

Effects of Long-term Rofecoxib on Gastric Intestinal Metaplasia: Results of a Randomized Controlled Trial

Wai K. Leung, Enders K.W. Ng, Francis K.L. Chan, Wing Y. Chan, Kui-fat Chan, Alex C.M. Auyeung, Candice C.H. Lam, James Y. W. Lau, and Joseph J. Y. Sung

Abstract Purpose: Gastric cancer and its premalignant gastric lesion, intestinal metaplasia (IM), frequently express cyclooxygenase-2 (COX-2) at high levels. We tested whether long-term use of specific COX-2 inhibitors regress gastric IM.

Experimental Design: This is a double-blind, randomized, placebo-controlled trial. Individuals with confirmed IM and *Helicobacter pylori* clearance were randomized to receive rofecoxib 25 mg daily or placebo. Endoscopy was done at baseline, at the end of year 1, and at the end of year 2, with multiple biopsies taken from the antrum and corpus. The primary end point was the proportion of subjects with regression of IM. Secondary end points were the severity of other histologic variables and the proportion of subjects with complete regression of IM.

Results: Two-hundred and thirteen subjects with confirmed IM were randomized. The proportion of subjects with the regression of IM did not differ significantly between rofecoxib and placebo groups (antrum, 24.5% versus 26.9%; $P = 0.74$; corpus, 4.3% versus 2.2%; $P = 0.68$). Patients on rofecoxib (19.1%) and on placebo (16.1%) had no IM detected in the stomach ($P = 0.59$). There was also no significant difference in the severity of IM between the two treatment groups ($P \geq 0.3$).

Conclusions: There was no trend to suggest that treatment with rofecoxib for 2 years resulted in the regression of gastric IM. Although our findings cast doubt on the reversibility of gastric IM by COX-2 inhibitor, further studies are needed to establish the role of COX-2 inhibitors in different stages of gastric carcinogenesis.

Gastric cancer is the second leading cause of cancer-related death in the world which is associated with >600,000 deaths each year (1). The gastric carcinogenesis process is generally believed to be a multi-step progression from chronic gastritis to atrophy, intestinal metaplasia (IM), dysplasia and cancer, which is usually triggered by chronic *Helicobacter pylori* infection (2). Individuals infected with *H. pylori* have an at least 2-fold increase in risk of developing gastric cancer (3) and attempts to halt or reverse this progression by eradication of *H. pylori* seem to be the most logical approach in the prevention of gastric cancer. Due to the long lead-time and relatively low incidence of gastric cancer development, most

chemoprevention studies used surrogate end point like changes in premalignant gastric lesions (4–7). With its easily recognized histologic appearance, gastric IM is a commonly used surrogate end point in chemoprevention trials. In a prospective study from Japan, individuals with IM in the stomach had a 6.4-fold increase in risk of gastric cancer (8). This finding further supports the importance of IM in gastric cancer progression. Results from several large-scale, randomized controlled trials however showed that eradication of *H. pylori* alone could only confer a marginal benefit in preventing the progression of gastric IM when compared with patients treated with placebo (4–6). The degree of regression was modest even up to 7 years posttreatment and a substantial proportion of individuals had deterioration of premalignant gastric lesions on follow-up examination (7). More importantly, the benefits of *H. pylori* eradication in the prevention of cancer development may be confined to individuals with no premalignant changes on baseline examination (6).

Overexpression of cyclooxygenase-2 (COX-2), which is associated with resistance to apoptosis and induction of angiogenesis, is believed to play a key role in cancer development and progression (9, 10). We have previously shown that gastric carcinoma and its precursor lesions have high levels of COX-2 expression (11). In an animal model of gastric carcinogenesis, treatment with a specific COX-2 inhibitor reduced the number of gastric tumors formed (12). Meta-analysis data of human studies

Authors' Affiliation: Institute of Digestive Disease, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong

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Requests for reprints: Wai K. Leung, Department of Medicine and Therapeutics, 9/F Clinical Sciences Building, Prince of Wales Hospital, Shatin, Hong Kong. Phone: 852-2632-3140; Fax: 852-2637-852; E-mail: wkleung@cuhk.edu.hk.

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also show that the use of nonsteroidal anti-inflammatory drugs reduce the risk of gastric cancer by ~20% (13). However, there is no human data on the use of selective COX-2 inhibitors in the chemoprevention of gastric cancer.

In this study, we hypothesized that among patients with gastric IM who had confirmed eradication of *H. pylori*, treatment with a specific COX-2 inhibitor promotes the regression of IM. Herein, we tested the effect of a specific COX-2 inhibitor in patients with confirmed gastric IM after *H. pylori* eradication. The present study was a prospective, randomized, double-blind, placebo-controlled study.

Patients and Methods

Study population. All study subjects were recruited from the Endoscopy Center of the Prince of Wales Hospital of Hong Kong. We invited first-degree relatives of patients with gastric adenocarcinoma and patients with dyspepsia who were between 18 and 70 years of age to undergo screening endoscopy for gastric IM. The study protocol was approved by the Clinical Research Ethics Committee of the Chinese University of Hong Kong and all participants gave written informed consent.

All eligible subjects underwent upper gastrointestinal endoscopy screening between April 2001 and October 2002. During each endoscopy, a total of eight gastric biopsies were taken from the antrum (two from the superior and inferior antrum at ~4 cm from the pylorus, one from the angular incisura, and one from the proximal part of the inferior antrum) and the corpus of the stomach (four biopsies from the distal and proximal part of the corpus along the greater and lesser curve) for histologic examination.

Gastric biopsy specimens were fixed in 10% buffered formalin and embedded in paraffin. The 4 μ m paraffin sections were stained with H&E, and Alcain blue-periodic acid Schiff (pH 2.5). Histologic sections of the antrum and the corpus were graded separately for the severity of acute polymorphonuclear cell infiltrates (AP), chronic mononuclear cell infiltrates (CM), glandular atrophy (GA), and IM as stipulated by the updated Sydney System (14). GA was defined by the loss of appropriate glands (15). For AP, CM, and GA, a global score of none (0), mild (1), moderate (2), or marked (3) was given (14). Due to the focal nature of IM, each gastric biopsy was scored separately for IM (0-3) and the mean score was compiled for the antrum and corpus, respectively.

H. pylori infection, which was defined by the presence of the bacterium on histology, was treated with a 1-week course of eradication therapy consisting of a proton pump inhibitor, amoxicillin, and clarithromycin prior to randomization. *H. pylori* eradication was confirmed by a negative urea breath test 8 weeks posttreatment. Only patients with confirmed *H. pylori* eradication were recruited. Subjects who were regular users of nonsteroidal anti-inflammatory drugs including COX-2-selective inhibitors, aspirin and corticosteroids, were excluded. Other exclusion criteria included previous gastrectomy, active peptic ulcer, pregnancy or lactating mother, a history of cardiovascular or cerebrovascular disease, active cancers, and abnormal complete blood counts or serum biochemistry.

Eligible subjects who were histologically confirmed to have gastric IM and negative tests for *H. pylori* were randomly assigned to receive either rofecoxib (Vioxx, Merck, Whitehouse Station, NJ) 25 mg once daily or an identical-looking placebo at a 1:1 ratio. Randomization was carried out in blocks of four by a computer-generated list of random numbers. An independent staff assigned treatments according to consecutive numbers that were kept in opaque and sealed envelopes. Consecutively numbered, sealed bottles of the study medications were dispensed by a research nurse.

Assessment. After randomization, patients were reviewed again on week 4 and then every 3 months until the end of the study period by

clinicians who were unaware of the patients' treatment allocation. At each visit, adverse events were monitored with a comprehensive symptom questionnaire as well as clinical laboratory evaluations. Compliance was monitored by pill counts. Nonsteroidal anti-inflammatory drugs, corticosteroids, aspirin, and non-study COX-2 inhibitors were prohibited during the study period.

Endoscopy was planned annually until the end of year 5. The same protocol for obtaining gastric biopsy was used as in baseline endoscopy. All gastric biopsies were interpreted by two pathologists who were blinded to the assigned treatment and treatment duration. The agreed grading was used in all cases to minimize potential interobserver variation.

Cellular apoptosis and proliferation. Cellular apoptosis of gastric epithelial cells was determined by the terminal deoxynucleotidyl transferase-mediated dUTP-digoxigenin nick end-labeling technique (DeadEnd Colorimetric TUNEL System; Promega, Madison, WI), whereas cellular proliferation was determined by immunoperoxidase staining against Ki-67 (MIB-1; Zymed, San Francisco, CA) as described previously (16). A quantitative method for calculating the percentage of apoptotic cells and Ki-67-stained nuclei was used. All sections were examined in high-power fields (400 \times). A random starting field was selected and every other field was examined throughout the antrum. The apoptotic index and Ki-67 labeling index were determined by counting the number of positively stained nuclei per 100 epithelial cells among 1,000 epithelial cells in the quantified regions.

End points. The primary end point was defined as the proportion of patients with regression of gastric IM. Regression was defined as a reduction in the mean IM score by at least 1 point when compared with baseline. Secondary end points were the proportion of patients with the absence of IM in all biopsies taken from the antrum and corpus, the severity of other histologic variables, and changes in apoptotic and proliferation index.

Statistical analysis. We assumed that long-term eradication of *H. pylori* led to the regression of gastric antral IM in 25% of the subjects (4, 5), and that chemoprevention with rofecoxib would be clinically worthwhile if the treatment could induce an additional 25% regression in 5 years after curing *H. pylori* infection. This assumption was based on very limited long-term data on changes of gastric IM available at the time of planning this study (4, 5). Accordingly, a sample of 85 subjects was required in each treatment arm to achieve a power of 90% at 5% level of significance. On the assumption that 20% of the study subjects would be lost to follow-up, a total sample of 213 subjects would be required for this study.

An independent data review committee did all the analyses according to the intention-to-treat principle, which included all patients who had taken at least one dose of study drugs and who had undergone follow-up endoscopy. The homogeneity of the two treatment groups at baseline was analyzed by χ^2 test for categorical data and Student's *t* test for continuous variables. The difference in histologic grading between the two treatment groups was compared by Mann-Whitney *U* test. The severity of IM before and after study medication within each treatment group was compared by Wilcoxon signed-rank test. The proportion of patients who were free of IM was compared by χ^2 test. The two-tailed independent *t* test was used to determine the difference in apoptotic and proliferation index of gastric epithelium between the two treatment groups.

We planned a yearly interim analysis with predefined criteria to assess the safety and efficacy of the two treatments. To terminate the trial if one treatment was markedly inferior to the other, we used a Peto-Haybittle type of stopping rule that prespecified a level of significance of 0.001 (17). Because long-term chemoprevention with a COX-2 inhibitor is expensive and not without side effects, we planned to terminate the trial if treatment with rofecoxib did not lead to a meaningful regression of gastric IM after 2 years of study medication. The latter was predefined as the upper limit of the 95% confidence interval for the difference between the two treatment outcomes to be <15% at the end of year 2.

The interim results at the end of year 1 did not justify early termination. At the end of year 2, the difference in the proportion of patients with regression of IM between the rofecoxib and placebo groups was -2.4% , suggesting that fewer patients in the rofecoxib group has regression of IM. Even in the best-case scenario, the upper limit of the 95% confidence interval for this difference was 10.1%, and we did not consider it justified to continue this trial. The study was therefore terminated after the second interim analysis.

Results

Patients. Among the 281 patients with IM, 213 underwent randomization: 106 were assigned to receive placebo and 107 to receive rofecoxib (Fig. 1). The reasons for exclusion from the trial included patient refusal (53 patients), early gastric cancer found on baseline endoscopy (3 patients), regular nonsteroidal anti-inflammatory drug users (3 patients), and other concurrent medical illnesses (9 patients).

The baseline demographic and histologic characteristics of the two treatment groups were comparable (Tables 1 and 2). At the end of year 2, 187 (87.8%) patients (93 in the placebo group and 94 in the rofecoxib group) returned for endoscopic examination. Ninety-eight percent of the patients took at least 80% of study medications. In the rofecoxib group, two patients developed cardiovascular complications (heart failure and atrial fibrillation) and one patient developed transient ischemic attack. Other adverse events leading to discontinuation of medication in the rofecoxib group included gastric ulcer in one, renal failure in one, recurrent aphthous ulcers in two, and epigastric pain in one. Serious adverse events encountered in

Table 1. Baseline characteristic of the patients

	Rofecoxib (N = 107)	Placebo (N = 106)
Male (%)	67 (62.6)	70 (66)
Mean age (y) \pm SD	51.1 \pm 9.3	51.3 \pm 8.1
Family history of stomach cancer (%)	34 (31.8)	32 (30.2)
Smoking history		
Nonsmokers (%)	68 (63.6)	59 (55.7)
Ex-smokers (%)	16 (15)	24 (22.6)
Current smokers (%)	23 (21.4)	23 (21.7)
Alcohol consumption		
Nondrinkers (%)	76 (71)	73 (68.9)
Current drinkers (%)	31 (29)	33 (31.1)
History of ulcer (%)	44 (41.1)	43 (40.6)
Gastric ulcer (%)	18 (16.8)	18 (17.0)
Duodenal ulcer (%)	25 (23.4)	22 (20.8)
Both gastric and duodenal ulcers (%)	1 (0.9)	3 (2.8)

the placebo group included myocardial infarction in two, ileal perforation in one, and lung cancer in one. There was no significant difference in the incidence of vascular complications between the two groups. No gastric cancer was detected on follow-up endoscopy in all study subjects.

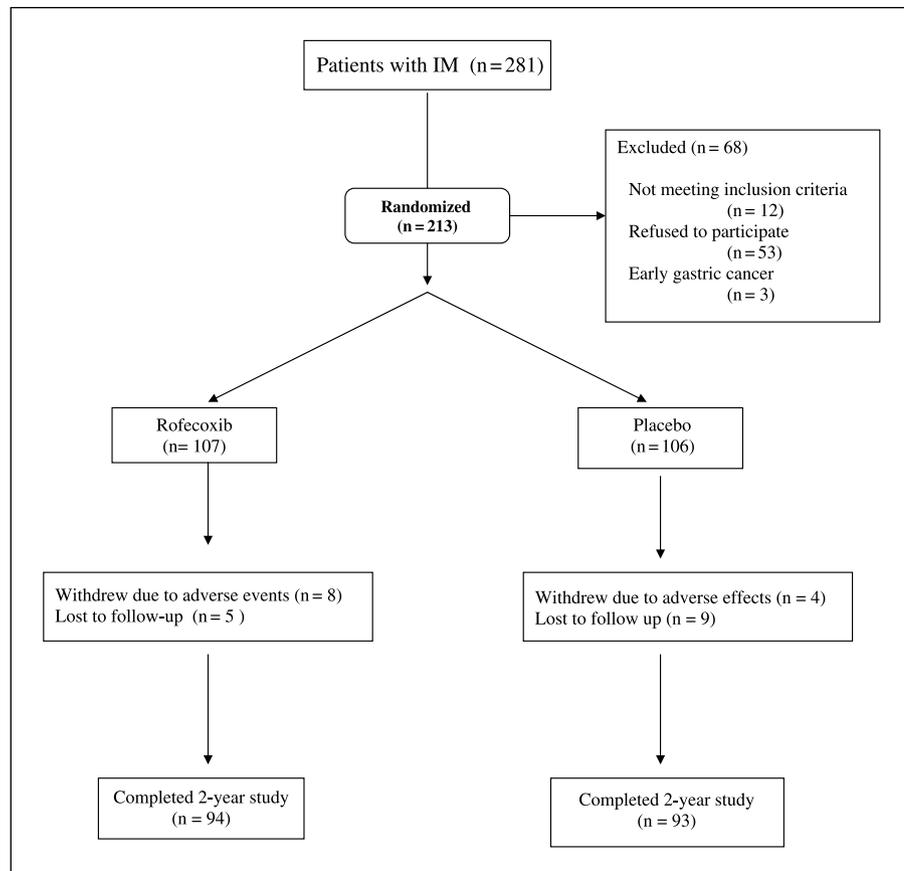


Fig. 1. Trial profile.

Table 2. Baseline histologic findings of patients

Histologic features	Rofecoxib	Placebo
Acute inflammation (antrum)		
Mean \pm SD	0.76 \pm 1.09	0.7 \pm 1.03
Median (range)	0 (0-3)	0 (0-3)
Acute inflammation (body)		
Mean \pm SD	0.37 \pm 0.81	0.35 \pm 0.69
Median (range)	0 (0-3)	0 (0-3)
Chronic inflammation (antrum)		
Mean \pm SD	1.67 \pm 0.72	1.63 \pm 0.71
Median (range)	2 (0-3)	2 (0-3)
Chronic inflammation (body)		
Mean \pm SD	1.03 \pm 0.82	0.92 \pm 0.81
Median (range)	1 (0-3)	1 (0-3)
Atrophy (antrum)		
Mean \pm SD	0.44 \pm 0.57	0.42 \pm 0.55
Median (range)	0 (0-2)	0 (0-2)
Atrophy (body)		
Mean \pm SD	0.11 \pm 0.42	0.11 \pm 0.37
Median (range)	0 (0-3)	0 (0-2)
IM score (antrum)		
Mean \pm SD	0.86 \pm 0.72	0.96 \pm 0.74
Median (range)	0.75 (0-3)	0.75 (0-3)
IM score (body)		
Mean \pm SD	0.17 \pm 0.38	0.13 \pm 0.42
Median (range)	0 (0-2.5)	0 (0-3)

Grading of IM and GA. The severity of IM and GA at the end of year 1 and year 2 is shown in Table 3. There was a significant reduction in the severity of IM and GA in the antrum at the end of year 1 when compared with baseline in both treatment groups [rofecoxib, $P = 0.02$ (IM), $P = 0.008$ (GA); placebo, $P < 0.001$ (IM), $P = 0.043$ (GA)]. At the end of year 2, significant differences from baseline were only observed in the antrum of subjects treated with placebo (IM, $P = 0.004$; GA, $P = 0.011$) but not with rofecoxib (IM, $P = 0.14$; GA, $P = 0.06$). There was no significant difference in the severity of IM and GA in the corpus between baseline and follow-up examinations in both treatment groups. However, there was no significant difference between the two treatment groups at all time points ($P > 0.09$; Table 3).

Proportion of patients with improvement. We also compared the proportion of patients with improvement (i.e., score ≤ 1), no change (i.e., same score), or deterioration (i.e., score ≥ 1) in the four histologic variables. As shown in Fig. 2, a considerable proportion of patients had improvement in gastric inflammation scores at the end of year 2. The proportion of patients with improvement in AP and CM infiltrates were comparable between the two treatment groups in the antrum (AP, $P = 0.93$; CM, $P = 0.3$) and in the corpus (AP, $P = 0.69$; CM, $P = 0.37$).

For antral IM, 24.5% of patients in the rofecoxib group and 26.9% in the placebo group had improvement (absolute difference, -2.4% ; 95% confidence interval for the difference, -14.9% to 10.1% ; $P = 0.74$). In the corpus, the proportion of patients with improvement (regression) in the mean IM score was 4.3% in the rofecoxib group and 2.2% in the placebo group

(absolute difference, 2.1% ; $P = 0.68$). Similarly, there was no significant difference in the proportion of patients with deterioration of IM in the two treatment groups in the antrum (14.9% in the rofecoxib group versus 10.8% in the placebo group; $P = 0.51$) as well as in the corpus (5.3% in the rofecoxib group versus 4.3% in the placebo group; $P = 1.0$). At the end of year 2, 19.1% (95% confidence interval, 11.8-28.6%) in the rofecoxib group and 16.1% (95% confidence interval, 9.3-25.2%) in the placebo group had no IM detected in the stomach ($P = 0.59$). In keeping with IM changes, there was no significant interval changes noted in the atrophy scores between patients treated with rofecoxib or placebo (antrum, $P = 0.49$; corpus, $P = 0.98$).

A subgroup analysis was done to assess for the potential effects of family history of gastric cancer on treatment response. Twenty percent of the patients with a family history of gastric cancer had an improvement in IM after treatment with rofecoxib as compared with 26.6% in those with no family history ($P = 0.61$).

Distribution of IM. As a considerable proportion of patients had histologic improvement at the end of year 2, there was a remarkable change in the distribution of IM with time in both treatment groups (Fig. 3). The proportion of patients with IM in the antrum decreased in both treatment groups (rofecoxib group, 75.7-67%, $P = 0.06$; placebo, 82.1-68.8%, $P = 0.06$). In keeping with this change, the proportion of patients with IM in the corpus decreased in both treatment groups (rofecoxib, 24.3-13.8%, $P = 0.06$; placebo, 18-15.1%, $P = 0.05$). Again, there was no significant difference in the distribution pattern of IM between the two study groups at the end of year 2 ($P = 0.18$).

Changes in apoptotic and proliferative index. We also determined the apoptotic and proliferative index in the antrum of 59 randomly selected patients (30 in the rofecoxib group and 29 in the placebo group) at the end of year 2. These indexes were counted separately for foci with and without IM. As shown in Table 4, there was no significant difference in both variables between the rofecoxib and placebo groups.

Discussion

The chemoprevention of gastric cancer is an important issue in many Asian countries where gastric cancer is prevalent. Despite the strong etiologic link between *H. pylori* and gastric cancer, the benefits of *H. pylori* eradication in preventing gastric cancer or progression of premalignant gastric lesions is suboptimal (4-7). There is a pressing need to identify other promising chemopreventive agents.

This is the first randomized controlled study that evaluated the effects of long-term treatment with a COX-2 inhibitor in patients with gastric IM after *H. pylori* eradication. This study was conducted in a Chinese population with high background gastric cancer incidence (1). In this study, we also recruited first-degree relatives of gastric cancer patients who are at higher risk of developing gastric cancer as well as premalignant gastric lesions (18, 19). We used the updated Sydney classification (14), which is a visual analog scale of severity, for the grading of histologic variables. Although this grading system has its limitations, this is thus far the most widely accepted grading system for gastritis and advanced gastric lesions such as IM. To overcome the possible sampling error of gastric IM, we took multiple gastric biopsies from the antrum and corpus of the

stomach according to a standard protocol. These biopsy sites cover the regions in which IM is usually more severe and extensive, as found in the Chinese population (20). In fact, the number of biopsies taken from this study was higher than all previously published studies on the chemoprevention of gastric cancer (4–6).

Despite the enthusiasm of using COX-2 inhibitor as a potential chemopreventive agent (9, 10), our results showed that there was no apparent benefit of using rofecoxib in regressing gastric IM. There was not even a trend favoring rofecoxib in all variables measured: the severity of IM, the proportion of patients with IM regression, the proportion of patients with disappearance of IM, and the distribution pattern of IM. Moreover, there was no significant difference in cell proliferation and apoptotic indexes between the two treatment groups.

Our findings are in keeping with a recent report on chemoprevention of esophageal squamous cell cancer with another COX-2 inhibitor, celecoxib (21). In that study, treatment with celecoxib for up to 10 months had no effect on histologic grade of esophageal dysplasia. However, preliminary results of the Adenomatous Polyp Prevention on Vioxx trial showed that the long-term use of rofecoxib was associated with a significantly reduced rate of colorectal adenoma recurrence (22). Although the dosage of rofecoxib used in the

Adenomatous Polyp Prevention on Vioxx study and the current study is identical, there are several fundamental differences between these two studies. The Adenomatous Polyp Prevention on Vioxx trial recruited patients with confirmed colorectal adenoma but all lesions were removed prior to the entry into the study. Hence, there was no residual premalignant lesion in the colon and all patients could be regarded to have normal colon on entry. In contrast, we recruited patients with gastric IM, which would inevitably persist in the stomach throughout the study period. Hence, these patients had abnormal gastric histology on entry, which may account for the disparate results between the two studies.

Intuitively, the apparent lack of effect of COX-2 inhibitors in regressing gastric IM and esophageal dysplasia (21) may suggest that these agents are more effective in preventing the development rather than regressing premalignant lesions. Although there is considerable difference between dysplasia and metaplasia, IM is thus far the best surrogate histologic marker to identify individuals at high risk of gastric cancer development (2, 8). To support this, we have previously shown that many molecular changes found in gastric cancer, including COX-2 overexpression and disrupted cell kinetic changes, are readily detected in IM (11, 23–25). Nonetheless, there may be a need to reexamine the use of IM as a surrogate end point in gastric chemoprevention study (26).

Table 3. Severity of IM and GA at baseline, year 1, and year 2 of follow-up

	Antrum			Corpus		
	Baseline	Year 1	Year 2	Baseline	Year 1	Year 2
IM						
Rofecoxib						
Mean ± SD	0.86 ± 0.72	0.71 ± 0.76	0.72 ± 0.67	0.17 ± 0.38	0.11 ± 0.27	0.10 ± 0.28
Median (IQR)	0.75 (0-3)	0.5 (0-1.19)*	0.63 (0-1)	0 (0-0)	0 (0-0)	0 (0-0)
Placebo						
Mean ± SD	0.96 ± 0.74	0.72 ± 0.73	0.71 ± 0.76	0.13 ± 0.42	0.12 ± 0.36	0.11 ± 0.43
Median (IQR)	0.75 (0.5-1.5)	0.5 (0-1.25)†	0.5 (0-1)‡	0 (0-0)	0 (0-0)	0 (0-0)
P§	0.25	0.77	0.71	0.20	0.28	0.67
GA						
Rofecoxib						
Mean ± SD	0.44 ± 0.57	0.28 ± 0.45	0.27 ± 0.44	0.11 ± 0.42	0.07 ± 0.29	0.02 ± 0.15
Median (IQR)	0 (0-1)	0 (0-1)¶	0 (0-1)	0 (0-0)	0 (0-0)	0 (0-0)
Placebo						
Mean ± SD	0.42 ± 0.55	0.29 ± 0.5	0.37 ± 0.59	0.11 ± 0.37	0.07 ± 0.25	0.08 ± 0.27
Median (IQR)	0 (0-1)	0 (0-1)¶	0 (0-1)**	0 (0-0)	0 (0-0)	0 (0-0)
P§	0.89	0.93	0.33	0.8	0.85	0.09

Abbreviation: IQR, interquartile range.

*Mann-Whitney *U* test (rofecoxib versus placebo).

†*P* = 0.02 versus baseline, Wilcoxon signed ranks test.

‡*P* < 0.001 versus baseline, Wilcoxon signed ranks test.

§*P* = 0.004 versus baseline, Wilcoxon signed ranks test.

¶*P* = 0.008 versus baseline, Wilcoxon signed ranks test.

¶*P* = 0.043 versus baseline, Wilcoxon signed ranks test.

***P* = 0.011 versus baseline, Wilcoxon signed ranks test.

In the Adenomatous Polyp Prevention on Vioxx trial, treatment with rofecoxib had a progressive reduction in adenoma number and size, which was obvious even at 12 months. In this study, there was an initial reduction in the severity of IM and GA at year 1 when compared with baseline, particularly in the antrum, in all study subjects (Table 3). However, there was no further reduction from year 1 to year 2. The early improvement in IM and GA, which were noticed in both rofecoxib- and placebo-treated groups, may be related to the effect of *H. pylori* eradication. In the absence of proper control group, this improvement may be falsely attributed to be the beneficial effects of COX-2 inhibitor. The overall proportion of patients with regression of IM at the end of year 2 was ~25% in this study. This figure was comparable to the long-term effects of *H. pylori* eradication in previous chemoprevention trials (15-20%; refs. 4, 5).

This study was terminated early based on predefined criteria of lack of efficacy. Although cancer chemoprevention is a usually a chronic process, there is a possibility that longer duration of treatment is needed. At the end of 2 years, fewer patients in the rofecoxib group had improvement in antral IM and even the upper limit of the difference between the two treatment groups decreased to <11%. The results of this interim analysis therefore may not support the continuation of rofecoxib for 3 more years to achieve a meaningful regression of IM. Apart from efficacy, other factors, including the cost of treatment, potential adverse effects related to

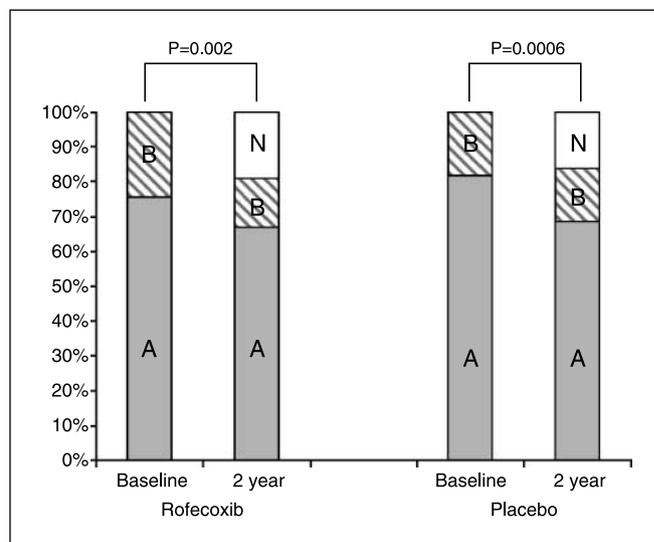


Fig. 3. The distribution of IM at baseline and at the end of year 2. A, antrum IM only; B, body IM; N, no IM detected. Rofecoxib (P = 0.002), placebo (P = 0.0006).

treatment, and compliance issues, have to be considered when determining the optimal duration of chemoprevention trials. Long-term use of COX-2 inhibitors is expensive when compared with a single course of anti-*H. pylori* treatment or vitamin supplementation (4-6). The long-term use of COX-2 inhibitors, rofecoxib, or high-dose celecoxib, was recently shown to be associated with a significantly higher risk of cardiovascular adverse events, particularly thrombotic events (27, 28). For rofecoxib, the increase in cardiovascular adverse events begin to surface at 18 months posttreatment and the incidence is estimated to be ~1.5 events per 100 patient-years, which is 2-fold higher than those receiving placebo (28). In our study, only one patient in the rofecoxib group developed transient ischemic attack (0.5 events/100 patient-years), whereas two patients in the placebo group developed coronary thrombotic events (1 event/100 patient-years). Although the results from this study did not show a higher vascular complication in patients taking rofecoxib, use of rofecoxib was associated with renal failure and heart failure in two patients. In light of the recent safety data, long-term use of COX-2 inhibitor for chemoprevention, particularly rofecoxib, may not be advisable.

In conclusion, treatment with rofecoxib for 2 years failed to regress gastric IM in patients after eradication of *H. pylori*.

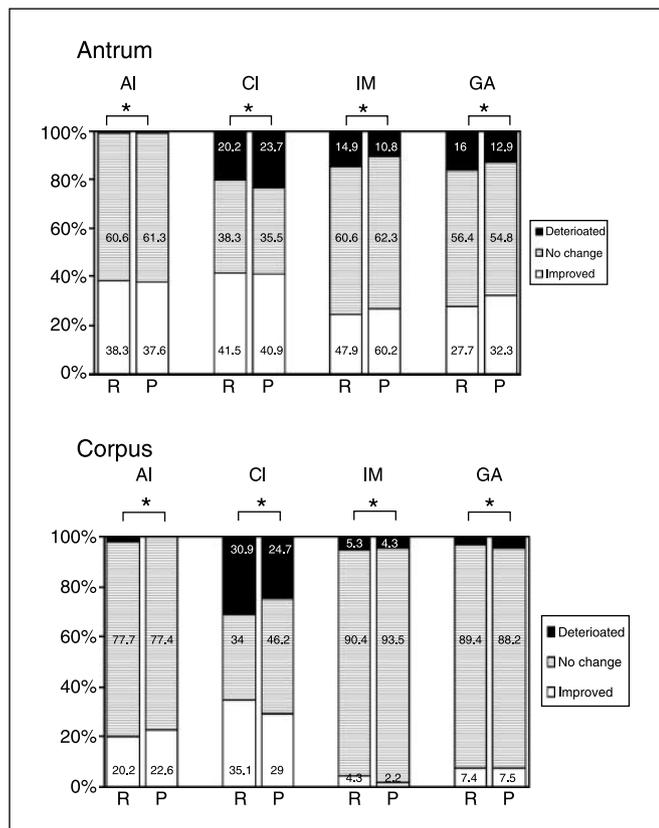


Fig. 2. Proportion of patients with changes in gastric histology at year 2 when compared with baseline. R, rofecoxib; P, placebo; AI, acute polymorphonuclear infiltrates; CI, chronic mononuclear infiltrates; IM, intestinal metaplasia; GA, glandular atrophy. *, P > 0.05.

Table 4. Changes in apoptotic and proliferative index in gastric epithelium with and without IM at the end of year 2

	Rofecoxib	Placebo	P
Apoptotic index			
Nonmetaplastic	0.34 ± 0.14	0.42 ± 0.23	0.14
IM	0.74 ± 0.44	0.64 ± 0.41	0.44
Proliferative index			
Nonmetaplastic	24.6 ± 7.4	26.8 ± 7.6	0.28
IM	44.0 ± 12.0	48.7 ± 15.7	0.25

Although our findings may cast doubt on the reversibility of gastric IM by COX-2 inhibition, we cannot totally exclude the potential beneficial effects of COX-2 inhibitors in other stages of gastric carcinogenesis. Further studies are still needed to

establish the role of COX-2 inhibitors on the prevention of development of gastric IM in individuals without preneoplastic gastric lesions or in treating patients with dysplasia or even gastric cancer.

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