Anti-inflammatory and Upper Gastrointestinal Effects of Celecoxib in Rheumatoid Arthritis
A Randomized Controlled Trial

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PROSTANOIC ACIDS ARE SYNTHESIZED IN RESPONSE TO PHYSIOLOGIC STIMULI THAT MODULATE AND MAINTAIN HOMEOSTASIS. Prostanoic acids are also produced during acute and chronic inflammatory processes, and it is generally accepted that they mediate many of the symptoms of inflammation such as edema and pain.1,2 The 2 isoforms of cyclooxygenase (COX), COX-1 and COX-2, catalyze the committed step in the synthesis of prostanoic acids from arachidonic acid.3 Recent pharmacological evidence reinforces the likelihood that these isoenzymes mediate different biological functions.45 COX-1 is constitutively expressed in many tissues and produces prostanoic acids that predomina ntly regulate normal cellular processes.6-8 In contrast, COX-2 activity is typically undetectable in most tissues; however, COX-2 expression can be rapidly induced by proinflammatory cytokines or by growth factors.6-11

Context In vitro studies have shown that celecoxib inhibits cyclooxygenase 2 (COX-2) but not COX-1, suggesting that this drug may have anti-inflammatory and analgesic activity without adverse upper gastrointestinal (GI) tract effects that result from COX-1 inhibition.

Objective To test whether celecoxib has efficacy as an anti-inflammatory and analgesic with reduced GI tract mucosal damage compared with conventional nonsteroidal anti-inflammatory drugs in patients with rheumatoid arthritis.

Design Randomized, multicenter, placebo-controlled, double-blind trial lasting 12 weeks, with follow-up at weeks 2, 6, and 12, from September 1996 through February 1998.

Setting Seventy-nine clinical sites in the United States and Canada.

Patients A total of 1149 patients aged 18 years or older with symptomatic rheumatoid arthritis who met inclusion criteria were randomized; 688 (60%) of these completed the study.

Interventions Patients were randomized to receive celecoxib, 100 mg, 200 mg, or 400 mg twice per day (n = 240, 235, and 218, respectively); naproxen, 500 mg twice per day (n = 225); or placebo (n = 231).

Main Outcome Measures Improvement in signs and symptoms of rheumatoid arthritis as assessed using standard measures of efficacy and GI tract safety as assessed by upper GI tract endoscopy before and after treatment, compared among treatment groups.

Results All dosages of celecoxib and naproxen significantly improved the signs and symptoms of arthritis compared with placebo. Maximal anti-inflammatory and analgesic activity was evident within 2 weeks of initiating treatment and was sustained throughout the 12 weeks. The incidence of endoscopically determined gastroduodenal ulcers in placebo-treated patients was 4 (4%) of 99, and the incidences across all dosages of celecoxib were not significantly different (P>.40): 9 (6%) of 148 with 100 mg twice per day, 6 (4%) of 145 with 200 mg twice per day, and 8 (6%) of 130 with 400 mg twice per day. In contrast, the incidence with naproxen was 36 (26%) of 137, significantly greater than either placebo or celecoxib (P<.001). The overall incidences of GI tract adverse effects were 19% for placebo; 28%, 25%, and 26% for celecoxib 100 mg, 200 mg, and 400 mg twice per day, respectively; and 31% for naproxen.

Conclusion In this study, all dosages of celecoxib were efficacious in the treatment of rheumatoid arthritis and did not affect COX-1 activity in the GI tract mucosa as evidenced by less frequent incidence of endoscopic ulcers compared with naproxen.
As a result of the research that characterized the role of COX-2 in prostanoic acid production, a class of anti-inflammatory and analgesic agents that primarily inhibit COX-2 while sparing COX-1 at therapeutic dosages has been developed. The clinical rationale for this effort is that by sparing COX-1 activity, COX-2–specific inhibitors are not expected to interfere with homeostatic prostanoic-dependent processes such as upper gastrointestinal (GI) tract mucosal protection and platelet aggregation. The potential clinical benefit of this strategy is important given that patients who take nonsteroidal anti-inflammatory drugs (NSAIDs), which inhibit both COX-1 and COX-2, incur a 3- to 10-fold higher risk of gastroduodenal injury and death than those who do not. Endoscopic studies have shown that the prevalence of gastroduodenal ulcers is 15% to 30% among users of conventional (ie, nonspecific) NSAIDs. Large, randomized trials have suggested that endoscopic ulcers are surrogate markers for NSAID-induced complications such as bleeding, perforation, and obstruction. Celecoxib has been shown to inhibit COX-2 and spare COX-1 activity in vitro while possessing effective anti-inflammatory and analgesic properties when studied in vivo. It is recommended for the treatment of osteoarthritis at 100 mg 2 times a day or 200 mg once daily, and for the treatment of rheumatoid arthritis (RA) at 100 to 200 mg twice per day. This randomized, placebo-controlled, double-blind, 12-week trial was conducted to test the hypothesis that celecoxib has efficacy as an anti-inflammatory and analgesic drug through COX-2 inhibition but has little effect on COX-1 activity at efficacious doses as evidenced by reduced GI tract mucosal damage defined by endoscopy. The efficacy and upper GI tract safety of celecoxib in treating RA was assessed and compared with the effects of naproxen and placebo.

**METHODS**

**Study Population**

Men and women outpatients aged 18 years or older who were eligible to participate in the study if they fulfilled the American College of Rheumatology (ACR-20) criteria for a diagnosis of RA and were in a functional class of I, II, or III. Additional selection criteria were based on disease activity. Patients were eligible to participate if the dosages of any glucocorticoids, disease-modifying antirheumatic drugs, or methotrexate had been stable and were expected to remain constant throughout the study. Patients were excluded from the study if they had active GI tract, renal, hepatic, or coagulation disorders; history of malignancy (unless removed surgically with no recurrence within 5 years); esophageal or gastroduodenal ulceration within the previous 30 days; or a history of gastric or duodenal surgery other than an oversew. In addition, patients were excluded if the upper GI tract endoscopy performed at baseline disclosed an esophageal, gastric, or duodenal ulcer or more than 10 erosions in the stomach or duodenum. Patients were not excluded for a history of peptic ulcer disease.

**Study Protocol**

This prospective, randomized, double-blind trial was conducted at 79 clinical sites in the United States and Canada in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. The protocol was approved by the institutional review board at each clinical site, and all patients were required to provide written informed consent. Quality control measures included site visits, verification of case report forms against source medical records, and site audits by sponsor personnel. Prior to enrollment, patients completed a physical examination and clinical laboratory testing. A baseline serological antibody test for Helicobacter pylori (FlexSure, Beckman-Coulter, Palo Alto, Calif) was included. Screening or baseline clinical assessments of arthritis included patients’ and physicians’ global assessment of arthritis, scored on a scale of 1 (very good) to 5 (very poor); the patients’ assessment of arthritis pain marked on a visual analog scale (VAS) from 0 mm (no pain) to 100 mm (severe pain); a complete count of tender/painful joints; a complete count of swollen joints (hip joints were not assessed); duration of morning stiffness; the health assessment questionnaire Functional Disability Index; and plasma levels of C-reactive protein.

Following a 2- to 7-day washout period of NSAIDs or any analgesic medication, symptomatic RA (flare) was confirmed at a baseline visit according to the following definition: physicians’ and patients’ global assessments of “fair,” “poor,” or “very poor” and the first 2 plus either the third or the fourth of the following: (1) the presence of at least 6 tender or painful joints with an increase of 20% or at least 2 joints; (2) a...
minimum of 3 swollen joints with an increase of 20% or at least 2 joints; (3) a minimum of 45 minutes of morning stiffness and increase of at least 15 minutes; or (4) patients’ assessment of pain of at least 40 mm on the VAS and an increase of at least 20% or 10 mm.

An upper GI tract endoscopic evaluation was performed within 7 days prior to the first dose of study medication. The mucosae of the stomach and duodenum were evaluated separately for the presence of petechiae, erosions, and ulcers. An ulcer was defined as any break in the mucosa at least 3 mm in diameter with unequivocal depth.

**Treatment**

Patients were assigned by a computer-generated randomization schedule to 1 of 5 treatment groups: placebo, celecoxib 100 mg twice per day, celecoxib 200 mg twice per day, celecoxib 400 mg twice per day, or naproxen 500 mg twice per day (FIGURE 1). Randomization was stratified by center using a block size of 10 treatments. All treatment regimens were fully masked so that all patients took the same number of capsules, and all regimens were identical in appearance and frequency.

**Concomitant Medications**

Stable doses of aspirin no more than 325 mg/d were allowed, and acetaminophen up to 2 g/d for no longer than 3 consecutive days was also allowed except within 48 hours prior to arthritis assessments, during which no analgesics were allowed. NSAIDs, injectable corticosteroids, and anticoagulants were prohibited. Stable doses of oral glucocorticoids (up to 10 mg of prednisone per day) or disease-modifying antirheumatic drugs (DMARDs) were allowed and antiulcer drugs were prohibited.

**Clinical Assessments**

Clinical efficacy and safety assessments were performed at weeks 2, 6, and 12. Efficacy assessments were identical to those performed at the screening and baseline visits. Safety was evaluated according to the incidence and type of adverse reactions and clinical laboratory abnormalities. At the final treatment (or early termination) visit, each patient underwent a second upper GI tract endoscopy, and a CLO test for H. pylori was performed on a tissue sample taken from the greater curvature of the stomach. In all cases, the endoscopist was blinded to the treatment a patient was receiving.

Patient demographic and baseline characteristics are shown in Table 1.

**Statistical Analysis**

Homogeneity of the treatment groups at baseline was analyzed using the $\chi^2$ (for sex and race), 2-way analysis of variance (for continuous demographic variables and baseline disease activity), and the Cochran-Mantel-Haenszel test (for patients’ and physicians’ global assessments). Differences among the treatment groups in concurrent medication use were analyzed with the Fisher exact test.

**Table 1. Patient Demographic and Baseline Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n = 231)</th>
<th>100 mg (n = 240)</th>
<th>200 mg (n = 235)</th>
<th>400 mg (n = 218)</th>
<th>Naproxen (n = 225)</th>
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<tbody>
<tr>
<td>Mean age, y (range)</td>
<td>54 (27-70)</td>
<td>54 (22-85)</td>
<td>55 (20-90)</td>
<td>54 (22-85)</td>
<td>55 (28-81)</td>
</tr>
<tr>
<td>Women, %</td>
<td>73</td>
<td>74</td>
<td>73</td>
<td>72</td>
<td>72</td>
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<tr>
<td>Weight, kg</td>
<td>77 (19)</td>
<td>79 (18)</td>
<td>77 (19)</td>
<td>78 (18)</td>
<td>79 (19)</td>
</tr>
<tr>
<td>Duration of disease, y</td>
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<td>11 (10)</td>
<td>11 (10)</td>
<td>10 (9)</td>
<td>10 (9)</td>
</tr>
<tr>
<td>Concurrent medications, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Aspirin use, ≤325 mg/d</td>
<td>8</td>
<td>10</td>
<td>11</td>
<td>6</td>
<td>8</td>
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<td>Corticosteroids</td>
<td>36</td>
<td>42</td>
<td>37</td>
<td>34</td>
<td>31</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>43</td>
<td>48</td>
<td>46</td>
<td>43</td>
<td>45</td>
</tr>
<tr>
<td>DMARDs</td>
<td>32</td>
<td>35</td>
<td>32</td>
<td>31</td>
<td>37</td>
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<td>Patient’s Global Assessment, %†</td>
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<tr>
<td>Fair</td>
<td>35</td>
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<td>37</td>
<td>44</td>
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<td>Poor</td>
<td>53</td>
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<td>48</td>
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<td>43</td>
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<tr>
<td>Very poor</td>
<td>11</td>
<td>12</td>
<td>14</td>
<td>15</td>
<td>11</td>
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<tr>
<td>Physician’s Global Assessment, %‡‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td>43</td>
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<tr>
<td>Very poor</td>
<td>8</td>
<td>8</td>
<td>11</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Arthritis pain visual analog scale, mm§</td>
<td>69 (19)</td>
<td>67 (20)</td>
<td>68 (20)</td>
<td>66 (21)</td>
<td>67 (18)</td>
</tr>
<tr>
<td>Functional Disability Index (HAQ)¶</td>
<td>1.4 (0.7)</td>
<td>1.4 (0.7)</td>
<td>1.5 (0.7)</td>
<td>1.4 (0.7)</td>
<td>1.5 (0.7)</td>
</tr>
<tr>
<td>C-reactive protein, mg/L</td>
<td>16.4 (17.6)</td>
<td>15.3 (15.2)</td>
<td>16.8 (18.6)</td>
<td>16.0 (20.9)</td>
<td>14.6 (15.3)</td>
</tr>
<tr>
<td>Duration of morning stiffness, min</td>
<td>276.5 (350.5)</td>
<td>279.4 (388.5)</td>
<td>305.3 (409.8)</td>
<td>310.9 (418.7)</td>
<td>312.6 (407.6)</td>
</tr>
</tbody>
</table>

*All data presented as mean (SD) unless otherwise indicated. DMARD indicates disease-modifying antirheumatic drug; HAQ, health assessment questionnaire.
†Scale ranged from 1 (very good) to 5 (very poor).
‡One patient in the 100-mg celecoxib group was rated “good” and the score for 1 naproxen patient was missing.
§Scale ranged from 0 (no pain) to 100 (very severe pain).
¶Scale ranged from 0 to 3, with lower score representing less disability.

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Figure 2. Changes in Signs and Symptoms of Rheumatoid Arthritis

Mean numbers of tender/painful joints (top panel) and swollen joints (bottom panel) at 2, 6, and 12 weeks. Statistically significant effects (P < .05 vs placebo) were observed in all celecoxib-treatment groups at all assessment times, and in the naproxen group at all but 1 assessment time. Asterisk indicates P < .05 for all doses of celecoxib and naproxen vs placebo. Dagger indicates P < .05 for all doses of celecoxib vs placebo. Celecoxib and naproxen were both administered twice daily for all dosages. One patient was withdrawn from the celecoxib 400-mg group because of a protocol violation.

Efficacy analyses were based on the intent-to-treat cohort, defined as all patients who took at least 1 dose of study medication. In all efficacy measures, including the composite ACR-20 analysis, missing values for any assessment time were imputed by carrying forward the last observed value for any patient who discontinued the study for any reason (including treatment failure) before completing 12 weeks. Continuous efficacy variables were compared among treatment groups using analysis of covariance with treatment and center as factors and the corresponding baseline value as a covariate. Hochberg’s step-up procedure was used to control for type-1 error associated with multiple-treatment comparisons at each time point within each efficacy variable.

For categorical efficacy variables (Patient’s and Physician’s Global Assessments and the ACR-20 responder criteria), the Cochran-Mantel-Haenszel test, stratified by center, was used to compare results among treatment groups. Incidence of withdrawal due to treatment failure was analyzed with the Fisher exact test.

The gastroduodenal ulcer incidences at week 12 were analyzed with Cochran-Mantel-Haenszel tests stratified by baseline status; 95% confidence intervals (CIs) for the ulcer incidences were also calculated. The overall effects of H pylori status and H pylori status by treatment interaction were examined using both analysis of covariance and Cochran-Mantel-Haenszel test. The effects of concurrent aspirin or corticosteroid use, history of gastroduodenal ulcers, and history of GI tract bleeding were analyzed in a similar manner.

The planned sample size was based on the expectation that 35% of patients receiving active treatment would show improvement compared with 20% of placebo-treated patients. A sample size of 200 patients per treatment group was sufficient to detect this difference with 80% power at an α level of .05 adjusted for 3 celecoxib doses vs placebo by the Bonferroni method. This sample size was also sufficient to detect an anticipated difference in endoscopic gastroduodenal ulcer rate of 3% (celecoxib 400 mg twice per day) vs 11% (naproxen 500 mg twice per day) at the same α level and power.

RESULTS

Patient Characteristics

A total of 1149 patients were enrolled. No significant differences among the treatment groups at entry were detected with respect to baseline characteristics (Table 1). The study was completed by 688 patients (60%). Figure 1 shows reasons for early discontinuation from the study and includes the numbers of patients withdrawing during each interval, indicating the extent of data extrapolation at each assessment time.

Baseline endoscopic scores were not significantly different among treatment groups. More than 50% of the patients had normal gastric and duodenal mucosae, and no patients had an...
ulcer. The incidence of *H pylori* positive serology results at baseline was also not statistically significantly different across the treatment groups, ranging from 23% to 34% of patients.

**Efficacy Results**

Celecoxib produced significant improvement in the signs and symptoms of RA for all efficacy measures. As shown by the reduced number of tender/painful and of swollen joints among those treated (FIGURE 2), celecoxib produced statistically significant and maximal effects by week 2, which were sustained through 12 weeks. All celecoxib doses generally demonstrated similar efficacy, and all were comparable to naproxen 500 mg twice per day.

The percentages of patients who responded (improved) by ACR-20 criteria at weeks 2, 6, and 12 are shown in FIGURE 3. The results show significant and comparable treatment effects among patients in all the dose groups of celecoxib and naproxen, with maximal effect achieved by week 2.

For other efficacy measures, week 12 results are presented in TABLE 2. In the patients' and physicians' global assessments, celecoxib was associated with statistically significant treatment effects compared with placebo. For patients' global assessment, all celecoxib dose groups had significantly better scores than the placebo group. However, for Physicians' Global Assessment, only those in the 200-mg and 400-mg, twice-per-day celecoxib-dose groups had significantly better scores than those in the placebo group.

Naproxen was not significantly different from placebo at week 12 in either measure of efficacy. In patients' assessment of arthritis pain and duration of morning stiffness, all active treatments showed significant improvement and were statistically distinct from placebo. Improvements in the health assessment questionnaire functional disability scores were significant for those taking celecoxib 200 mg and 400 mg twice per day (P<.001 for both) and those taking naproxen compared with those taking placebo (P = 0.08). Neither celecoxib nor naproxen was associated with demonstrable effects on C-reactive protein levels.

Withdrawals from the study due to treatment failure were significantly lower for all active treatment groups (P<.001 for all) than for the placebo group: 104 (45%) of placebo patients compared with 67 (28%) of patients receiving 100 mg, 50 (21%) receiving 200 mg, and 59 (27%) receiving 400 mg of celecoxib twice per day, and 65 (29%) of patients receiving naproxen (Figure 1).

**Endoscopic Results**

FIGURE 4 shows the incidences of ulceration over the 12-week course of the trial in patients who completed the study and underwent final endoscopic evaluation. Any endoscopic finding other than ulcer was categorized as unknown if the data were obtained before the 12-week visit; only patients with endoscopy results categorized as known, including all patients found to have an ulcer at any time, are included in the analysis. In 99 patients receiving placebo, gastroduodenal ulcers developed in 4 (4% [95% CI, 0.1%-7.9%]); in 148 receiving 100-mg celecoxib, ulcers developed in 9 (6% [95% CI, 2.2%-10.0%]); in 145 receiving 200-mg celecoxib, ulcers developed in 6 (4% [95% CI, 0.9%-7.3%]); and in 130 receiving 400-mg celecoxib twice daily, ulcers developed in 8 (6% [95% CI, 2.1%-10.4%]). In comparison, of 137 patients receiving naproxen, 36 developed gastroduodenal ulcers (26% [95% CI, 18.9%-33.7%]). There were no statistically significant differences in the incidence of gastroduodenal ulcers between the placebo group and any of the celecoxib groups (P>.40) and no evidence of a dose response, whereas the incidence of ulceration in the naproxen group was significantly greater than in each of the

### Table 2. Effect of Treatment on Signs and Symptoms at 12 Weeks

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 231)</th>
<th>100 mg (n = 240)</th>
<th>200 mg (n = 235)</th>
<th>400 mg (n = 217)</th>
<th>Naproxen (n = 225)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR-20 Responders Index</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. (%) of patients responding</td>
<td>66 (29)</td>
<td>95 (40)†</td>
<td>103 (44)†</td>
<td>85 (39)†</td>
<td>81 (36)†</td>
</tr>
<tr>
<td>No. (%) with improvement on Patient’s Global Assessment</td>
<td>36 (16)</td>
<td>52 (22)†</td>
<td>71 (30)†‡¶§</td>
<td>55 (25)†</td>
<td>42 (19)</td>
</tr>
<tr>
<td>No. (%) with improvement on Physician’s Global Assessment</td>
<td>35 (15)</td>
<td>51 (21)</td>
<td>70 (30)†‡¶§</td>
<td>54 (25)†</td>
<td>45 (20)</td>
</tr>
<tr>
<td>Tender and painful joints</td>
<td>−7.6 (0.94)</td>
<td>−11.6 (0.91)†</td>
<td>−12.4 (0.91)†</td>
<td>−11.7 (0.92)†</td>
<td>−9.5 (0.88)</td>
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<tr>
<td>Swollen joints</td>
<td>−5.5 (0.64)</td>
<td>−7.5 (0.75)†</td>
<td>−9.1 (0.72)†</td>
<td>−7.0 (0.74)†</td>
<td>−6.9 (0.67)†</td>
</tr>
<tr>
<td>Arthritis Pain VAS, mm</td>
<td>−9.3 (2.0)</td>
<td>−16.9 (1.7)†</td>
<td>−20.7 (1.9)†</td>
<td>−18.1 (2.0)†</td>
<td>−16.9 (1.8)†</td>
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<tr>
<td>HAQ Functional Disability Index</td>
<td>−0.1 (0.04)</td>
<td>−0.1 (0.03)</td>
<td>−0.3 (0.04)</td>
<td>−0.2 (0.04)</td>
<td>−0.2 (0.03)</td>
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<tr>
<td>C-reactive protein, mg/L</td>
<td>0.6 (2.2)</td>
<td>−0.8 (1.6)</td>
<td>−0.9 (2.0)</td>
<td>4.6 (3.4)</td>
<td>−2.0 (2.7)</td>
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<tr>
<td>Duration of morning stiffness, min</td>
<td>8.9 (31.7)</td>
<td>−97.8 (26.8)†</td>
<td>−153.0 (27.7)†</td>
<td>−126.4 (33.2)†</td>
<td>−90.1 (28.3)†</td>
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</table>

*Values are expressed as mean (SEM) unless otherwise indicated. ACR indicates American College of Rheumatology; VAS, visual analog scale; and HAQ, health assessment questionnaire.†P<.05 vs placebo.‡P<.05 vs celecoxib 100 mg twice daily.¶Values reported are change from baseline. Negative change indicates improvement.§Scale ranged from 1 (very good) to 5 (very poor). Patient improvement was defined as a reduction of at least 2 grades from baseline for grades 3 to 5 or a change in grade from 2 to 1.

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An ulcer was defined as any break in the mucosa at least 3 mm in diameter with unequivocal depth. For each patient there were 3 possible outcomes: known ulcer, known no ulcer, and unknown. Any endoscopic finding other than ulcer was categorized as unknown if the data were obtained before the 12-week visit. Naproxen-treated patients had a significantly greater incidence of gastroduodenal ulcers than did patients treated with either celecoxib or placebo ($P<.001$). The incidences of gastroduodenal ulcers in the celecoxib treatment groups were similar to that in placebo-treated patients ($P>.40$). Error bars indicate 95% confidence intervals. Asterisk indicates $P<.001$ vs all other treatments. Celecoxib were detected. The incidences of other treatment groups ($P<.001$). A comparison of the effects of *H pylori* status, concurrent aspirin or corticosteroid use, history of GI tract bleeding, or history of GI tract ulcers on the incidence of gastroduodenal ulcers within treatment groups showed that none of these factors was associated with an effect on ulceration.

**General Safety**

All doses of celecoxib were well tolerated in this study. The incidences of adverse events among the celecoxib treatment groups were generally higher than in the placebo group but did not suggest a dose response. The adverse events with the highest incidence were headache, upper respiratory tract infection, dyspepsia, diarrhea, and abdominal pain (Table 3).

The incidences of the most frequently reported GI tract adverse events (dyspepsia, diarrhea, abdominal pain, nausea, and flatulence) combined were 19% for placebo; 28% for 100 mg, 25% for 200 mg, and 26% for 400 mg of celecoxib twice per day; and 31% for naproxen.

No adverse renal effects of celecoxib were detected. The incidences of peripheral edema and hypertension were low (0%-2%) and were similar among all treatment groups (Table 3). As representative measures, mean blood pressures and creatinine values decreased slightly over the 12 weeks in all treatment groups (Table 4).

Serious adverse events (representing hospitalizations or malignancies detected during study participation) were reported for 5 patients (2%) receiving placebo; 4 patients (2%) receiving 100 mg, 5 (2%) receiving 200 mg, and 4 (2%) receiving 400 mg of celecoxib twice per day; and 4 patients (2%) receiving naproxen. None of these events was considered to be related to study medication.

One clinically significant upper GI tract ulcer complication occurred during the study. An 80-year-old woman who received naproxen 500 mg twice per day developed an ulcer on the superior wall of the duodenal bulb and a large postbulbar ulcer on the anterosuperior wall of the duodenum, creating a partial gastric outlet obstruction after 22 days of treatment.

**COMMENT**

We tested the hypothesis that an agent that inhibits COX-2 while sparing COX-1 will be as effective as conventional NSAIDs (that inhibit both COX-1 and COX-2) but at therapeutic doses will not interfere with other prostaglandin-dependent homeostatic processes such as representative measures, mean blood pressure, and creatinine levels.
as upper GI tract mucosal integrity.\textsuperscript{7,6,20,30,41,42} The results of our study provide evidence supporting the hypothesis. Celecoxib demonstrated anti-inflammatory and analgesic efficacy comparable with naproxen, with a significantly lower incidence of gastroduodenal ulceration than naproxen, and not significantly different from placebo.

All doses of celecoxib were associated with anti-inflammatory and analgesic efficacy. This efficacy was reflected by improvements in all efficacy measures beginning at week 2 and sustained over 12 weeks. Total daily celecoxib doses of 200 mg to 400 mg were maximally efficacious, with no further benefit observed with the 400 mg twice per day regimen (800 mg/d). The efficacy of celecoxib was comparable with naproxen, and the improvement in patients treated with naproxen was similar to previously reported results from RA efficacy trials investigating the efficacy of naproxen and other NSAIDs.\textsuperscript{33,44}

Approximately 20\% to 30\% of patients who take conventional NSAIDs develop persistent adverse effects, and more than 10\% are estimated to discontinue treatment as a result.\textsuperscript{45} In this study, the GI tract tolerability of celecoxib was found to be intermediate between that for placebo and that for naproxen, as shown by incidences of GI tract adverse events and withdrawals due to GI tract adverse events. (Because crude incidences are not normalized for differing lengths of exposure, the ability to interpret these data is limited.) Overall, celecoxib was well tolerated.

It is well established that conventional NSAID therapy can lead to gastroduodenal ulceration and associated serious complications of perforation, hemorrhage, and gastric outlet obstruction.\textsuperscript{19,20} There is evidence to suggest that NSAID-induced ulcers and their resulting complications are largely caused by NSAID-mediated inhibition of mucosal prostaglandin production, primarily mediated by COX-1 activity.\textsuperscript{45,46} Prostaglandins have been shown to mediate gastroduodenal mucosal protection by several interrelated mechanisms.\textsuperscript{47,48} In animal models, NSAID-induced GI tract toxicity has been isolated to inhibition of COX-1 activity.\textsuperscript{17,50}

The results of this study provide clinical evidence for the association of celecoxib with improved endoscopic upper GI tract safety compared with naproxen. Moreover, the incidence rates of gastroduodenal ulcers associated with celecoxib, even at 4 times the recommended dose, were not significantly different from that observed with placebo. However, it should be noted that the study was not powered to show equivalence between celecoxib and placebo.

The incidence of gastroduodenal ulcers among patients receiving placebo in our study is similar to that observed in previous studies in which the point prevalence of gastroduodenal ulcers in normal asymptomatic volunteers was examined by upper GI tract endoscopy.\textsuperscript{49,50} The prevalence of gastroduodenal ulcers in untreated patients in these previous studies ranged from 1.7\% to 4.3\%. The incidence of gastroduodenal ulcers among patients who received naproxen in our study was 26\%, which is similarly consistent with previous endoscopic studies of upper GI tract damage induced by naproxen or other NSAIDs.\textsuperscript{23-26}

The precise cause of the ulcers that develop in the patients treated with either placebo or celecoxib in our study is uncertain. Neither \emph{H pylori}--positive status nor low-dose aspirin use (\textles 325 mg/d), both known ulcerogenic factors,\textsuperscript{31,52} were shown to be a factor contributing to gastroduodenal ulcer formation.

The observed differences in upper GI tract ulceration between celecoxib and naproxen are important since ulcers are generally thought to be precursors for potentially fatal ulcer complications (perforation, bleeding, or obstruction).\textsuperscript{27,28} If true, this data would indicate that drugs that inhibit COX-2 while sparing COX-1 may result in a decreased rate of ulcer complications compared with conventional NSAIDs.

Overall, these results provide evidence of the clinical benefits of celecoxib in the treatment of RA. Current therapeutic strategies for RA usually consist of combination therapy including NSAIDs together with corticosteroids and disease-modifying agents.\textsuperscript{52} In this 12-week study, celecoxib produced improvement in the signs and symptoms of RA comparable with the effects of naproxen but with a significantly reduced incidence of endoscopically identified gastroduodenal ulcers. Thus, one of the major impediments that can limit the effective use of conventional NSAIDs, upper GI tract toxic effects, may potentially be obviated by the use of celecoxib.

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EFFECTS OF CELECOXIB IN PATIENTS WITH RHEUMATOID ARTHRITIS

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