0)	0 (0.0)
Superficial IM	62	19 (30.6)	1 (1.6)	37 (59.7)	5 (8.1)	0 (0.0)	0 (0.0)	0 (0.0)
Deep IM	154	25 (16.2)	3 (1.9)	76 (49.4)	46 (29.9)	3 (1.9)	0 (0.0)	1 (0.6)
Ind DYS	418	55 (13.2)	7 (1.7)	231 (55.3)	110 (26.3)	9 (2.2)	1 (0.2)	5 (1.2)
Low-grade DYS	77	3 (3.9)	2 (2.6)	38 (49.4)	28 (36.4)	5 (6.5)	0 (0.0)	1 (1.3)
High-grade DYS	1	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	919							

CAG, chronic atrophic gastritis; DYS, dysplasia; IM, intestinal metaplasia; Ind DYS, indefinite dysplasia.

proportions of subjects with progression in any of the treatment groups and placebos by intention-to-treat analysis or per-eradication-protocol analysis (all p>0.05). However, compared with placebo, the proportions of regression were significantly increased in the celecoxib (51.7% vs 42.3% by intention-to-treat analysis, and 52.8% vs 41.2% by per-eradication-protocol analysis) and anti-*H pylori* treatment (54.1% vs 42.3% and 59.3% vs 41.2%, respectively) arms. ORs were 1.55 (95% CI 1.01 to 2.38) for celecoxib and 1.80 (95% CI 1.16 to 2.78) for anti-*H pylori* treatment by intention-to-treat analysis, and 1.72 (95% CI 1.07 to 2.76) for celecoxib and 2.19 (95% CI 1.32 to 3.64) for anti-*H pylori* treatment by per-eradication-protocol analysis. No statistically significant favourable effects were found for *H pylori* eradication followed by celecoxib.

To investigate whether specific types of advanced gastric lesions (such as IM, Ind DYS or DYS) were affected by different treatment arms, we examined changes in the distribution of histopathology categories by treatment arm. No statistically significant effects were seen in any histopathology categories by treatment arm (data not shown). We also analysed the proportions of regression and progression by treatment group and site, such as antrum, angulus or body of the stomach; similar trends for regression and progression were observed and none reached statistical significance (data not shown).

Effect on incidence of gastric cancer

Nine incident GCs were diagnosed during the trial (from 2004 to 2006) and follow-up period (from 2007 to 2009): four in 2005, three in 2006, two in 2007, and zero in 2008 and 2009. One (0.4%) of 234 subjects was identified in the placebo group, three (1.4%) of 220 subjects in the anti-*H pylori* combined with COX-2 inhibitor group, three (1.3%) of 233 subjects in the anti-*H pylori* group, and two (0.9%) of 232 subjects in the COX-2 inhibitor group. Because seven of the nine GCs were identified during the treatment period from 2004 to 2006, we did not evaluate the treatment effect on the incidence of GC. Information on baseline gastric pathology, TNM (tumour, node, metastases) stage and histopathological type for these GC cases are shown in table 5. Of the nine GC cases, eight (88.9%) were intestinal type, and one (11.1%) was diffuse type. Seven (77.8%) of the nine GC cases were T1 stage.

Adverse effects

As previously published with regard to the safety of celecoxib,[27] we assessed a number of potential adverse effects of celecoxib, and there were no significant effects on gastrointestinal tract symptoms (peptic ulcer, constipation, diarrhoea, nausea, gastric spasm, bloating and abdominal pain) or cardiovascular events (myocardial infarction, ischaemia and stroke). No severe adverse events were found during the 2-year trial; the details were reported previously.[27] No deaths were associated with assignment to either the celecoxib or combination group.

DISCUSSION

The primary objective of this study is to assess the effect of a selective COX-2 inhibitor alone and in combination with *H pylori* eradication on the advanced gastric lesions. We found that *H pylori* eradication or celecoxib treatment alone led to a higher rate of regression than placebo. No beneficial effects on the regression of advanced gastric lesions were observed for *H pylori* eradication followed by celecoxib. To the best of our knowledge, this is the first population-based study exploring the effect of celecoxib on the evolution of advanced gastric lesions.

Table 4 Regression and progression of histopathology by different treatment arms*

Group	No change n	Regression n	OR (95% CI)*	p Value	Progression n	OR (95% CI)*	p Value
Intention-to-treat analysis							
Placebo	78	99	1.00		57	1.00	
Anti-Hp+celecoxib	59	114	1.50 (0.97 to 2.32)	0.067	47	1.06 (0.63 to 1.78)	0.833
Anti-Hp+placebo	55	126	1.80 (1.16 to 22.78)	0.009	52	1.24 (0.74 to 2.09)	0.411
Celecoxib+placebo	61	120	1.55 (1.01 to 22.38)	0.046	51	1.13 (0.68 to 1.89)	0.637
Per-protocol analysis							
Placebo†	67	82	1.00		50	1.00	
Anti-Hp+celecoxib‡	47	84	1.48 (0.91 to 2.40)	0.117	30	0.83 (0.45 to 1.51)	0.537
Anti-Hp+placebo‡	36	96	2.19 (1.32 to 3.64)	0.002	30	1.08 (0.58 to 2.02)	0.805
Celecoxib+placebo†	49	102	1.72 (1.07 to 2.76)	0.026	42	1.14 (0.65 to 2.00)	0.658

*ORs and 95% CIs were calculated by logistic regression and adjusted for age, sex, smoking and drinking status.
†The participants who remained *H pylori* positive.
‡The participants in whom *H pylori* was eradicated (negative by carbon-13 urea breath test after 45 days).
Anti-Hp, anti-*H pylori* treatment.

Table 5 Characteristics of the GC cases

No	Sex	Age (2002)	2002 Baseline histology	Treatment group (2004)	GC diagnosis (year)	GC type	TNM stage
1	M	57	DYS (low)	Celecoxib+placebo	2005	Intestinal	T1
2	M	64	Ind DYS	Anti-Hp+placebo	2005	Intestinal	T1
3	M	48	Ind DYS	Placebo	2005	Diffuse	T1
4	F	63	Ind DYS	Anti-Hp+celecoxib	2005	Intestinal	T1
5	M	44	IM (deep)	Anti-Hp+placebo	2006	Intestinal	T2
6	M	62	Ind DYS	Anti-Hp+celecoxib	2006	Intestinal	T1
7	M	51	Ind DYS	Celecoxib+placebo	2006	Intestinal	T1
8	M	57	DYS (low)	Anti-Hp+celecoxib	2007	Intestinal	T2
9	M	41	Ind DYS	Anti-Hp+placebo	2007	Intestinal	T1

Anti-Hp, anti-*H pylori* treatment; CAG, chronic atrophic gastritis; DYS, dysplasia; F, female; GC, gastric cancer; IM, intestinal metaplasia; Ind DYS, indefinite dysplasia; M, male; TNM, tumour, node, metastases.

Several randomised intervention trials have confirmed the effects of *H pylori* eradication on premalignant gastric lesions or GC.[9–13] Our previous randomised trial in Linqu revealed that *H pylori* eradication caused a significant decrease of 40% in the prevalence of advanced gastric lesions, as well as favourable effects on GC.[9] The present finding confirmed that *H pylori* eradication could enhance the regression of advanced gastric lesions.

COX-2 overexpression may be an important step in *H pylori*-associated gastric carcinogenesis.[15] Although several studies have shown that long-term use of aspirin or non-aspirin NSAIDs can prevent the development of GC,[28 29] no randomised study of celecoxib on GC prevention or its precursors has yet been reported. Our finding provides new evidence and supports the hypothesis that celecoxib has a beneficial effect on the regression of *H pylori*-associated advanced gastric lesions.

Various mechanisms have been proposed to explain the effect of celecoxib on the regression of *H pylori*-associated gastric lesions.[29 30] *H pylori* can upregulate the expression of COX-2 and increase prostaglandin E_2 (PGE_2) synthesis both in vitro and in vivo,[31 32] which can stimulate cell proliferation, mutagenesis and mitogenesis and inhibit apoptosis. Inhibition of COX-2 expression by celecoxib may inhibit these processes.[15 21] In addition to its direct COX-2 inhibiting effect, celecoxib has been reported to inhibit NF-κB activation,[33 34] which is a major mediator of *H pylori*-induced inflammation.

In contrast with the positive findings for *H pylori* eradication and celecoxib alone, our study did not support additional beneficial effects for *H pylori* eradication followed by celecoxib treatment on the regression of advanced gastric lesions. There are several possible explanations for this negative result. During the *H pylori*-induced COX-2/PGE_2 carcinogenesis sequence, COX-2 expression in *H pylori*-infected subjects should be decreased after *H pylori* eradication. Indeed, several studies including the present one (data not shown) have confirmed that COX-2 expression is significantly decreased after *H pylori* eradication.[16 35] A recent study has provided new experimental evidence that PGE_2 may act as an immune modulator of the *H pylori*–host interaction, and systemic administration of PGE_2 may prevent development of premalignant gastric lesions or even reverse pre-existing lesions in a mouse model.[30] Although the result was not obtained directly from a human study, it suggests that over-inhibition of COX-2 may affect the immunomodulatory role of PGE_2 during gastric carcinogenesis.

Despite the relatively long period of this study (from 2004 to 2006 for the trial and 2007 to 2009 for the follow-up), we were unable to assess the effect of celecoxib or *H pylori* eradication on GC incidence because of the small sample size. Moreover, the baseline pathology of the nine incident GCs in 2002 showed Ind DYS (six cases) and DYS (two cases) (table 5); thus the treatment effect of either celecoxib or *H pylori* eradication on such advanced lesions may be limited.

We did not find statistically significant beneficial effects on the progression of advanced gastric lesions in any of the treatment arms. As subjects with early gastric lesions such as NAG or mild/moderate CAG were not included in our study population, the effects of different treatment arms on the progression of gastric lesions may not be detected among those with more advanced gastric lesions, such as IM, Ind DYS or DYS (77.8% of the subjects).

In addition, the rate of regression with placebo was about 41% in our study, which seems higher than our previous 4.5-year gastroscopy-based cohort study (743/2628=28.2% from table 2).[4] However, we calculated the rate of regression in subjects with advanced gastric lesions (≥ severe CAG), which was similar to the present study (743/1596=46.5% from table 2).[4] Because only subjects with advanced gastric lesions (≥ severe CAG) were enrolled in the present study, the chances of regression were higher than in those with a full spectrum of gastric pathology, including NAG or mild/moderate CAG. A high rate of regression in the placebo group tends to diminish the true treatment differences, therefore the effects of active treatments may be diluted.

In this study, there were 418 subjects with Ind DYS at baseline, and 110 remained in the same class at the end of the trial, whereas the proportion of subjects with low-grade DYS (77/919=8.4%) at baseline was much lower than in our previous study (mild DYS, 503/2628=19.1%).[4] This may be because some cases diagnosed as mild DYS in 1999 would correspond to Ind DYS in the present study according to the Padovo International Classification.[23] In addition, all subjects enrolled in our study were *H pylori* positive only. *H pylori* may induce cellular hyperproliferation or atypia, and the pathologist may be unable to decide for certain if the lesion being considered represents neoplastic or non-neoplastic cells.[23] To test if some atypical cases may be resolved after removal of the source of *H pylori*, we further analysed the samples with Ind DYS at baseline and the end of the trial. At baseline, 135 (32.3%) were foveolar hyperproliferation and 283 (67.3%) were hyperproliferative IM, whereas at the end of the trial, only three (2.7%) were foveolar hyperproliferation and 107 (97.3%) hyperproliferative IM. This result strongly supports our hypothesis that foveolar hyperproliferation is mainly affected by *H pylori*-induced inflammation, and would have disappeared after treatment of *H pylori* in this population.

The safety of celecoxib is an important issue in this intervention trial. The epidemiological data suggest that regular intake of celecoxib at a low dosage (from 200 mg to 400 mg,

daily) is safe and can reduce cancer risk.[36 37] The result of a meta-analysis of 72 studies of celecoxib (≤400 mg daily) shows no evidence of increased cardiovascular risk associated with celecoxib.[21] We selected 200 mg (twice daily) of celecoxib for our intervention trial, and no severe adverse events were found during the 2-year treatment period.[27]

A strength of our study is that it is a randomised, placebo-controlled factorial design with good quality control in a well-defined population. This 2×2 factorial design allows us to assess the effects of a selective COX-2 inhibitor or *H pylori* eradication, alone or combined, on the evolution of advanced gastric lesions. The high treatment compliance and excellent follow-up also enhanced the reliability of the study. In addition, seven of the nine GC cases were diagnosed in the early stages (TNM stage T1), indicating the high quality of the endoscopy and histological examinations. Our study also has some limitations, such as the use of 'the most severe diagnosis' to categorise participants, which could not provide any prognostic or therapeutic information. A more efficient system for assessing gastric mucosa, such as the OLGA staging system,[38] will be used in our future studies.

In conclusion, a single anti-*H pylori* treatment or long-term use of celecoxib has a favourable effect on the regression of *H pylori*-associated advanced gastric lesions, but *H pylori* eradication followed by celecoxib is not recommended.

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Patient consent Obtained.

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Contributors All authors directly participated in the planning, execution, or analysis of the study. All authors have read and approved the final version submitted. All authors accept responsibility for its content. Study organisation was by WY, and BCYW designed the study. WY, BCYW, LZ and SL supervised the execution of the study. LZ, JM, KP, WL and HHXX were responsible for the field administration and data collection. LS, XZ and JL were responsible for the endoscopic examination. J-yL and AL were responsible for the pathological diagnosis. GF and KP performed the statistical analyses. WY, LZ, KP and BCYW drafted the manuscript.

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Effects of selective COX-2 inhibitor and *Helicobacter pylori* eradication on precancerous gastric lesions

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