COMPARISON OF UPPER GASTROINTESTINAL TOXICITY OF ROFECOXIB AND NAPROXEN IN PATIENTS WITH RHEUMATOID ARTHRITIS

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ABSTRACT

Background Each year, clinical upper gastrointestinal events occur in 2 to 4 percent of patients who are taking nonselective nonsteroidal antiinflammatory drugs (NSAIDs). We assessed whether rofecoxib, a selective inhibitor of cyclooxygenase-2, would be associated with a lower incidence of clinically important upper gastrointestinal events than is the nonselective NSAID naproxen among patients with rheumatoid arthritis.

Methods We randomly assigned 8076 patients who were at least 50 years of age (or at least 40 years of age and receiving long-term glucocorticoid therapy) and who had rheumatoid arthritis to receive either 50 mg of rofecoxib daily or 500 mg of naproxen twice daily. The primary end point was confirmed clinical upper gastrointestinal events (gastroduodenal perforation or obstruction, upper gastrointestinal bleeding, and symptomatic gastroduodenal ulcers).

Results Rofecoxib and naproxen had similar efficacy against rheumatoid arthritis. During a median follow-up of 9.0 months, 2.1 confirmed gastrointestinal events per 100 patient-years occurred with rofecoxib, as compared with 4.5 per 100 patient-years with naproxen (relative risk, 0.5; 95 percent confidence interval, 0.3 to 0.6; $P<0.001$). The respective rates of complicated confirmed events (perforation, obstruction, and severe upper gastrointestinal bleeding) were 0.6 per 100 patient-years and 1.4 per 100 patient-years (relative risk, 0.4; 95 percent confidence interval, 0.2 to 0.8; $P=0.005$). The incidence of myocardial infarction was lower among patients in the naproxen group than among those in the rofecoxib group (0.1 percent vs. 0.4 percent; relative risk, 0.2; 95 percent confidence interval, 0.1 to 0.7); the overall mortality rate and the rate of death from cardiovascular causes were similar in the two groups.

Conclusions In patients with rheumatoid arthritis, treatment with rofecoxib, a selective inhibitor of cyclooxygenase-2, is associated with significantly fewer clinically important upper gastrointestinal events than treatment with naproxen, a nonselective inhibitor. (N Engl J Med 2000;343:1520-8.)

NONSTEROIDAL antiinflammatory drugs (NSAIDs) are among the most commonly used medications in the world.[1] A major factor limiting their use is gastrointestinal toxicity. Although endoscopic studies reveal that gastric or duodenal ulcers develop in 15 to 30 percent of patients who regularly take NSAIDs,[2] the chief concern is clinically important gastrointestinal problems, such as bleeding. It has been estimated that more than 100,000 patients are hospitalized and 16,500 die each year in the United States as a result of NSAID-associated gastrointestinal events.[3,4]

Most NSAIDs inhibit both cyclooxygenase-1 and cyclooxygenase-2, isoenzymes involved in the synthesis of prostaglandins.[5] Cyclooxygenase-1 is constitutively expressed and generates prostanoids involved in the maintenance of the integrity of gastrointestinal mucosa and platelet aggregation,[6] whereas at sites of inflammation, cyclooxygenase-2 is induced to generate prostaglandins that mediate inflammation and pain.[7] The antiinflammatory effects of nonselective NSAIDs (those that inhibit both cyclooxygenase-1 and cyclooxygenase-2) therefore appear to be mediated through the inhibition of cyclooxygenase-2,[8] whereas their harmful effects in the gastrointestinal tract as well as their antiplatelet effects are believed to occur primarily through the inhibition of cyclooxygenase-1.[5]

Agents that selectively inhibit cyclooxygenase-2 have antiinflammatory and analgesic effects that are simi-

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lar to those of nonselective NSAIDs,[9-12] but they induced significantly fewer ulcers in endoscopic trials.[12-15] Whether such a decrease in the number of ulcers translates into a similar decrease in the number of clinical gastrointestinal events is a matter of controversy. We performed a prospective, randomized, double-blind comparison of rofecoxib and naproxen in more than 8000 patients with rheumatoid arthritis.

METHODS

Study Population

Patients with rheumatoid arthritis who were at least 50 years old (or at least 40 years old and receiving long-term glucocorticoid therapy) and who were expected to require NSAIDs for at least one year were eligible. Patients were excluded if they had a history of another type of inflammatory arthritis, upper gastrointestinal surgery, or inflammatory bowel disease; an estimated creatinine clearance of 30 ml or less per minute; a positive test for fecal occult blood (this test was performed at base line in all patients); an unstable medical condition; a history of cancer or alcohol or drug abuse in the five years before the study; a history of cerebrovascular events in the two years before the study; or a history of myocardial infarction or coronary bypass in the year before the study. Patients with morbid obesity and those who required or who had been receiving treatment with aspirin, ticlopidine, anticoagulants, cyclosporine, misoprostol, sucralfate, or proton-pump inhibitors or treatment with histamine H_2–receptor antagonists in prescription-strength doses were also excluded from the study. Patients enrolled in the study were not thought to require the use of these agents by their treating physicians.

Study Design

The study was conducted at 301 centers in 22 countries. Three to 14 days after discontinuing NSAIDs, eligible patients were randomly assigned to receive either 50 mg of rofecoxib (Vioxx, Merck, Whitehouse Station, N.J.) once daily or 500 mg of naproxen (Novopharm Biotech, Toronto) twice daily. The groups were stratified according to the presence or absence of a history of gastroduodenal ulcer, upper gastrointestinal bleeding, and gastroduodenal perforation. Blinding was achieved through the use of a matching placebo for each study medication.

Patients were permitted to take acetaminophen, non-NSAID analgesic medications, glucocorticoids, and disease-modifying drugs (e.g., methotrexate) to control their rheumatoid arthritis. Patients were also allowed to take antacids and H_2-receptor antagonists in the following maximal doses: ranitidine, 150 mg daily; famotidine, 20 mg daily; cimetidine, 400 mg daily; and nizatidine, 150 mg daily. Nonstudy NSAIDs were not allowed. After randomization, the patients returned to the clinic at six weeks and at four months and every four months thereafter until the end of the study. Patients were contacted by telephone at week 10 and every four months thereafter. Compliance was assessed by pill counts at clinic visits and by questioning of patients during the scheduled telephone calls. Serum was obtained from all patients for *Helicobacter pylori* testing (HM-CAP, Enteric Products, Stonybrook, N.Y.). Investigators were not informed of the results of these tests during the study.

The institutional review board or ethics review committee at each center approved the protocol, and all patients gave written informed consent. A steering committee oversaw the study design, conduct of the trial, analyses of data, and drafting of this report. This committee was composed of 14 members, 2 of whom were employees of the sponsoring pharmaceutical company. An independent data and safety monitoring board monitored the patients' safety. An independent, external (end-point) committee whose members were unaware of the patients' treatment assignments reviewed the data to determine which patients had reached the study end points. Because highly selective cyclooxygenase-2 inhibitors do not inhibit platelet aggregation, which is mediated by cyclooxygenase-1, there was a possibility that the incidence of thrombotic cardiovascular events would be lower among patients treated with nonselective cyclooxygenase inhibitors than among those treated with cyclooxygenase-2–selective inhibitors. Therefore, cardiovascular events were also assessed for a future meta-analysis by independent committees whose members were unaware of the patients' treatment assignments. A separate analysis of these events, however, was not specified in the study design.

Study End Points

Patients who had potential clinical upper gastrointestinal events were evaluated and treated according to the standard practice of the physicians who were caring for them. Patients who stopped taking the study medication before the study ended were followed until the end of the study to determine whether an upper gastrointestinal event had occurred. Only events that were confirmed by the end-point committee according to prespecified criteria (Table 1) and that occurred during treatment or within 14 days after the discontinuation of treatment were included in the primary analysis.

In addition, the protocol called for the analysis of all episodes of gastrointestinal bleeding, including confirmed and unconfirmed episodes of upper gastrointestinal bleeding, and bleeding from a site beyond the duodenum that resulted in hospitalization, discontinuation of treatment, or a decrease in the hemoglobin level of at least 2 g per deciliter.

Assessment of Efficacy

For each patient both the investigator and the patient answered a Global Assessment of Disease Activity question at base line (after the discontinuation of prestudy NSAIDs), 6 weeks, 4 months, and 12 months and at the end of the study or when treatment was discontinued. The score can range from 0 ("very well") to 4 ("very poor"), and higher scores indicate more disease activity. The Modified Health Assessment questionnaire was administered only to patients enrolled at centers in the United States at base line, at six weeks, and at the end of the study or when treatment was discontinued. This questionnaire evaluates the extent of functional disability in eight types of tasks performed on a daily basis. The level of effort required to perform each task is assessed on a 4-point scale on which a score of 0 indicates no difficulty in performing the task and a score of 3 indicates an inability to perform the task.[16] Higher scores indicate more severe disability.

Statistical Analysis

The primary hypothesis was that the risk of confirmed upper gastrointestinal events (gastroduodenal perforation or obstruction, upper gastrointestinal bleeding, and symptomatic gastroduodenal ulcers) would be lower among patients who were taking rofecoxib than among those who were taking naproxen. Secondary hypotheses were that the risk of confirmed complicated events (perforation, obstruction, and severe upper gastrointestinal bleeding) and the risk of both confirmed and unconfirmed upper gastrointestinal events would be lower among patients who were taking rofecoxib.

Cox proportional-hazards analysis was used to compare the effect of treatment; the presence or absence of a history of gastrointestinal events was a stratification factor in the analysis.[17,18] The scores for the Global Assessment of Disease Activity question and Modified Health Assessment questionnaire were analyzed in terms of the mean change from base line during the treatment period. The primary population for analysis comprised all randomized patients. Subgroup analyses were conducted with use of Cox regression analysis.[17,18] Interactions between treatments and subgroups were assessed to determine whether the effect of rofecoxib as compared with that of naproxen was consistent in the subgroups. We assessed data on general safety by evaluating 95 percent confidence intervals of the differences in the proportions of the treatment groups with each adverse event.[19] All statistical tests were two-sided.

TABLE 1. CRITERIA FOR GASTROINTESTINAL EVENTS.

EVENT	CRITERIA REQUIRED FOR CONFIRMATION OF EVENT
Perforation due to nonmalignant gastric or duodenal ulcer	Evidence of perforation on endoscopy, at surgery, on radiography (evidence of free intraabdominal air or extravasation of contrast medium), or at autopsy
Obstruction due to gastric or duodenal ulcer	Occurrence of nausea and vomiting ≥24 hours postprandially and evidence of narrowing of distal portion of stomach or duodenum as a result of a nonmalignant ulcer on endoscopy, at surgery, on radiography, or at autopsy
Upper gastrointestinal bleeding	Episode of hematemesis or aspiration of bloody gastric fluid witnessed by health care provider; episode of melena witnessed by health care provider; evidence of active bleeding on endoscopy, at surgery, or on angiography; positive test for fecal occult blood with documented upper gastrointestinal lesion judged to be the source and associated with either clinically significant bleeding or decrease in volume* or evidence of visible vessel, clot, or pigmented spot on ulcer at endoscopy; or episode of hematemesis or melena reported by patient with upper gastrointestinal lesion judged to be the source and associated with either clinically significant bleeding or decrease in volume* or evidence of visible vessel, clot, or pigmented spot on ulcer at endoscopy
Gastric or duodenal ulcer	Evidence of gastric or duodenal ulcer on endoscopy, at surgery, on contrast-enhanced radiography of the upper gastrointestinal tract, or at autopsy

*A decrease in volume was defined by the finding of a decrease in hemoglobin of at least 2 g per deciliter; by the finding of an orthostatically induced change in pulse of more than 20, change in systolic blood pressure of more than 20 mm Hg, or change in diastolic blood pressure of more than 10 mm Hg; by the finding of other evidence of a clinically significant reduction in circulatory volume (e.g., clinically significant hypotension that is corrected by volume replacement); or by the need for blood transfusion.

RESULTS

Characteristics of the Patients

Between January 1999 and July 1999, we screened 9539 patients and enrolled 8076; 4047 were randomly assigned to receive rofecoxib, and 4029 to receive naproxen. The major reasons for exclusion were a contraindication to prolonged NSAID therapy (in the case of 246 patients), a positive test for fecal occult blood (203 patients), and a failure to meet inclusion criteria (355 patients). The median follow-up was 9.0 months in both treatment groups (range, 0.5 to 13). A total of 5742 patients (71.1 percent) continued to take their assigned medication until the end of the study. Rates of discontinuation were similar in the two groups: 29.3 percent in the rofecoxib group (16.4 percent because of adverse events, 6.3 percent because of a lack of efficacy, and 6.6 percent for other reasons) and 28.5 percent in the naproxen group (16.1 percent because of adverse events, 6.5 percent because of a lack of efficacy, and 5.9 percent for other reasons). Ninety-nine percent of the patients in both groups took their medication on at least 75 percent of the study days. The base-line characteristics were similar in the two groups (Table 2).

Efficacy

Rofecoxib and naproxen had similar efficacy against rheumatoid arthritis (Table 3). In addition, the rates of discontinuation of treatment owing to a lack of efficacy were low in both groups (6.3 percent in the rofecoxib group and 6.5 percent in the naproxen group).

Adverse Gastrointestinal Events

Confirmed upper gastrointestinal events occurred in 177 patients. In 53 of these patients the event was complicated. An additional 13 patients had events that were reported by investigators but that were judged by the end-point committee to be unconfirmed.

The time to the development of a confirmed upper gastrointestinal event is shown in Figure 1. The rates per 100 patient-years and incidences of the prespecified clinical events are shown in Tables 4 and 5, respectively. The relative risk of confirmed upper gastrointestinal events for patients in the rofecoxib group as compared with those in the naproxen group was 0.5 (95 percent confidence interval, 0.3 to 0.6; $P<0.001$), whereas the relative risk of complicated confirmed upper gastrointestinal events was 0.4 (95 percent confidence interval, 0.2 to 0.8; $P=0.005$). The relative risk of complicated upper gastrointestinal bleeding for patients in the rofecoxib group as compared with those in the naproxen group was 0.4 (95 percent confidence interval, 0.2 to 0.7; $P=0.004$), whereas the relative risk of bleeding beyond the duodenum was 0.5 (95 percent confidence interval, 0.2 to 0.9; $P=0.03$).

A per-protocol analysis of the 7925 patients without substantial protocol violations demonstrated relative risks of confirmed upper gastrointestinal events and complicated confirmed events of 0.4 (95 percent confidence interval, 0.3 to 0.6; $P<0.001$) and 0.4 (95 percent confidence interval, 0.2 to 0.7; $P=0.003$), respectively. The results of an intention-to-treat analysis of all confirmed upper gastrointestinal

TABLE 2. BASE-LINE CHARACTERISTICS OF THE PATIENTS.*

CHARACTERISTIC	ROFECOXIB GROUP (N=4047)	NAPROXEN GROUP (N=4029)
Age — yr	58±9	58±10
Female sex — no. (%)	3223 (79.6)	3215 (79.8)
Race or ethnic group — no. (%)		
White	2761 (68.2)	2750 (68.3)
Black	207 (5.1)	202 (5.0)
Asian	101 (2.5)	85 (2.1)
Hispanic	501 (12.4)	516 (12.8)
Other	477 (11.8)	476 (11.8)
Duration of disease — no. (%)		
Unknown	3 (0.1)	6 (0.1)
<2 yr	430 (10.6)	455 (11.3)
2–10 yr	1991 (49.2)	1996 (49.5)
>10 yr	1623 (40.1)	1572 (39.0)
Positive test for rheumatoid factor — no. (%)	2946 (72.8)	2967 (73.6)
Prior use of NSAIDs — no. (%)	3321 (82.1)	3331 (82.7)
Treatment for rheumatoid arthritis — no. (%)		
Glucocorticoids	2260 (55.8)	2263 (56.2)
Methotrexate	2263 (55.9)	2269 (56.3)
Other disease-modifying drugs	1847 (45.6)	1826 (45.3)
Low-dose H_2-receptor antagonists — no. (%)†	365 (9.0)	335 (8.3)
History of clinical gastrointestinal events	314 (7.7)	316 (7.8)
Global Disease Activity score‡		
Patient's assessment	2.0±0.9	2.0±0.9
Investigator's assessment	1.9±0.8	1.9±0.8
American College of Rheumatology functional class — no. (%)§		
I	881 (21.8)	830 (20.6)
II	2160 (53.4)	2199 (54.6)
III	928 (22.9)	932 (23.1)
IV	78 (1.9)	68 (1.7)

*Plus–minus values are means ±SD. NSAIDs denotes nonselective nonsteroidal antiinflammatory drugs.

†A low dose was defined as a maximal daily dose of 150 mg of ranitidine, 20 mg of famotidine, 400 mg of cimetidine, and 150 mg of nizatidine.

‡Scores can range from 0 ("very well") to 4 ("very poor"). Higher scores indicate more disease activity.

§According to the American College of Rheumatology's system of classification, functional class I indicates complete ability to perform usual activities of daily living, and class IV indicates limited ability to perform usual activities of daily living.

events throughout the study, including those that occurred at any time after the discontinuation of treatment, were similar and remained statistically significant (data not shown).

Subgroup analyses showed the following relative risks of clinical gastrointestinal events among the patients in the rofecoxib group as compared with those in the naproxen group: patients with no prior gastrointestinal events (relative risk, 0.5; 95 percent confidence interval, 0.3 to 0.7), patients with prior gastrointestinal events (relative risk, 0.4; 95 percent confidence interval, 0.2 to 0.8), patients with no glucocorticoid therapy at base line (relative risk, 0.7; 95 percent confidence interval, 0.4 to 1.2), and patients with glucocorticoid therapy at base line (relative risk, 0.4; 95 percent confidence interval, 0.2 to 0.6). The relative risks in these subgroups and the other prespecified subgroups (defined according to sex, race or ethnic group, and location of study center) were not significantly different, indicating that there was no significant interaction between the treatments and the subgroups.

Treatment with rofecoxib was associated with a significantly lower incidence of clinical gastrointestinal events regardless of the results of serologic tests for *H. pylori*. However, the relative risks of clinical events among *H. pylori*–negative patients and *H. pylori*–positive patients were significantly different (P=0.04, data not shown). Finally, the relative risk of gastrointestinal events remained significantly lower (0.1; 95 percent confidence interval, 0.02 to 1.0) in the rofecoxib group than in the naproxen group even in a subgroup at very low risk (i.e., patients who were younger than 65 years, who were negative for *H. pylori*, who had no history of a clinical gastrointestinal event, and who were not taking glucocorticoids at base line).

General Safety

The safety of both rofecoxib and naproxen was similar to that reported in previous studies.[20,21] The mortality rate was 0.5 percent in the rofecoxib group and 0.4 percent in the naproxen group. The rate of death from cardiovascular causes was 0.2 percent in both groups. Ischemic cerebrovascular events occurred in 0.2 percent of the patients in each group. Myocardial infarctions were less common in the naproxen group than in the rofecoxib group (0.1 percent vs. 0.4 percent; 95 percent confidence interval for the difference, 0.1 to 0.6 percent; relative risk, 0.2; 95 percent confidence interval, 0.1 to 0.7). Four percent of the study subjects met the criteria of the Food and Drug Administration (FDA) for the use of aspirin for secondary cardiovascular prophylaxis (presence of a history of myocardial infarction, angina, cerebrovascular accident, transient ischemic attack, angioplasty, or coronary bypass)[22] but were not taking low-dose aspirin therapy. These patients accounted for 38 percent of the patients in the study who had myocardial infarctions. In the other patients the difference in the rate of myocardial infarction between groups was not significant (0.2 percent in the rofecoxib group and 0.1 percent in the naproxen group). When the data showing a reduction in the rate of myocardial infarction in the naproxen group became available after the completion of this trial, Merck, the manufacturer of rofecoxib, notified all investigators in ongoing studies of a change in the exclusion criteria to allow patients to use low-dose aspirin. There was no association between hypertension and myocardial infarction; only a single patient (in the rofecoxib group) had both hypertension and a myocardial infarction as adverse events.

TABLE 3. EFFECTIVENESS OF ROFECOXIB AND NAPROXEN FOR RHEUMATOID ARTHRITIS.*

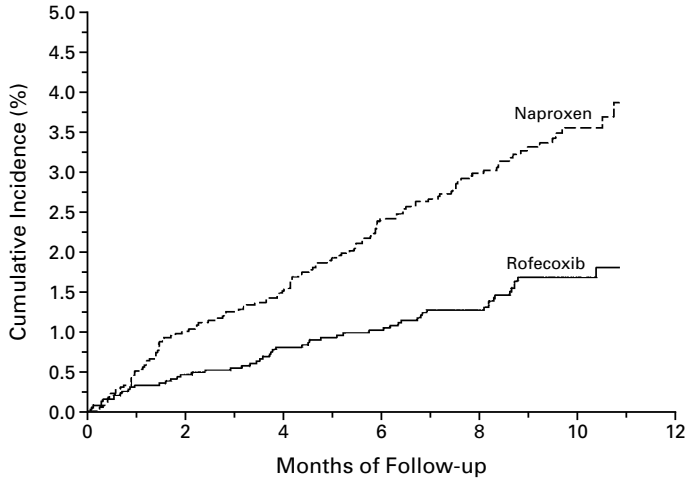
VARIABLE	BASE-LINE SCORE		CHANGE IN SCORE DURING TREATMENT		
	ROFECOXIB GROUP	NAPROXEN GROUP	ROFECOXIB GROUP	NAPROXEN GROUP	LEAST-SQUARES MEAN DIFFERENCE BETWEEN GROUPS (95% CI)†
Global Disease Activity score‡					
Patient's assessment	1.96±0.93	1.99±0.94	−0.51±0.93	−0.53±0.94	0.00 (−0.03 to 0.03)
Investigator's assessment	1.85±0.80	1.87±0.78	−0.49±0.84	−0.52±0.85	0.01 (−0.02 to 0.04)
Modified Health Assessment score§	0.59±0.49	0.59±0.49	−0.11±0.37	−0.12±0.36	0.01 (−0.01 to 0.04)

*Plus–minus values are means ±SD.

†The values were calculated by analysis of variance in a model that included treatment assignment and presence or absence of a history of gastrointestinal events and the base-line value as covariates. CI denotes confidence interval.

‡Scores can range from 0 ("very well") to 4 ("very poor"). Higher scores indicate more disease activity.

§Scores can range from 0 (no difficulty in performing a task) to 3 (unable to perform the task). Higher scores indicate more severe disability. The questionnaire was administered only to patients enrolled at centers in the United States (1735 in the rofecoxib group and 1732 in the naproxen group).



NO. AT RISK

Rofecoxib	4047	3641	3402	3180	2806	1073	533
Naproxen	4029	3644	3389	3163	2796	1071	513

Figure 1. Cumulative Incidence of the Primary End Point of a Confirmed Upper Gastrointestinal Event among All Randomized Patients.

The most common adverse events leading to discontinuation of treatment, excluding the gastrointestinal end points, were dyspepsia, abdominal pain, epigastric discomfort, nausea, and heartburn. In the rofecoxib group, significantly fewer patients discontinued treatment as a result of any one of these five upper gastrointestinal symptoms than in the naproxen group (3.5 percent vs. 4.9 percent). The rates of discontinuation for any gastrointestinal events, including gastrointestinal end points, were also significantly lower in the rofecoxib group than in the naproxen group (7.8 percent vs. 10.6 percent). The incidence of adverse effects related to renal function was low and was similar in the two groups (1.2 percent in the ro-

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