Celecoxib Is Efficacious and Well Tolerated in Treating Signs and Symptoms of Ankylosing Spondylitis

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ABSTRACT. ***Objective.*** To evaluate the efficacy and safety of celecoxib in patients with ankylosing spondylitis (AS).

Methods. This was a 12-week randomized, double-blind, placebo-controlled study with 4 treatment arms: celecoxib 200 mg qd, celecoxib 400 mg qd, naproxen 500 mg bid, and placebo. Patients (age 18–75 yrs) requiring daily treatment with nonselective nonsteroidal antiinflammatory drugs, and with a pain intensity on visual analog scale (VAS) ≥ 50 mm worsening by 30% compared with a preinclusion visit (14 days prior) were studied. Primary endpoints were least-squares mean changes from baseline in pain intensity, disease activity (patient global assessment VAS), and functional impairment [Bath Ankylosing Spondylitis Functional Index (BASFI)]. Adverse events were monitored throughout the study.

Results. Of 611 randomized patients, 137 were allocated to celecoxib 200 mg, 161 to celecoxib 400 mg, 157 to naproxen, and 156 to placebo. Improvements in least-squares mean pain intensity, disease activity, and BASFI scores were significantly greater in the celecoxib 200 mg, celecoxib 400 mg, and naproxen groups than in the placebo group ($p \leq 0.001$) at Week 12 and the interim timepoints, Weeks 1, 3, and 6. Celecoxib 400 mg was as effective as naproxen; however, naproxen was more effective than celecoxib 200 mg. Celecoxib was well tolerated, with an adverse event profile similar to placebo. However, 3 naproxen-treated patients experienced serious treatment-related gastrointestinal (GI) adverse events (one severe gastric ulcer, one moderate GI hemorrhage, one severe GI hemorrhage).

Conclusion. In this 12-week study, celecoxib 200 mg qd and 400 mg qd were efficacious and well tolerated in treating signs and symptoms of AS. (J Rheumatol 2006;33:1805–12)

Key Indexing Terms:
ANKYLOSING SPONDYLITIS CYCLOOXYGENASE INHIBITORS
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Ankylosing spondylitis (AS), the prototype of the spondyloarthropathies, is a chronic debilitating disease that is characterized by axial skeletal ankylosis and inflammation at the entheses[1]. It predominantly affects the spine, although peripheral joints may also be affected[2]. Disease onset typically starts during adolescence and peaks around age 28 years. Men are more commonly affected by AS than women, with a ratio of about 3:1.

The progressive expression of AS makes management challenging, and thus the goal of treatment is not only to relieve clinical symptoms but also to prevent or slow its progression. Treatment of AS aims to relieve pain, stiffness, and loss of function associated with the inflammatory process and, ideally, to block the underlying inflammatory structural damage that causes deformities and ankylosis.

Nonselective nonsteroidal antiinflammatory drugs (NSAID), which rapidly reduce the signs and symptoms of axial involvement of AS, are first-line treatment[2]. Further, physiotherapy, including exercise, is a necessary adjunct to pharmacotherapy that can significantly relieve symptoms and improve range of motion[3].

Disease modifying antirheumatic drugs (DMARD) such as sulfasalazine and methotrexate are considered second-line treatment, but are only effective in alleviating peripheral joint symptoms/signs of spondyloarthropathies and have no effect on structural spinal changes in the long term[4-7].

There is increasing evidence that tumor necrosis factor-α (TNF-α) is involved in the pathogenesis of AS, and recent data have shown that the TNF-α inhibitors etanercept and infliximab are effective for the treatment of patients with AS[8,9]. In the United States, etanercept and infliximab are indicated for reducing the signs and symptoms in patients with active AS. However, the longterm safety profile of TNF inhibition in this population is unknown, and some experts have advised restricting use of these agents to patients with moderate to severe AS who have failed or cannot tolerate NSAID[10].

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Most patients with active AS require regular pain relief; however, as nonselective NSAID are associated with gastrointestinal (GI) toxicity, it has been suggested that these first-line agents should be administered only when the disease is causing pain[2]. As the newer cyclooxygenase (COX)-2-selective inhibitors have a more favorable GI safety profile than nonselective NSAID, they may provide a better alternative. The COX-2-selective inhibitor celecoxib has been shown to be better tolerated than nonselective NSAID, with significantly fewer cases of dyspepsia, nausea, and abdominal pain in patients with osteoarthritis (OA) and rheumatoid arthritis (RA)[11-14]. In addition, celecoxib is associated with a significantly lower incidence of endoscopically detected gastroduodenal ulcers compared with naproxen and other nonselective NSAID[15-17].

Celecoxib has previously been shown to be effective in improving the signs and symptoms of OA and RA. Further, celecoxib 100 mg bid, given for 6 weeks, has been shown to significantly relieve pain and improve function in patients with AS[18]. As well, in an extension of the 6-week study, continuous treatment with either celecoxib 100 mg bid or an NSAID for up to 2 years was shown to reduce radiographic progression[19].

In our 12-week study, celecoxib 200 mg qd and celecoxib 400 mg qd were compared with naproxen and placebo to evaluate the analgesic efficacy and effects on disease activity and functional capacity of celecoxib in patients with AS.

MATERIALS AND METHODS

This was a randomized, double-blind, placebo-controlled parallel-group study in patients with AS. The study was divided into a 14-day pretreatment period that included a preinclusion/screening visit, and a 12-week treatment period. The treatment period included a baseline visit and assessment visits at Weeks 1, 3, 6, and 12 (or early termination).

Patients discontinued their previous NSAID at the beginning of the 14-day preinclusion/screening period. However, rescue medication was allowed in the form of acetaminophen (APAP) up to 2000 mg/day until 8 h before the baseline visit. The protocol was approved by the institutional review board at each center. All patients gave written informed consent.

Patients aged 18 to 75 years with a diagnosis of AS as defined by modified New York criteria (clinical and radiologic)[20] with axial involvement and requiring daily treatment with NSAID during the previous 30 days were included. Patients with or without peripheral enthesopathy, and large peripheral joint synovitis (hips, knees, and/or shoulders) were included. Patients with distal small-joint synovitis were excluded to ensure as pure a population of patients as possible. Patients with any known inflammatory enteropathy (ulcerative colitis, Crohn's disease), any extraarticular signs (e.g., uveitis, cardiac involvement), or any vertebral compression were excluded. Patients with psoriasis were not excluded from the study.

Patients included in the study had pain intensity ≥ 50 mm on a 100 mm visual analog scale (VAS), worsening by 30% compared with that recorded at the preinclusion visit following discontinuation of existing therapy. They had taken no analgesic for at least 8 h or antiinflammatory medication for at least 72 h prior to study start. Women of childbearing potential had to be using and continue to use effective contraception throughout the trial, and had to have a negative pregnancy test at the time of inclusion.

Patients were excluded if they needed to wear a corset during the course of the trial, if they required commencement of physiotherapy, reeducation or manipulation, or if they required concomitant use of muscle relaxants, hypnotics, anxiolytics, sedatives, tranquilizers or antidepressants (unless taking stable doses for 2 weeks prior to inclusion). Patients who received corticosteroids in the 6 weeks preceding study start were excluded, as were those requiring concomitant use of anticoagulants, ticlopidine, or lithium. Patients receiving methotrexate > 25 mg/wk or anti-TNF agents were excluded. Sulfasalazine was allowed if the patient was taking a stable dose for 60 days prior to screening.

Patients with a history of gastroduodenal ulcer confirmed by endoscopy in the 30 days prior to inclusion or with current GI bleeding were not permitted to enter the study. Patients with known hypersensitivity to analgesics, NSAID, celecoxib, COX-2-selective inhibitors in general, naproxen, lactose, sulfonamides, or APAP were excluded, as were those with a history of asthma, chronic disease (rheumatologic or other that might interfere with the results of the study), or current or previous malignancy.

Patients were randomized to receive celecoxib 200 mg qd, celecoxib 400 mg qd, naproxen 500 mg bid, or placebo. The first dose of study medication was taken at the baseline visit after all study procedures had been completed in patients who met the inclusion criteria and other procedures had been performed. Rescue APAP was provided to patients to be taken as needed, but only up to a dose of 2000 mg/day.

Clinical efficacy assessments were performed at baseline and after 1, 3, 6, and 12 weeks. The primary efficacy measures were least-squares mean changes from baseline to Week 12 for patient's assessment of global pain intensity (100 mm VAS, where 0 = no pain and 100 = extreme pain), patient global assessment of disease activity (100 mm VAS, where 0 = disease inactive and 100 = disease extremely active), and functional ability assessed by patient responses on the 10-item Bath Ankylosing Spondylitis Functional Index (BASFI; 100 mm VAS, where 0 = easy and 100 = impossible)[21]. The BASFI is reliable and sensitive to change and is widely used in AS clinical trials to define and monitor functional impairment.

The secondary efficacy measures included: least-squares mean changes from baseline to the interim timepoints (Weeks 1, 3, and 6) for the primary efficacy measures patient's assessment of global pain intensity (VAS), patient's global assessment of disease activity (VAS), and BASFI; least-squares mean changes from baseline to Weeks 1, 3, 6, and 12 for physician's global assessment of disease activity (VAS), morning stiffness duration, and nocturnal pain (VAS and verbal); number of APAP tablets consumed since previous visit; and incidence of and time to withdrawal due to treatment failure.

Exploratory efficacy measures included the Assessments in Ankylosing Spondylitis (ASAS) 20 Improvement Criteria[22], Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)[23], modified Brief Pain Inventory-short form[24,25], C-reactive protein (CRP), Articular Index, fingertips-to-floor distance, Schober Index (mobility), and chest expansion.

General clinical safety measures, including adverse events, clinical laboratory tests, and physical examinations (including vital signs) were monitored by the investigator. Adverse events were evaluated at each assessment visit (baseline, Weeks 1, 3, 6, 12).

It was calculated that a sample size of 150 patients per treatment group allowed detection of a least-squares mean change from baseline between treatment groups of 10 mm in the patient's assessment of global pain intensity, assuming a standard deviation (SD) of 28.44 mm, an α level of 0.025 (2-sided), and a power of 0.80. All efficacy analyses were performed on data from the intent-to-treat (ITT) population cohort, defined as patients who were randomized to treatment and took at least one dose of study medication. The analyses of primary efficacy variables at Week 12 were considered the primary endpoints (primary analyses) and were used to determine the efficacy of celecoxib using a 2-way analysis of covariance (ANCOVA) with center and treatment as effects and baseline as a covariate. The primary comparisons were prespecified to be between celecoxib and placebo.

Least-squares mean changes from baseline to each visit were analyzed for patient's assessment of global pain intensity (VAS), patient's global assessment of disease activity (VAS), functional impairment (BASFI), physician's assessment of disease activity (VAS), nocturnal pain (visual and verbal), number of APAP tablets consumed, total BASDAI score, and CRP, using a 2-way ANCOVA. Pairwise treatment group comparisons for morning stiffness were

analyzed using Wilcoxon rank-sum tests. The results of the pairwise comparisons for the 2 celecoxib treatment groups (200 mg and 400 mg) versus placebo for the primary endpoints were analyzed using Hochberg's step-down procedure.

Incidence of withdrawal due to lack of efficacy was analyzed by an overall Cochran-Mantel-Haenszel (CMH) test; pairwise comparisons between the treatment groups were performed using Fisher's exact test. The time to withdrawal due to lack of efficacy was analyzed by log-rank test; time to withdrawal within each treatment group was plotted using Kaplan-Meier product limit plots. An overall log-rank test on the time to withdrawal was performed.

ASAS improvement criteria responder analyses were performed using a CMH test at Weeks 1, 3, 6, and 12. Descriptive analyses were performed on the observed data for the Articular Index, fingertips-to-floor distance, Schober Index, and chest expansion.

RESULTS

Of the 611 patients included in this study, 156 were randomized to placebo, 137 to celecoxib 200 mg qd, 161 to celecoxib 400 mg qd, and 157 to naproxen 500 mg bid. The majority of patients were male, Caucasian, and aged 40–45 years. There were no significant differences among the treatment groups in demographic data or clinical variables at baseline (Table 1).

In total, 408 (67%) patients completed the study: 72 (46%) in the placebo group, 100 (73%) in the celecoxib 200 mg qd group, 118 (73%) in the celecoxib 400 mg qd group, and 118 (75%) in the naproxen group. The most common reason for withdrawal was lack of efficacy, with a higher proportion of patients in the placebo group (38%) withdrawing for this reason than in the celecoxib 200 mg (18%), celecoxib 400 mg (14%), or naproxen (11%) groups.

Improvements in least-squares mean pain intensity (VAS), disease activity (VAS), and BASFI scores from baseline to Week 12 were significantly greater in the celecoxib 200 mg qd, celecoxib 400 mg qd, and naproxen groups than in the placebo group ($p \leq 0.001$; Figure 1). There was no significant difference in least-squares mean change in pain intensity between the 3 active treatment groups. However, the least-squares mean reductions in disease activity score ($p < 0.05$) and BASFI ($p < 0.01$) were significantly greater in the naproxen group than in the celecoxib 200 mg qd group.

Improvements in least-squares mean pain intensity (VAS), disease activity (VAS), and BASFI scores from baseline to Weeks 1, 3, and 6 in the celecoxib 200 mg, celecoxib 400 mg, and naproxen groups were significantly greater than in the placebo group ($p < 0.001$; Figure 2). However, least-squares mean reductions were significantly greater in the naproxen group compared with the celecoxib 200 mg group in pain intensity scores at Week 6 ($p < 0.05$) and in disease activity and BASFI scores at Weeks 3 and 6 ($p < 0.05$). Further, least-squares mean reductions in disease activity score were significantly greater in the naproxen group than the celecoxib 400 mg group at Week 1 ($p < 0.05$).

Improvements in median morning stiffness duration from baseline to Week 12 were significantly greater in patients receiving celecoxib 200 mg, celecoxib 400 mg, and naproxen than in those receiving placebo (Table 2). There was no significant difference between the celecoxib groups. However, there was a significantly greater reduction in duration of morning stiffness in the naproxen group compared with the celecoxib 200 mg group.

Improvements in least-squares mean nocturnal pain scores (VAS and verbal) from baseline to Weeks 1, 3, 6, and 12 in the celecoxib 200 mg and celecoxib 400 mg groups were significantly greater ($p < 0.001$) than in the placebo group. Improvements in least-squares mean nocturnal pain scores (VAS) in the naproxen group were significantly greater than in the placebo group at Weeks 1, 3, 6 and 12 ($p < 0.001$), the

Table 1. Baseline demographics and clinical characteristics of study groups.

	Placebo, n = 156	Celecoxib 200 mg qd, n = 137	Celecoxib 400 mg qd, n = 161	Naproxen 500 mg bid, n = 157	p
Age, yrs, mean ± SD	43.8 ± 11.5	43.9 ± 11.9	45.1 ± 11.6	45.4 ± 12.6	0.469
Sex, n (%)					
Male	114 (73)	108 (79)	112 (70)	117 (75)	0.338
Female	42 (27)	29 (21)	49 (30)	40 (25)	
Race, n (%)					
Caucasian	117 (75)	106 (77)	126 (78)	119 (76)	0.791
Asian	10 (6)	3 (2)	6 (4)	6 (4)	
African American	1 (1)	1 (1)	4 (2)	4 (3)	
Other	28 (18)	27 (20)	25 (16)	28 (17)	
Height, cm, mean ± SD	171.0 ± 10.0	171.8 ± 10.7	170.1 ± 9.8	170.2 ± 10.3	0.353
Weight, kg, mean ± SD	82.5 ± 18.0	82.3 ± 17.4	82.7 ± 18.1	82.3 ± 20.4	0.961
Patient's global assessment of pain intensity, mean ± SD	73.5 ± 16.6	70.8 ± 15.6	71.4 ± 15.4	71.7 ± 15.6	0.309
Patient's global assessment of disease activity, mean ± SD	69.1 ± 21.4	65.9 ± 20.5	65.3 ± 22.5	66.1 ± 20.1	0.278
Functional Index (BASFI), mean ± SD	54.4 ± 22.2	50.0 ± 25.2	51.7 ± 24.2	52.0 ± 21.8	0.307

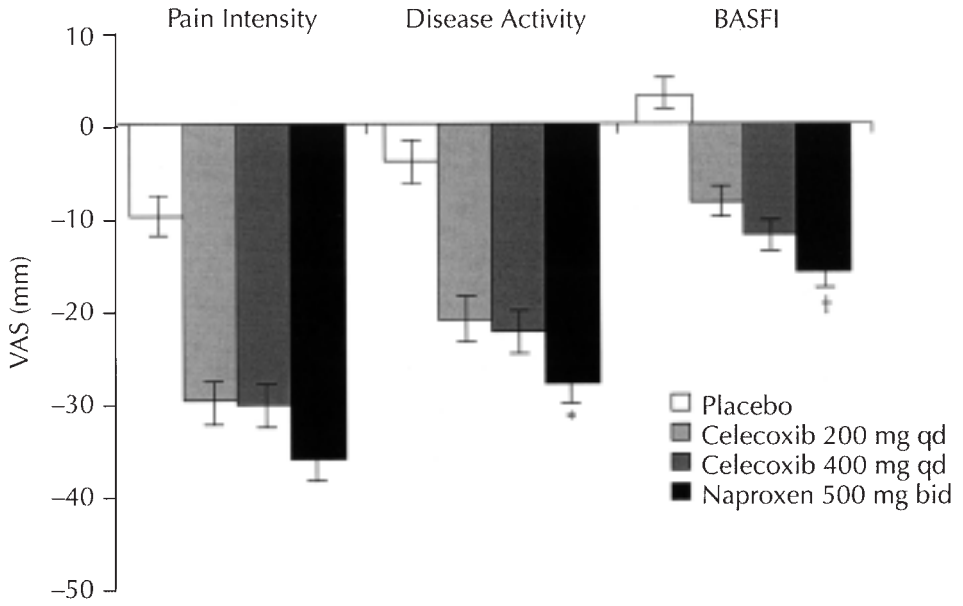

Figure 1. Least-squares mean (± SE) changes from baseline to Week 12 in pain intensity score (VAS), disease activity score (VAS), and functional impairment (BASFI) score (VAS). $p < 0.001$ for all active treatments vs placebo; *$p < 0.05$ vs celecoxib 200 mg qd; †$p < 0.01$ vs celecoxib 200 mg qd.

celecoxib 200 mg group at Week 12 ($p = 0.023$), and the celecoxib 400 mg group at Week 1 ($p = 0.018$).

At baseline, patients receiving placebo, celecoxib, or naproxen consumed around 2 APAP tablets per day on average. However, by Week 12, consumption of APAP in the celecoxib and naproxen groups had decreased to slightly less than 1 tablet per day on average. APAP consumption did not change throughout the study in placebo-treated patients. The differences between celecoxib- and placebo-treated patients, and between naproxen- and placebo-treated patients, were significant ($p < 0.001$). The proportion of patients who were responders based on the ASAS 20 Improvement Criteria is illustrated in Figure 3. There were significant between-group differences in the number of responders at each week ($p < 0.001$); however, no pairwise comparisons were performed.

Improvements in least-squares mean BASDAI scores from baseline to Weeks 1, 3, 6, and 12 in patients receiving celecoxib 200 mg, celecoxib 400 mg, and naproxen were significantly greater than in patients receiving placebo ($p < 0.001$), reflecting a greater reduction in overall levels of pain, fatigue, and stiffness (Table 2). In addition, improvements in least-squares mean BASDAI scores were significantly greater in patients receiving naproxen than in those receiving celecoxib 200 mg ($p \leq 0.023$).

The percentage of patients who reported having experienced pain in the past 24 hours was lowest in the celecoxib 400 mg group (86.3%), compared with the naproxen (87.9%), celecoxib 200 mg (89.1%), and placebo (98.1%) groups. Patients in the 3 active groups had significant improvements in pain intensity and pain interference in function compared with placebo, demonstrated by significantly greater least-squares mean changes in the modified Brief Pain Inventory-short form score from baseline to Weeks 1, 3, 6, and 12 ($p < 0.001$).

Changes in CRP values from baseline to Week 12 in patients receiving celecoxib and naproxen were significantly different from changes in those receiving placebo (Table 2). Articular Index scores, fingertips-to-floor distances, Schober Index, and chest expansion measurements improved from baseline to Week 12 to a greater degree in the active treatment groups than in the placebo group.

The most frequently reported adverse events, occurring in ≥ 3% of all patients, are shown in Table 3. These included headache, nasopharyngitis, upper respiratory tract infection, nausea, and dyspepsia. Most adverse events were mild to moderate in severity. The most frequent treatment-related adverse events were GI disorders; these were experienced by 7% of placebo-treated patients, 7% and 11% of celecoxib 200 mg and celecoxib 400 mg-treated patients, respectively, and 15% of naproxen-treated patients. The most common treatment-related GI disorder was dyspepsia, experienced by 5% of patients in the naproxen group, 4% and 6% in the celecoxib 200 mg and 400 mg groups, and 3% in the placebo group. Nine patients experienced at least one incident of treatment-related edema — 3 celecoxib 200 mg patients, 4 celecoxib 400 mg patients, and 2 naproxen patients.

Serious adverse events were experienced by 2 placebo-treated patients, one celecoxib 200 mg patient, one celecoxib 400 mg patient, and 3 naproxen patients. One placebo-treated patient experienced severe gall bladder pain, and another severe carotid artery stenosis; both were considered by the

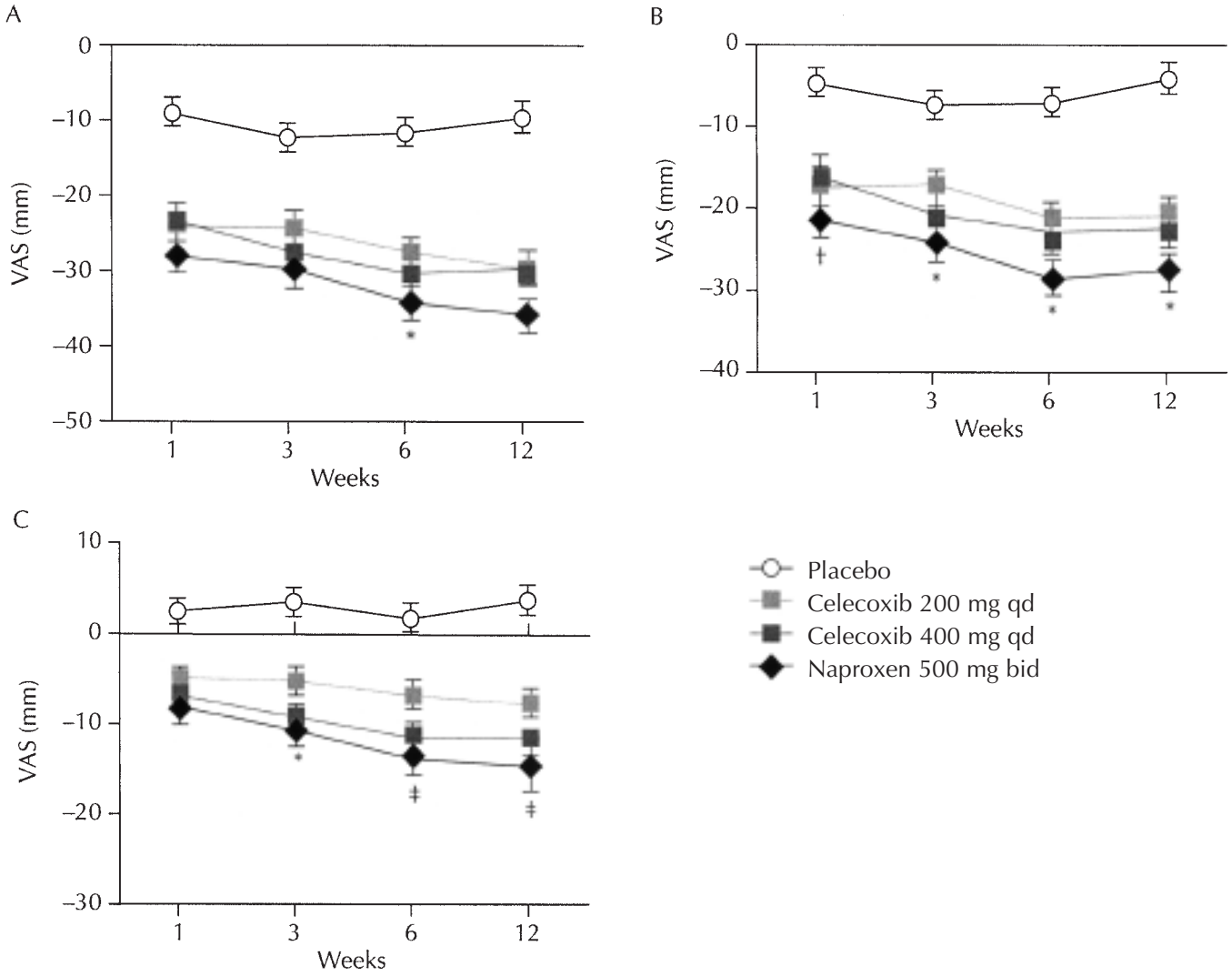

Figure 2. Least-squares mean (± SE) changes from baseline to Weeks 1, 3, 6, and 12 in (A) pain intensity score (VAS), (B) disease activity score (VAS), and (C) BASFI score. $p < 0.001$ for all active treatments vs placebo; *$p < 0.05$ vs celecoxib 200 mg qd; †$p < 0.05$ vs celecoxib 400 mg qd; ‡$p < 0.01$ vs celecoxib 200 mg qd.

investigator not to be treatment-related. One celecoxib 200 mg patient experienced severe decreased blood pressure that was considered treatment-related, and one celecoxib 400 mg patient experienced severe renal calculus that was considered not to be treatment-related by the investigator. One naproxen treated patient experienced a severe gastric ulcer, severe pulmonary embolism, and severe deep vein thrombosis; the gastric ulcer was considered to be treatment-related, but the other 2 events were not considered to be treatment-related. Another naproxen patient experienced a moderate GI hemorrhage that was considered to be treatment-related, and a third naproxen patient experienced a severe GI hemorrhage and severe chest pain; the GI hemorrhage was considered to be treatment-related, but the chest pain was not considered treatment-related. The chest pain occurred on study Day 1 and resolved on Day 2. An electrocardiogram showed no changes, and echocardiogram revealed normal left ventricular systolic function, mild left ventricular hypertrophy, and mild aortic insufficiency. An adenosine cardiolite study revealed no ischemia, and cardiac markers were normal. Eleven (7%) placebo-treated patients, 3 (2%) celecoxib 200 mg patients, 9 (6%) celecoxib 400 mg patients, and 9 (6%) naproxen patients withdrew from the study due to at least one adverse event.

DISCUSSION

In this 12-week, randomized clinical study, celecoxib 200 mg and 400 mg qd were efficacious in treating the signs and symptoms of AS, as assessed by pain intensity (global pain intensity), disease activity (patient's global assessment of disease activity), and physical function (BASFI) scores. These findings are consistent with a 6-week study of patients with AS, in which celecoxib 200 mg was associated with significant improvements in both pain and physical function[18]. However, our study was better powered than the 6-week

Table 2. Change from baseline for secondary outcome measures.

	Placebo, n = 156	Celecoxib 200 mg qd, n = 137	Celecoxib 400 mg qd, n = 161	Naproxen 500 mg bid, n = 157
Physician's global assessment of disease activity, least-squares mean				
Week 1	–4.26	–15.6*	–14.7*	–21.9*†‡
Week 3	–7.56	–18.7*	–19.9*	–23.8*
Week 6	–8.15	–19.0*	–22.1*	–26.6*†
Week 12	–5.75	–18.7*	–23.4*	–26.7*†
Nocturnal Pain (VAS), least-squares mean				
Week 1	–3.23	–16.2*	–14.9*	–21.0*‡
Week 3	–4.18	–18.2*	–21.1*	–22.4*
Week 6	–5.87	–22.3*	–23.1*	–26.6*
Week 12	–3.05	–20.3*	–22.3*	–28.5*†‡
BASDAI, least-squares mean				
Week 1	–2.07	–12.5*	–14.3*	–17.9*†
Week 3	–3.48	–13.9*	–18.4*	–19.3*†
Week 6	–3.97	–16.3*	–20.7*	–22.3*†
Week 12	–1.74	–15.4*	–19.5*	–22.9*
Morning stiffness, min, median				
Week 12	0	–5*	–20*	–30*†
CRP, mg/l, least-squares mean				
Week 12	1.17	–2.46*	–2.64*	–3.60*

* $p \leq 0.05$ vs placebo; † $p \leq 0.05$ vs celecoxib 200 mg; ‡ $p \leq 0.05$ vs celecoxib 400 mg.

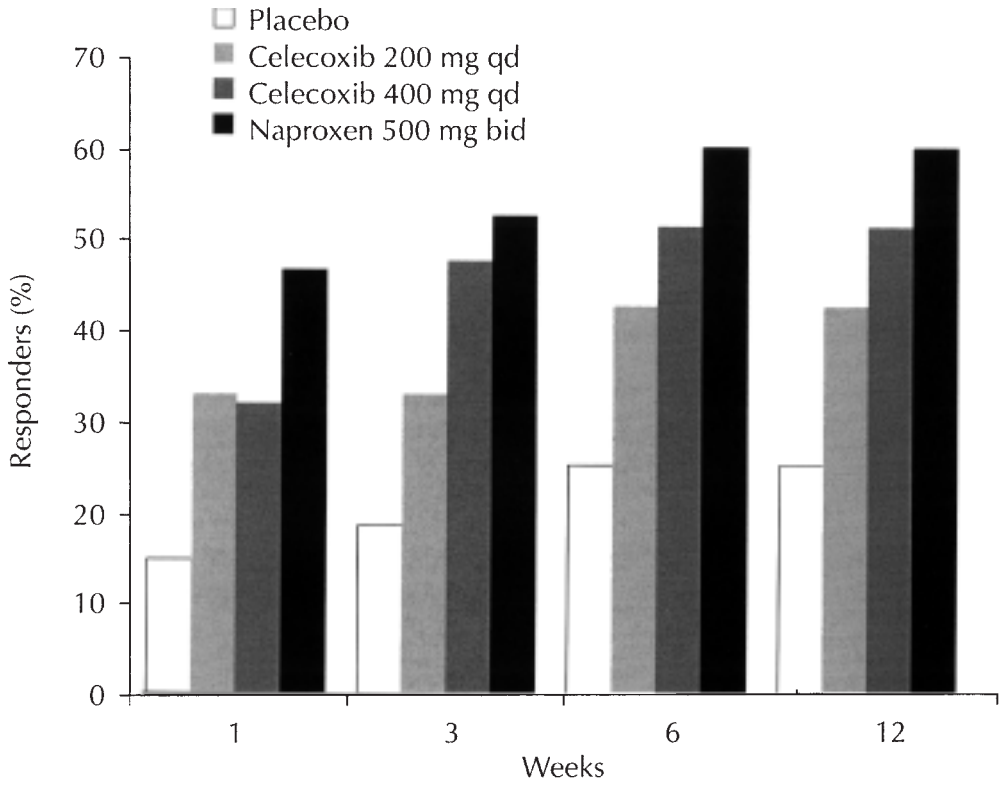

Figure 3. ASAS responder rate at Weeks 1, 3, 6, and 12. $p < 0.001$ for all active treatments vs placebo.

Table 3. Adverse events occurring in ≥ 3% of patients in any treatment group.

Adverse Event, n (%)	Placebo, n = 156	Celecoxib 200 mg qd, n = 137	Celecoxib 400 mg qd, n = 161	Naproxen 500 mg bid, n = 157
Any event	82 (52.6)	73 (53.3)	85 (52.8)	78 (49.7)
Headache	11 (7.1)*	7 (5.1)	13 (8.1)*	3 (1.9)
Nausea	3 (1.9)	4 (2.9)	9 (5.6)	7 (4.5)
Nasopharyngitis	4 (2.6)	10 (7.3)	9 (5.6)	5 (3.2)
Dermatitis	3 (1.9)	3 (2.2)	8 (5.0)	0 (0.0)
Arthralgia	0 (0.0)	5 (3.6)†	6 (3.7)†	1 (0.6)
Dyspepsia	5 (3.2)	6 (4.4)	6 (3.7)	11 (7.0)
Diarrhea	3 (1.9)	5 (3.6)	5 (3.1)	6 (3.8)
Fatigue	5 (3.2)	3 (2.2)	3 (1.9)	5 (3.2)
Upper respiratory tract infection	7 (4.5)	3 (2.2)	3 (1.9)	5 (3.2)
Sinusitis	4 (2.6)	0 (0.0)	2 (1.2)	5 (3.2)
Constipation	2 (1.3)	0 (0.0)	1 (0.6)	5 (3.2)
Sore throat	5 (3.2)‡	1 (0.7)	0 (0.0)	1 (0.6)

* Occurred in significantly more patients in the placebo and celecoxib 400 mg groups than in the naproxen group. † Occurred in significantly more patients in the celecoxib 200 mg and celecoxib 400 mg groups than in the placebo group. ‡ Occurred in significantly more patients in the placebo group than in the celecoxib 400 mg group.

study, was of longer duration, and compared different dosages of celecoxib with naproxen rather than ketoprofen.

In our study, both doses of celecoxib (200 mg qd and 400 mg qd) and naproxen 500 mg bid showed superior efficacy compared with placebo at all timepoints (Weeks 1, 3, 6, and 12). Further, the results obtained in the placebo group were consistent with those in previous clinical trials[26,27]. The 12-week duration of the study was chosen in accord with regulatory guidance for demonstration of efficacy in chronic pain, specifically AS. The study showed that celecoxib 400 mg qd was as effective as naproxen 500 mg bid; however, naproxen was generally more effective than celecoxib 200 mg qd, although these differences were not consistently statistically significant and may not be clinically meaningful. A dose-response relationship was also seen with celecoxib, with a trend toward greater efficacy at the higher celecoxib dose. These findings suggest that celecoxib 200 mg is efficacious; however, some patients may benefit from the higher celecoxib dose. The authors of a 6-week, placebo-controlled study with a 12-month double-blind extension phase suggest that, although a short-term study (6 weeks) may be sufficient to confirm the efficacy of a NSAID compared with placebo in AS, longer-term evaluation is required to better define tolerability and to detect a difference between active dosing arms[27]. In our study, although nearly 40% of placebo patients withdrew due to lack of efficacy, there was sufficient power to demonstrate efficacy of the active treatment arms. However, the occurrence of a number of serious adverse events in the naproxen group during this time suggests that a study of greater than 12 weeks' duration may not be necessary to detect differences between a COX-2 selective inhibitor and a NSAID.

Celecoxib has previously been shown to be efficacious in treating the signs and symptoms of OA and RA[16,28-30], where the beneficial antiinflammatory effects of celecoxib are at least as effective as those of nonselective NSAID, such as naproxen, but differences in their safety profiles are evident. One of the main concerns with nonselective NSAID use is the increased risk of GI adverse events, such as ulceration, perforation, and bleeding. However, it is well established that COX-2 selective inhibitors are associated with a lower incidence of gastroduodenal ulcers than nonselective NSAID, and a similar incidence to that of placebo[13,15,16,28].

Although evaluation of safety was not the primary objective of this study and the study was not adequately powered to assess safety events, the overall incidence of adverse events was low and similar in all treatment groups. However, it should be noted that many patients with AS would traditionally be classified into a low-risk group for serious GI complications (men aged < 50 yrs with no history of concomitant corticosteroid or intermittent NSAID use). Despite this, naproxen was associated with treatment-related serious adverse events of a gastric ulcer and 2 GI bleeds, which were not observed in the celecoxib or placebo groups. In addition, there were no thrombotic events in the placebo or celecoxib groups; however, one patient in the naproxen group had a severe pulmonary embolism and deep venous thrombosis. Therefore, COX-2 selective inhibitors may provide a safer alternative to nonselective NSAID in the AS patient population.

The results of this study suggest that celecoxib 200 mg or 400 mg qd may be of benefit to patients with spondyloarthropathies with axial involvement and may result in fewer serious GI adverse events than naproxen after 12 weeks' treatment.

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