Efficacy and Tolerability of Celecoxib in the Treatment of Acute Gouty Arthritis: A Randomized Controlled Trial

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ABSTRACT. ***Objective.*** To evaluate the analgesic efficacy of high-dose celecoxib in the treatment of moderate to extreme pain and inflammation associated with acute gouty arthritis.

Methods. A multinational, randomized, double-blind, double-dummy, active-controlled trial was done with patients (aged ≥ 18 years) with acute gouty monoarthritis or oligoarthritis (onset of pain ≤ 48 h before enrollment). Patients were treated for 8 days with 1 week followup and were randomized 1:1:1:1 to receive celecoxib 50 mg bid, celecoxib 400 mg (followed by 200 mg later on Day 1 and then 200 mg bid for 7 days), celecoxib 800 mg (followed by 400 mg later on Day 1 and then 400 mg bid for 7 days), or indomethacin 50 mg tid.

Results. Of 443 patients screened, 402 were randomized and 400 received treatment. Baseline demographics were comparable among treatments. Patients receiving high-dose celecoxib (800/400 mg) experienced a significantly greater reduction in pain intensity on Day 2 compared with low-dose celecoxib 50 mg bid [least squares (LS) mean difference –0.46; p = 0.0014]. For high-dose celecoxib 800/400 mg, the change in pain scores from baseline to Day 2 was comparable with indomethacin 50 mg tid (LS mean difference 0.11; p = 0.4331). There were significant differences in adverse events when the combined celecoxib groups (29.5%) were compared with patients taking indomethacin (43.1%; p = 0.0116). There was no change in median serum creatinine levels for any treatment. There were more discontinuations due to adverse events (8.8% vs 3%; p = 0.0147) with indomethacin than with the combined celecoxib groups.

Conclusion. High-dose celecoxib (800/400 mg) was significantly more effective than low-dose celecoxib (50 mg bid) and comparable to indomethacin in the treatment of moderate to extreme pain in patients with acute gouty arthritis. Further, celecoxib was well tolerated. (J Rheumatol First Release Aug 1 2012; doi:10.3899/jrheum.110916)

Key Indexing Terms:
ACUTE GOUTY ARTHRITIS
NONSTEROIDAL ANTIINFLAMMATORY DRUGS
CYCLOOXYGENASE-2 SELECTIVE NSAID
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The prevalence of gout is increasing worldwide, placing a significant burden on healthcare resources and society as a whole[1]. Gout is the most common form of inflammatory arthritis in men and elderly patients[1,2,3]. It is characterized by a deposition of monosodium urate crystals in the joints and soft tissues[2,4]. Gout often presents as an acute inflammation of a single joint, often the first metatarsophalangeal joint (podagra)[1]. Subsequent attacks may more frequently involve other joints or multiple joints, including the midtarsi, ankles, and knees. If inadequately treated, gout can lead to joint deformity, functional impairment, and widespread tophus formation in articular and subcutaneous tissues[5].

Because of their efficacy and availability, nonsteroidal antiinflammatory drugs (NSAID) are often recommended for the treatment of acute gouty arthritis[6,7,8,9,10], and are included in the guidelines of the European League Against Rheumatism[10] and the New Zealand Rheumatism Association[11]. Although head-to-head studies of NSAID have shown comparable efficacy in patients with acute gouty arthritis[12,13,14,15], in many countries including the United States, indomethacin has been considered a standard for treatment in acute gouty arthritis and has been used as a comparator in

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many clinical trials[13,15,16]. However, it has also been associated with frequent gastrointestinal (GI) tract adverse events (AE) and central nervous system AE[15,16,17,18]. Other treatment options available only in some countries for patients with acute gouty arthritis are the cyclooxygenase-2 (COX-2) selective NSAID. The efficacy of these drugs in the treatment of acute gouty arthritis has been established in 3 randomized clinical trials[15,19,20]. Etoricoxib 120 mg once daily was comparable in efficacy to indomethacin 50 mg 3 times daily (tid)[19] while lumiracoxib was also shown to be as effective as indomethacin 50 mg tid for the treatment of acute gouty arthritis[15].

The COX-2 selective NSAID celecoxib has been shown to be as effective as other NSAID (with a superior GI toxicity profile) in the treatment of osteoarthritis (OA) and rheumatoid arthritis[21,22,23], but there have been no studies of this agent in the treatment of patients with acute gouty arthritis. Our study was, therefore, performed to evaluate the efficacy and tolerability of a high dose of celecoxib in the treatment of moderate to extreme pain associated with acute gouty arthritis.

MATERIALS AND METHODS

Study design. The study (Clinical Trials Registration Number NCT00549549) was a randomized, double-blind, double-dummy, active-controlled trial conducted at 100 centers in 13 countries (Canada, Colombia, Costa Rica, Italy, Mexico, Peru, Philippines, the Republic of Korea, the Russian Federation, Spain, Taiwan, Thailand, and the United States). The protocol was approved by the institutional review boards or independent ethics committees at all centers, and the study was conducted in accord with the principles of the Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practice guidelines, and local regulatory requirements.

Our study consisted of an 8-day treatment period followed by a 1-week followup period. The primary objective was to evaluate the efficacy of a high-dose celecoxib regimen (celecoxib 800/400 mg: 800 mg, with 400 mg 12 h later on Day 1, followed by 400 mg bid for 7 days), compared with a low-dose regimen (50 mg bid: 50 mg, with 50 mg 12 h later on Day 1, followed by 50 mg bid for 7 days) in patients with acute gouty arthritis. These doses were chosen because the higher dose regimens have been shown to be effective in patients with postoperative pain after dental surgery[24], while the 50 mg bid regimen was selected as a placebo surrogate because this is the lowest dose that has shown any efficacy in OA and dental surgery pain. Secondary objectives included pairwise comparisons of 4 treatment groups (celecoxib 800/400, celecoxib 400/200 mg, celecoxib 50 mg bid, and indomethacin 50 mg tid) concerning their analgesic, antiinflammatory, and safety profiles.

Patients. Adult patients (age ≥ 18 years) were eligible for inclusion in the study if they had acute gouty arthritis according to the American College of Rheumatology preliminary criteria for the classification of the acute arthritis of primary gout[25], with onset of pain < 48 h before enrollment. Patients were also required to have moderate, severe, or extreme pain in an index joint identified by the investigator over the previous 24 h on the 5-point (0–4) Likert patient's assessment of pain intensity scale (scores of 2, 3, or 4, respectively) and, in the opinion of the investigator, to be candidates for daily therapy with NSAID, analgesics, or both. Patients receiving allopurinol could be included if the dose had remained stable for at least 1 week before the start of the study. Women of childbearing potential were required to use adequate contraception throughout the study.

Patients were excluded if they had polyarticular gout (> 4 joints affected), chronic joint damage or persistent inflammation from gout, or any other form of arthritis (except for mild or moderate OA that did not affect the index joint). Patients were also excluded if they were taking NSAID/analgesics (or had taken these within 5 half-lives of the appropriate agent), oral or injectable corticosteroids (< 2 weeks before the study start), acetylsalicylic acid (> 325 mg/day), intraarticular injections of hyaluronic acid (in the index joint), anticoagulants, and colchicine (> 1.2 mg/day). Two percent or less of patients in any group were taking low-dose colchicine and there were no significant differences among the groups. Patients were also excluded if they had a history of gout that was unresponsive to NSAID; a known allergy or hypersensitivity to COX-2 inhibitors, NSAID, or acetylsalicylic acid; previous myocardial infarction (MI); any significant uncontrolled disease/condition that in the opinion of the investigator would have contraindicated study participation or confounded interpretation of the results; certain known laboratory abnormalities (or any abnormalities of concern to the investigator); or a positive pregnancy test. Median baseline creatinine levels (mg/dl) were 1.2, 1.2, 1.3, and 1.2, respectively, for celecoxib 50 mg, 200/400 mg, 400/800 mg, and indomethacin. All patients must have provided written informed consent before inclusion in the study.

Treatment. Patients were randomized 1:1:1:1 to receive 1 of the 3 celecoxib regimens or indomethacin. Randomization was performed using an interactive telephone system, based on a computer-generated schedule, and was stratified according to the extent of disease (monoarticular vs oligoarticular) and by country. Blinding was maintained by the use of placebo capsules that were identical in appearance to the celecoxib and indomethacin capsules. Rescue medication, including NSAID and analgesics, could be given at any time at the investigator's discretion if adequate pain relief was not achieved during study treatment. Patients requiring rescue medication were recorded as having lack of efficacy, withdrawn, and asked to return to the clinic for an early termination visit before taking the rescue medication.

Efficacy and safety evaluations. Patients rated the intensity of pain in the index joint over the preceding 24 h at baseline and before the morning dose of study medication on Days 2 to 14. Pain was rated on the 5-point Likert scale: 0 = no pain, 1 = mild pain, 2 = moderate pain, 3 = severe pain, and 4 = extreme pain; all reported pain scores were recorded in diaries kept by the patients. Using the same scale, patients also rated the intensity of pain in the index joint 2, 4, 8, and 12 h after the first dose of study medication on Day 1, and before and 8 h after the morning dose on Day 2. In addition, patients provided a global evaluation of their study medication on Day 9, using a 5-point scale (1 = poor, 2 = fair, 3 = good, 4 = very good, 5 = excellent). The treating physicians assessed signs and symptoms of inflammation on Days 1, 5, 9, and 14 (or earlier if the patient withdrew from the study). Tenderness and swelling were rated on a 4-point scale (tenderness: 0 = no tenderness; 1 = patient complained of pain to touch; 2 = patient complained of pain and winced; 3 = patient complained of pain, winced, and withdrew; swelling: 0 = none; 1 = palpable; 2 = visible; 3 = bulging beyond joint margins). Redness and warmth were assessed as present or absent.

The primary endpoint was the change in pain intensity in the index joint from baseline to Day 2 (24-h recall of pain during Day 2, assessed on Day 3). Secondary endpoints included (1) changes from baseline in physicians' assessments of the index joint on Days 5, 9, and 14; (2) changes from baseline in patients' 24-h assessments of pain intensity on Days 1 to 13; (3) changes from baseline in patients' assessments of pain intensity on Days 1 (2, 4, 8, and 12 h) and 2 (0 and 8 h); (4) time-weighted average (TWA, calculated as the area under the curve of pain intensity differences from baseline to a timepoint) changes in patients' assessments of pain intensity over 8 (TWA-8), 12 (TWA-12), and 24 (TWA-24) h after the first dose of study medication during Day 1; and (5) the incidence of and time to withdrawal due to lack of efficacy. Safety and tolerability were also assessed throughout the duration of the study. Safety evaluations included monitoring of AE with descriptions of severity as mild, moderate, or severe and a standard definition of serious AE, physical examinations, measurement of vital signs, and clinical laboratory investigations (hematology, clinical chemistry, and urinalysis). Laboratory tests were undertaken at baseline and at Day 14 only. In addition, in a posthoc analysis, the glomerular filtration rate was calculated using the modification of diet in renal disease formula and summarized by treatment, based on 5 chronic kidney disease (CKD) stages.

Statistical analysis. The sample size determination was based on the hypothesis that the mean difference in the primary endpoint between the high-dose and low-dose celecoxib regimens would be 0.5, with an intragroup SD of 1.1. A sample size of 100 patients per group would provide about 90% power to demonstrate superior efficacy of the high-dose regimen, assuming a 2-sided significance level of 0.05.

Statistical analyses of efficacy were performed on the intent-to-treat population, which included all randomized patients who received at least 1 dose of study medication and had at least 1 postbaseline evaluation. The primary analysis was conducted using an analysis of covariance with randomization stratum (monoarticular vs oligoarticular), region, and treatment group as factors, and baseline assessments of pain intensity over 24 h as covariate. The same model was used in secondary analyses. Binary endpoints were analyzed using the Cochran-Mantel-Haenszel test stratified by randomization strata. Time to withdrawal because of lack of efficacy was analyzed using the log-rank test and the Kaplan-Meier plot. Efficacy assessments made after taking rescue medication were excluded from the efficacy analyses. No multiplicity adjustment was made for secondary comparisons. The last observation carried forward method was used for missing data if applicable. For the statistical analysis, SAS/STAT software (SAS Institute Inc., Cary, NC, USA) was used.

RESULTS

Patients. Patients were recruited from 75 centers. A total of 443 patients were screened; of these, 402 patients were randomized and 400 patients received treatment (Figure 1). Forty-one patients discontinued during the screening phase; 39 were excluded because they did not meet the entry criteria and 2 were excluded for other reasons. Overall, baseline patient demographics and disease characteristics were comparable between the different treatment regimens (Table 1).

Primary efficacy endpoint. At baseline, the mean patient's assessment of pain intensity score ranged from 2.73 to 3.03 for the 4 treatment groups, with a median score of 3 (severe)

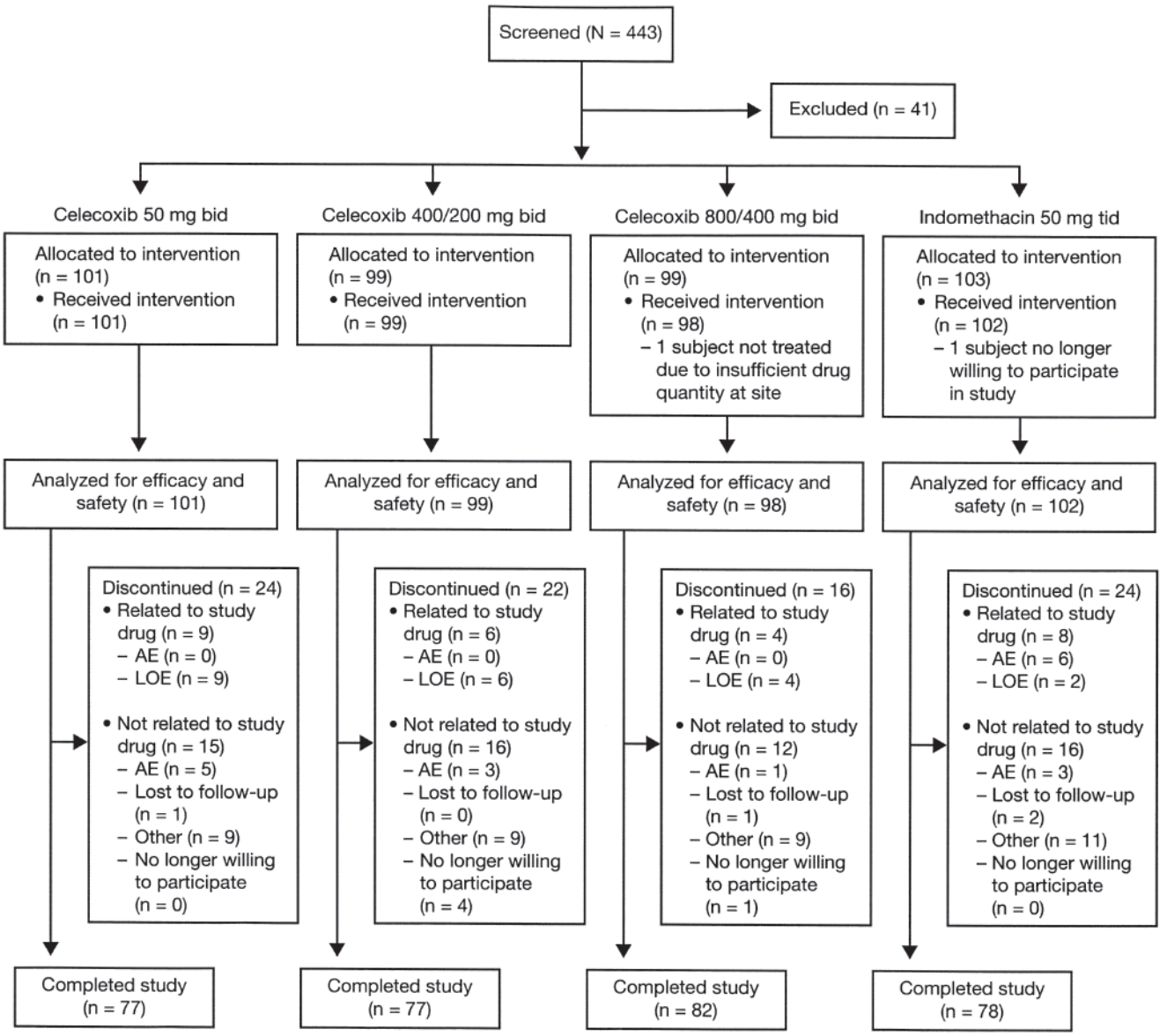


Figure 1. The CONSORT procedure (Consolidated Standards of Reporting Trials). AE: adverse event; LOE: lack of efficacy.

Table 1. Patient demographics and disease characteristics.

Characteristics	Celecoxib, 50 mg bid, n = 101	Celecoxib, 400/200 mg, n = 99	Celecoxib, 800/400 mg, n = 98	Indomethacin, 50 mg tid, n = 102
Sex, n				
Men	91	90	90	95
Women	10	9	8	7
Age, yrs, n (%)				
18–44	28 (27.7)	28 (28.3)	26 (26.5)	34 (33.3)
45–64	56 (55.4)	55 (55.6)	60 (61.2)	54 (52.9)
≥ 65	17 (16.8)	16 (16.2)	12 (12.2)	14 (13.7)
Mean (SD)	52.4 (11.9)	52.3 (12.0)	51.0 (11.3)	49.6 (12.7)
Range	28–80	25–90	26–79	23–76
Race, n (%)				
White	53 (52.5)	64 (64.6)	54 (55.1)	55 (53.9)
Black	11 (10.9)	3 (3.0)	10 (10.2)	9 (8.8)
Asian	22 (21.8)	18 (18.2)	19 (19.4)	19 (18.6)
Other	15 (14.9)	14 (14.1)	15 (15.3)	19 (18.6)
Body mass index, kg/m^2				
Mean (SD)	30.2 (5.7)	30.3 (5.1)	31.2 (7.1)	30.6 (5.9)
Range	14.5–45.7	19.6–47.8	20.1–64.7	17.3–47.4
n*	99	97	97	102
Gout pattern, n (%)				
Monoarticular	82 (81.2)	78 (78.8)	72 (73.5)	78 (76.5)
Oligoarticular	19 (18.8)	21 (21.2)	26 (26.5)	24 (23.5)
Diabetes†	10	6	10	5
Hypertension††	45	45	39	45
Angina pectoris	1	1	0	3

* No. patients for whom body mass index data were available. † No. patients with this condition; includes the following preferred terms: diabetes mellitus, type 2 diabetes mellitus, and diabetic neuropathy. †† No. patients with this condition; includes the following preferred terms: hypertension and essential hypertension. Bid: twice daily; tid: 3 times daily.

and range of scores from 2 (moderate) to 4 (extreme) for all groups (Table 2). Following treatment, all groups reported a reduction in pain from baseline.

Patients receiving high-dose celecoxib experienced a significantly greater reduction in patient's assessment of pain intensity on Day 2 compared with low-dose celecoxib [least

Table 2. Changes from baseline in patient's assessment of pain intensity over 24 hours on Day 2 (measured before the morning dose on Day 3) among the intent-to-treat population.

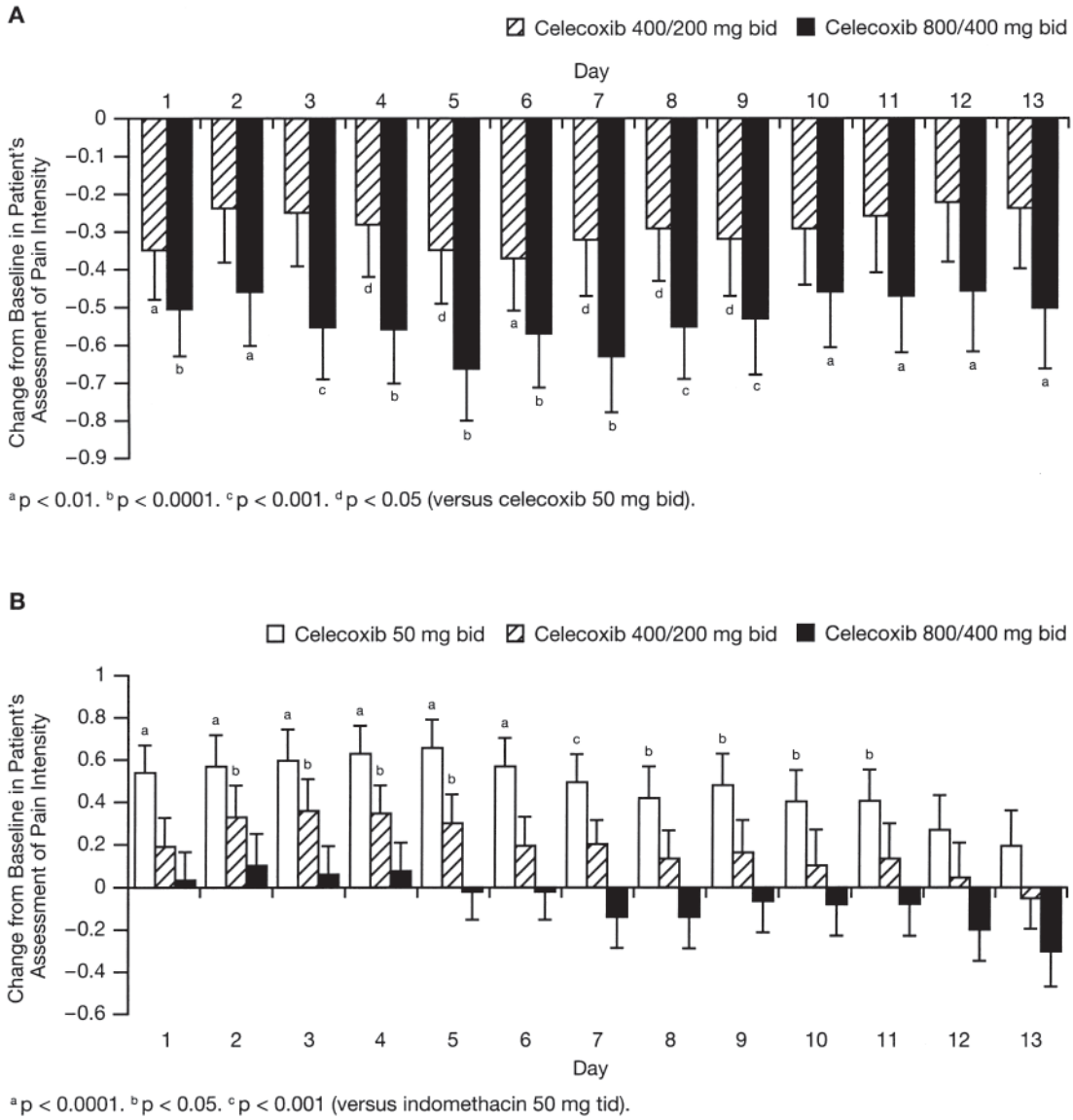
	Celecoxib, 50 mg bid, n = 100	Celecoxib, 400/200 mg, n = 99	Celecoxib, 800/400 mg, n = 96	Indomethacin 50 mg tid, n = 102
Baseline				
n	100	99	96	102
Mean (SD)	3.03 (0.67)	2.73 (0.62)	2.84 (0.69)	2.83 (0.76)
Range	2.0–4.0	2.0–4.0	2.0–4.0	2.0–4.0
Day 2 (change from baseline)				
n	97	96	94	98
Mean (SD)	–1.14 (1.10)	–1.23 (0.97)	–1.51 (1.11)	–1.62 (0.97)
Range	–4.0 to 1.0	–3.0 to 1.0	–4.0 to 1.0	–3.0 to 1.0
Vs celecoxib 50 mg bid				
LS mean difference (SE)	—	–0.24 (0.14)	–0.46 (0.14)	—
95% CI	—	–0.52 to 0.04	–0.74 to –0.18	—
p	—	0.0947	0.0014	—
Vs indomethacin 50 mg tid				
LS mean difference (SE)	0.57 (0.14)	0.33 (0.14)	0.11 (0.14)	—
95% CI	0.29 to 0.84	0.05 to 0.60	–0.17 to 0.39	—
p	< 0.0001	0.0196	0.4331	—

Bid: twice daily; LS: least squares; SE: standard error; tid: 3 times daily.

squares (LS) mean difference –0.46, p = 0.0014; Table 2]. The effect of high-dose celecoxib was not significantly different from that of indomethacin 50 mg tid (LS mean difference 0.11, p = 0.4331). There were also no significant differences observed between celecoxib 400/200 mg and low-dose celecoxib (LS mean difference –0.24, p = 0.0947). The reductions in pain intensity observed in patients receiving celecoxib 400/200 mg and low-dose celecoxib were significantly smaller than those seen with indomethacin (LS mean differences 0.33, p = 0.0196, and 0.57, p < 0.0001, respectively).

Secondary efficacy endpoints. For the physician's assessment of the index joint, reductions in tenderness and swelling were observed for all the celecoxib treatment groups studied and were similar to those seen with indomethacin. Specific scores obtained on 4-point scales for tenderness decreased by 1.74, 1.66, and 1.94 for the 3 celecoxib groups and by 1.64 for indomethacin. Decreases in swelling for the same respective groups were 1.55, 1.63, 1.78, and 1.58. In terms of the physician's assessment of the index joint for redness and warmth, again there were no significant differences observed between any of the treatment groups studied.

For patients receiving high-dose celecoxib there were significantly greater improvements in the patient's assessment of pain intensity on Days 1 to 13 compared with the low-dose celecoxib regimen (Figure 2A). When compared with indomethacin, the high-dose celecoxib regimen was not significantly different on any of the Days 1 to 13. Although indomethacin tended to show a greater change from Day 1 to



[a] p < 0.01. [b] p < 0.0001. [c] p < 0.001. [d] p < 0.05 (versus celecoxib 50 mg bid).

[a] p < 0.0001. [b] p < 0.05. [c] p < 0.001 (versus indomethacin 50 mg tid).

Figure 2. Change from baseline in the 5-point Likert scale of patient's assessment of pain intensity, Days 1 to 13. A. High-dose celecoxib versus celecoxib 50 mg bid (least squares mean difference, standard error). B. Three doses of celecoxib versus indomethacin 50 mg tid (least squares mean difference, standard error).

4, from Day 5 until study completion patients reported a tendency to greater pain reduction with celecoxib than indomethacin (Figure 2B).

For the TWA at various times on Day 1, there were significant differences in the patient's assessment of pain between the high-dose celecoxib and low-dose celecoxib regimens over all TWA periods (at 24 h: LS mean difference 0.29, p = 0.0077). However, there were no significant differences between the high-dose celecoxib and indomethacin regimens at any of these timepoints, although patients receiving indomethacin did experience a greater reduction in pain when compared with either the low-dose or celecoxib 400/200 mg regimen. There were also no significant differences between the celecoxib 400/200 mg and low-dose celecoxib treatment groups.

Overall, significantly more patients withdrew during treatment because of a lack of efficacy with low-dose celecoxib than with indomethacin (10.0% and 2.9%, respectively; p = 0.0213). For the purposes of this analysis, withdrawal owing to lack of efficacy included patients who discontinued because of insufficient clinical response, or who discontinued because of an AE of gout, gouty arthritis, or disease progression.

Safety findings. For all treatments, headache (16 patients) and worsening of gout symptoms (33 patients) were the most frequently reported AE. Most AE were also mild or moderate in severity, with no more than 5% of severe AE in any group (Table 3). There were significant differences in the frequency of AE considering all doses of celecoxib (29.5%) versus indomethacin (43.1%; p = 0.0116). There was also a significantly greater proportion of patients in the indomethacin group (8.8%) who discontinued treatment because of an AE compared with patients treated with celecoxib (3.0% all doses; p = 0.0147). The highest dose of celecoxib was also associated with significantly fewer discontinuations than indomethacin (p = 0.0319; Table 3). There were no deaths reported and only 1 serious AE, a facial bone fracture in an indomethacin-treated patient; this was not believed to be related to treatment. In terms of the physical examination, vital signs, and clinical laboratory evaluations, there were no consistent clinically significant changes observed during the course of the study for any treatment. Although some patients had elevated serum creatinine levels at baseline, there was no change in median serum creatinine levels for any treatment. At both baseline and final visit, no patients had stage 5 CKD; some patients had stage 4 CKD at baseline and final visit but this was a rare event. For the high-dose celecoxib group, 30.6% of patients were classified as having stage 3 CKD at baseline compared with 34.0% at the final visit. For the indomethacin group, 29.4% and 38.3% of patients had stage 3 CKD at baseline and final visit, respectively. Increases in sitting systolic blood pressure > 30 mm Hg were reported for 1.0%, 0%, 1.1%, and 2.0% of patients in the low-dose celecoxib, celecoxib 400/200 mg, high-dose celecoxib, and indomethacin groups, respectively; no differences were statistically significant. No patients had an increase in sitting diastolic blood pressure > 30 mm Hg.

DISCUSSION

The results of this study showed that high-dose celecoxib was more effective than low-dose celecoxib and provided a reduction in pain intensity 2 days after the start of treatment com-

Table 3. Summary of adverse events (AE).

Adverse Events	Celecoxib, 50 mg bid, n = 101	Celecoxib, 400/200 mg, n = 99	Celecoxib, 800/400 mg, n = 98	Indomethacin 50 mg tid, n = 102
Total no. AE	59	43	51	80
Patients with AE, n (%)*	33 (32.7)	27 (27.3)	28 (28.6)	44 (43.1)
Gouty arthritis	6 (5.9)	9 (9.1)	9 (9.2)	9 (8.8)
Headache	5 (5.0)	4 (4.0)	3 (3.1)	4 (3.9)
Diarrhea	3 (3.0)	2 (2.0)	2 (2.0)	5 (4.9)
Dizziness	2 (2.0)	1 (1.0)	2 (2.0)	6 (5.9)
Arthralgia	1 (1.0)	4 (4.0)	3 (3.1)	2 (2.0)
Upper abdominal pain	1 (1.0)	0 (0.0)	1 (1.0)	5 (4.9)
Dyspepsia	2 (2.0)	0 (0.0)	2 (2.0)	3 (2.9)
Nausea	2 (2.0)	0 (0.0)	1 (1.0)	3 (2.9)
Pain in extremity	0 (0.0)	1 (1.0)	3 (3.1)	1 (1.0)
Pyrexia	4 (4.0)	1 (1.0)	0 (0.0)	0 (0.0)
Patients with severe AE, n (%)	5 (5.0)	3 (3.0)	2 (2.0)	1 (1.0)
Patients with serious AE, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Discontinuations due to AE, n (%)	5 (5.0)	3 (3.0)	1 (1.0)**	9 (8.8)**
Worsening of gout/gouty arthritis	2 (2.0)	3 (3.0)	1 (1.0)	2 (2.0)
Other	3 (3.0)	0 (0.0)	0 (0.0)	7 (6.8)
Dose reduced/temporary discontinuations due to AE, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Deaths, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

* AE occurring in > 2% of patients. ** p = 0.0319 for higher-dose celecoxib versus indomethacin.

parable with indomethacin 50 mg tid. High-dose celecoxib also appeared to have a greater effect during the later stages of treatment. Like many previous studies, this study focused on the response during the first few days of treatment. It is clinically important to observe the treatment response throughout the acute episode until full resolution. Compared with the high-dose celecoxib regimen, the other celecoxib regimens studied produced smaller reductions in pain than indomethacin.

Although NSAID are widely used in the treatment of acute gouty arthritis, strong efficacy data are lacking[7,8]. Indeed, a systematic review of 13 randomized trials[7] concluded that the only compelling data come from 2 trials[19,20] that demonstrated that etoricoxib 120 mg/day was equivalent in efficacy to indomethacin 50 mg tid. There have been no direct head-to-head comparisons between COX-2 selective NSAID; however, our findings suggest that celecoxib produces comparable analgesia to indomethacin 50 mg tid, but only at the high dose.

Overall, celecoxib was well tolerated in our study and the incidence of AE with all 3 celecoxib regimens combined was lower than that seen with indomethacin. However, caution should be exercised when using any NSAID in patients with acute gouty arthritis who may also present with a number of comorbidities, including cardiovascular disease. Little is known about the association between NSAID treatment duration and risk of cardiovascular disease. A recent review of a Danish database[26] reported that even short-term treatment with most NSAID (except naproxen) was associated with increased risk of death and recurrent MI in patients with prior MI. Patients with previous MI had been excluded from our study. Although patients with other "significant" medical conditions had been planned to be excluded, a number of patients, as noted above, were included with stage 3 and 4 CKD. Celecoxib or other NSAID should not be considered appropriate for patients with serious renal disease.

Patients with both polyarticular and/or chronic gouty arthritis were also excluded from the trial but in clinical practice these patients also require treatment.

Some outcome measures, such as redness and local temperature, are very subjective. We found there were no differences among treatment groups in swelling, tenderness, redness, warmth, or in the physicians' assessments of joints. It may be true that these signs of inflammation did not differ among the individual treatment groups, but it also raises questions about how accurately these were recorded.

Finally, not all patients completed the trial, the number of scheduled visits may have been insufficient to fully understand the effects on inflammation, and like other trials in acute gout, the current trial may have been too short in duration to allow followup to complete resolution of all flares.

This randomized controlled trial showed that high-dose celecoxib was significantly more effective than very low-dose celecoxib 50 mg bid in the treatment of moderate to extreme pain associated with acute gouty arthritis. Further, high-dose celecoxib 800/400 mg was shown to be comparable in efficacy to indomethacin 50 mg tid. There was also an interesting observation that the duration of pain relief appeared longer with high-dose celecoxib than with indomethacin, although further studies will be required to confirm and analyze this. Overall, high-dose celecoxib appeared to be well tolerated in the treatment of moderate to extreme pain associated with acute gouty arthritis.

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