Gastroduodenal Safety and Tolerability of Lumiracoxib Compared with Ibuprofen and Celecoxib in Patients with Osteoarthritis

CHRISTOPHER J. HAWKEY, PETR SVOBODA, IRENA F. FIEDOROWICZ-FABRYCY, EVGENY L. NASONOV, EDUARD G. PIKHLAK, MARC COUSIN, XAVIER GITTON, and GODEHARD HOEXTER

ABSTRACT. ***Objective.*** To compare the incidence of gastroduodenal ulcers in patients with osteoarthritis (OA) treated with therapeutic doses of the novel COX-2 selective inhibitor, lumiracoxib (COX189, Prexige®), and the standard nonsteroidal antiinflammatory drug (NSAID) ibuprofen. The COX-2 selective inhibitor celecoxib was included as an active control.

Methods. In this randomized, multicenter, double-blind, parallel-group study, eligible patients were randomized to receive lumiracoxib 200 mg (n = 264) or 400 mg (n = 260) once daily (qd), ibuprofen 800 mg (n = 260) 3 times daily (tid), or celecoxib 200 mg qd (n = 258) for 13 weeks. The incidence of gastroduodenal ulcers and erosions was determined by endoscopy prior to randomization, and after 4 weeks and 13 weeks of treatment (end of study). Frequencies of adverse events were also recorded.

Results. The cumulative incidence of gastroduodenal ulcers ≥ 3 mm in diameter was significantly lower in the lumiracoxib groups (200 mg: 4.3%; 400 mg: 4.0%) than in the ibuprofen group (15.7%; $p < 0.001$) and similar to the celecoxib group (3.2%). In the ibuprofen group, a significantly greater number of patients (6.0%) had > 10 gastroduodenal erosions compared with lumiracoxib 200 mg (1.2%; $p < 0.01$), lumiracoxib 400 mg (1.6%; $p < 0.05$), and celecoxib (2.4%; $p < 0.05$). A greater number of patients in the ibuprofen group discontinued treatment due to an adverse event compared with both lumiracoxib groups and the celecoxib group.

Conclusion. In patients with OA, lumiracoxib 200 mg or 400 mg qd was associated with a significantly lower risk of gastroduodenal ulceration than ibuprofen 800 mg tid, and was similar to celecoxib 200 mg qd. (J Rheumatol 2004;31:1804–10)

Key Indexing Terms:
GASTRODUODENAL ULCERS LUMIRACOXIB IBUPROFEN CELECOXIB

Osteoarthritis (OA) is a chronic and often progressive condition requiring longterm symptomatic pain management. Nonsteroidal antiinflammatory drugs (NSAID) are the most widely prescribed agents for this condition, and are well established for management of the chronic pain associated with OA[1,2]. However, these agents are a common cause of serious morbidity and mortality associated with gastrointestinal (GI) ulcers and ulcer complications. The incidence of symptomatic ulcers and ulcer complications associated with standard NSAID was reported in 1998 to be around 1–4% per year[3].

NSAID are believed to damage the GI tract principally as a result of inhibition of the constitutive cyclooxygenase (COX)-1 enzyme that helps to maintain GI mucosal integrity by synthesizing prostaglandins. Recognition of a second cyclooxygenase enzyme (COX-2) that is upregulated at sites of inflammation stimulated the development of agents that selectively inhibited COX-2. Four oral COX-2 selective inhibitors are currently available for use in various countries for the management of OA: celecoxib, valdecoxib, rofecoxib, and etoricoxib. Clinical studies have supported the much improved GI safety of this class of agents, which are effective in pain management yet cause significantly fewer endoscopically detected GI ulcers than standard nonselective NSAID such as ibuprofen or naproxen[4–6].

Lumiracoxib is a novel COX-2 selective inhibitor, chemically distinct from existing COX-2 selective agents in that

From the University Hospital Nottingham, Nottingham, United Kingdom; Research Center for Traumatology and Surgery, Ministry of Health, Moravia, Czech Republic; Klinika Reumatologii, Panstwowy Szpital Kliniczny, Szczecin, Poland; Rheumatology Institute, Russian Academy of Medical Sciences, Moscow; Moscow Clinical Research Centre of Arthrology, Moscow, Russia, and Novartis Pharma AG, Basel, Switzerland.

Supported by a grant from Novartis Pharma AG, Basel, Switzerland.

C.J. Hawkey, DM, FRCP, Professor of Gastroenterology, University Hospital, Nottingham, UK; P. Svoboda, MD, PhD, Associate Professor, Trauma Hospital, Medical School, Masaryk University, Brno, Czech Republic; I.F. Fiedorowicz-Fabrycy, MD, PhD, Department of Rheumatology, Pomeranian Medical University, Szczecin, Poland; E.L. Nasonov, MD, PhD, Director, State Research Institute of Rheumatology, Russian Academy of Medical Sciences, Moscow; E.G. Pikhlak, MD, PhD, Chief Physician, Moscow Clinical Research Centre of Arthrology, Moscow, Russia; M. Cousin, PhD, CRD Scientific Advisor; X. Gitton, PhD, Senior Clinical Research Manager, CRD (Arthritis); G. Hoexter, MSc, Senior Statistician, Novartis Pharma AG, Basel, Switzerland.

Address reprint requests to Prof. C.J. Hawkey, Division of Gastroenterology, University Hospital Nottingham, Queen's Medical Centre, Nottingham NG7 2UH, UK. E-mail: cj.hawkey@nottingham.ac.uk

Submitted November 6, 2003; revision accepted March 17, 2004.

it does not contain a sulfur-containing moiety but has a carboxylic acid group, making it a mildly acidic molecule[7]. Lumiracoxib is rapidly absorbed, with a short plasma half-life ($t_{½}$ of 3–6 h)[8], yet several clinical studies suggest 24-hour efficacy[9–11]. Rapid plasma clearance, alongside prolonged efficacy, suggests that lumiracoxib could provide at least equally effective pain relief in OA as standard NSAID, with improved tolerability resulting from its COX-2 selective inhibition.

We designed a large, multicenter, 13-week study to determine the incidence of endoscopically detected gastroduodenal ulcers in adult patients with OA treated with lumiracoxib, and to compare this with the incidence of ulceration and erosions in patients treated with ibuprofen. The celecoxib arm was included as an active control treatment.

MATERIALS AND METHODS

Patients. The study population consisted of male and female patients aged ≥ 18 years with a diagnosis of primary OA of the hip, knee, or hand according to the American College of Rheumatology (ACR) criteria[12–14] or of the spine (cervical or lumbar, confirmed by radiograph) and functional status of I–III according to the revised ACR criteria. Patients were required to have been symptomatic for at least 3 months prior to enrollment, to be receiving NSAID or other analgesic therapy, and to have a baseline pain assessment of moderate, severe, or extreme (Likert scale) in the affected joint. In addition, only patients with no ulceration of the gastroduodenal mucosa, with ≤ 10 gastroduodenal erosions and with no lesion of the esophageal mucosa (confirmed by endoscopy) were considered for enrollment.

The main exclusion criteria were: any other inflammatory arthritis, active GI disease, history of gastroduodenal bleeding, pyloric or duodenal obstruction, past gastroduodenal surgery, active malignancy or history of malignancy, a serum creatinine value exceeding 1.2 times the upper limit of normal (ULN), and an aspartate or alanine transaminase exceeding 1.5 times the ULN. Eligibility for inclusion in this study was not influenced by *Helicobacter pylori* status.

Study design. This was a randomized, multicenter, double-blind, controlled, parallel-group study, conducted in accord with the principles of Good Clinical Practice and the Declaration of Helsinki at 83 clinical centers in Bulgaria, the Czech Republic, France, Hungary, Ireland, Poland, Romania, Russia, South Africa, Spain, and the UK. Independent ethics committees approved the protocol and all patients provided written informed consent prior to any study procedure. Quality control procedures included regular monitoring visits with verification of case report forms against medical records, and audits conducted by sponsor personnel at selected sites.

At screening, patients underwent clinical laboratory testing. After a 7-day NSAID washout period, patients underwent baseline gastroduodenal endoscopy. Biopsy specimens were obtained from the gastric antrum and body for rapid urease testing (CLOtest) and histologic (Giemsa) stain evaluation for *H. pylori*. Eligible patients were subsequently randomized within 7 days to receive lumiracoxib 200 mg once daily (qd), lumiracoxib 400 mg qd, celecoxib 200 mg qd, or ibuprofen 800 mg three times daily (tid) for up to 13 weeks. Study medication was provided in blister packages. Blinding was maintained by using matching placebo tablets and capsules. Randomization was performed in blocks of 4 from a computer-generated list. Each site was provided with sealed envelopes containing treatment assignments, which were returned and destroyed after study completion. Study personnel remained blinded until the clinical database was locked. There were 4 planned study visits (baseline and at Weeks 4, 8, and 13). Endoscopies were conducted prior to randomization and at Weeks 4 and 13.

Patients were allowed to take acetaminophen (up to 2 g/day) and antacids (e.g., calcium carbonate or magnesium carbonate tablets up to a maximum of 8 per day) as rescue medication. These were dispensed and monitored by the investigator at each study visit. NSAID, gastroprotective agents (histamine H2-receptor antagonists, proton pump inhibitors, misoprostol), anticoagulants and antiplatelet agents (with the exception of low dose aspirin, maximum daily dose ≤ 325 mg) were not permitted. Corticosteroids were not allowed except for ocular, topical, nasal, inhaled, or intraarticular (maximum 3) preparations.

Patients completed a pain assessment using a 5 point Likert categorical scale (none, mild, moderate, severe, or extreme) and both patients and investigators completed categorical global assessments of disease activity at baseline and at Weeks 4, 8, and 13. Adverse events (spontaneously reported and investigator-assessed) were recorded at Weeks 4, 8, and 13. Vital signs and routine biochemistry, hematology, and urinalysis were assessed at each study visit.

Statistical analyses. Sample size was calculated based on the expected cumulative incidence of endoscopically detectable gastroduodenal ulcers (≥ 3 mm diameter). With 158 patients per treatment arm, the study had 90% power to detect a statistically significant difference (5% level, 2-sided test) between the lumiracoxib and ibuprofen treatment arms — assuming a 20% and 7% ulcer incidence rate in the ibuprofen 800 mg and lumiracoxib 400 mg groups, respectively. Allowing for a 20% dropout rate, we estimated that 198 patients per treatment arm would be required to maintain the statistical power of the study.

The primary endpoint of the study was the cumulative incidence of endoscopically detectable gastroduodenal ulcers (≥ 3 mm in diameter) at study end (Week 13) in the modified safety population (defined as all patients who underwent at least one post-baseline endoscopy). A multiple logistic model was employed, taking into account as main effects the logarithm of age, whether at least one unscheduled endoscopy was performed, the number of post-baseline endoscopies, and treatment. A 2-sided 5% level of significance was applied for all comparisons. Secondary safety variables at Weeks 4 and 13 included the cumulative incidence of gastroduodenal ulcers (≥ 5 mm) and esophageal ulcers (any size), and the change from baseline in esophageal mucosal score. The incidence of gastroduodenal ulcers at Week 4 (≥ 3 mm) was a secondary safety variable. Secondary safety variables at Week 13 only included the mean number of gastroduodenal erosions and the incidence of > 10 detectable gastroduodenal erosions.

Efficacy analyses (overall joint pain, global assessment of disease activity, and number of rescue medication tablets required) were performed using a multiple logistic model taking treatment as the main effect. Improvement in efficacy was defined as an endpoint assessment of "very good" or an improvement of ≥ 2 grades on a categorical scale. Descriptive statistics are presented for demographic variables, vital signs, laboratory values, and adverse events.

RESULTS

We randomized a total of 1042 patients to receive lumiracoxib 200 mg qd (n = 264), lumiracoxib 400 mg qd (n = 260), celecoxib 200 mg qd (n = 258), or ibuprofen 800 mg tid (n = 260). Patient disposition, discontinuation, and the proportion of patients who deviated from protocol criteria during the study are detailed in Figure 1. The most common reason for early discontinuation was the emergence of an adverse event (discussed below).

There were no clinically or statistically relevant differences between the treatment groups with respect to baseline demographics or disease characteristics (Table 1). The majority of patients were female (76.7%), aged between 41 and 65 years (63.3%), and Caucasian (98.2%). At baseline,

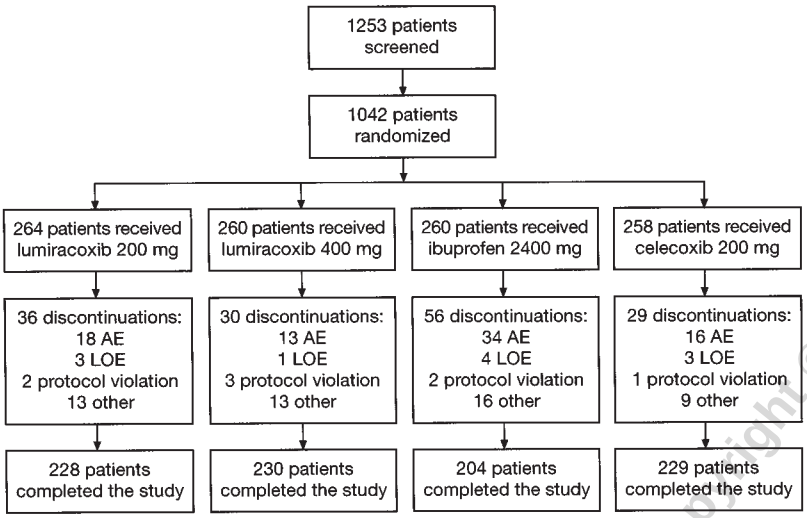

Figure 1. Patient disposition, showing randomization scheme, discontinuations, and intention-to-treat population.

Table 1. Patient characteristics.

	Lumiracoxib 200 mg qd, n = 264	Lumiracoxib 400 mg qd, n = 260	Ibuprofen 800 mg tid, n = 260	Celecoxib 200 mg qd, n = 258
Mean age, yrs ± SD	58.8 ± 10.89	58.1 ± 10.72	57.9 ± 11.13	59.9 ± 9.73
Male/female. %	20.8/79.2	25.4/74.6	23.8/76.2	23.3/76.7
Caucasian, n (%)	260 (98.5)	256 (98.5)	254 (97.7)	253 (98.1)
Mean height, cm ± SD	163.3 ± 8.00	164.8 ± 8.97	164.6 ± 0.95	163.9 ± 8.49
Mean weight, kg ± SD	77.6 ± 15.13	78.6 ± 14.95	78.3 ± 13.91	77.1 ± 14.31
Body mass index, kg/m^2 ± SD	29.1 ± 5.28	29.0 ± 5.28	28.9 ± 4.45	28.7 ± 5.15
Mean disease duration, yrs ± SD	8.0 ± 7.40	7.6 ± 7.37	6.9 ± 6.83	8.1 ± 7.10
Number of patients with				
Prior NSAID therapy (%)	215 (81.4)	213 (81.9)	224 (86.2)	214 (82.9)
History of GI events (%)	85 (32.2)	91 (35.0)	90 (34.6)	89 (34.5)
Baseline erosions (%)	27 (10.2)	20 (7.7)	32 (12.3)	30 (11.6)
H. pylori positive (%)	183 (69.3)	189 (72.7)	185 (71.2)	169 (65.5)
≥ 1 alcoholic drink/day (%)	22 (8.3)	26 (10.0)	25 (9.6)	20 (7.8)

most patients were assessed as having moderate or severe pain and patient/physician global ratings were poor to fair. The proportion of patients who tested positive for *H. pylori* was slightly lower in the celecoxib group than in the other 3 treatment groups.

Safety and tolerability

Esophageal and gastroduodenal evaluation. The cumulative incidence of gastroduodenal ulcers ≥ 3 mm in diameter at study end (Week 13) in the modified safety population was significantly lower among patients treated with lumiracoxib (200 mg qd, 4.3%; 400 mg qd, 4.0%) than among patients treated with ibuprofen 800 mg tid (15.7%; both $p < 0.001$) (Figure 2). No significant difference in the cumulative incidence was observed between either lumiracoxib 200 mg qd or 400 mg qd and celecoxib 200 mg qd (3.2%). A similar pattern was seen for the per-protocol population (subset of modified safety population excluding those with a major protocol violation) in that the incidence of gastroduodenal ulceration with lumiracoxib 200 mg qd (4.1%) and 400 mg qd (4.2%) was significantly lower compared with ibuprofen (16.0%; $p < 0.001$ and $p < 0.01$, respectively) and comparable with celecoxib (3.4%). *H. pylori* status had no influence on the incidence of gastroduodenal ulcers ≥ 3 mm in any treatment group.

When rates for gastric and duodenal ulceration (≥ 3 mm) were examined separately in the modified safety population, the cumulative incidence of gastric ulceration was significantly lower in the lumiracoxib groups (200 mg qd, 2.7%; and 400 mg qd, 2.4%) than in the ibuprofen group (8.9%; both $p < 0.05$) and similar to celecoxib (2.8%). The cumulative incidence of duodenal ulceration ≥ 3 mm in the lumira-

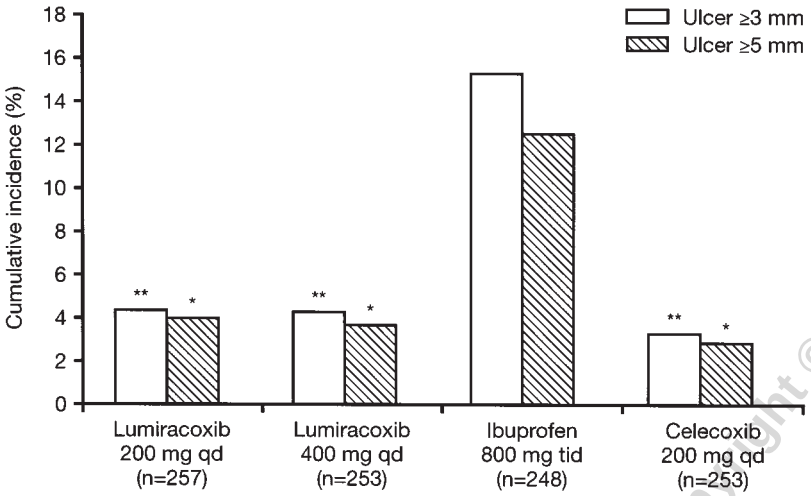

Figure 2. Cumulative incidence of gastroduodenal ulcers (≥ 3 mm and ≥ 5 mm diameter) among patients treated with lumiracoxib 200 mg qd (n = 257), lumiracoxib 400 mg qd (n = 253), ibuprofen 800 mg tid (n = 248), or celecoxib 200 mg qd (n = 253) for up to 13 weeks (modified safety population). *p < 0.005 vs ibuprofen; *p < 0.001 vs ibuprofen. n = modified safety population (all patients who underwent at least one post-baseline upper GI endoscopy).

coxib 200 mg qd and 400 mg qd groups (both 1.6%) was again significantly lower than in the ibuprofen group (8.1%; $p < 0.001$ and $p = 0.001$, respectively) and similar to celecoxib (0.4%).

The cumulative incidence of gastroduodenal ulcers ≥ 5 mm in diameter showed a similar pattern to that seen for ulcers ≥ 3 mm. The cumulative incidence of gastroduodenal ulcers ≥ 5 mm at study end was significantly lower in both the lumiracoxib 200 mg qd (3.9%) and 400 mg qd (3.6%) groups compared with the ibuprofen 800 mg tid group (12.5%; both $p < 0.005$) and similar to the celecoxib 200 mg qd group (2.8%) (Figure 2). When analyzed separately, the incidence of gastric ulcers ≥ 5 mm in diameter was lower with lumiracoxib 200 mg qd (2.3%; $p < 0.05$), lumiracoxib 400 mg qd (2.0%; $p = 0.053$), and celecoxib (2.4%; $p = 0.068$) compared with ibuprofen 800 mg tid (6.5%). The incidence of duodenal ulceration ≥ 5 mm in the lumiracoxib 200 mg qd and 400 mg qd groups (both 1.6%) was again significantly lower than in the ibuprofen group (6.9%; both $p < 0.01$) and similar to celecoxib (0.4%).

The number of patients with erosions at baseline was lower in patients receiving lumiracoxib 400 mg qd than in the other treatment groups, but this was not statistically significant (Table 1). Irrespective of the number of erosions they presented at baseline, fewer patients had erosions or ulcers at study end in the lumiracoxib 200 mg, lumiracoxib 400 mg, and celecoxib groups compared with the ibuprofen group (Table 2).

Significantly fewer patients taking either dose of lumiracoxib or celecoxib had > 10 gastroduodenal erosions compared with ibuprofen, and significantly more had no visible injury of the gastric or duodenal mucosa (Table 3). There was no significant difference between the celecoxib group and the 2 lumiracoxib groups. In addition, the proportion of patients with normal gastric mucosa was significantly higher in the lumiracoxib 200 mg qd (72.4%), lumiracoxib 400 mg qd (76.7%), and celecoxib (75.5%) groups than in the ibuprofen (55.2%) group (all $p < 0.001$). Similarly, the proportion of patients with normal duodenal mucosa was significantly higher in the lumiracoxib 200 mg qd (83.7%; $p < 0.05$), lumiracoxib 400 mg qd (87.4%; $p < 0.001$), and celecoxib (87.7%; $p < 0.001$) groups compared with the ibuprofen (74.2%) group (Table 3). Very few patients had any evidence of lower level mucosal injury and there were no obvious differences between treatment groups or with study visit. Only one patient (taking lumiracoxib 400 mg qd) developed an esophageal ulcer.

Adverse events. The proportion of patients who experienced any adverse event was similar across treatment groups, but highest among patients who received ibuprofen (77.7%; Table 4). The most commonly reported adverse events (in ≥ 5% of patients in any treatment group) were upper abdominal pain, dyspepsia, nausea, influenza, nasopharyngitis, and headache. Compared with patients receiving ibuprofen, fewer patients receiving lumiracoxib or celecoxib had adverse events or resulted in study drug discontinuation.

The incidence of serious adverse events was similar across treatment groups, but fewer serious adverse events were considered by the investigator to be study treatment-related in the lumiracoxib groups than in the other groups (lumiracoxib 200 mg qd, n = 1; lumiracoxib 400 mg qd, n = 1; ibuprofen, n = 6; celecoxib, n = 6). There were 2 serious GI events in the celecoxib group and 3 in the ibuprofen group involving GI ulceration or bleeding that were consid-

Table 2. Change in the gastroduodenal mucosa during the study.

	Patients with Erosions at Study End, n	Patients with a Normal Mucosa at Study End, n	Patients who Developed Ulcers at Study End, n
Patients with erosions at baseline*			
Lumiracoxib 200 mg qd (n = 27)	5	18	1
Lumiracoxib 400 mg qd (n = 20)	3	11	3
Ibuprofen 800 mg tid (n = 32)	11	12	7
Celecoxib 200 mg qd (n = 30)	6	19	1
Patients with no erosions at baseline**			
Lumiracoxib 200 mg qd (n = 237)	18	189	10
Lumiracoxib 400 mg qd (n = 240)	16	204	7
Ibuprofen 800 mg tid (n = 228)	39	146	32
Celecoxib 200 mg qd (n = 228)	13	191	7

* 24 post-baseline assessments could not be made: lumiracoxib 200 mg (n = 4), lumiracoxib 400 mg (n = 6), ibuprofen (n = 9), and celecoxib (n = 5). ** 117 post-baseline assessments could not be made: lumiracoxib 200 mg (n = 30), lumiracoxib 400 mg (n = 20), ibuprofen (n = 43), and celecoxib (n = 24).

Table 3. Gastroduodenal injury after 13 weeks: number of patients (%); analyzed using modified safety population.

	Lumiracoxib 200 mg qd, n = 257	Lumiracoxib 400 mg qd, n = 253	Ibuprofen 800 mg tid, n = 248	Celecoxib 200 mg qd, n = 253
> 10 gastroduodenal erosions	3 (1.2)**	4 (1.6)*	15 (6.0)	6 (2.4)*
No visible injury of gastric musosa	186 (72.4)***	194 (76.7)***	137 (55.2)	191 (75.5)***
No visible injury of duodenal musosa	215 (83.7)*	221 (87.4)***	184 (74.2)	222 (87.7)***

* $p < 0.05$ versus ibuprofen. ** $p < 0.01$ versus ibuprofen. *** $p < 0.001$ versus ibuprofen.

Table 4. Adverse events (AE): number of patients (%).

Adverse Events	Lumiracoxib 200 mg qd, n = 264	Lumiracoxib 400 mg qd, n = 260	Ibuprofen 800 mg tid, n = 260	Celecoxib 200 mg qd, n = 258
Total no. with AE	196 (74.2)	187 (71.9)	202 (77.7)	183 (70.9)
Primary organ/system affected				
Gastrointestinal	133 (50.4)	124 (47.7)	144 (55.4)	120 (46.5)
Infections and infestations	79 (29.9)	78 (30.0)	75 (28.8)	58 (22.5)
Musculoskeletal, connective tissue, bone	16 (6.1)	19 (7.3)	14 (5.4)	27 (10.5)
Nervous system	41 (15.5)	48 (18.5)	50 (19.2)	44 (17.1)
AE reported in ≥ 5% of patients				
Upper abdominal pain	44 (16.7)	60 (23.1)	75 (28.8)	41 (15.9)
Dyspepsia	74 (28.0)	69 (26.5)	69 (26.5)	63 (24.4)
Nausea	13 (4.9)	9 (3.5)	14 (5.4)	12 (4.7)
Influenza	16 (6.1)	21 (8.1)	18 (6.9)	8 (3.1)
Nasopharyngitis	34 (12.9)	24 (9.2)	25 (9.6)	19 (7.4)
Headache	34 (12.9)	39 (15.0)	39 (15.0)	31 (12.0)
AE considered possibly related to study drug				
Total	121 (45.8)	113 (43.5)	140 (53.8)	111 (43.0)
Discontinuations related to AE				
Total	20 (7.6)	14 (5.4)	35 (13.5)	16 (16.2)
GI disorders	13 (4.9)	12 (4.5)	28 (10.8)	10 (3.9)

ered related to study treatment, compared to one in the lumiracoxib 200 mg qd group (abdominal pain) and one in the lumiracoxib 400 mg qd group (abdominal pain with superficial gastric ulceration). A single fatality due to hemopericardium occurred in the ibuprofen group, but was not considered related to study treatment.

Antacid rescue medication. The number of patients requiring antacid rescue medication was significantly

greater in the ibuprofen group than in the lumiracoxib 400 mg qd group (89.1% vs 83.0%; p = 0.05). There was no significant difference in the proportion of patients using antacid rescue medication in the lumiracoxib 200 mg qd (84.7%), the celecoxib (84.6%), and the ibuprofen groups. The mean number of tablets taken per day ranged from 1.2 to 1.4 across all treatment groups.

Efficacy. Although this study was not specifically designed to measure efficacy, mean change from baseline in pain and global disease activity were analyzed. There were no clinical or statistically significant differences between treatments in terms of the proportion of patients experiencing an improvement in overall joint pain intensity or global disease activity (patient's or physician's assessment; Figure 3).

DISCUSSION

Our large, multicenter, 13-week study aimed to determine if the incidence of endoscopically detected gastroduodenal ulcers was lower in patients with OA treated with lumiracoxib, compared with those treated with ibuprofen, using celecoxib as an active control treatment. The results show that, at the therapeutic dosages of 200 mg qd and 400 mg qd, the novel COX-2 selective inhibitor lumiracoxib is associated with significantly less gastric damage and fewer adverse events and consequently fewer discontinuations than the standard nonselective NSAID ibuprofen (800 mg tid).

A recent metaanalysis of drug usage in OA[15] showed that ibuprofen, one of the most widely prescribed standard NSAID globally, was associated with a lower overall risk of adverse events and risk from complicated upper GI events than a wide variety of other NSAID. It is a common first-line therapy for OA and has been used as the comparator in recent trials assessing the safety and tolerability of COX-2 selective inhibitors[4,6]. Ibuprofen was thus considered an appropriate comparator in this trial.

In this study, we found the cumulative frequency of gastroduodenal ulcers ≥ 3 mm in diameter to be significantly lower after treatment with lumiracoxib 200 mg qd and lumiracoxib 400 mg qd compared with ibuprofen 800 mg tid (Figure 2). A 5 mm ulcer diameter is frequently assessed in NSAID ulcer trials to exclude erosions, and is considered an acceptable standard for assessing the risk of developing increasingly serious lesions[16]. In our study, the secondary analysis of gastroduodenal ulcers ≥ 5 mm in diameter showed that both doses of lumiracoxib were associated with a significantly lower cumulative incidence of gastroduodenal ulcers ≥ 5 mm than ibuprofen. These findings, together with the fact that significantly fewer patients in the ibuprofen group had normal gastric or duodenal mucosa compared with either lumiracoxib group, not only illustrates the superior tolerability profile of lumiracoxib over ibuprofen but suggests there is no dose-related effect of lumiracoxib on the gastroduodenal mucosa.

Further support is provided by the observation that more patients in the ibuprofen group experienced adverse events considered possibly related to the study drug than in any other treatment group. Moreover, the proportion of patients treated with ibuprofen who discontinued because of GI adverse events was more than double that in either of the lumiracoxib or celecoxib groups. This suggests that GI events account for the majority of drug-related discontinuations with ibuprofen, a finding consistent with other comparative studies of COX-2 selective inhibitors and standard NSAID[17–19].

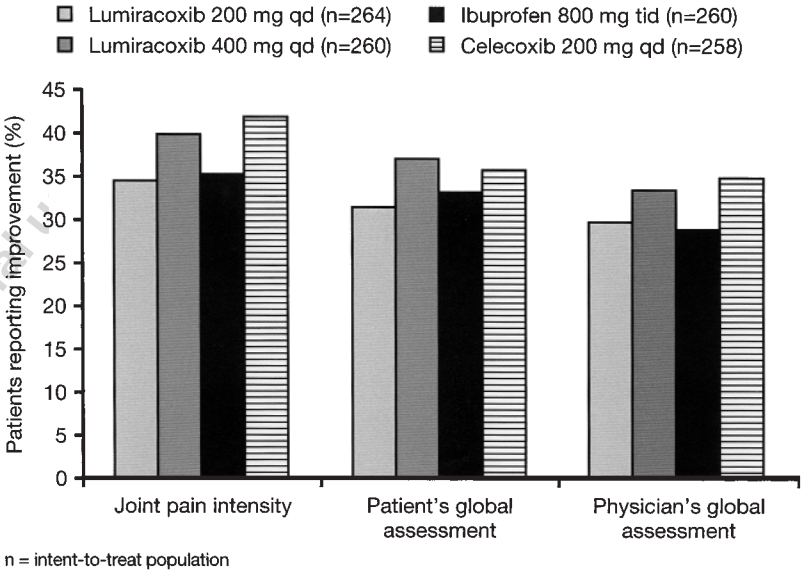

Figure 3. Percentage of patients with improvements in joint pain intensity and disease activity (global assessment by patients and physicians).

In summary, lumiracoxib at therapeutic doses is associated with a gastroduodenal safety and tolerability profile that is markedly superior to ibuprofen and similar to celecoxib. This profile shows lumiracoxib to be a well-tolerated alternative to standard NSAID.

REFERENCES

1. Moskowitz RW. The role of anti-inflammatory drugs in the treatment of osteoarthritis: a United States viewpoint. Clin Exp Rheumatol 2001;19 Suppl 25:S3–S8.
2. Dougados M. The role of anti-inflammatory drugs in the treatment of osteoarthritis: a European viewpoint. Clin Exp Rheumatol 2001;19 Suppl 25:S9–S14.
3. Singh G. Recent considerations in nonsteroidal anti-inflammatory drug gastropathy. Am J Med 1998;105:31S–38S.
4. 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.
5. Goldstein JL, Correa P, Zhao WW, et al. Reduced incidence of gastroduodenal ulcers with celecoxib, a novel cyclooxygenase-2 inhibitor, compared to naproxen in patients with arthritis. Am J Gastroenterol 2001;96:1019–27.
6. Hawkey C, Laine L, Simon T, et al. Comparison of the effect of rofecoxib (a cyclooxygenase 2 inhibitor), ibuprofen, and placebo on the gastroduodenal mucosa of patients with osteoarthritis: a randomized, double-blind, placebo-controlled trial. The Rofecoxib Osteoarthritis Endoscopy Multinational Study Group. Arthritis Rheum 2000;43:370–7.
7. Mangold JB, Gu H, Rodriguez LC, Scott G, Bonner J, Rordorf C. Pharmacokinetics and metabolism of lumiracoxib in healthy male subjects [abstract]. Drug Metab Rev 2002;34 Suppl 1:141.
8. Scott G, Rordorf C, Blood P, Branson J, Milosavljev, Greig G. Dose escalation study to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of COX189 in healthy subjects [abstract]. Ann Rheum Dis 2002;61 Suppl 1:242.
9. Schnitzer TJ, Geusens P, Hasler P, et al. Efficacy and safety of COX189 in osteoarthritis: a multi-national study [abstract]. Arthritis Rheum 2000;43 Suppl:S336.
10. Benevolenskaya L, Tüzün S, Hagin E, Moore A, Gimona A. Lumiracoxib is effective in relieving symptoms of knee or hip osteoarthritis after 4 weeks of treatment: results from a randomized, placebo-controlled trial [abstract]. Ann Rheum Dis 2003;62 Suppl 1:246.
11. Grifka J, Zacher J, Brown J, et al. Lumiracoxib is effective and well tolerated in patients with osteoarthritis of the hand: results from a randomized, placebo-controlled trial [abstract]. Ann Rheum Dis 2003;62 Suppl 1:222.
12. Altman R, Alarcon G, Appelrouth D, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hip. Arthritis Rheum 1991;34:505–14.
13. Altman R, Asch E, Bloch G, et al. Development of criteria for the classification and reporting of osteoarthritis: classification of osteoarthritis of the knee. Arthritis Rheum 1986;29:1039–49.
14. Altman R, Alarcon G, Appelrouth D, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hand. Arthritis Rheum 1990;33:1601–10.
15. Garcia Rodriguez LA. Nonsteroidal antiinflammatory drugs, ulcers and risk: a collaborative meta-analysis. Semin Arthritis Rheum 1997;26 Suppl 1:16–20.
16. Graham DY. High-dose famotidine for prevention of NSAID ulcers? Gastroenterology 1997;112:2143–5.
17. Langman MJ, Jensen DM, Watson DJ, et al. Adverse upper gastrointestinal effects of rofecoxib compared with NSAIDs. JAMA 1999;282:1929–33.
18. Hawkey CJ, Jackson L, Harper SE, Simon TJ, Mortensen E, Lines CR. Review article: the gastrointestinal safety profile of rofecoxib, a highly selective inhibitor of cyclooxygenase-2, in humans. Aliment Pharmacol Ther 2001;15:1–9.
19. Simon LS, Weaver AL, Graham DY, et al. Anti-inflammatory and upper gastrointestinal effects of celecoxib in rheumatoid arthritis: a randomized controlled trial. JAMA 1999;282:1921–8.