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Efficacy of Celecoxib, a Cyclooxygenase 2–Specific Inhibitor, in the Treatment of Ankylosing Spondylitis

A Six-Week Controlled Study with Comparison Against Placebo and Against a Conventional Nonsteroidal Antiinflammatory Drug

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Objective. **To evaluate the short-term efficacy of celecoxib, a cyclooxygenase 2–specific inhibitor, in the treatment of ankylosing spondylitis (AS).**

Methods. **The study was a 6-week randomized, double-blind, placebo-controlled trial with 3 treatment arms: placebo, ketoprofen 100 mg twice daily, and celecoxib 100 mg twice daily. Patients who had AS according to the modified New York criteria, without peripheral synovitis and with active disease (pain ≥40 mm on a 100-mm visual analog scale [VAS] and an increase in pain of at least 30% after nonsteroidal antiinflammatory drug withdrawal) were eligible for study. Primary outcome measures were change in pain intensity (VAS) and change in functional impairment (Bath Ankylosing Spondylitis Functional Index [BASFI]).**

Results. **Of the 246 randomized patients, 76 were allocated to receive placebo, 90 ketoprofen, and 80 celecoxib. There were no statistically significant differences between treatment groups at study entry. During the 6 weeks of the study, the decrease in pain and functional impairment was greater in the active treatment groups than in the placebo group, with a trend in favor of celecoxib when the 2 active treatments were compared. The mean changes were −13 mm, −21 mm, and −27 mm ($P = 0.006$) for pain and 1, −6, and −12 ($P = 0.0008$) for BASFI score in the placebo, ketoprofen, and celecoxib groups, respectively. During treatment, the number of patients reporting epigastric pain was 6 (8%), 13 (14%), and 10 (13%) in the placebo, ketoprofen, and celecoxib groups, respectively.**

Conclusion. **The results of this study confirm the clinically relevant antiinflammatory effect of celecoxib at a 200-mg daily dosage, with significant improvement of both pain and function in patients with AS.**

The group of diseases collectively labeled spondylarthropathies consists of several disorders: reactive arthritis, psoriatic arthritis, arthritis related to inflammatory bowel disease, a subgroup of juvenile chronic arthritis, and ankylosing spondylitis (AS), the latter being the prototype of this group of interrelated disorders (1). The rheumatic manifestations of these diseases include spinal symptoms, but also extraspinal joint disease and enthesopathic lesions (2). The monitoring and, to a lesser degree, the diagnosis and treatment of these diseases are related more to their clinical presentation than to the individual diagnosis (3). The objectives of treatment of the axial involvement of spondylarthropathy are to reduce and/or prevent the deleterious clinical effects of the 3 main clinical characteristics of the disease, i.e., inflammation, ankylosis, and abnormal postures.

Nonsteroidal antiinflammatory drugs (NSAIDs) are considered to be the cornerstone of drug therapy for such axial involvement. Most of the clinical trials evaluating NSAIDs clearly demonstrate substantial, quick

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relief of symptoms. Because of the lack of knowledge of whether this symptomatic effect obtained in the short term will correlate with an improvement in the long-term prognosis, and due to the poor tolerability of conventional NSAIDs, the usual recommendation is to restrict the intake of NSAIDs to periods when the disease is causing pain (4).

Conventional NSAIDs inhibit the 2 isozymes cyclooxygenase 1 (COX-1) and COX-2. COX-1 is responsible for production of prostaglandins critical to the maintenance of gastric mucosal integrity and platelet function, and COX-2 is responsible for the biosynthesis of inflammatory prostaglandins (5).

Celecoxib has a high affinity for COX-2 enzyme at therapeutic doses (6). Experience in clinical trials conducted to date has consistently shown that treatment with celecoxib has been associated with improvement in the signs and symptoms of osteoarthritis and rheumatoid arthritis, with no appreciable effects on platelet function and no significantly increased rates of gastroduodenal ulcer as compared with placebo treatment (7–9). The effect of celecoxib on AS symptoms has not been evaluated previously. In the present study, we assessed the short-term efficacy of celecoxib 200 mg daily and ketoprofen (a widely used conventional NSAID) 200 mg daily, compared with placebo in the treatment of AS.

PATIENTS AND METHODS

Patient population. Outpatients fulfilling the modified New York criteria for AS (10) were recruited in 76 rheumatology centers, in France, after written informed consent was obtained. Other defined criteria for inclusion were 1) daily NSAID intake during the month preceding the screening visit; 2) NSAID washout period of 2–14 days before the baseline visit; and 3) a flare of the disease at baseline, defined both by pain scored as ≥40 mm on a 100-mm visual analog scale (VAS) and by an increase in pain of at least 30% between the screening and the baseline visits.

Patients with peripheral articular disease, defined by the presence of active (with swelling) peripheral arthritis (excluding hip and shoulder) at the screening visit and those with active inflammatory bowel disease were excluded, as were those with concomitant severe medical illness. Patients who had received corticosteroids during the previous 6 weeks and/or any disease-modifying antirheumatic drug with a change in dosage during the previous 6 months were excluded. Also excluded were patients with peptic ulcer confirmed by endoscopy within the year preceding the screening visit. At the screening visit, concomitant therapies with gastrointestinal (GI)–protective effects (misoprostol, proton pump inhibitors) were stopped when there was no history of gastroduodenal ulcers and were initiated and/or continued when there was a positive history of gastroduodenal ulcers.

Study design. The study was a multicenter, randomized, double-blind, placebo- and conventional NSAID–controlled trial of 6 weeks' duration. The design was approved by the Ethics Committee of Cochin Hospital.

Study drugs. After confirmation that the patient fulfilled the defined eligibility criteria, patients were randomly assigned to receive placebo, celecoxib 100 mg twice daily, or ketoprofen 100 mg twice daily. Patients took 4 capsules per day (2 at breakfast and 2 at dinner), every day during the 6 weeks of the trial, regardless of the level of symptoms. Compliance was evaluated by pill count at each visit. Acetaminophen (500-mg tablets, maximum of 6 tablets/day) was used as analgesic treatment during the study, when needed.

Assessment criteria. Clinical assessments were performed at baseline and after 1, 3, and 6 weeks, by the same investigator. The primary criteria were patient-reported global pain intensity over the 2 previous days (recorded using a 100-mm VAS) and patient-reported functional impairment (according to the Bath Ankylosing Spondylitis Functional Index [BASFI]) (11). The secondary criteria were patient's overall assessment of disease activity (100-mm VAS), patient-reported nocturnal pain intensity (100-mm VAS), and mobility (Schober test).

Other outcome measures included 1) degree of pain at physical examination, determined using a previously reported spinal articular index (12) that focuses on the cervical, thoracic, and lumbar spine as well as the sacroiliac joints (each area scored on a 0–4 scale; maximum possible score 16); 2) degree of clinical inflammation, assessed by the duration of morning stiffness; 3) degree of sleep impairment, measured using a 1–4 scale; 4) range of chest expansion in centimeters; and 5) overall assessment of the disease activity by the investigator. At each visit, the investigators checked for treatment compliance and tolerability. At the baseline visit and at week 6, blood samples were collected to evaluate hematologic, liver, and renal function and the C-reactive protein (CRP) level.

Sample size. The sample size needed in order to demonstrate a statistically significant difference between active NSAID and placebo in the change in pain intensity from baseline to 6 weeks was calculated. It was considered important to detect a difference of half a standard deviation (i.e., if the standard baseline deviation is 30 mm, then a difference of 15 is deemed clinically relevant). We calculated that a sample size of 80 patients per treatment group would allow demonstration of this difference with an α level of 0.05 and a power of at least 0.80 (2-tailed).

Statistical analysis. The efficacy analysis was conducted on the intent-to-treat (ITT) population, defined as all patients randomized in the study and receiving at least 1 dose of study drug, with the last-observation-carried-forward technique. For patients who withdrew without a treatment assessment, the baseline value was reported as the final value. For patients who withdrew after an intermediate visit, the last value recorded during treatment was reported as the final value.

The primary efficacy criteria (absolute changes in global pain intensity [VAS] and in functional impairment [BASFI]) were evaluated using a two-way analysis of covariance, with treatment and center as factors and baseline value as covariate. In cases of significant treatment effect, a pairwise comparison was conducted using the Hochberg procedure. For both primary variables, the ratio of celecoxib effect to ketoprofen effect was calculated and the 95% confidence interval (95% CI) of the ratio was estimated. The secondary criteria (overall assessment of disease activity by patient, nocturnal pain, Schober test) and the other outcome measures were analyzed in the same way as the primary criteria.

Responders were defined as patients in whom global

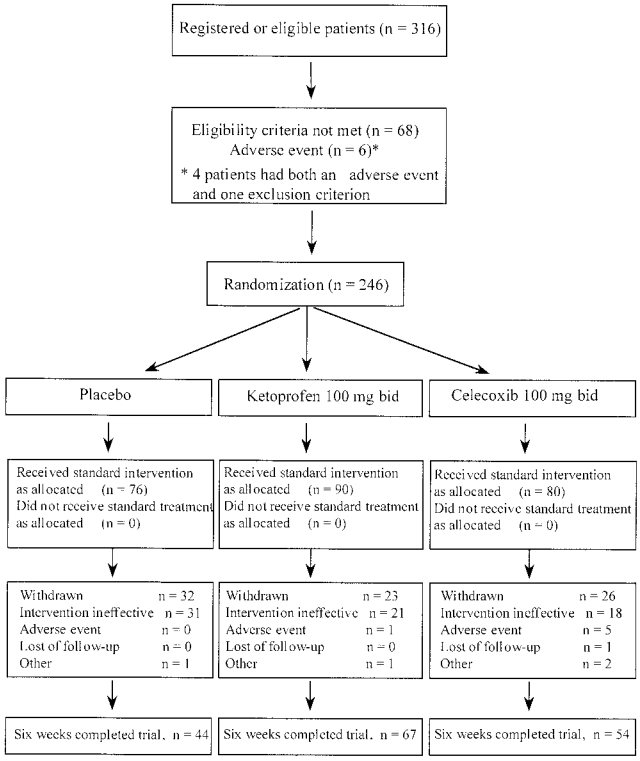

Figure 1. Patients and study course.

pain intensity decreased by at least 50% during the study period and who did not have to discontinue the drug because of lack of efficacy. Based on previous experiences (13–16), we anticipated a 20% placebo effect and a 50% active drug effect after 6 weeks of therapy. The number of responders was compared between treatment groups, by chi-square test.

An acceptable level of treatment compliance was defined a priori as an intake of capsules of at least 70% of the theoretical quantity expected to be taken. The safety analyses were performed on all randomized patients.

RESULTS

Patients and study course. Of the 316 patients screened, 246 were included in the trial (Figure 1). The most frequent reasons for noninclusion were a lack of flare after the NSAID washout period (68.6%) and a failure to achieve a washout of NSAIDs (11.4%).

Table 1 summarizes the patients' characteristics at the start of the trial. All 246 patients were included in the ITT analysis. There was no statistically significant difference in demographic data or clinical variables among the 3 treatment groups at baseline. The main reasons for discontinuation of the study drug were lack of efficacy in 23% of the patients in both active treatment groups and 41% of the patients in the placebo group. Compliance was good: the mean capsule intake was 97.5%, 100%, and 97.4% of the theoretical total in the celecoxib, ketoprofen, and placebo groups, respectively.

Assessment of efficacy. The mean ± SD changes in the global pain variable (VAS) were −13 ± 29 mm in the placebo group and −21 ± 26 mm in the ketoprofen group ($P = 0.0512$). The mean ± SD changes in the functional impairment variable (BASFI) were 1.3 ± 17.7 in the placebo group and −6.0 ± 20.8 in the ketoprofen group ($P = 0.0436$) (Table 2). Moreover, the percentage of patients in the placebo group who experienced an improvement in pain of at least 50% during the 6-week study (19.7%) was very close to that expected (20%). In the ketoprofen group, this percentage was 36% ($P = 0.0024$). The results obtained in the celecoxib group were also significantly different from those observed with placebo treatment (mean changes in pain and functional impairment were −27 ± 30 [$P = 0.0068$] and −12 ± 22 [$P = 0.0006$], respectively) (Table 2). The

Table 1. Baseline characteristics of the 246 randomized and treated ankylosing spondylitis patients, by treatment group*

Characteristic	Treatment group		
	Placebo (n = 76)	Ketoprofen 100 mg twice daily (n = 90)	Celecoxib 100 mg twice daily (n = 80)
Age, mean ± SD years	40 ± 11	38 ± 11	38 ± 11
% male	71	67	70
Body mass index, mean ± SD	24.6 ± 4.0	23.4 ± 3.3	24.1 ± 4.0
Disease duration, mean ± SD years	11 ± 9	11 ± 10	11 ± 9
History of peripheral articular disease, %	26.3	30.0	37.5
History of acute anterior uveitis, %	15.8	23.3	28.8
Family history of spondylarthropathy, %	34	31	38
HLA–B27 positive, %	84	89	84

* There were no statistically significant differences between groups for any of these baseline variables.

Table 2. Baseline values and mean changes in clinical and biologic variables during the 6 weeks of the study, by treatment group*

Variable	Baseline†			Changes during the study			
	Placebo (n = 76)	Ketoprofen 100 mg twice daily (n = 90)	Celecoxib 100 mg twice daily (n = 80)	Placebo (n = 76)	Ketoprofen 100 mg twice daily (n = 90)	Celecoxib 100 mg twice daily (n = 80)	P‡
Pain							
Global pain, VAS	70 ± 15	66 ± 15	70 ± 16	−13 ± 29	−21 ± 26§	−27 ± 30¶	0.0061
Spinal articular index	8.4 ± 2.7	7.9 ± 2.7	8.9 ± 2.9	−0.79 ± 2.38	−1.57 ± 2.78	−2.32 ± 3.16	0.0076
Function, BASFI	42 ± 25	39 ± 19	47 ± 23	1.3 ± 17.7	−6.0 ± 20.8#	−11.9 ± 22.0**	0.0008
Overall assessment, VAS							
Patient	66 ± 20	60 ± 24	67 ± 20	−8.8 ± 26.0	−16.7 ± 31.0	−24.5 ± 31.3	0.0028
Physician	59 ± 17	57 ± 18	59 ± 17	−5.6 ± 25.8	−16.6 ± 28.2	−18.6 ± 26.7	0.0025
Inflammation							
Night pain, VAS	54 ± 29	53 ± 28	56 ± 32	−0.2 ± 29.3	−16.0 ± 31.7	−17.7 ± 33.9	0.0002
Sleep disturbance, % yes††	67.1	67.8	61.3	59.2	34.4	38.8	0.003
Morning stiffness, minutes	86 ± 127	91 ± 149	83 ± 79	7 ± 128	−27 ± 154	−28 ± 74	NS
CRP, mg/liter	14.1 ± 16.0	14.5 ± 16.6	20.2 ± 28.5	−0.31 ± 9.13	−1.69 ± 8.15	−2.48 ± 11.32	NS
Range of motion							
Modified Schober test, mm	12.8 ± 1.5	12.8 ± 1.3	12.5 ± 1.4	0.16 ± 0.87	0.55 ± 1.07	0.48 ± 1.00	0.0314
Finger-to-floor distance, mm	23.1 ± 15.8	24.4 ± 16.4	27.2 ± 15.3	0.28 ± 9.75	−3.59 ± 12.16	−3.25 ± 9.0	NS
Chest expansion, cm	4.5 ± 2.0	4.8 ± 2.2	4.2 ± 2.1	−0.13 ± 0.99	0.24 ± 1.35	0.27 ± 1.54	NS

* Values are the mean ± SD. VAS = visual analog scale; BASFI = Bath Ankylosing Spondylitis Functional Index; CRP = C-reactive protein.
† There were no statistically significant differences at baseline for any of these variables.
‡ Determined by two-way analysis of covariance and, for the 2 main assessment criteria (pain and functional impairment), by pairwise comparison using the Hochberg procedure. NS = not significant.
§ $P = 0.0512$ versus placebo.
¶ $P = 0.0068$ versus placebo.
# $P = 0.0436$ versus placebo.
** $P = 0.0006$ versus placebo.
†† Score of 3 or 4 on a 1–4 scale.

trend in favor of the celecoxib group when compared with the ketoprofen group did not reach statistical significance for these variables. The ratio of the celecoxib effect to the ketoprofen effect was 1.30 (95% CI 0.98–1.62]) for pain intensity and 1.98 (95% CI 0.80–3.96) for functional impairment. The percentage of patients who experienced an improvement of at least 50% in the celecoxib group (48%) was very close to that expected (50%) and significantly different from placebo (20%) ($P = 0.001$).

The results observed for all of the other clinical variables and CRP levels are summarized in Table 2. All 3 secondary clinical assessments (patient global assessment, night pain, and Schober test) confirmed the efficacy of the active treatments. The remaining efficacy assessments yielded comparable results. The mean ± SD numbers of acetaminophen tablets used daily as analgesic rescue were similar in the celecoxib and ketoprofen groups (1.4 ± 1.6 and 1.3 ± 1.2, respectively) and lower than in the placebo group (1.8 ± 1.6) ($P = 0.09$).

A detailed analysis of the changes in pain and functional impairment over time (Figure 2) showed that the improvement in both the ketoprofen and the celecoxib groups was observed at the first treatment visit (which occurred after 7 days of treatment). The changes in the biologic variables (CRP) showed a trend in favor of the active treatment groups when compared with placebo (Table 2).

Assessment of tolerability. During the study, the incidence of any adverse event was statistically significantly higher in the 2 active treatment groups compared with the placebo group (42%, 60%, and 68% in the placebo, ketoprofen, and celecoxib groups, respectively) ($P = 0.005$). Moreover, the number of patients who had to withdraw from the study because of side effects was greater in the active treatment groups compared with the placebo group (0, 1, and 5 patients in the placebo, ketoprofen, and celecoxib groups, respectively). The patient in the ketoprofen group withdrew after 14 days of therapy because of abdominal symptoms (constipation, abdominal pain, and rectal bleeding). The 5 patients in the celecoxib group withdrew for various reasons, many of which were not considered to be drug related (renal colic in 1 patient, atrial fibrillation in 1, pruritus in 1, abdominal pain in 1, and heartburn in 1).

The adverse events with the highest incidence were upper GI symptoms (epigastric pain, heartburn, nausea, abdominal pain), diarrhea, headache, upper

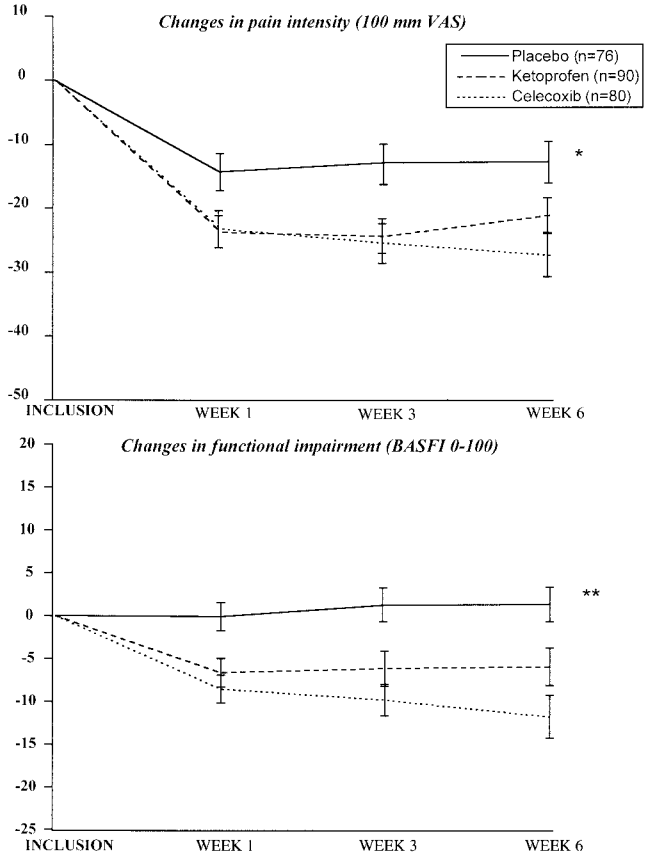

Figure 2. Changes over time in pain as assessed by visual analog scale (VAS) and in functional impairment as assessed by the Bath Ankylosing Spondylitis Functional Index (BASFI), by treatment group. * = $P = 0.0061$ for overall treatment effect on day 42 and $P = 0.0068$ for celecoxib versus placebo on day 42; ** = $P = 0.0008$ for overall treatment effect on day 42, $P = 0.0436$ for ketoprofen versus placebo on day 42, and $P = 0.0006$ for celecoxib versus placebo on day 42 (by two-way analysis of covariance and pairwise comparisons using the Hochberg procedure).

respiratory tract infection, and pruritus (Table 3). Epigastric pain occurred in 6 patients (7.9%), 13 patients (14.4%), and 10 patients (12.5%) in the placebo, ketoprofen, and celecoxib groups, respectively ($P = 0.42$).

One serious adverse event was reported in each active treatment group. In the celecoxib group, 1 patient died following discontinuation of treatment due to lack of efficacy. This event was considered unrelated to the drug. In the ketoprofen group, a gastric ulcer was diagnosed, with endoscopy performed, due to severe epigastric pain after 11 days of treatment.

One patient in the ketoprofen group had a significant decrease in the hemoglobin level, from 12.3 gm/dl to 8.8 gm/dl. There were no clinically significant changes in levels of creatinine or liver function enzymes in any of the 3 groups.

DISCUSSION

This study demonstrated that celecoxib 100 mg twice daily showed similar efficacy and safety to ketoprofen 100 mg twice daily during the 6-week period of treatment of AS; both celecoxib and ketoprofen demonstrated superior efficacy and safety when compared with placebo. The results obtained in the placebo group appear to mimic those observed in previous clinical trials (13–16). In addition, this trial confirmed the lack of placebo effect with the instruments used to evaluate the functional impairment of the patients, contrasting with a more relevant placebo effect in the instruments for evaluating patient global assessment and/or the level of pain (17,18).

In this study, celecoxib was compared with both an inactive control (placebo) and an active control (ketoprofen). Ketoprofen was chosen because of its well-known antiinflammatory effect (19) and because of a pharmacokinetic profile similar to that of celecoxib. A twice-daily dosage (once in the morning and once in the evening) was chosen for both drugs. The choice of the dosage of the active comparator is usually a concern when conducting clinical trials. The dosage of 100 mg twice daily for ketoprofen was considered to be the most appropriate since this is the dosage that is recommended and usually prescribed by rheumatologists in daily practice (20).

The present findings suggest that celecoxib at a daily dosage of 200 mg is sufficient to produce a substantial beneficial effect in 50% of patients with AS. The antiinflammatory effect is usually defined by an improvement in clinical variables that can be assessed by the patient, e.g., nocturnal pain, morning stiffness, general level of pain, and functional improvement. The

Table 3. Adverse events with an overall incidence of ≥5%, by treatment group*

Event	Placebo (n = 76)	Ketoprofen (n = 90)	Celecoxib (n = 80)
Epigastric pain	6 (7.9)	13 (14.4)	10 (12.5)
Diarrhea	1 (1.3)	6 (6.7)	6 (7.5)
Nausea	3 (3.9)	5 (5.6)	4 (5.0)
Heartburn	4 (5.3)	3 (3.3)	3 (3.8)
Abdominal pain	–	2 (2.2)	4 (5.0)
Headache	6 (7.9)	3 (3.3)	6 (7.5)
Bronchitis	–	3 (3.3)	4 (5.0)
Pharyngitis	4 (5.3)	6 (6.7)	1 (1.3)
Pruritus	1 (1.3)	3 (3.3)	4 (5.0)

* Values are the no. (%) of patients.

ability of conventional NSAIDs to provide a beneficial effect on biologic parameters of inflammation is considered to be questionable or marginal. In AS, the CRP level has been found to be correlated with clinical parameters of disease severity (such as decreased chest expansion) and predictive of structural disease progression (21,22). In this study, there was a trend in favor of an NSAID effect on the CRP level, with mean decreases of 0.3, 1.7, and 2.5 mg/liter in the placebo, ketoprofen, and celecoxib groups, respectively (see Table 2).

The beneficial antiinflammatory effect of celecoxib, which can be considered at least comparable with that of conventional NSAIDs, must be analyzed with respect to its safety profile. The evaluation of the safety profile of celecoxib was not the primary objective of the present study. It is important to note that treatment with GI-protective agents was maintained in select patients, in accordance with the study design. Nevertheless, our results confirm the acceptable short-term safety profile of celecoxib. One of the main concerns with the use of NSAIDs is the risk of occurrence of ulcers and their potential clinical complications, i.e., bleeding and perforation. Studies in other diseases have clearly demonstrated a better safety profile of celecoxib when compared with conventional NSAIDs (7–9). In those studies, the incidence of gastroduodenal ulcers in celecoxib-treated patients was similar to that in placebo-treated patients (8) and significantly lower than that observed with diclofenac (9) or naproxen (8). Regarding upper GI effects, the analysis of the present study has limited clinical relevance due to the relatively small sample size compared with the larger-scale trials performed with rheumatoid arthritis and osteoarthritis patients.

The results of this study strongly suggest that celecoxib 200 mg daily may be of benefit for patients with spondylitis with painful axial involvement. However, previous studies have suggested that a 6-week clinical trial is not of sufficient duration to detect the optimal dosage of NSAIDs to be used in AS (16). Therefore, further trials of longer duration and comparing different dosages are necessary to define the optimal dosage of celecoxib in these patients.

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