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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

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Objective. **To compare the clinical efficacy of rofecoxib, a specific inhibitor of cyclooxygenase 2 (COX-2), with that of diclofenac in patients with osteoarthritis (OA) and to evaluate the safety and tolerability of rofecoxib.**

Methods. **We performed a randomized, double-blind, active comparator–controlled trial in 784 adults with OA of the knee or hip. Patients were randomized to 1 of 3 treatment groups: 12.5 mg of rofecoxib once daily, 25 mg of rofecoxib once daily, and 50 mg of diclofenac 3 times daily. Clinical efficacy and safety were evaluated over a 1-year continuous treatment period.**

Results. **Rofecoxib at dosages of 12.5 and 25 mg demonstrated efficacy that was clinically comparable to that of diclofenac, as assessed by all 3 primary end points according to predefined comparability criteria. Results from secondary end points were consistent with those of the primary end points. There were small statistical differences favoring diclofenac for 2 of the end points. All treatments were well tolerated.**

Conclusion. **Rofecoxib was well tolerated and provided efficacy that was clinically comparable, according to predefined statistical criteria, to that of 150 mg of diclofenac per day in this 1-year study. Specific inhibition of COX-2 provided therapeutic efficacy in OA.**

Nonsteroidal antiinflammatory drugs (NSAIDs) are widely used in the treatment of osteoarthritis (OA) (1,2). Although NSAIDs effectively control mild-to-moderate joint pain associated with OA, their use is accompanied by the risk of significant gastrointestinal (GI) toxicity, including GI perforation, ulceration, and bleeding (PUB) (3–5).

NSAIDs act by inhibiting the synthesis of prostaglandins by the enzyme cyclooxygenase (COX) (6,7). Two COX isoforms are now recognized. COX-1, which is constitutively expressed, sustains the routine physiologic function of prostaglandins, including gastric mucosal protection; COX-2 is induced chiefly in response to pathologic processes, including pain and inflammation (5–8). Prostaglandins synthesized by the inducible COX-2 isoform mediate acute inflammatory responses in animal models (9).

In vitro and ex vivo assays have shown that NSAIDs are non–isoform specific, inhibiting both the COX-1 and COX-2 isoforms (10–16). Since prostaglandins are involved in the maintenance of GI mucosal integrity and since only the COX-1 isoform is present in the normal GI mucosa, the GI toxicity of NSAIDs has been proposed to result largely from inhibition of COX-1 activity (12,17–20). The therapeutic effects of NSAIDs may be primarily attributable to COX-2 inhibition (9,21,22). Therefore, agents that specifically inhibit COX-2 were developed and evaluated because of their potential to provide clinical efficacy comparable to

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that of NSAIDs with a reduced risk of GI toxicity (23–25).

Rofecoxib (VIOXX®; Merck, Rahway, NJ) is a specific inhibitor of COX-2 in humans. Using ex vivo human whole blood assays, rofecoxib showed dose-related inhibition of COX-2 activity (26). The degree of COX-2 inhibition was similar to that of NSAIDs. At doses of 15–40 times the proposed clinical dose, rofecoxib had no dose-dependent inhibition of COX-1 (27).

This report describes the results of a large, randomized, clinical trial comparing rofecoxib, 12.5 and 25 mg once daily, with diclofenac sodium, 50 mg 3 times daily, in the treatment of patients with knee and hip OA. In this study, rofecoxib provided efficacy in OA that, according to predefined statistical criteria, was clinically comparable to a high dose of the NSAID diclofenac. In a study using serial endoscopy for the presence of ulcers in OA patients, rofecoxib demonstrated a GI safety profile equivalent to that of placebo and significantly better than that of ibuprofen (28). Our findings, together with those reported by Laine et al (28), show that in the treatment of OA, rofecoxib is as effective as diclofenac and has the potential to improve the GI safety profile.

PATIENTS AND METHODS

All patients gave written informed consent before screening and enrollment in the study. The study protocol and procedures were approved by the institutional review boards for all investigative sites. The investigators who participated in the Rofecoxib Protocol 035 Study Group are listed in Appendix A.

Study design. Patients were screened (screening visit) to ensure study eligibility. Upon confirmation of eligibility (see entry criteria), patients were randomized (randomization visit) by a computer-generated allocation schedule to 1 of 3 treatment groups: rofecoxib 12.5 mg once daily, rofecoxib 25 mg once daily, or diclofenac 50 mg 3 times daily (150 mg/day). Study blinding was maintained by using a matching placebo for each study medication. Patients took 3 tablets each morning and 1 tablet at both midday and evening. Patients were provided open-label acetaminophen (maximum dosage of 2.6 gm/day) that could be taken for OA pain that was not adequately controlled by the study medication.

Patients returned to the study center following 2, 4, 8, 12, 19, 26, 33, 39, 45, and 52 weeks of therapy to assess both efficacy and safety. Patients who did not enter a voluntary extension at the end of the 1-year treatment period returned 7–10 days after their last dose of study medication for post-therapy safety assessments.

Entry criteria. Patients were a minimum of 40 years old and had both clinical and radiographic evidence of OA. Patients with OA of the knee or hip were eligible for study. Radiographic criteria for OA of the knee were joint space narrowing and the presence of osteophytes; the radiographic criterion for OA of the hip was joint space narrowing. The study joint (either the knee or the hip) had to be the primary source of pain or disability. Patients were in functional class I, II, or III according to the Steinbrocker criteria (29). The study included 2 groups of OA patients, based on the treatment they received for OA at the time of enrollment: those who took NSAIDs and those who took acetaminophen.

The NSAID group was assessed at the screening visit, and patients who satisfied entry criteria discontinued their NSAID therapy. Following a washout period, patients' pain when walking was assessed on a patient-reported 100-mm visual analog scale (VAS). Patients were randomized into the study if they had at least moderate pain when walking (40 mm) and a minimum increase in pain when walking (15 mm) compared with the level at screening. In addition, the physician's assessment of disease status had to be worse compared with the screening level.

The acetaminophen group was randomized if at both the screening and randomization visits (no acetaminophen allowed within 12 hours of assessments), the patients reported at least moderate pain when walking (40 mm). In addition, the patient's and physician's assessments of disease status had to be fair, poor, or very poor.

Women were postmenopausal or demonstrably nongravid. Patients were excluded if they had significant renal impairment, clinically significant abnormalities on physical or laboratory examinations at the screening visit, positive results on fecal occult blood testing, class III/IV angina or uncontrolled congestive heart failure, uncontrolled hypertension, a stroke or transient ischemic attack within 2 years of study, active hepatic disease, a history of recent neoplastic disease, or an allergy to acetaminophen or NSAIDs. Patients were excluded if they required aspirin at any dose, corticosteroids, warfarin, or ticlopidine.

Patients with a history of gastroduodenal ulcer or GI bleeding were allowed to participate.

Efficacy measurements and end points. Well-validated measurements of efficacy were obtained at screening, randomization, and following 2, 4, 8, 12, 26, 39, and 52 weeks of treatment. At each of these visits, the patients completed the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (30), and both the patients and the physicians completed an assessment of disease status. Patients and physicians completed an assessment of response to therapy following 2, 4, 8, 12, and 26 weeks of treatment.

There were 3 primary end points for this study: pain when walking (100-mm VAS, which is question 1 of the WOMAC), patient's assessment of response to therapy (5-point scale, where 0 = none and 4 = excellent), and physician's assessment of disease status (5-point scale, where 0 = very poor and 4 = very well). All 3 end points were used to determine clinical and statistical comparability, as described in the statistical section (see below).

Other end points were patient's assessment of disease status (100-mm VAS, where 0 = very well and 100 = very poor), physician's assessment of response to therapy (5-point scale, where 0 = none and 4 = excellent), WOMAC subscales of Pain, Stiffness, and Functional Ability (100-mm VAS), study-joint tenderness (0–3 scale, where 0 = no pain and 3 = patient states that there is pain; winces and withdraws), and amount of rescue acetaminophen consumed (number of 325-mg tablets).

Safety assessments. Spontaneously reported adverse experiences were recorded throughout the study. Vital signs

Table 1. Baseline characteristics of the patients, according to treatment group*

Characteristic	Rofecoxib 12.5 mg (n = 259)	Rofecoxib 25 mg (n = 257)	Diclofenac, 150 mg (n = 268)	Total (n = 784)
Female sex, no. (%)	169 (65.3)	175 (68.1)	185 (69.0)	529 (67.5)
Race, no. (%)				
White	236 (91.1)	229 (89.1)	237 (88.4)	702 (89.5)
African American	19 (7.3)	23 (8.9)	23 (8.6)	65 (8.3)
Other	4 (1.5)	5 (1.9)	8 (3.0)	17 (2.2)
Age, mean ± SD years	62.8 ± 10.2	62.8 ± 10.3	62.5 ± 10.1	63.6 ± 10.2
Weight, mean ± SD kg	92.4 ± 22.2	87.9 ± 19.6	88.0 ± 21.0	89.4 ± 21.0
Duration of OA, mean ± SD years	11.1 ± 8.9	11.5 ± 8.7	11.4 ± 9.4	8.7 ± 9.0
Functional class, no. (%)				
Class I	31 (12.0)	39 (15.2)	38 (14.2)	109 (13.9)
Class II	173 (66.8)	176 (68.5)	168 (62.7)	517 (65.9)
Class III	54 (20.8)	42 (16.3)	62 (23.1)	158 (20.2)
Study joint, no. (%)				
Hip	61 (23.6)	68 (26.5)	61 (22.8)	190 (24.2)
Knee	198 (76.4)	189 (73.5)	207 (77.2)	594 (75.8)
Previous OA medication use, no. (%)				
NSAIDs	240 (92.7)	238 (92.6)	242 (90.3)	720 (91.8)
Acetaminophen	19 (7.3)	19 (7.4)	26 (9.7)	64 (8.2)
Primary outcome measure†				
Pain when walking (WOMAC), 0–100-mm VAS	75.9 ± 15.0	77.5 ± 14.7	75.8 ± 15.4	76.4 ± 15.0
Physician's assessment of disease status, 0–4 Likert scale	2.9 ± 0.7	2.9 ± 0.7	3.0 ± 0.7	2.9 ± 0.7

* Duration of osteoarthritis (OA) was determined by patient report. Functional class was determined according to the Steinbrocker criteria. NSAIDs = nonsteroidal antiinflammatory drugs; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; VAS = visual analog scale.
† The third primary outcome measure, patient's assessment of response to therapy, was not examined past week 26 and does not have baseline (randomization) values because it assessed the patient's response to therapy.

were monitored at every visit. Laboratory investigations, including hematology, blood chemistry, and a urinalysis, were performed at all visits. For all clinical adverse experiences, the investigator recorded the intensity, the relation to test drug, the outcome, and any action taken. The investigator also determined if a laboratory adverse event was study-drug related.

Statistical analysis. This study tested the hypothesis that rofecoxib, 12.5 mg and 25 mg once daily, would have clinical efficacy comparable to that of diclofenac, 50 mg 3 times daily. As a comparability trial, specific predefined criteria were established. Clinical comparability was declared if the following criteria were met: for all 3 primary end points, the 95% confidence intervals (95% CIs) of the difference in the mean treatment response between 2 treatments were within ±10 mm on a 100-mm VAS and ±0.5 on a Likert scale. These clinical comparability bounds are more conservative than those proposed by a consensus of academic rheumatologists and employed in a study comparing meloxicam with diclofenac (31,32). This study had >99% power to demonstrate compa-

Table 2. Numbers of patients who entered, completed, and discontinued the study, according to treatment group

Study status	Rofecoxib 12.5 mg	Rofecoxib 25 mg	Diclofenac, 150 mg	Total
Entered the study, no. of patients	259	257	268	784
Completed the study, no. (%)	161 (62.2)	142 (55.3)	145 (54.1)	448 (57.1)
Discontinued the study, no. (%)	98 (37.8)	115 (44.7)	123 (45.9)	336 (42.9)
Clinical adverse experience	37 (14.3)	32 (12.5)	41 (15.3)	110 (14.0)
Laboratory adverse experience	1 (0.4)	2 (0.8)	14 (5.2)	17 (2.2)
Lack of efficacy	36 (13.9)	56 (21.8)	43 (16.0)	135 (17.2)
Deviation from protocol	10 (3.9)	12 (4.7)	11 (4.1)	33 (4.2)
Patient withdrew consent	9 (3.5)	9 (3.5)	11 (4.1)	29 (3.7)
Other*	5 (1.9)	4 (1.6)	3 (1.1)	12 (1.5)

* Includes patients who moved and patients who were lost to followup.

rable efficacy (according to the criteria cited) between 25 mg of rofecoxib and diclofenac if their true difference is 0.

For the determination of comparability, the 3 primary end points were analyzed as the averaged response over the 52-week treatment period (first 26 weeks only for patient's assessment of response to therapy). All data collected from discontinuation and unscheduled visits were included in this analysis; no missing values were imputed. The comparability analysis was also performed on data from the first 12 weeks and the first 26 weeks.

The responses of primary and secondary end points were analyzed using an analysis of covariance model, with treatment, study center, and history of ulcer or upper GI bleeding as main effects, and baseline as the covariate. For end points without baseline measurements (i.e., patient's/physician's assessment of response to therapy), the baseline value of a relevant variable (i.e., patient's/physician's assessment of disease status) was used as the covariate in the model.

RESULTS

Between November 1996 and April 1997, 1,128 patients were screened, and 784 (69.5%) were enrolled into the study. Patients not randomized were excluded for a variety of reasons, including failure to meet OA diagnostic criteria (13.8%), abnormalities found on screening physical or laboratory examinations (12.1%), failure to satisfy randomization OA activity criteria (1.3%), and their reconsideration of participation in the study (4.2%). All treatment groups had similar baseline characteristics and primary efficacy outcome measures at enrollment (Table 1). All randomized patients with OA of the knee and 96% of those with OA of the hip fulfilled the American College of Rheumatology classification criteria for OA of those regions (33,34).

A total of 448 of the 784 patients (57.1%) completed 1 year of study therapy (Table 2); the overall discontinuation incidence was similar among treatment groups. There were no statistically significant differences in the incidence of discontinuation because of lack of efficacy of the study therapy or clinical adverse experience among the treatment groups. The increased discontinuation rate because of laboratory adverse experiences in the diclofenac group was due to elevations in serum transaminases, as discussed later in the Results (see below).

Efficacy. Figure 1 presents the response over time for all 3 primary end points. Both pain when walking and physician's assessment of disease status, the 2 end points evaluated at baseline (randomization), demonstrated significant improvements from baseline for all treatment groups. The mean response for the primary end point of patient's assessment of response to therapy was similar among all treatment groups. This end point was not examined past week 26 and does not have baseline values because it assessed the patients' response to therapy.

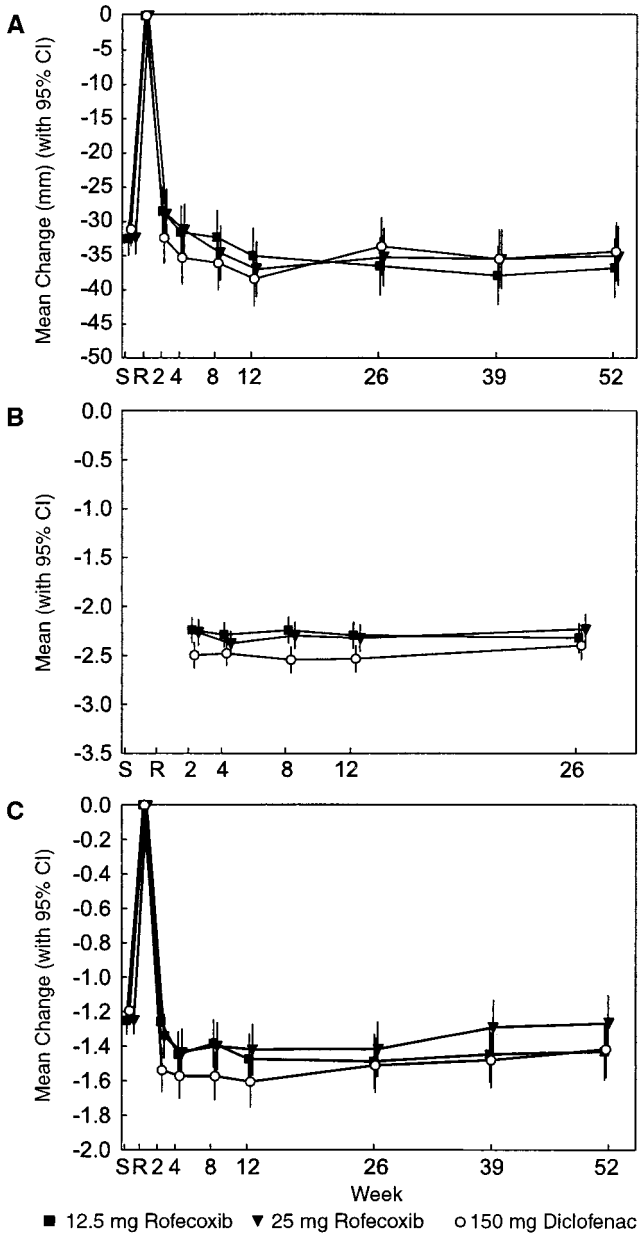

Figure 1. Treatment response over time for the 3 primary clinical efficacy end points: **A**, pain when walking (baseline mean 76.4 mm on a 100-mm visual analog scale), **B,** patient's assessment of response to therapy (not assessed at baseline visit), and **C,** physician's assessment of disease status (baseline mean 2.9 on a 5-point scale, where 0 = very poor and 4 = very well). Scales in **A** and **C** were normalized to the randomization mean; the scale in **B** was inverted for consistency with other end points. On all graphs, decreasing values indicate improvement. S = screening visit; R = randomization visit; 95% CI = 95% confidence interval.

For all primary end points, treatment responses

Table 3. Comparability analysis for the 3 primary end points over 1 year or 6 months of treatment, as indicated*

Primary end point	Comparing 25 mg of rofecoxib with 150 mg of diclofenac	Comparing 12.5 mg of rofecoxib with 150 mg of diclofenac
Pain when walking (WOMAC question 1), 0–100-mm VAS	1.98 (−1.66, 5.62)	1.81 (−1.85, 5.44)
Patient's assessment of response to therapy, 0–4 Likert scale†	0.19 (0.05, 0.33)	0.24 (0.10, 0.38)
Physician's assessment of disease status, 0–4 Likert scale	0.17 (0.05, 0.29)	0.13 (0.01, 0.25)

* Comparability was defined as the difference in the least squares mean (95% confidence interval), and must be within ±10 mm on the visual analog scale (VAS) and ±0.5 units on the Likert scale. Positive mean differences favor diclofenac over rofecoxib. WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.
† Data for this end point were not collected after week 26; therefore, the analysis concerns the first 26 weeks of treatment.

were seen within 2 weeks (first time point measured) for all treatment groups. The treatment responses were sustained throughout the entire year of treatment (or 26 weeks for patient's assessment of response to therapy) at a generally consistent level.

The primary hypothesis of this study was that rofecoxib would provide comparable clinical efficacy to that of diclofenac in the treatment of OA. To test this hypothesis, comparability criteria for the 3 primary end points were prespecified (as discussed in Patients and Methods). The difference in the mean treatment response between 2 treatments is calculated as treatment A minus treatment B, and this difference has an associated 95% CI. The 2 treatments would be considered clinically comparable if the 95% CI of the difference does not extend beyond the predefined bound of ±10 mm on the VAS and ±0.5 on the Likert scale.

Table 3 presents the comparability data. For all 3 primary end points, the 95% CIs for the difference in the mean treatment response for each of the treatment pairs (25 mg of rofecoxib and diclofenac; 12.5 mg of rofecoxib and diclofenac) were within the predefined comparability bound. Thus, both 12.5 and 25 mg of rofecoxib demonstrated clinical efficacy comparable to that of 150 mg diclofenac over 1 year of continued treatment. The same conclusion was reached when comparability was analyzed for the first 12 weeks or the first 26 weeks of treatment.

There were small differences favoring diclofenac compared with rofecoxib for 2 end points that reached statistical significance: patient's assessment of response to therapy and physician's assessment of disease status.

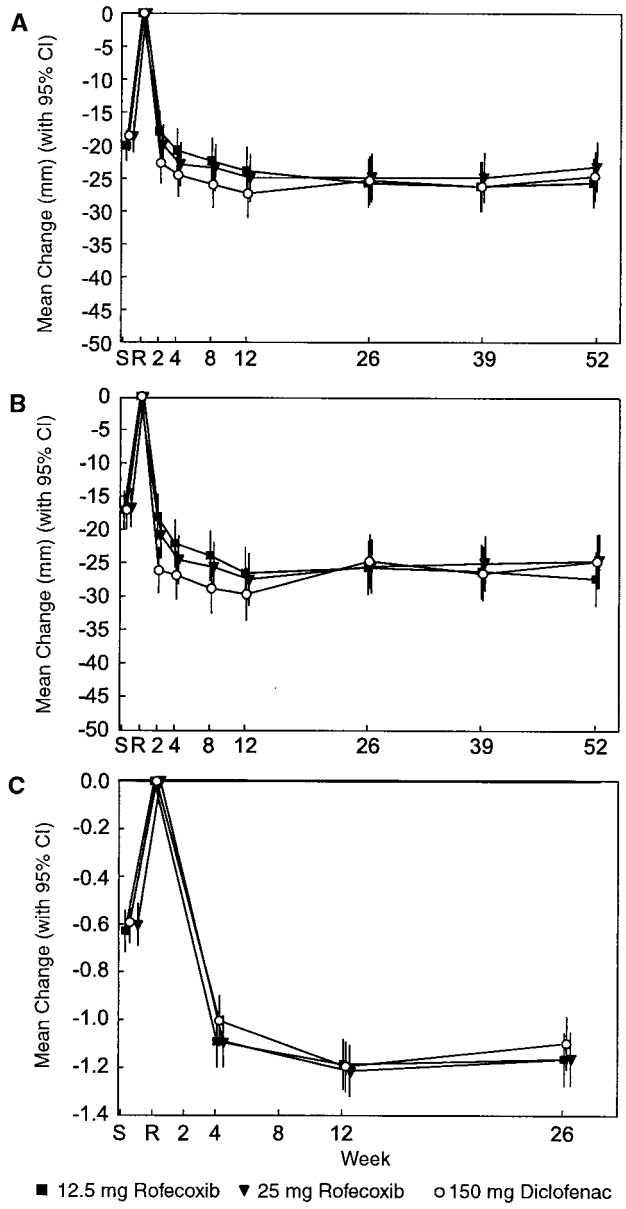

Figure 2. Treatment responses over time for the 3 secondary end points: **A,** Physical Function subscale of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (baseline mean 69.6 on a 100-mm visual analog scale [VAS]), **B,** Stiffness subscale of the WOMAC (baseline mean 72.9 on a 100-mm VAS), and **C,** study-joint tenderness (baseline mean 2.0 on a 0–3 scale, where 0 = no pain and 3 = patient states that there is pain; winces and withdraws). Study-joint tenderness was not assessed after week 26. Scales were normalized to the randomization mean. On all graphs, decreasing values indicate improvement. S = screening visit; R = randomization visit; 95% CI = 95% confidence interval.

Table 4. Summary of secondary efficacy end points over the 12-month treatment period*

Efficacy end point	Rofecoxib 12.4 mg (n = 259)	Rofecoxib 25 mg (n = 257)	Diclofenac, 150 mg (n = 268)
Pain subscale (WOMAC), 0–100-mm VAS	−26.7 (−29.5, −23.9)	−27.3 (−30.1, −24.42)	−29.6 (−32.4, −26.8)
Physical Function subscale (WOMAC), 0–100-mm VAS	−23.4 (−26.4, −20.4)	−23.8 (−26.8, −20.7)	−25.8 (−28.9, −22.8)
Stiffness subscale (WOMAC), 0–100-mm VAS	−24.5 (−27.7, −21.3)	−25.2 (−28.4, −22.0)	−27.7 (−30.9, −24.5)
Patient's assessment of disease status, 0–100-mm VAS	−28.5 (−31.7, −25.3)	−27.1 (−30.3, −23.9)	−31.5 (−34.7, −28.3)
Physician's assessment of response to therapy, 0–4 Likert scale†	−2.5 (−2.66, −2.43)	−2.5 (−2.61, −2.39)	−2.8 (−2.9, −2.6)
Study-joint tenderness, 0–3 Likert scale	−1.1 (−1.2, −1.0)	−1.2 (−1.3, −1.1)	−1.1 (−1.2, −1.0)
Acetaminophen use (for rescue), tablets/day	0.8 (0.7, 0.9)	0.8 (0.7, 0.9)	0.7 (0.6, 0.8)

* Values are the least squares mean (95% confidence interval), representing the mean change from the time of randomization. Negative values indicate improvement in the end point compared with randomization (visit 2), except for acetaminophen use. See Table 1 for definitions.
† Data for this end point were not collected after week 26; therefore, the analysis concerns the first 26 weeks of treatment.

However, these differences and their respective 95% CIs were within the comparability bounds predefined for this study.

OA is a complex disease with multiple clinical manifestations. Secondary end points were collected to assess the response to treatment in a variety of domains. The secondary end points of the WOMAC Stiffness subscale, WOMAC Physical Function subscale, and study-joint tenderness (Figure 2) demonstrated significant changes from baseline in all treatment groups. Results for additional secondary end points were consistent with the finding of clinical comparability among treatment groups (Table 4).

The consistency of the treatment effects of rofecoxib and diclofenac among patients of various subgroups was compared. Treatment-by-factor analysis for the 3 primary end points showed that there was no statistically significant interaction with treatment for various subgroups, including location of the study joint (knee or hip), previous OA medication (NSAID or acetaminophen), age, and sex.

Safety. All safety data are reported for the entire 1-year treatment period. The incidence of each clinical adverse event and drug-related (as assessed by the investigator) adverse event was similar among the treatment groups. The most frequent adverse events were upper respiratory infection and sinusitis; the most frequent GI adverse events were nausea, diarrhea, and heartburn (Table 5). The differences in incidence of GI adverse events were not statistically significant.

The incidence of patients who discontinued the study because of clinical adverse events was similar among the 3 treatment groups (Table 2). The majority of discontinuations were because of adverse experiences related to the GI or cardiovascular systems. Patients discontinued because of GI symptoms at a similar incidence (4.6%, 3.1%, and 3.7% in the 12.5-mg rofecoxib, 25-mg rofecoxib, and diclofenac groups, respectively). Patients discontinued because of cardiovascular events at a similar incidence (2.3%, 3.1%, and 3.7% in the 12.5-mg rofecoxib, 25-mg rofecoxib, and diclofenac groups, respectively). The most frequent individual adverse experiences resulting in discontinuation were diarrhea, dyspepsia, epigastric discomfort, and myocardial infarction (Table 5). No single adverse experience accounted for discontinuation in >2 patients per treatment group.

A total of 2, 2, and 3 patients in the 12.5-mg rofecoxib, 25-mg rofecoxib, and diclofenac groups, respectively, experienced a symptomatic gastric or duodenal ulcer. There were no episodes of GI bleeding in this study.

The incidence of drug-related lower extremity

Table 5. Summary of adverse experiences*

	Rofecoxib 12.5 mg (n = 259)	Rofecoxib 25 mg (n = 257)	Diclofenac, 150 mg (n = 268)
Any clinical adverse event	86.9	84.0	86.2
Any drug-related clinical adverse event†	30.9	30.4	32.5
Most frequent adverse event			
Upper respiratory infection	23.9	25.7	17.9
Sinusitis	8.9	7.4	7.1
Most frequent GI adverse event			
Nausea	6.2	7.4	9.7
Diarrhea	6.9	12.1	10.4
Heartburn	5.4	5.1	3.0
Any laboratory adverse event	14.4	18.4	27.4
Discontinuation due to adverse event			
Diarrhea	0.4	0.8	0.4
Dyspepsia	0.4	0.8	0.0
Epigastric discomfort	0.8	0.0	0.7
Myocardial infarction	0.4	0.4	0.7

* Values are percentages of patients. GI = gastrointestinal.
† Determined by the investigator to be possibly, probably, or definitely medication related.

Table 6. Blood pressure and serum creatinine levels over time*

Variable, treatment group	Screening visit	Week 12	Week 26	Week 52
Systolic blood pressure (mm Hg)				
Rofecoxib 12.5 mg	136.7 ± 16.5	136.2 ± 15.6	134.4 ± 17.3	136.8 ± 17.4
Rofecoxib 25 mg	135.6 ± 15.4	136.9 ± 16.7	133.9 ± 14.9	136.8 ± 17.0
Diclofenac 150 mg	136.4 ± 16.3	134.9 ± 14.7	134.3 ± 15.4	133.7 ± 16.3
Diastolic blood pressure (mm Hg)				
Rofecoxib 12.5 mg	80.8 ± 7.8	79.9 ± 8.2	80.1 ± 8.2	80.2 ± 8.0
Rofecoxib 25 mg	80.4 ± 8.4	81.0 ± 9.4	79.5 ± 9.0	81.5 ± 9.6
Diclofenac 150 mg	81.0 ± 8.7	79.9 ± 9.3	79.1 ± 9.7	79.8 ± 8.9
Serum creatinine (mg/dl)				
Rofecoxib 12.5 mg	1.14 ± 0.2	1.15 ± 0.2	1.14 ± 0.2	1.11 ± 0.2
Rofecoxib 25 mg	1.13 ± 0.2	1.16 ± 0.2	1.16 ± 0.2	1.13 ± 0.2
Diclofenac 150 mg	1.13 ± 0.2	1.15 ± 0.2	1.15 ± 0.2	1.10 ± 0.2

* Values are the mean ± SD.

edema (reported by the patient) over the year of treatment was similar among the treatment groups (3.9%, 1.9%, and 3.4% in the 12.5-mg rofecoxib, 25-mg rofecoxib, and diclofenac groups, respectively). The clinical significance of these events was minor, since over the entire 1-year duration of the study, only a single patient (12.5-mg rofecoxib group) discontinued therapy because of lower extremity edema and most cases resolved with continuation of treatment. There were 4 episodes of congestive heart failure: 1 in the 12.5-mg rofecoxib group and 3 in the diclofenac group. There were no meaningful changes in blood pressure or serum creatinine levels over the year of treatment among the 3 groups (Table 6). No patient had a clinical episode of acute renal failure.

There were more laboratory adverse events in the diclofenac group compared with the rofecoxib groups, largely due to a greater incidence of increased serum aminotransferase levels. The diclofenac group had pronounced mean changes in alanine and aspartate aminotransferase levels compared with the rofecoxib groups (Figure 3). These elevations caused 11 diclofenac patients (4.1%) to discontinue therapy, compared with none of the patients in the rofecoxib groups.

Because of its action in inhibiting the function of platelets, prolonged therapy with low-dose aspirin reduces the risk of thromboembolic cardiovascular events (35). Although a similar epidemiologic case has not been made for NSAIDs, there has been a theoretical concern that specific inhibition of COX-2, which does not effect platelet function, may not protect the cardiovascular system to the same extent as NSAIDs. In this 1-year study that included patients with cardiovascular risk factors (hypertension in 45%, angina in 3%, hypercholesterolemia in 16%, and diabetes in 7%), the incidence of thromboembolic cardiovascular events, such as myocardial infarction, stroke, transient ischemic attack, and peripheral arterial occlusions, was numerically lower in the rofecoxib groups (1.5%, 2.3%, and 3.4% in the 12.5-mg

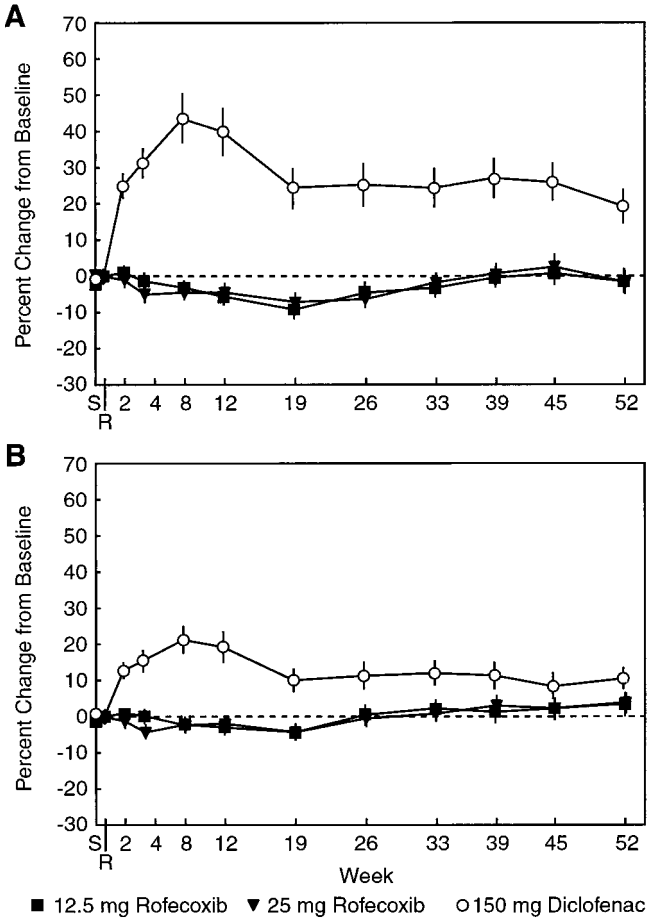

Figure 3. Aminotransferase values over time, expressed as the geometric mean percentage of change from baseline. **A,** Alanine aminotransferase; **B,** aspartate aminotransferase. See Figure 1 for definitions.

rofecoxib, 25-mg rofecoxib, and diclofenac groups, respectively).

DISCUSSION

The discovery of 2 isoforms of COX, the target enzyme inhibited by NSAIDs, poses a number of questions concerning the role of COX-1 and COX-2 in the efficacy and safety of this widely prescribed class of drugs. Previous studies have demonstrated that specific COX-2 inhibitors are efficacious in the treatment of OA, but did not answer the question as to how that efficacy compares with the efficacy of NSAIDs (36).

In this study, the efficacy of rofecoxib was comparable to that of a high dose of the NSAID diclofenac. Predefined clinical comparability criteria were used for the primary analysis because the scientific question of interest was whether rofecoxib had clinical efficacy comparable to that of an NSAID in the treatment of OA. Small statistical differences favoring diclofenac compared with 25 mg of rofecoxib were seen for 2 of the end points: <0.20 Likert units for patient's assessment of response to therapy and physician's assessment of disease status. These differences and the associated 95% CI were well within the clinical comparability bounds prespecified for this study. These bounds are more conservative than those recommended by a panel of expert rheumatologists (31). In addition, 0.2 Likert units is markedly smaller than the recently determined minimal perceptible clinical improvement of 0.5 units for these end points in OA studies (37). Thus, both the 12.5-mg and the 25-mg doses of rofecoxib are clinically comparable by the strict, prespecified comparability criteria to diclofenac for all 3 primary end points.

In addition, the effects of rofecoxib on a variety of the clinical manifestations of OA, as assessed by secondary end points, were comparable to those of diclofenac for all end points. These results were obtained in a representative population of OA patients, and the results were consistent across study joint, age, and sex.

There are several potential limitations to this study. No placebo group was included in the study because of the inability to maintain patients who have painful OA symptoms on a regimen of placebo for 1 year. The treatment responses in this study were markedly similar to those of rofecoxib groups in other placebo-controlled trials that clearly demonstrated significant differences compared with placebo (36,38). In addition, the responses seen with rofecoxib were comparable to those seen with high doses of diclofenac, an NSAID widely accepted as efficacious in the treatment of OA.

All studies are subject to dropouts, which affect the interpretation of the data. The 43% incidence of discontinuation for this 1-year study was less than that of a long-term study of OA comparing naproxen with acetaminophen (39). When adjusted for duration of exposure, it is lower than the 30–34% discontinuation rate for 12-week OA studies without placebo controls (40,41). The overall incidence of discontinuation was similar among all treatment groups. The effects of dropouts on the results were minimized by employing an intention-to-treat analysis and by not imputing values for patients who discontinued.

Overall, during 1 year of treatment, all treatments were generally well tolerated. It is important to note that no adverse event unique to the specific inhibition of COX-2 was observed in the rofecoxib treatment groups. The overall incidences of adverse events and discontinuations for clinical adverse events were similar among the treatment groups.

The hypothesis of improved GI safety and tolerability for inhibitors that are specific for COX-2 cannot be answered with the results of a single trial. Early published results for rofecoxib and celecoxib demonstrate an improved GI safety profile compared with NSAIDs (42,43). An endoscopic study of OA patients confirmed the significantly improved GI safety profile of rofecoxib in comparison to standard NSAID therapy (28). In that study, patients who received rofecoxib (25 and 50 mg) had significantly fewer endoscopic gastroduodenal ulcers compared with those who received ibuprofen (2.4 gm) over 6 months of treatment (9.6%, 14.7%, and 45.8% for the 25-mg rofecoxib, 50-mg rofecoxib, and ibuprofen groups, respectively). In addition, the incidence of endoscopic gastroduodenal ulcers in the rofecoxib group was equivalent to placebo for the 12-week placebo treatment period.

In the present 1-year study, there were fewer symptomatic ulcers in the combined rofecoxib groups (0.8%) compared with the diclofenac group (1.2%). The numbers of patients in the study were too small to support a conclusion of a decrease in the incidence of PUB events. A combined analysis of all OA clinical studies has been performed and demonstrated a statistically important decrease in PUBs for rofecoxib-treated patients compared with NSAID-treated patients (44). Thus, based both on the endoscopy data and the analysis of clinical PUB events, rofecoxib appears to have a meaningful improvement in GI safety compared with NSAIDs.

Treatment with rofecoxib for 1 year did not have

an effect on serum aminotransferase levels. In contrast, the elevations in serum aminotransferase levels in the diclofenac group were consistent with the published experience (45).

The most common renal effects of NSAIDs attributable to the inhibition of COX are a reduction in glomerular filtration rate (GFR) and reductions in the excretion of sodium, with the potential for fluid retention and edema. The intrarenal distribution and regulation of renal COX-2 by sodium intake suggests a role for this enzyme in renal physiology and in the renal effects of NSAIDs (46,47). It has been previously shown that the acute (24–48 hours postdose) sodium-retaining effect of 50-mg rofecoxib is comparable to that of the NSAID indomethacin (48). This effect resolves over the 14 days of treatment with rofecoxib, in contrast to the persistence of this effect with indomethacin. In addition, rofecoxib did not significantly affect the GFR (48). In this 1-year study, the renal effects of rofecoxib were similar to those of diclofenac, as assessed by spontaneous reports of lower extremity edema. Most of these events resolved while continuing study therapy, and few patients discontinued treatment because of these events. There were no significant effects on the mean diastolic or systolic blood pressure or on serum creatinine levels.

In summary, the specific inhibition of COX-2 with rofecoxib at a dosage of 12.5 mg and 25 mg once daily provided comparable clinical efficacy to that of diclofenac 50 mg 3 times daily in the treatment of OA of the knee and hip. Rofecoxib was generally well tolerated.

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REFERENCES

1. Lane NE. Pain management in osteoarthritis: the role of COX-2 inhibitors. J Rheumatol 1997;24 Suppl 49:20–4.
2. Brandt KD. Osteoarthritis. In: Isselbacher KJ, Braunwald E, Wilson J, Martin J, Fauci A, Kasper D, editors. Harrison's principles of internal medicine. 12th ed. New York: McGraw-Hill; 1991. p. 1475–9.
3. Fries JF. NSAID gastropathy: the second most deadly rheumatic disease? Epidemiology and risk appraisal. J Rheumatol 1991;18 Suppl 28:6–10.
4. Garcia Rodriguez LA, Cattaruzzi C, Troncon MG, Agostinis L. Risk of hospitalization for upper gastrointestinal tract bleeding associated with ketorolac, other nonsteroidal anti-inflammatory drugs, calcium antagonists, and other antihypertensive drugs. Arch Intern Med 1998;158:33–9.
5. Richardson C, Emery P. The clinical implications of inhibition of the inducible form of cyclo-oxygenase. Drug Saf 1996;15:249–60.
6. Vane JR, Botting RM. New insights into the mode of action of anti-inflammatory drugs. Inflamm Res 1995;44:1–10.
7. De Brum-Fernandes AJ. New perspectives for nonsteroidal anti-inflammatory therapy. J Rheumatol 1997;24:246–8.
8. Donnelly MT, Hawkey CJ. COX-II inhibitors: a new generation of safer NSAIDs? Aliment Pharmacol Ther 1997;11:227–36.
9. Masferrer JL, Zweifel BS, Manning PT, Hauser SD, Leahy KM, Smith WG, 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.
10. O'Neill GP, Mancini JA, Kargman S, Yergey J, Kwan MY, Falgueyret JP, et al. Overexpression of human prostaglandin G/H synthase-1 and -2 by recombinant vaccinia virus: inhibition by nonsteroidal anti-inflammatory drugs and biosynthesis of 15-hydroxyeicosatetraenoic acid. Mol Pharmacol 1994;45:245–54.
11. Laneuville O, Breuer DK, Dewitt DL, Hla T, Funk CD, Smith WL. Differential inhibition of human prostaglandin endo-peroxide H synthases-1 and -2 by nonsteroidal anti-inflammatory drugs. J Pharmacol Exp Ther 1994;271:927–34.
12. Meade EA, Smith WL, deWitt DL. Differential inhibition of prostaglandin endoperoxide synthase (cyclooxygenase) isozymes by aspirin and other non-steroidal anti-inflammatory drugs. J Biol Chem 1993;268:6610–4.
13. Kargman S, Charleson S, Cartwright M, Frank J, Riendeau D, Mancini J, et al. Characterization of prostaglandin G/H synthase 1 and 2 in rat, dog, monkey, and human gastrointestinal tracts. Gastroenterology 1996;111:445–54.
14. Berg J, Christoph T, Widerna M, Bodenteich A. Isoenzyme specific cyclooxygenase inhibitors: a whole cell assay system using the human erythroleukemic cell line HEL and the human monocytic cell line mono mac 6. J Pharmacol Toxicol Methods 1997;37:179–86.
15. Wong E, DeLuca C, Boily C, Charleson S, Cromlish W, Denis D, et al. Characterization of autocrine inducible prostaglandin H synthase-2 (PGHS-2) in human osteosarcoma cells. Inflamm Res 1997;46:51–9.
16. Miralpeix M, Camacho M, Lopez-Belmonte J, Canalias F, Beleta J, Palacios JM, et al. Selective induction of cyclo-oxygenase-2 activity in the permanent human endothelial cell line HUV-EC-C: biochemical and pharmacological characterization. Br J Pharmacol 1997;121:171–80.
17. Langman MJS, Weil J, Wainwright P, Lawson DH, Rawlins MD, Logan RFA, et al. Risks of bleeding peptic ulcer associated with individual non-steroidal anti-inflammatory drugs. Lancet 1994;343:1075–8.
18. Fries JF. Assessing and understanding patient risk. Scand J Rheumatol Suppl 1992;92:21–4.
19. Gabriel SE, Jaakkimainen L, Bombardier C. Risk for serious gastrointestinal complications related to use of nonsteroidal anti-inflammatory drugs: a meta-analysis. Ann Intern Med 1991;115:787–96.
20. Bakhle YS, Botting RM. Cyclooxygenase-2 and its regulation in inflammation. Med Inflamm 1996;5:305–23.
21. Seibert K, Masferrer JL. Role of inducible cyclooxygenase (COX-2) in inflammation. Receptor 1994;4:17–23.
22. Chan CC, Boyce S, Brideau C, Ford-Hutchinson AW, Gordon R, Guay D, et al. Pharmacology of a selective cyclooxygenase-2 inhibitor, L745.337—a novel nonsteroidal anti-inflammatory agent with an ulcerogenic sparing effect in rat and nonhuman primate stomach. J Pharmacol Exp Ther 1995;274:1531–7.
23. Vane JR, Botting RM. New insights into the mode of action of anti-inflammatory drugs. Inflamm Res 1995;44:1–10.
24. Griswold DE, Adams JL. Constitutive cyclooxygenase (COX-1) and inducible cyclooxygenase (COX-2): rationale for selective inhibition and progress to date. Med Res Rev 1996;16:181–206.
25. Prasit P, Riendeau D. Selective cyclooxygenase 2 inhibitors. Annu Rep Med Chem 1997;30:179–88.

26. Brideau C, Kargman S, Liu S, Dallob AL, Ehrich EW, Rodger IW, et al. A human whole blood assay for clinical evaluation of biochemical efficacy of cyclooxygenase inhibitors. Inflamm Res 1996;45:68–74.
27. Ehrich E, Dallob A, van Hecken A, Depré M, DeLepeleire I, Brideau C, et al. Demonstration of selective COX-2 inhibition by MK-966 in humans [abstract]. Arthritis Rheum 1996;39 Suppl 9:S81.
28. Laine L, Harper S, Simon T, Bath R, Johanson J, Schwartz H, et al. A randomized trial comparing the effects of rofecoxib, a cyclooxygenase 2-specific inhibitor, with that of ibuprofen on the gastroduodenal mucosa of patients with osteoarthritis. Gastroenterology 1999;117:776–83.
29. Steinbrocker O, Traeger CH, Batterman RC. Therapeutic criteria in rheumatoid arthritis. JAMA 1949;140:659–62.
30. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol 1988;15:1833–40.
31. Bellamy N, Carette S, Ford PM, Kean WF, leRiche NGH, Lussier A, et al. Osteoarthritis antirheumatic drug trials. III. Setting the delta for clinical trials—results of a consensus development (Delphi) exercise. J Rheumatol 1992;19:451–7.
32. Hawkey C, Kahan A, Steinbruck K, Alegre C, Baumelou E, Begaud B, et al. Gastrointestinal tolerability of meloxicam compared to diclofenac in osteoarthritis patients. Br J Rheumatol 1998;37:937–45.
33. Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, et al. Development of criteria for the classification and reporting of osteoarthritis: classification of osteoarthritis of the knee. Arthritis Rheum 1986;29:1039–49.
34. Altman R, Alarcón G, Appelrouth D, Bloch D, Borenstein D, Brandt K, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hip. Arthritis Rheum 1991;34:505–14.
35. The Steering Committee of the Physicians' Health Study Research Group. Preliminary report: findings from the aspirin component of the ongoing physicians' health study. N Engl J Med 1988;318: 262–4.
36. Ehrich E, Schnitzer T, Kivitz A, Weaver A, Wolfe F, Morrison B, et al. MK-966, a highly selective cox-2 inhibitor, was effective in the treatment of osteoarthritis of the knee and hip in a 6-week placebo controlled study [abstract]. Arthritis Rheum 1997;40 Suppl 9:S85.
37. Ehrich E, Davies G, Watson W, Bolognese J, Seidenberg B, Bellamy N. Minimal perceptible clinical improvement in osteoarthritis: WOMAC and global assessments, influence of age, gender and geographic region [abstract]. Arthritis Rheum 1999;42 Suppl 9:S143.
38. Saag K, Fisher C, McKay J, Ehrich E, Zhao P-L, Bolognese J, et al, for the MK-0966 Phase III Protocol 033 Study Group. MK-0966, a specific cox-2 inhibitor, has clinical efficacy comparable to ibuprofen in the treatment of knee and hip osteoarthritis in a 6-week controlled clinical trial [abstract]. Arthritis Rheum 1998;41 Suppl 9:S196.
39. Williams HJ, Ward JR, Egger MJ, Neuner R, Brooks RH, Clegg DO, et al. Comparison of naproxen and acetaminophen in a two-year study of treatment of osteoarthritis of the knee. Arthritis Rheum 1993;36:1196–206.
40. Ward DE, Veys EM, Bowdler JM, Roma J. Comparison of aceclofenac with diclofenac in the treatment of osteoarthritis. Clin Rheumatol 1995;14:656–62.
41. Bellamy N, Buchanan WW, Chalmers A, Ford PM, Kean WF, Gunnar RG, et al. A multicenter study of tenoxicam and diclofenac in patients with osteoarthritis of the knee. J Rheumatol 1993;20:999–1004.
42. Simon LS, Lanza FL, Lipsky PE, Hubbard RC, Talwalker S, Schwartz BD, et al. Preliminary study of the safety and efficacy of SC-58635, a novel cyclooxygenase 2 inhibitor: efficacy and safety in two placebo-controlled trials in osteoarthritis and rheumatoid arthritis, and studies of gastrointestinal and platelet effects. Arthritis Rheum 1998;41:1591–602.
43. Lanza FL, Rack MF, Simon TJ, Quan H, Bolognese JA, Hoover ME, et al. Specific inhibition of cyclooxygenase-2 (COX-2) with MK-0966 is associated with less gastroduodenal damage than either aspirin or ibuprofen. Aliment Pharmacol Ther 1999;13: 761–7.
44. Langman M, Jensen D, Watson DJ, Harper S, Zhao P, Bolognese J, et al. Adverse upper gastrointestinal effects of rofecoxib compared with NSAIDs. JAMA 1999;282:1929–33.
45. Purcell P, Henry D, Melville G. Diclofenac hepatitis. Gut 1991; 32:1381–5.
46. Guan Y, Chang M, Cho W, Zhang Y, Redha R, Davis L, et al. Cloning, expression, and regulation of rabbit cyclooxygenase-2 in renal medullary interstitial cells. Am J Physiol 1997;273:F18–26.
47. Yang T, Singh I, Pham A, Sun D, Smart A, Schnermann J, et al. Differential response of renal cortical and inner medullary cyclooxygenase-2 (COX-2) expression to dietary salt [abstract]. J Am Soc Nephrol 1997;8:S621.
48. Catella-Lawson F, McAdam B, Morrison BW, Kapour S, Kuobu D, Antes L, et al. Effects of specific inhibition of cyclooxygenase-2 on sodium balance, hemodynamics, and vasoactive eicosanoids. J Pharmacol Exp Ther 1999;289:735–41.

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