Celecoxib versus diclofenac in long-term management of rheumatoid arthritis: randomised double-blind comparison

Paul Emery, Henning Zeidler, Tore K Kvien, Mario Guslandi, Raphael Naudin, Helen Stead, Kenneth M Verburg, Peter C Isaakson, Richard C Hubbard, G Steven Geis

Summary

Background Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit cyclo-oxygenase (COX), which leads to suppression of COX-1-mediated production of gastrointestinal-protective prostaglandins. Gastrointestinal injury is a common outcome. We compared the efficacy, safety, and tolerability of long-term therapy with celecoxib, a COX-1 sparing inhibitor of COX-2, with diclofenac, a non-specific COX inhibitor.

Methods 655 patients with adult-onset rheumatoid arthritis of at least 6 months’ duration were randomly assigned oral celecoxib 200 mg twice daily or diclofenac SR 75 mg twice daily for 24 weeks. Anti-inflammatory and analgesic activity and tolerability were assessed at baseline, every 4 weeks, and at week 24. We assessed gastrointestinal safety by upper-gastrointestinal endoscopy within 7 days of the last treatment dose at centres where the procedure was available. Analysis was by intention-to-treat.

Findings 430 patients underwent endoscopy (celecoxib n=212, diclofenac n=218). The two drugs were similar in management of rheumatoid arthritis pain and inflammation. Gastrroduodenal ulcers were detected endoscopically in 33 (15%) patients treated with diclofenac and in eight (4%) in the celecoxib group (p<0·001). The rate of withdrawal for any gastrointestinal-related adverse event, most commonly abdominal pain, diarrhoea, and dyspepsia, was nearly three times higher in the diclofenac-treated group than in the celecoxib group (16 vs 6%; p<0·001).

Interpretation Celecoxib showed sustained anti-inflammatory and analgesic activity similar to diclofenac, with a lower frequency of upper gastrointestinal ulceration or gastrointestinal adverse events, and tolerability was better.

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Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs), in the treatment of rheumatoid arthritis, act by inhibiting cyclo-oxygenase (COX), which converts arachidonic acid to prostaglandins. A well established limitation of NSAIDs is the risk of clinically important injury to gastrointestinal mucosa, such as ulceration, perforation, and haemorrhage. COX exists in two isoforms. Cyclo-oxygenase-1 (COX-1), a wide-ranging essential enzyme, produces prostaglandins involved in cytoprotective and regulatory functions in gastrointestinal mucosa, platelets, and renal cells; gastric prostaglandins are derived almost exclusively from COX-1. Cyclo-oxygenase-2 (COX-2), predominantly a cytokine-induced enzyme, produces prostaglandins that mediate pain and inflammation.

With the exception of the brain, reproductive organs, and kidney, COX-2 is expressed at low concentrations in most normal tissue, but is upregulated in inflammatory cells such as activated macrophages and synoviocytes. All NSAIDs inhibit COX-1 and COX-2, each to varying degrees. This observation has led to the hypothesis that the therapeutic effects of NSAIDs are achieved by COX-2 inhibition, but many of the toxic effects, most commonly gastrointestinal injury, result from COX-1 inhibition. By contrast with conventional (ie, non-specific) NSAIDs, celecoxib was designed to inhibit specifically COX-2. Celecoxib inhibits COX-2 selectively in vitro as well as in vivo, and has effective anti-inflammatory and analgesic properties with fewer gastrointestinal toxic effects in animals and in healthy volunteers. To test clinically the hypothesis that celecoxib has anti-inflammatory and analgesic properties through COX-2 inhibition without gastrointestinal toxicity associated with inhibition of COX-1, we assessed the long-term efficacy, gastrointestinal safety, and overall tolerability of celecoxib compared with diclofenac for management of rheumatoid arthritis. We chose to compare celecoxib with diclofenac because it is a commonly prescribed NSAID believed to have a favourable gastrointestinal safety profile.

Patients and methods

132 centres in Europe, Israel, South Africa, Australia, and New Zealand took part in this study, in accordance with the Helsinki Declaration. All patients gave written, informed consent.

Study population

We enrolled 655 men and women. Patients were eligible for inclusion if they had a diagnosis of adult-onset rheumatoid arthritis of at least 6 months’ duration, according to American Rheumatism Association criteria, a functional capacity classification of III or less, and were anticipated to require continuous treatment with an NSAID for the duration of the trial. Exclusion criteria included a diagnosis of any concomitant rheumatic condition; active or suspected peptic ulceration or gastrointestinal bleeding; an important coagulation defect or
any other disorder that might preclude NSAID use; malignant disease (but not patients with at least 5-year remission after surgery); renal or hepatic disorder; inflammatory bowel disease; diclofenac intolerance; or hypersensitivity to COX-2 inhibitors, sulphonamides, or NSAIDs. Patients were also excluded if they had any clinically abnormal values on pretreatment laboratory tests. Women of childbearing age were excluded if they were pregnant, might become pregnant, or were lactating. Patients were also excluded if they had received any of the following treatments: any disease-modifying antirheumatic drug (DMARD) or oral corticosteroid given before the first dose of study drug, an injected corticosteroid given at week 24 or at the time of withdrawal.

Methods
This study was a double-blind, double-dummy, randomised, parallel trial. Eligible patients were enrolled after screening and were not required to undergo washout of NSAID before study entry. Patients were assigned by computer-generated random numbers to celecoxib 200 mg (GD Searle and Co, Skokie, IL, USA) or diclofenac SR 75 mg (Voltarol 75 slow-release, Ciba-Geigy, UK) twice daily. The drugs were identical in appearance.

Withdrawals because of treatment failure. We assessed treatment compliance by counting the number of capsules in returned bottles. Use of antiinflammatory analgesics, NSAIDs (including low-dose aspirin) other than the study drug, or chronic use of an analgesic or antiulcer drug was prohibited during the study.

Assessments
Screening by medical history, physical examination, and clinical laboratory tests was done during a pretreatment visit up to 7 days before the first dose of study medication. Efficacy and tolerability were assessed at the baseline visit, every 4 weeks during treatment, and at week 24 or at the time of withdrawal.

The main determinants of the primary outcome—efficacy in the treatment of arthritis—were the physician’s and patient’s assessments of arthritis, number of tender or painful joints (68 joints), and number of swollen joints (66 joints). Patients graded tenderness on a scale of zero (not tender) to three, and swelling on a scale of zero (none) to three (bulging synovial proliferation with cystic characteristics). Secondary arthritis assessments consisted of the number of patients responding according to the American College of Rheumatology responder index (ACR-20). Functional disability score with the modified health assessment questionnaire (0–100 mm), duration of morning stiffness, pain visual analogue scale, C-reactive protein concentration, and withdrawals because of treatment failure.

Gastrointestinal safety was based on a single upper gastrointestinal endoscopic assessment at week 24, at time of withdrawal, or no more than 7 days after the last dose of study drug. Upper gastrointestinal endoscopy was done only at study sites where the procedure was available. Injury to stomach and duodenal mucosa were assessed separately with the following scale: no visible lesions present (0); one to ten petechiae (1); more than ten petechiae (2); one to five erosions (3); six to ten erosions (4); 11–25 erosions (5); more than 25 erosions (6); or ulcer (7). An ulcer was defined as any break in the mucosa of at least 3 mm in diameter with unequivocal depth. These patients were also tested for the presence of Helicobacter pylori.

Gastrointestinal and overall tolerability were based on clinical laboratory tests (including haematological, biochemical, and urine analyses), physical examinations, observed or reported adverse events, and withdrawals because of adverse events. Data on any potential upper-gastrointestinal ulcer complications (perforation, bleeding, or gastric-outlet obstruction) were assessed by an external committee of independent gastroenterologists who were unaware of treatment status, according to pre-established criteria.

Statistical analysis
On the assumption of a 30% withdrawal rate, we calculated that a sample size of 240 patients in each treatment group would show, with a 5% level of significance (α=0·05, two-sided) and a power of 90% (β=0·10), a treatment difference of 16% (80% vs 64%) in the proportion of patients who did not worsen after 24 weeks on overall assessment. A target sample size of 144 patients in each treatment group for development of ulcer was calculated to detect 95% CI in ulcer rate of 2–4% for celecoxib and 15–25% for diclofenac, with a 5% level of significance (α=0·05, two-sided) and a power of 90% (β=0·10).

We measured treatment efficacy by primary and secondary arthritis assessments. The analyses were completed on the intention-to-treat population with the last observation carried forward. Primary arthritis assessments were analysed by analysis of covariance with treatment and centre as factors and the corresponding baseline score as a covariate factor; changes from baseline were also analysed by the Cochran-Mantel-Haenszel method, stratified by centre. We analysed secondary assessments by ANCOVA, apart from the ACR-20 responder index, which was analysed by the Cochran-Mantel-Haenszel method, stratified by centre, to confirm the corresponding ANCOVA results. Withdrawals because of absence of arthritis efficacy were analysed by Fisher’s exact test.

All analyses of treatment safety and tolerability were based on intention-to-treat. Analyses of results from upper gastrointestinal endoscopy included between-group comparison of occurrence of ulcers, analysed by the Cochran-Mantel-Haenszel test and stratified by centre. In the analysis of upper gastrointestinal endoscopy results, we grouped pyloric channel ulcers with gastric ulcers. The differential effects of Helicobacter pylori status or concomitant corticosteroid use on ulcer occurrence were analysed by ANOVA, with treatment, centre, and H pylori status as factors, and by the Cochran-Mantel-Haenszel test, stratified by treatment.

Results
326 patients received celecoxib and 329 received diclofenac. 212 on celecoxib and 218 on diclofenac underwent upper gastrointestinal endoscopy. 158 patients were withdrawn because of: pre-existing protocol violations (4); protocol non-compliance (8); treatment failure (48); and adverse events (98) (figure 1).

At baseline, the groups were similar for demography, general health, duration of rheumatoid arthritis, history of gastrointestinal disease, and NSAID intolerance (table 1). In general, baseline rheumatoid arthritis status was similar in the two groups although the diclofenac group showed a significantly higher mean pain score (visual analogue score), and a significantly longer duration of morning stiffness. The groups were similar for use of other arthritis drugs, apart from a significantly higher number of patients using anticoagulants, NSAIDs (including low-dose aspirin) other than the study drug, or chronic use of an analgesic or antiulcer drug was prohibited during the study.

* p=0·014. RA=rheumatoid arthritis; GI=gastrointestinal; DMARDs=disease-modifying antirheumatic drugs.

Table 1: Baseline characteristics

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on diclofenac than on celecoxib who were receiving concomitant corticosteroid therapy.

No baseline differences in medical history, demographics, or disease characteristics were apparent between patients who underwent an end-of-study endoscopy and those who did not (data not shown).

**Arthritis assessments**

Celecoxib and diclofenac did not differ for almost all measures of pain and inflammation associated with rheumatoid arthritis (table 2), or for distribution of patients classified by change in rheumatoid arthritis disease status on global assessment of arthritis condition. The mean number of tender or painful or swollen joints decreased over time in the two groups (figure 2). The difference between treatment groups was not significant at any time, apart from week 16, when the number of tender or painful joints was significantly lower in the celecoxib treatment group. The similarity of treatments was confirmed by least squares means analyses, which showed that changes from baseline did not differ between treatment groups.

Secondary arthritis assessments showed that the two treatments were similarly effective in managing rheumatoid arthritis pain and inflammation (table 2). Least squares means analyses confirmed no between-group differences in the change from baseline in any of the secondary measures. In the patient's assessment of pain, the reduction in perceived pain from baseline to week 24, was 6·6 mm for celecoxib and 8·6 mm on the visual analogue scale for diclofenac.

The absolute decrease in duration of morning stiffness from baseline to week 24 was 13·9 min in the diclofenac compared with 2·7 min in the celecoxib group, but between-patient variability was high in this measure, as shown by the large SDs at baseline and at week 24. The mean score on the functional disability index did not differ for the two treatment groups, at baseline or at week 24. Concentrations of C-reactive protein did not change substantially in either treatment group. Significant differences were seen between treatment groups only at weeks 4 and 8, when the mean concentration of C-reactive protein was significantly lower in the celecoxib than in the diclofenac group (p<0·05).

80 (25%) patients in the celecoxib group and 73 (22%) patients in the diclofenac group showed improvement on the American College of Rheumatology-20 responder index at week 24; significant differences between treatment

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**Table 2: Mean (SD) arthritis assessment results at week 24**

<table>
<thead>
<tr>
<th></th>
<th>Celecoxib</th>
<th>Diclofenac</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary assessments</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physician’s assessment*</td>
<td>2·9 (0·7)</td>
<td>2·6 (0·8)</td>
</tr>
<tr>
<td>Patient’s assessment*</td>
<td>3·0 (0·8)</td>
<td>2·7 (0·9)</td>
</tr>
<tr>
<td>Number of tender or</td>
<td>20·3 (14·4)</td>
<td>14·5 (14·1)</td>
</tr>
<tr>
<td>painful joints</td>
<td>21·7 (14·4)</td>
<td>16·4 (14·7)</td>
</tr>
<tr>
<td>Number of swollen joints</td>
<td>14·9 (10·2)</td>
<td>10·7 (10·1)</td>
</tr>
<tr>
<td><strong>Secondary assessments</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain VAS (mm)</td>
<td>47·4 (21·5)</td>
<td>40·8 (25·5)</td>
</tr>
<tr>
<td>Duration of morning stiffness (min)</td>
<td>70·0 (71·8)</td>
<td>67·3 (140·6)</td>
</tr>
<tr>
<td>MHAQ functional</td>
<td>1·2 (0·7)</td>
<td>1·1 (0·7)</td>
</tr>
<tr>
<td>disability index</td>
<td>1·2 (0·6)</td>
<td>1·1 (0·7)</td>
</tr>
<tr>
<td>C-reactive protein (mg/L)</td>
<td>15·1 (32·1)</td>
<td>17·4 (22·9)</td>
</tr>
</tbody>
</table>

**Notes:**

- VAS=visual analogue scale. MHAQ=modified health assessment questionnaire.
- *Independent assessments, graded from 1 (very good: symptom-free with no limitation of normal activities) to 5 (very poor: very severe symptoms that are intolerable, and inability to carry out all normal activities).

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**Figure 1: Trial profile**

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**Figure 2: Mean (SE) number of tender or painful (upper) joints and swollen (lower) joints**

*p=0·012.
groups in the distribution of these responses were not detected. Time to withdrawal and number of patients withdrawn for lack of treatment efficacy were similar in each treatment group (26 [8%] on celecoxib and 22 [7%] on diclofenac).

Safety

More gastroduodenal ulcers were detected on endoscopy in patients receiving diclofenac than in those given celecoxib (figure 3, table 3). Mean ulcer size was 1·0 cm (SD 0·7, range 0·3–4·0) in the diclofenac and 0·5 (0·2, 0·3–0·8) in the celecoxib group. When analysed separately by site of ulceration, more patients on diclofenac than on celecoxib had ulcers in the stomach or duodenum (figure 3). Similarly, significantly more ulcers or mucosal erosions, or both, (corresponding to endoscopy scores of 3–7) were detected in the stomach and in the duodenum, of patients receiving diclofenac than at the corresponding sites in those on celecoxib (table 3). More ulcers were detected in patients positive for H pylori than in those negative for H pylori in the two groups (figure 3). Similarly, significantly more ulcers or mucosal erosions, or both, (corresponding to endoscopy scores of 3–7) were detected in the stomach and in the duodenum, of patients receiving diclofenac than at the corresponding sites in those on celecoxib (table 3). More ulcers were detected in patients positive for H pylori than in those negative for H pylori in the two groups (table 3). Corticosteroid use had no effect on the number of ulcers that were detected in either treatment group (table 3).

Tolerability

Gastrointestinal-related adverse events, mostly mild to moderate in severity, were reported by 159 (48%) patients taking diclofenac and by 118 (36%) patients taking celecoxib. Abdominal pain was significantly lower in the diclofenac group (21% vs 11%) than in the celecoxib group (21% vs 11%) (table 4). Frequencies of other gastrointestinal adverse events were not significantly higher for diclofenac than for celecoxib.

Five gastrointestinal-related adverse events required admission of patients on diclofenac. These included one patient with multiple gastric erosions, requiring a transfusion of four units of blood, and one with a gastric ulcer, resulting in anaemia. The other three gastrointestinal events were gastritis in two patients and intestinal stenosis in one.

The rate of withdrawal for gastrointestinal-related adverse events was nearly three times higher among patients on diclofenac (51 [16%]) than on celecoxib (18 [6%], p<0.001).

239 (73%) patients in the diclofenac group and 222 (68%) in the celecoxib group reported one or more adverse events. The difference was not significant. The most frequently reported events are shown in table 4. Less common adverse events included peripheral oedema (11 [3%] for celecoxib vs 5 [2%] for diclofenac) and hypertension (4 [1%] vs 5 [2%]). 64 (19%) patients on diclofenac withdrew because of an adverse event, compared with 34 (10%) patients treated with celecoxib (p=0.001). Time to withdrawal for any adverse event was significantly earlier for patients on diclofenac than those on celecoxib (p=0.001).

Mean haemoglobin values were significantly decreased at all follow-up visits in patients treated with diclofenac (figure 4), whereas those for celecoxib remained much the same. At 24 weeks, the mean change in haemoglobin was −0·24 g/dL with diclofenac and −0·01 g/dL with celecoxib.

Mean systolic and diastolic blood pressures fell by about 1–2 mm Hg in each group during the study; no difference between groups was significant. Mean weights remained within 0·2 kg of baseline values.

Mean creatinine values were 93·3 μmol/L and 93·2 μmol/L at baseline and 95·5 μmol/L and 97·2 μmol/L at the final visit in the celecoxib and diclofenac groups, respectively. Mean urea values were 6·0 mmol/L in each group at baseline and 6·4 mmol/L and 6·7 mmol/L at the final visit, respectively.

Throughout the study, changes from mean baseline values for liver-function enzymes (alkaline phosphatase, aspartate aminotransferase, and alanine aminotransferase) were significantly increased (p<0.05) in the diclofenac-treated group. In the celecoxib-treated group, mean values for liver-function enzymes stayed the same or declined slightly.

Table 3: Gastrointestinal ulcer frequency

<table>
<thead>
<tr>
<th>Ulcer frequency by concomitant corticosteroid use</th>
<th>Celecoxib (n=326)</th>
<th>Diclofenac (n=329)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroid use</td>
<td>2/90 (3%)</td>
<td>12/102 (12%)</td>
<td>NS</td>
</tr>
<tr>
<td>No corticosteroid use</td>
<td>6/332 (5%)</td>
<td>21/116 (18%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Among patients with known H pylori status only.

Table 4: Most frequently-reported adverse events

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Celecoxib (n=312)</th>
<th>Diclofenac (n=218)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>36 (11%)</td>
<td>68 (21%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>36 (11%)</td>
<td>68 (21%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>39 (12%)</td>
<td>46 (14%)</td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>39 (12%)</td>
<td>46 (14%)</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>32 (10%)</td>
<td>42 (13%)</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>32 (10%)</td>
<td>42 (13%)</td>
<td></td>
</tr>
<tr>
<td>Upper-respiratory-tract infection</td>
<td>19 (6%)</td>
<td>30 (9%)</td>
<td></td>
</tr>
<tr>
<td>Upper-respiratory-tract infection</td>
<td>19 (6%)</td>
<td>30 (9%)</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>15 (5%)</td>
<td>27 (8%)</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>15 (5%)</td>
<td>27 (8%)</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>6 (2%)</td>
<td>17 (5%)</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>6 (2%)</td>
<td>17 (5%)</td>
<td></td>
</tr>
</tbody>
</table>

*p<0.05.
Gastrointestinal tolerability was better with celecoxib than for diclofenac. Lack of gastrointestinal tolerability limits the clinical usefulness of NSAIDs; about 20–30% of patients who take NSAIDs develop persistent gastrointestinal symptoms, and more than 10% of all patients discontinue treatment. However, gastrointestinal symptoms may, or may not, be associated with gastroduodenal ulceration or more serious ulcer complications. Also, the degree to which gastrointestinal symptoms are the result of non-specific inhibition of COX or some other mechanism remains to be established.

Our results provide clinical evidence for celecoxib’s upper-gastrointestinal safety. Over 24 weeks, the prevalence of endoscopically identified gastroduodenal ulcers in patients with rheumatoid arthritis taking celecoxib was nearly four-fold lower than in those given diclofenac. A similar pattern was seen in less severe upper-gastrointestinal injury, such as erosions. The prevalence of gastroduodenal ulcers with diclofenac is consistent with previous endoscopic studies of diclofenac or NSAIDs. On the other hand, the 4% prevalence of gastroduodenal ulcer detected in the celecoxib group agrees with previously reported point prevalence (1.7–4.3%) of gastroduodenal ulcers detected by upper gastrointestinal endoscopy in healthy symptom-free volunteers or untreated patients.

The pathogenesis of the ulcers that developed in patients given celecoxib could not be established. Ulcer formation was not significantly correlated with evidence of H pylori infection, although the ulcer prevalence in celecoxib-treated patients negative for H pylori was 1% (a value within the range of background rates) compared with nearly 8% in patients with evidence of H pylori infection. At baseline, significantly more patients in the diclofenac group were receiving corticosteroids, but we found no relationship between corticosteroid use and ulcer frequency in the two groups. This absence of an association is in contrast with other studies that showed use of concomitant corticosteroid therapy with an NSAID was a risk factor for ulcer complications.

The potential clinical importance of the low frequency of upper gastrointestinal ulceration with celecoxib is predicated on the observation that gastroduodenal ulcers detected by endoscopy are judged to be reasonable surrogate markers for serious ulcer complications (perforation, bleeding, or obstruction). Although direct investigation of ulcer complications is needed to confirm this result, our results suggest that the rate of ulcer complications with celecoxib might be lower than that noted with conventional NSAIDs.

**Contributors**

P Emery, H Zeidler, T Kvien, and M Guslandi were clinical investigators in the study. R Nasud, H Stead, and R Hubbard participated in developing the protocols and in analysing and interpreting the results, and provided medical supervision of the study conduct. P Isaksen and G Geis participated in developing the protocol and in analysing and interpreting the results. R Verburg participated in analysing and interpreting the results. All authors participated in preparing the final version of the paper.

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