STOMACH

Incidence of gastroduodenal ulcers in patients with rheumatoid arthritis after 12 weeks of rofecoxib, naproxen, or placebo: a multicentre, randomised, double blind study

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Gut 2003;**52**:820–826

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Accepted for publication 17 December 2002

Background: Previous studies in patients with osteoarthritis have suggested that the selective cyclooxygenase (COX)-2 inhibitor rofecoxib results in less gastrointestinal damage than non-selective non-steroidal antiinflammatory drugs (NSAIDs). This study compared the incidence of endoscopically detected gastroduodenal ulcers in rheumatoid arthritis patients treated with rofecoxib or a non-selective NSAID.

Methods: In this multicentre, randomised, double blind, 12 week study, patients with rheumatoid arthritis were allocated to rofecoxib 50 mg once daily (n=219), naproxen 500 mg twice daily (n=220), or placebo (n=221). Endoscopy was performed at baseline and at six and 12 weeks. Life-table analysis and log rank tests were used to analyse the incidence of gastroduodenal ulcers ⩾3 mm. Gastric or duodenal ulcers ⩾5 mm and erosions were also evaluated as secondary end points. Tolerability was assessed by adverse events.

Results: The cumulative incidence of ulcers ⩾3 mm at 12 weeks was significantly higher in patients on naproxen (25.5%) than in patients receiving rofecoxib (6.8%; difference 18.7% (95% confidence interval (CI) 11.7%, 25.7%); p<0.001) or placebo (2.9%; difference 22.6% (95% CI 16.1%, 29.1%); p<0.001). The difference between rofecoxib (6.8%) and placebo (2.9%) did not reach statistical significance (p=0.066). Results were similar for ulcers ⩾5 mm and for mean changes from baseline in the number of gastroduodenal erosions. The overall incidence of clinical adverse events was similar among treatment groups (61% of patients on placebo, 62% in patients on rofecoxib, and 66% in patients on naproxen).

Conclusions: Rofecoxib 50 mg daily (twice the dose recommended for this patient population) resulted in a lower incidence of endoscopically detected gastroduodenal ulcers and erosions than treatment with naproxen 500 mg twice daily.

The potential of non-steroidal antiinflammatory drugs (NSAIDs) to cause gastrointestinal toxicity is well known, with an estimated 100 000 hospitalisations occurring annually in the USA due to NSAID related serious gastrointestinal complications.[1] Chronic use of NSAIDs puts patients at risk for perforations, ulcers, or haemorrhage of the gastroduodenal mucosa.[2 3] It has been postulated that these deleterious effects are a result of inhibition of cyclooxygenase (COX)-1, the isoform of the enzyme cyclooxygenase believed to catalyse the synthesis of gastroprotective prostaglandins.[3] By contrast, NSAIDs are thought to achieve their anti-inflammatory or analgesic efficacy by inhibition of COX-2, the isoform involved in inflammatory responses.[3] The lack of selectivity of traditional NSAIDs for a particular COX isoform is a likely explanation for the apparent inseparability of the toxic effect of COX-1 inhibition and the therapeutic effect of COX-2 inhibition seen with these agents. This has led to the development of COX-2 selective inhibitors, based on the premise that preferential inhibition of the isoform relevant to inflammation (COX-2) would be expected to convey the same therapeutic benefit of traditional NSAIDs with significantly less gastrointestinal toxicity due to inhibition of COX-1.[3]

Current knowledge of the COX-2 inhibitor rofecoxib has been consistent with the COX-2 hypothesis, in that rofecoxib is not only as effective as non-selective NSAIDs but is also well tolerated both in general and in terms of the gastrointestinal system.[4–8] Specifically, while naproxen 500 mg twice daily caused a 70% reduction in gastric mucosal prostaglandin synthesis, rofecoxib 25 mg and 50 mg had no such effect.[9 10] Similarly, faecal blood loss and intestinal permeability, both thought to be useful markers of the potential of an NSAID to cause clinically significant gastrointestinal toxicity,[11 12] were increased in healthy subjects who received indomethacin 150 mg or ibuprofen 250 mg, but not in subjects receiving rofecoxib 25 mg or 50 mg.[13 14]

Endoscopic evaluation of the effect of rofecoxib on the gastrointestinal mucosa has further demonstrated its favourable gastrointestinal safety profile in comparison with non-selective NSAIDs. In healthy subjects treated for seven days, ibuprofen 2400 mg and aspirin 2600 mg were each associated with an increased incidence of erosions in healthy subjects in comparison with placebo, whereas rofecoxib 250 mg (a supratherapeutic dose) given daily for seven days was not.[15] Consistent with these results, two endoscopy studies in more than 1500 osteoarthritis (OA) patients over the age of 50 years showed that the incidence of ulcers over three months in patients receiving daily rofecoxib 25 mg or 50 mg was similar to that in patients on placebo and less than that in patients on

Abbreviations: COX, cyclooxygenase; NSAIDs, non-steroidal anti-inflammatory drugs; OA, osteoarthritis; PUBs, gastrointestinal perforations, ulcers, or bleeding episodes; RA, rheumatoid arthritis.

ibuprofen 2400 mg.[16 17] Moreover, the clinical relevance of these endoscopic findings was demonstrated by an analysis of the results of eight phase II/III studies involving over 5400 OA patients.[18] In this analysis, rofecoxib resulted in a significantly lower incidence of gastrointestinal perforations, ulcers, and bleeding episodes (PUBs) compared with non-selective NSAIDs.[18]

In addition to their role in the treatment of OA and pain, NSAIDs are also an important component of treatment for rheumatoid arthritis (RA). Because high and/or chronic dosing with NSAIDs, as well as concomitant use of corticosteroids, may put RA patients at greater risk for upper gastrointestinal ulcers compared with placebo, the safety of rofecoxib has also been scrutinised in this patient population.[19–23] A large scale outcomes study of rofecoxib in RA patients (the VIGOR trial) showed that rofecoxib 50 mg daily was associated with significantly fewer upper gastrointestinal events (symptomatic ulcers, perforations, bleeds, and obstructions) than naproxen 500 mg twice daily, results similar to those observed in OA patients.[24] An endoscopy study was conducted to examine further the gastrointestinal safety profile of rofecoxib compared with that of NSAIDs in RA patients.

METHODS

Study population

All patients participating in the study gave written informed consent and the study was conducted in conformance with applicable country or local ethics requirements. The study was conducted at 48 sites in 18 countries. Patients between the ages of 21 and 85 years were enrolled, with a confirmed clinical diagnosis of RA and a requirement of at least three months of NSAID therapy. Patients were excluded if they had an oesophageal, gastric, or duodenal ulcer, pyloric obstruction, or erosive oesophagitis at baseline endoscopy.

Patients were also excluded if they had any of the following: creatinine level >2.0 mg/dl; creatinine clearance ⩽30 ml/min; bleeding diathesis; requirement for anticoagulants, low dose aspirin, ticlopidine, or clopidogrel; unstable medical disease including current angina or congestive heart failure; previous upper gastrointestinal surgery; faecal occult blood; history of inflammatory bowel disease, history of myocardial infarction, coronary angioplasty, or coronary artery bypass graft within one year, cerebrovascular event or active hepatic disease within the past two years, or malignancy within the past five years. The study population included patients infected with *Helicobacter pylori*, a prior history of a gastroduodenal PUB, or the presence of gastroduodenal erosions at baseline endoscopy.

Design

This was a randomised, double blind, placebo controlled, parallel group study.

Procedures

Following a two week washout period from non-selective NSAIDs and any antisecretory or cytoprotective drugs, patients who met entry criteria underwent baseline upper gastrointestinal endoscopy and determination of *H pylori* status by gastric biopsy with a rapid urease test (CLOtest) and by histology. Patients were then randomised to one of three treatment groups: rofecoxib 50 mg once daily, naproxen 500 mg twice daily, or placebo, for 12 weeks. Matching placebo for each medication was used to maintain blinding. Treatment allocation was stratified by history of significant upper gastrointestinal disease (gastroduodenal ulcer or upper gastrointestinal haemorrhage or perforation), and each stratum was further stratified according to concomitant use of oral corticosteroids during the study. Stable doses of non-study antirheumatic medications other than NSAIDs and antisecretory or cytoprotective drugs were permitted, as were injectable or oral corticosteroids (⩽10 mg prednisone or equivalent daily). Rescue medications (acetaminophen/paracetamol for pain and Gelusil aluminum hydroxide/magnesium hydroxide/simethicone (Warner-Lambert) for minor dyspepsia) were provided. Patients were prohibited from using the following medications throughout the study: H_2 receptor antagonists, proton pump inhibitors, prostaglandin analogues, other gastroprotective agents, calcium containing antacids, anticoagulants, antiplatelet therapy, and cyclosporin.

Patients were evaluated clinically at study weeks 3, 6, 9, and 12. Endoscopy was performed at baseline, at study weeks six and 12, at unscheduled discontinuation, and when deemed clinically necessary by the investigator. At endoscopy, the number and size of gastric and/or duodenal ulcers (defined as mucosal breaks with an unequivocal depth of at least 3 mm in the longest dimension) were recorded, and gastroduodenal mucosal erosions were counted. If an ulcer was detected, the patient was immediately discontinued from the study and underwent discontinuation procedures and ulcer treatment. Safety assessments also included physical examination and vital signs, laboratory parameters, and monitoring of clinical and laboratory adverse events throughout the study.

Statistical analysis

The cumulative incidence of gastric and/or duodenal ulcers ⩾3 mm over 12 weeks was the primary end point of the study. A survival analysis was used to analyse time to event data for ulcer incidence, and the log rank test was used to compare the cumulative incidence of ulcers among treatment groups. Twelve week cumulative rates were estimated via Kaplan-Meier, and the Breslow-Crowley method[25] was used to calculate 95% confidence intervals (CIs); 95% CIs were also calculated for between treatment differences and the ratio of the 12 week cumulative rates for the prespecified comparisons. Although the study was not designed to compare rofecoxib with placebo, p values were calculated for comparisons with placebo.

Twelve week cumulative ulcer incidence rates of 7.5% for rofecoxib, 7.5% for placebo, and 25% for naproxen were assumed. The study had 98% power to detect such differences between rofecoxib or placebo versus naproxen, based on a two sided test with $\alpha=0.05$.

Assessment of treatment effect on ulcer incidence was made for patient subgroups to explore the consistency of effects across subgroups. These classifications were defined at baseline by the following: age (<65 or ⩾65 years), sex, race (White or non-White), history of symptomatic PUB, *H pylori* status, baseline number of gastric and/or duodenal erosions (=0 or ⩾0), prior NSAID use, tobacco use, corticosteroid use, and geographical region (USA or international). A Cox proportional hazards model was used to test qualitative treatment by subgroup interactions.

Cumulative incidence of ulcers ⩾5 mm over 12 weeks, and mean change from baseline number of erosions over 12 weeks were assessed as secondary end points. Continuous variables were analysed with an analysis of covariance model (with prespecified factors of treatment, gastrointestinal history, corticosteroid use, and baseline covariate where appropriate). Adverse event data were analysed by Fisher's exact test.

RESULTS

Patient characteristics

Figure 1 shows the disposition of patients throughout the study. Of the 660 patients enrolled at the randomisation visit, 509 completed the study. Nine, 11, and 22 patients discontinued due to adverse experiences on placebo, rofecoxib, and naproxen, respectively, while 11, four, and two patients, respectively, discontinued due to lack of efficacy. As shown in table 1, there were no clinically meaningful differences among groups with regard to age, sex, race, history of gastrointestinal

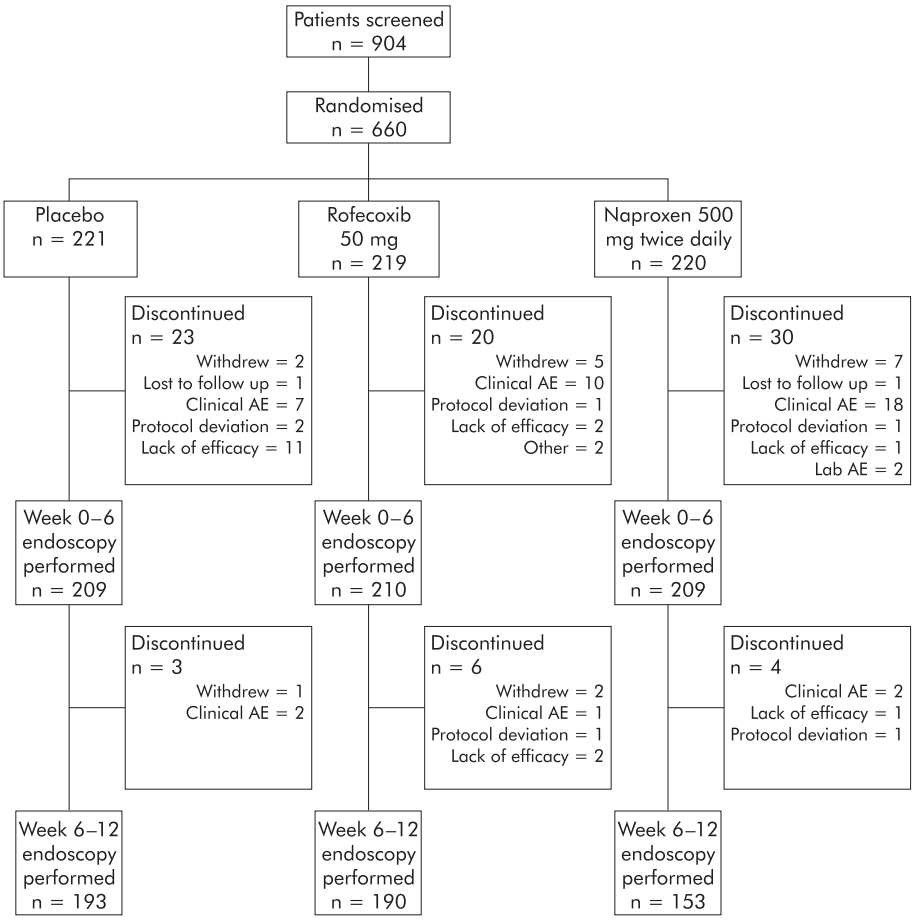

Figure 1 Study flow chart.

Table 1 Patient baseline characteristics

Patient characteristic	Placebo (n=221)	Rofecoxib 50 mg (n=219)	Naproxen 500 mg twice daily (n=220)
Female (%)	82	86	78
Mean age (y)	51	53	51
⩾65 years (%)	16	20	16
% from USA	22	21	22
% White	48	52	52
History of upper GI events (PUBs) (%)	10	11	14
H pylori positive (%)	61	61	57
% with baseline gastroduodenal erosions	11	13	14
Tobacco use (%)	38	34	40
Corticosteroids (%)	61	56	59
Prior NSAID use (%)	70	68	57

NSAIDs, non-steroidal antiinflammatory drugs; GI, gastrointestinal; PUBs, gastrointestinal perforations, ulcers, or bleeding episodes.

events, *H pylori* status, tobacco use, presence of gastroduodenal erosions, or prior NSAID use.

Incidence of ulcers and erosions

The six and 12 week incidences of ulcers ⩾3 mm are shown in fig 2. The 12 week cumulative incidence of gastroduodenal ulcers ⩾3 mm in patients on naproxen 500 mg twice daily (25.5%) was significantly greater than that in patients on rofecoxib 50 mg (6.8%; between treatment difference 18.7% (95% CI 11.7%, 25.7%); p⩽0.001) or placebo (2.9%; difference 22.6% (95% CI 16.1%, 29.1%); p<0.001) whereas the incidence in patients on rofecoxib did not differ significantly from that in patients on placebo (2.9%; p=0.066). Findings for ulcers ⩾5 mm were similar and are shown in fig 3. The 12 week cumulative incidence of ulcers ⩾5 mm was 2.9%, 5.3%, and 17.1% in patients on placebo, rofecoxib, and naproxen, respectively (difference for naproxen *v* rofecoxib (95% CI) 11.8% (5.7%, 18.0%), p⩽0.001; difference for naproxen *v* placebo 14.2%, p⩽0.001). The incidence in the rofecoxib group did not differ significantly from that in the placebo group (2.9%; p=0.210). As shown in fig 4, the least squares mean change from baseline in the number of erosions was significantly higher in patients on naproxen versus those on rofecoxib (difference (95% CI) 4.05 (93.37, 4.73); p<0.001) and in patients on naproxen versus patients on placebo (difference (95% CI) 4.41 (3.73, 5.08); p⩽0.001). There was no significant difference between patients on placebo and patients on rofecoxib.

A similar pattern of treatment effects was seen when gastric and duodenal ulcers were examined separately. The cumulative incidence of gastric ulcers ⩾3 mm at 12 weeks was 2.0% for placebo, 5.9% for rofecoxib, and 22.1% for naproxen. The

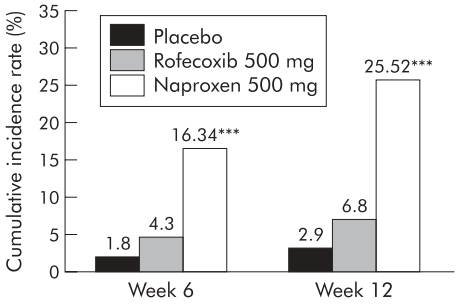

Figure 2 Cumulative incidence rate (%) of gastroduodenal ulcers ≥3 mm (intention to treat) in the placebo, rofecoxib 50 mg, and naproxen 500 mg twice daily groups. ***p<0.001 for naproxen versus rofecoxib or placebo.

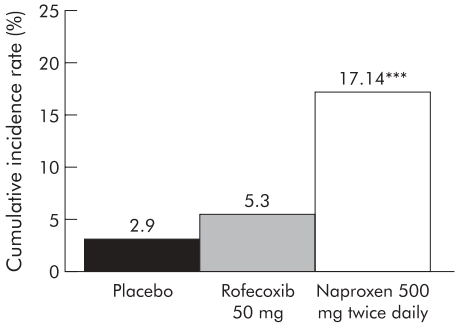

Figure 3 Cumulative incidence rate (%) of gastroduodenal ulcers ≥5 mm at week 12 (intention to treat) in the three groups. ***p<0.001 for naproxen versus rofecoxib or placebo.

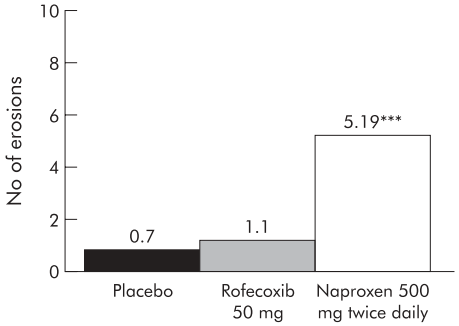

Figure 4 Least squares mean change from baseline number of gastroduodenal erosions at week 12 (intention to treat) in the three groups. ***p<0.001 for naproxen versus rofecoxib or placebo.

cumulative incidence of duodenal ulcers ≥3 mm at 12 weeks was 0.9% for placebo, 1.0% for rofecoxib, and 5.2% for naproxen.

Risk modifiers

Between treatment comparisons for ulcer (≥3 mm) incidence in subgroups defined by baseline patient characteristics were found to be generally consistent across all levels of all subgroups. Age ≥65 years, White race, and presence of prior gastrointestinal history were risk factors for gastroduodenal ulcers, as demonstrated by statistically significant main effects. There was no significant main effect of *H pylori* status (p=0.077) and no significant interaction between *H pylori* status and treatment (p=0.500). The cumulative incidence of ulcers ≥3 mm at 12 weeks in *H pylori* negative patients was 3.6% for placebo, 3.9% for rofecoxib, and 33.3% for naproxen. In *H pylori* positive patients, the cumulative incidence of ulcers ≥3 mm at 12 weeks was 2.3% for placebo, 8.3% for rofecoxib, and 17.9% for naproxen.

Tolerability

Table 2 summarises the tolerability assessments. There was no significant difference among treatment groups in the overall incidence of adverse events, although the incidence of drug related adverse events was higher in patients on naproxen and those on rofecoxib compared with those on placebo (p=0.002 for naproxen *v* placebo; p=0.030 for rofecoxib *v* placebo). Patients taking naproxen had a significantly higher rate of discontinuations due to an adverse event compared with the placebo group (p=0.036).

Comparison of the incidence of serious clinical adverse experiences among treatment groups showed no significant differences (2.7% for placebo, 1.8% for rofecoxib, and 4.1% for naproxen) (table 2). One death was reported among patients taking naproxen (hepatic and multiple organ failure in a patient discovered to be seropositive for hepatitis B). This was considered definitely not related to the study drug by the investigator. No serious laboratory adverse events were reported, and rates of all laboratory adverse experiences were generally similar among treatment groups (12.7 % in patients on placebo, 14.2% in patients on rofecoxib, and 18.3% in patients on naproxen) except for slightly more numerous reports of decreases in haematocrit and haemoglobin in patients taking naproxen compared with the two other groups.

The three adverse events most commonly reported over the entire study were epigastric discomfort, dyspepsia, and heartburn, each of which was reported in at least 5% of patients in each treatment group. No significant difference was observed among treatment groups for the incidence of dyspepsia (6.3% on placebo, 10.0% on rofecoxib, and 7.3% on naproxen) or heartburn (5.0% on placebo, 9.1% on rofecoxib, and 7.3% on naproxen); however, the rofecoxib group (9.1%) and the placebo group (8.6%) both had significantly lower incidences of epigastric discomfort compared with the naproxen group (17.3%; p≤0.016 for rofecoxib or placebo *v* naproxen). The percentages of patients who discontinued because of an adverse event involving the digestive system or abdominal pain were 0.9% on placebo, 3.7% on rofecoxib, and 6.8% on naproxen. The difference between the naproxen and placebo groups was statistically significant (5.9%; p=0.001) but the difference between the rofecoxib and placebo groups was not (p=0.062). There were seven PUBs (one patient on placebo, two patients on rofecoxib, and four patients on naproxen).

Because COX inhibition has known renal and vascular effects, analyses were prespecified for comparisons between groups for adverse experiences involving hypertension, oedema, or congestive heart failure (table 3). The reported incidences of hypertension were 2.3% for the placebo group, 6.4% for the rofecoxib group, and 0.9% for the naproxen group, and lower extremity oedema was reported for 1.8% of patients on placebo, 1.4% of patients on rofecoxib, and 0% of patients on naproxen. No patient discontinued treatment with the study drug due to either hypertension or lower extremity oedema. Likewise, there were no between treatment group differences observed for the incidences of congestive heart failure adverse events, which were reported for one patient in the study (rofecoxib group). This patient's event was considered not serious and not related to study drug by the investigator.

DISCUSSION

In the present study, rofecoxib 50 mg (twice the recommended dose for the treatment of RA) resulted in significantly fewer endoscopically detected gastroduodenal ulcers ≥3 mm at 12 weeks compared with naproxen 500 mg twice daily. This was also true for ulcers ≥5 mm, which some clinical experts have

Table 2 Summary of safety data (% of patients)

	Placebo (n=221)	Rofecoxib 50 mg (n=219)	Naproxen 500 mg twice daily (n=220)
One or more clinical adverse events	61.1	62.1	66.4
Drug related adverse event*	25.8	35.6†	39.5†
Serious adverse event	2.7	1.8	4.1
Discontinued due to an adverse event	4.1	5.0	9.1†

*Determined by the investigator to be possibly, probably, or definitely drug related.
†p<0.05

Table 3 Percentages of patients with adverse events of interest for selective COX-2 inhibitors

	Placebo (n=221)	Rofecoxib 50 mg (n=219)	Naproxen 500 mg twice daily (n=220)
Hypertension	2.3	6.4	0.9
Discontinued due to hypertension	0.0	0.0	0.0
Lower extremity oedema	1.8	1.4	0.0
Discontinued due to lower extremity oedema	0.0	0.0	0.0
Congestive heart failure	0.0	0.5	0.0
Discontinued due to congestive heart failure	0.0	0.5	0.0
Haemoglobin decreased	1.4	3.7	5.5
Haematocrit decreased	2.3	4.1	7.8

argued may be more clinically meaningful than those ⩾3 mm.[26] The latter findings are particularly compelling in view of the fact that ulcers ⩾3 mm but <5 mm resulted in immediate patient discontinuation, a stipulation which may have interrupted the development of some larger ulcers (⩾5 mm) and led to a conservative comparison with rofecoxib. Despite this, a significant advantage with rofecoxib 50 mg persisted compared with naproxen 500 mg twice daily. Rofecoxib 50 mg also demonstrated significantly lower increases in the number of gastroduodenal erosions at 12 weeks compared with naproxen 500 mg twice daily.

A prior history of PUBs was observed to be a positive risk factor for ulcer, as reported previously.[19 23 27] Patients with a prior history of PUBs are known to have an increased risk of ulceration when taking NSAIDs.[28–30] Age ⩾65 years and White race (*v* non-white) were also identified as risk factors for the development of gastroduodenal ulceration in this study. While older age has been previously identified as a potential risk factor for the development of endoscopic ulcers in patients with RA, race has not been previously identified as a factor in other studies. The clinical significance of this finding is unclear. However, the advantage of rofecoxib 50 mg over naproxen 500 mg twice daily was maintained in all these subgroups. *H pylori* status was not a risk factor for the development of ulcers in this study.

There were no statistically significant differences in the incidence of ulcers or erosions for the comparison of rofecoxib with placebo whereas naproxen showed a significant increase relative to placebo on all measures. There was a numerical increase in ulcers and erosions for rofecoxib relative to placebo, raising the possibility that this dose of rofecoxib may slightly increase ulcer rates in RA patients, unlike findings previously reported in OA. A previous combined analysis of OA endoscopy studies established statistical equivalence to placebo for a daily dose of 25 mg, but not for 50 mg.[16] This suggests that the numerical increase versus placebo seen in this study may have been less pronounced (or non-existent) at a lower dose.

Interestingly, the ulcer incidence rate in patients on placebo (2.9%) was lower than the incidence rates previously observed in two studies of similar design which assessed the incidence of gastroduodenal ulceration over 12 weeks in patients with OA.[16 31] These previous studies showed placebo ulcer incidences over 12 weeks of 9.92% and 5.10%, respectively. The significant variability in the incidence of endoscopic ulcers in patients taking placebo in these individual trials is consistent with the conclusion that small between treatment group differences in rates of endoscopic ulcer may not reflect clinically significant differences in drug effect. By contrast, the highly statistically significant differences from the naproxen 500 mg twice daily group in ulcer incidence in both the placebo and rofecoxib 50 mg groups are consistent with the results of a large clinical outcomes trial in RA patients that demonstrated a significant decrease in the incidence of clinical events of PUBs with rofecoxib 50 mg (a higher dose than recommended) compared with naproxen 500 mg twice daily (a standard dose).[24] This large study also compared a standard dose of naproxen with a dose of rofecoxib that is higher than recommended.

Rofecoxib 50 mg demonstrated a favourable safety profile compared with naproxen 500 mg twice daily and was well tolerated over the 12 week treatment period. The overall incidence of clinical and laboratory or serious adverse experiences was generally similar between the rofecoxib 50 mg, naproxen 500 mg twice daily, and placebo groups. Naproxen had the highest rate of drug related adverse experiences and placebo had the lowest rate. The rate of discontinuation due to adverse experiences was numerically similar between the rofecoxib 50 mg and placebo groups whereas the incidence of discontinuation due to adverse experiences was significantly greater in patients on naproxen 500 mg twice daily compared with those on placebo.

The adverse event profile was also supportive of better gastrointestinal tolerability for rofecoxib 50 mg than for naproxen 500 mg twice daily. Naproxen resulted in a significantly increased incidence of discontinuations due to adverse experiences of the digestive system or of abdominal pain whereas the incidence of these adverse experiences in patients on rofecoxib was less than that in patients on naproxen and not significantly different from placebo. Due to the small sample size and low incidence of upper gastrointestinal PUBs in this study, a significant difference in the incidence between treatment groups was not expected and therefore these data were not analysed. Data have previously

been published showing that upper gastrointestinal PUBs are reduced with rofecoxib compared with non- selective NSAIDs.[18 24] Previous data have also shown a reduced incidence of falls in haemoglobin with rofecoxib and celecoxi,[24 30] probably as a result of reduced whole gut blood loss.[13] The size of our study means that differences were not statistically significant.

Consistent with previous studies,[32–34] rofecoxib 50 mg was associated with a small increase in the incidence of physician reported adverse events of hypertension. A review of all hypertensive adverse experiences showed that these were generally of minor clinical impact and that most affected patients had pre-existing diagnoses of hypertension. No patient discontinued due to adverse experiences of hypertension; all patients continued on study drug and either had spontaneous resolution of their adverse experience or had adjustment made to their non-study medications such that the hypertension was treated. No association between hypertension adverse experiences and untoward outcomes (for example, unstable angina, myocardial infarction, or cerebrovascular events) was observed. In the group as a whole, mean changes in blood pressure showed that changes in systolic or diastolic readings occurred early in the course of therapy and tended to be transient (resolving on treatment). It should be noted that these results were observed with a dose of rofecoxib that is twice the dose recommended for chronic treatment of RA.

In summary, the findings of this study demonstrated that treatment with rofecoxib 50 mg once daily was well tolerated in RA patients and resulted in lower incidences of endoscopically detected gastroduodenal ulcers and erosions compared with naproxen 500 mg twice daily.

APPENDIX

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REFERENCES

1 **Wolfe MM**, Lichtenstein DR, Singh G. Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs. *N Engl J Med* 1999;**340**:1888–99.
2 **Loebl DH**, Craig R, Culic D, *et al*. Gastrointestinal blood loss: effect of aspirin, fenoprofen, and acetaminophen in rheumatoid arthritis as determined by sequential gastroscopy and radioactive fecal markers. *JAMA* 1977;**237**:976–81.
3 **Hawkey CJ**, Jackson L, Harper SE, *et al*. The gastrointestinal safety profile of rofecoxib, a highly selective inhibitor of cyclooxygenase-2, in humans. *Aliment Pharmacol Ther* 2001;**15**:1–9.
4 **Cannon GW**, Caldwell JR, Holt P, *et al*. Rofecoxib, a specific inhibitor of cyclooxygenase 2, with clinical efficacy comparable with that of diclofenac sodium: results of a one-year, randomized, clinical trial in patients with osteoarthritis of the knee and hip. Rofecoxib Phase III Protocol 035 Study Group. *Arthritis Rheum* 2000;**43**:978–87.
5 **Day R**, Morrison B, Luza M, *et al*. A randomized trial of the efficacy and tolerability of the COX-2 inhibitor rofecoxib vs. ibuprofen in patients with osteoarthritis. Rofecoxib/Ibuprofen Comparator Study Group. *Arch Intern Med* 2000;**160**:1781–7.
6 **Ehrich EW**, De Dallob A, Lepeliere I, *et al*. Characterization of rofecoxib as a cyclooxygenase-2 isoform inhibitor and demonstration of analgesia in the dental pain model. *Clin Pharmacol Ther* 1999;**65**:336–47.
7 **Merck & Co**., Inc. Vioxx (Rofecoxib Tablets and Oral Suspension). *Physicians Desk Reference*. Montvale, NJ: Medical Economics Company, 2000;1912–15.
8 **Morrison BW**, Daniels SE, Kotey P, *et al*. Rofecoxib, a specific cyclooxygenase-2 inhibitor, in primary dysmenorrhea: a randomized controlled trial. *Obstet Gynecol* 1999;**94**:504–8.
9 **Wright N**, Garlick N, Calder N, *et al*. Evidence that the COX-2 specific inhibitor rofecoxib at 50 mg spares gastric mucosal prostaglandin synthesis in humans. *Gut* 1999;**45**(suppl V):A25.
10 **Cryer B**, Gottesdiener K, Gertz B, *et al*. In *vivo* effects of rofecoxib, a new cyclooxygenase (COX)-2 inhibitor, on gastric mucosal prostaglandin (PG) and serum thromboxane B2 (TXB2) synthesis in healthy humans (abstract). *Am J Gastroenterol* 1999;**91**:1907.
11 **Bjarnason I**, Zanelli G, Smith T, *et al*. The pathogenesis and consequence of nonsteroidal anti-inflammatory drug induced small intestinal inflammation in man. *Scand J Rheumatol* 1987;**64**(suppl 69):55–62.
12 **Ridolfo**, AS, Crabtree, RE, Johnson, DW, *et al*. Gastrointestinal microbleeding: comparisons between benoxaprofen and other nonsteroidal anti-inflammatory agents. *J Rheumatol* 1980;*7*(suppl 6):36–47.
13 **Hunt R**, Bowen B, Mortensen E, *et al*. A randomized trial measuring fecal blood loss after treatment with rofecoxib, ibuprofen, or placebo in healthy subjects. *Am J Med* 2000;**109**:201–6.
14 **Sigthorsson G**, Crane R, Simon T, *et al*. Cox-2 inhibition with rofecoxib does not increase intestinal permeability in healthy subjects. A double-blind, crossover study comparing rofecoxib with placebo and indomethacin. *Gut* 2000;**47**:527–32.
15 **Lanza FL**, Rack MF, Simon TJ, *et al*. Specific inhibition of cyclooxygenase-2 with MK-0966 is associated with less gastroduodenal damage than either aspirin or ibuprofen. *Aliment Pharmacol Ther* 1999;**13**:761–7.
16 **Hawkey C**, Laine L, Simon T, *et al*. A randomized, double-blinded comparison of the effect of rofecoxib (a drug specifically inhibiting COX-2), ibuprofen, or placebo on the gastroduodenal mucosa of osteoarthritis patients. *Arthritis Rheum* 2000;**43**:370–7.
17 **Laine L**, Harper S, Simon T, *et al*. A randomized trial comparing the effect of rofecoxib, a cyclooxygenase 2-specific inhibitor, with that of ibuprofen on the gastroduodenal mucosa of patients with osteoarthritis. *Gastroenterology* 1999;**117**:776–83.
18 **Langman M**, Jensen DM, Watson DJ, *et al*. Adverse upper gastrointestinal effects of rofecoxib compared with NSAID's. *JAMA* 1999;**282**:1929–33.
19 **Fries JF**. NSAID gastropathy: the second most deadly rheumatic disease? Epidemiology and risk appraisal. *J Rheumatol* 1991;**18**(suppl 28):6–10.
20 **Seibert K**, Zhang Y, Leahy K, *et al*. Pharmacological and biochemical demonstration of the role of cyclooxygenase 2 in inflammation and pain. *Proc Natl Acad Sci U S A* 1994;**91**:12013–7.
21 **Vane J**. Towards a better aspirin. *Nature* 1994;**367**:215–16.
22 **Masferrer JL**, Zweifel BS, Manning PT, *et al*. Selective inhibition of inducible cyclooxygenase 2 in vivo is antiinflammatory and nonulcerogenic. *Proc Natl Acad Sci U S A* 1994;**91**:3228–32.
23 **Gabriel SE**, Jaakkimainen L, Bombardier C. Risk for serious gastrointestinal complications related to use of nonsteroidal anti-inflammatory drugs. *Ann Intern Med* 1991;**115**:787–96.
24 **Bombardier C**, Laine L, Reicin A, *et al* for the VIGOR Study Group. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. *N Engl J Med* 2000;**343**:1520–8.
25 **Breslow EN**, Crowley J. A large sample study of the life table and product limit estimates under random censorship. *Ann Stat* 1974;**2**:437–53.
26 **Graham DY**. High-dose famotidine for prevention of NSAID ulcers. *Gastroenterology* 1997;**112**:2143–5.
27 **Taha AS**, Sturrock RD, Russell RI. Mucosal erosions in long term non-steroidal anti- inflammatory drug users: predisposition to ulceration and relation to *Helicobacter pylori*. *Gut* 1995;**36**:334–6.
28 **Graham DY**, White RH, Moreland LW, *et al*. Duodenal and gastric ulcer prevention with misoprostol in arthritis patients taking NSAIDs. *Ann Intern Med* 1993;**119**:257–62.
29 **Griffin MR**, Piper JM, Daugherty JR, *et al*. Nonsteroidal anti-inflammatory drug use and increased risk for peptic ulcer disease in elderly persons. *Ann Intern Med* 1991;**114**:257–63.
30 **Silverstein FE**, Graham DY, Senior JR, *et al*. Misoprostol reduces serious gastrointestinal complications in patients with rheumatoid arthritis receiving nonsteroidal anti-inflammatory drugs. *Ann Intern Med* 1995;**123**:241–9.
31 **Hawkey CJ**, Laine L, Harper SE, *et al* for the Rofecoxib Osteoarthritis Endoscopy Mutinational Study Group. Influence of risk factors on endoscopic and clinical ulcers in patients taking rofecoxib or ibuprofen in two randomized controlled trials. *Aliment Pharmacol Ther* 2001;**15**:1593–601.

32 **Saag K**, van-der-Heijde D, Fisher C, *et al*. Rofecoxib, a new cyclooxygenase 2 inhibitor, shows sustained efficacy, comparable with other nonsteroidal anti-inflammatory drugs: a 6-week and a 1-year trial in patients with osteoarthritis. *Arch Fam Med* 2000;**9**:1124–34.
33 **Truitt KE**, Lee M, DeTora LM, *et al*. Results of a pivotal (phase III) placebo and active comparator controlled efficacy trial of rofecoxib 12.5 and 25 mg in adult patients with rheumatoid arthritis (RA). *Arthritis Rheum* 2001;44(9 suppl):S369.
34 **Truitt KE**, Guesens PP, DeTora LM, *et al*. Results of a pivotal (phase III) placebo and active comparator controlled efficacy trial of rofecoxib 25 and 50 mg in adult patients with rheumatoid arthritis (RA). *Ann Rheum Dis* 2001;**60**(suppl 1):161