

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

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Background

Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit cyclooxygenase (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.

Gastroduodenal 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 better tolerability.

Key words

celecoxib, specific cyclooxygenase-2 inhibitor, diclofenac, non-steroidal anti-inflammatory agents, rheumatoid arthritis, anti-inflammation, arthralgia; gastroduodenal ulcer; safety, randomised clinical trial

Introduction

Rheumatoid arthritis (RA) is a chronic, systemic disease characterised by periods of severe inflammation. One currently available class of agents used to treat RA, non-steroidal anti-inflammatory drugs (NSAIDs), acts by inhibiting cyclooxygenase (COX), the enzyme that converts arachidonic acid to prostaglandins.^{1,2} Unfortunately, NSAID therapy is frequently associated with clinically significant injury to gastrointestinal (GI) mucosa, including ulceration, perforation, and haemorrhage.^{3,4}

It is now known that COX exists in two isoforms.⁵⁻⁷ Cyclooxygenase-1 (COX-1), a ubiquitous constitutive enzyme, produces prostaglandins involved in cytoprotective and regulatory functions in GI mucosa, platelets, and renal cells^{8,9}; gastric prostaglandins are derived almost exclusively from COX-1.¹⁰ Cyclooxygenase-2 (COX-2), predominantly a cytokine-induced enzyme, produces prostaglandins that mediate pain and inflammation.¹¹⁻¹³ COX-2 is expressed in very low levels in most normal tissue, but is up-regulated in inflammatory cells such as activated macrophages and synoviocytes.^{12,14,15}

All currently available NSAIDs inhibit both COX-1 and COX-2, each to varying degrees.^{16,17} The therapeutic effects of NSAIDs are achieved by COX-2 inhibition, but the toxic effects, most commonly gastroduodenal injury, result from COX-1 inhibition.¹⁰ Theoretically, a new class of therapeutic agents, specific COX-2 inhibitors (SCIs), would be expected to achieve analgesic and anti-inflammatory effects without incurring injury to the gastroduodenal mucosa. Celecoxib is the first member of this novel class of

agents. In in vitro systems and at concentrations reflective of human therapeutic usage, celecoxib has demonstrated highly selective COX-2 inhibitory activity, with significantly less inhibition of COX-1.^{18,19}

In two large, 12-week clinical trials conducted in the United States and Canada, improvement in symptomatic osteoarthritis (OA) or RA with celecoxib 100 mg or 200 mg BID was comparable to that with naproxen 500 mg BID.²⁰ The incidence of gastroduodenal ulcer with celecoxib 100 mg BID (6%), 200 mg BID (4%), and 400 mg BID (6%) was comparable to that seen in patients treated with a placebo (4%); in patients treated with naproxen, the incidence was 26%.²⁰ The clinical trial reported here extends these two prior studies, evaluating long-term efficacy, GI safety, and overall tolerability of celecoxib compared with diclofenac in managing RA. Diclofenac was chosen as the comparator because it is a commonly prescribed NSAID with a favourable GI safety profile.²¹⁻²³

Patients and methods

This international study was conducted in 132 centres in Europe, Israel, South Africa, Australia, and New Zealand, in accordance with the Helsinki Declaration. All patients gave their written, informed consent.

Study population

Patients of either sex were eligible for inclusion if they had a diagnosis of adult-onset RA of at least 6 months' duration, according to American Rheumatism Association (ARA) criteria,²⁴ and a functional capacity classification of III or less.²⁵ Exclusion criteria included a diagnosis of: any concomitant rheumatic condition; active or suspected peptic ulceration or GI bleeding; a significant coagulation defect or any other condition that might preclude NSAID use; malignancy (but not those with at least 5-year post-resection remission); renal or hepatic disorder; inflammatory bowel disease; diclofenac intolerance; or hypersensitivity to COX-2 inhibitors, sulfonamides or NSAIDs. Patients also were excluded if they had any clinically significant abnormal values on pretreatment clinical laboratory tests. Women of childbearing age were excluded if they were pregnant, at risk of becoming pregnant, or lactating. Patients who used the following

therapies also were excluded: any disease-modifying antirheumatic drug (DMARD) or oral corticosteroid (if initiated less than 12 weeks before the first dose of study medication), or injected corticosteroid (if administered within 4 weeks before the first dose of study medication); or any other investigational medication within 30 days before the first dose of study medication. Patients were excluded if treatment was anticipated with an anticoagulant, or NSAID (including low-dose aspirin) other than the study medication, or chronic use of an analgesic or anti-ulcer drug.

Methods

This study was a double-blind, double-dummy, randomised, parallel trial. Patients were assigned by computer-generated randomisation to receive non-identifiable, oral medications twice daily: celecoxib 200 mg (G.D. Searle & Co., Skokie, IL, USA) or diclofenac SR 75 mg (Voltarol[®] 75 slow-release, Ciba-Geigy, UK). Identification of study medications was concealed from patients and investigators by a two-part label system. In case of an emergency, the treatment code could have been broken if deemed necessary by an investigator. Patients were withdrawn from the study for protocol violation or noncompliance, adverse signs or symptoms, or if they were lost to follow up. Investigators withdrew patients from the study at any time if their arthritic condition did not improve or worsened (treatment failure). Treatment compliance was measured by counting the number of capsules in returned bottles.

Assessments

Patient screening, by medical history, physical examination, and clinical laboratory tests, took place during a pretreatment visit. Efficacy and tolerability assessments were conducted at the baseline visit, at 4-week intervals during treatment, and at week 24 or the final visit if the patient did not complete the study.

Efficacy in the treatment of arthritis was based on primary arthritis assessments — physician's and patient's global assessment of the arthritis condition^{26,27}; and physician's assessment of joint tenderness, pain, and swelling^{26,27}; and secondary arthritis assessments — physician observed anti-arthritic efficacy according to the American College of Rheumatology responder index (ACR-20), including C-reactive

protein levels²⁸; and patient's evaluations using the Modified Health Assessment Questionnaire (MHAQ) functional disability index (at baseline and week 24)²⁹; the Pain-Visual Analogue Scale (VAS)³⁰; duration of early morning stiffness; the SF-36 Health Survey of health-related quality of life³¹; and withdrawals due to treatment failure.

GI safety was based on a single upper GI (UGI) endoscopic examination, conducted at week 24, the final visit, or no more than 7 days after the last dose of study medication. UGIs were performed on patients at study sites where the procedure was available. A serologic assay for *Helicobacter pylori* also was performed for these patients.

GI and overall tolerability were based on clinical laboratory tests (including haematology, biochemistry and urinalysis), physical examinations, observed or reported treatment-emergent adverse events, and withdrawals due to treatment-emergent adverse events. Clinically significant adverse GI events were defined by an external committee of independent gastroenterologists using pre-established criteria.

Statistics

Determination of target sample sizes for arthritis and ulcer assessments was based on results from a previous study that compared diclofenac 75 mg with diclofenac 75 mg/misoprostol 200 µg (Arthrotec[®] 75, G.D. Searle & Co., Skokie, IL, US).³² A target sample size of 160 patients in each treatment group for arthritis assessments, and 144 patients in each treatment group for ulcer incidence, were calculated to provide 90% power ($\beta=.10$) to detect differential effects of treatment at the 5% significance level ($\alpha=.05$, two-sided).

Efficacy in the treatment of arthritis was measured by primary and secondary arthritis assessments. These analyses were completed on the intention-to-treat population (all study participants who received at least one dose of study medication) with a last-observation-carried-forward approach. Primary arthritis assessments were analysed by analysis of covariance (ANCOVA) 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 (CMH) method, stratified by centre. Secondary assessments were analysed by ANCOVA, except for the ACR-20

responders index, which was analysed by the CMH method, stratified by centre, to confirm the corresponding ANCOVA results. The incidence of withdrawal due to lack of arthritis efficacy was analysed by Fisher's Exact test.

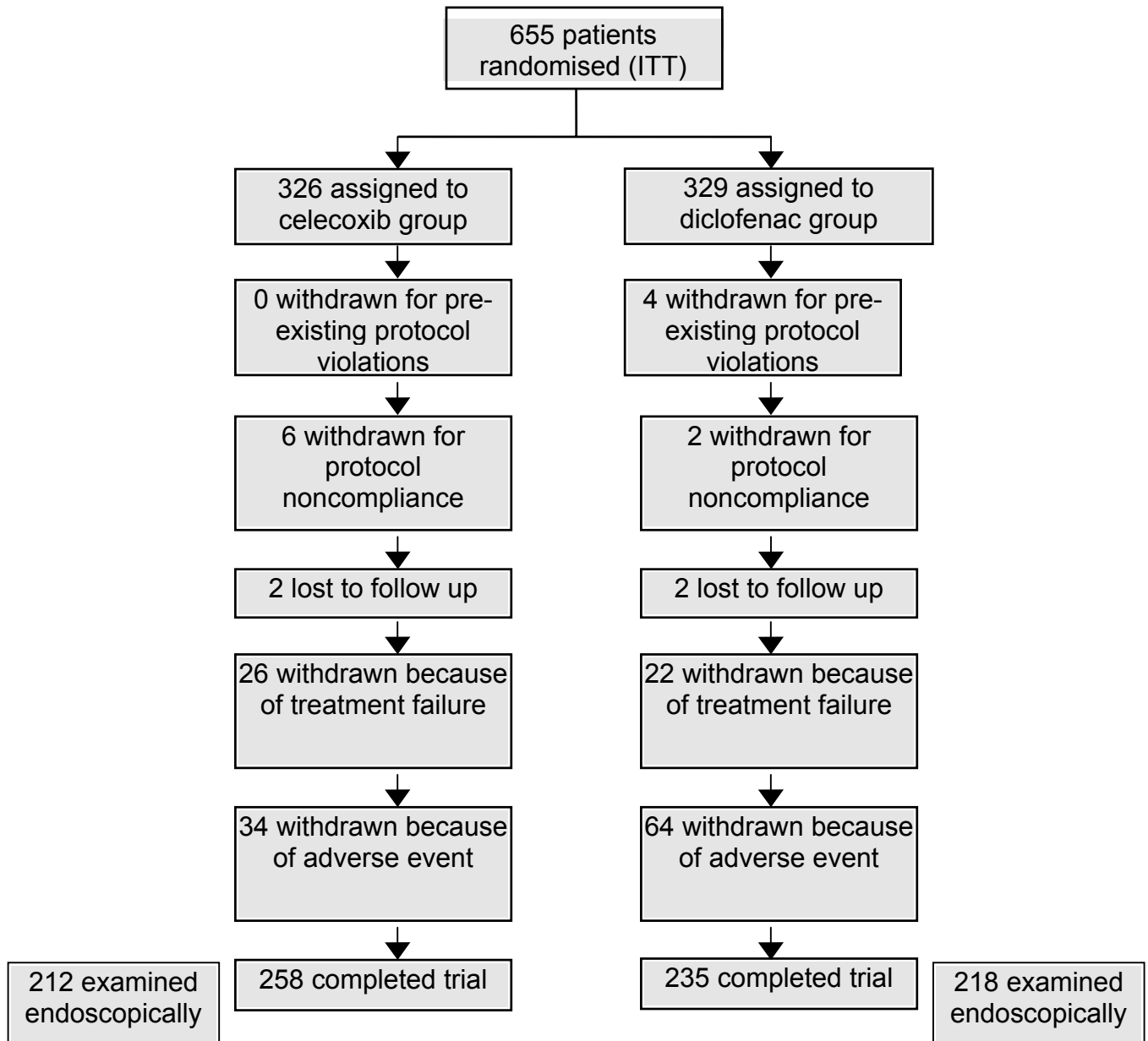
All analyses of treatment safety and tolerability were completed on an intention-to-treat basis. Analyses of results from endoscopic evaluations included between-group comparisons of the incidence of ulcer, analysed by the CMH test and stratified by centre. The differential effects of *H pylori* status or concomitant corticosteroid use on ulcer incidence were each determined by ANOVA, with treatment, centre, and *H pylori* status as factors, and by the CMH test, stratified by treatment.

Results

Study population

The intention-to-treat cohort was 655 patients, 326 patients in the celecoxib group and 329 in the diclofenac group. A UGI endoscopic examination was conducted for 430 patients, 212 in the celecoxib group and 218 in the diclofenac group. Patient disposition is diagrammed in Figure 1.

Figure 1. Patient Disposition



At baseline, the treatment groups were comparable with respect to demographic characteristics, general health, duration of RA disease, history of GI disease, and NSAID intolerance. The status of RA at baseline was comparable between treatment groups except for two patient assessments — a significantly higher mean pain score (VAS) in the diclofenac group, and a significantly longer duration of morning stiffness in the diclofenac group; neither was considered clinically significant. The groups were similar with regard to the use of other arthritis medications, except for a small but

significantly ($P=.014$) higher number of patients in the diclofenac group who were receiving concomitant corticosteroid therapy. Prominent patient baseline characteristics are listed in Table 1.

Table 1: Baseline patient characteristics

Characteristic	Celecoxib (n=326)	Diclofenac (n=329)
Demographics		
Age (mean years \pm SD)	55.90 \pm 11.78	54.50 \pm 11.82
Sex		
Female	247 (76%)	234 (71%)
Male	79 (24%)	95 (29%)
Medical history		
RA disease duration (mean years \pm SD)	11.01 \pm 9.10	9.90 \pm 7.72
History of GI bleeding	4 (1%)	1 (<1%)
History of ulcer	28 (9%)	27 (8%)
Concurrent medication		
Corticosteroids	124 (38%)*	157 (48%)*
DMARDs [†]		
Methotrexate	141 (43%)	145 (44%)
Other DMARDs	148 (45%)	151 (46%)

* $P=.014$.

[†]Disease-modifying antirheumatic drugs.

Primary arthritis assessments

In virtually all measures, celecoxib was equal to diclofenac in the management of pain and inflammation associated with RA (Table 2). There were no statistical differences in the distribution of patients categorised by change in RA disease status, as determined

by physician's or patient's global assessment of arthritis condition (Figures 2a and 2b). The mean number of tender/ painful or swollen joints decreased over time in both groups (Figures 2c and 2d). The difference between treatment groups was not significant at any time point, apart from week 16, when the number of tender or painful joints was significantly lower in the celecoxib treatment group ($P=.012$). The similarity of treatments was confirmed by least squares means analyses, which show that changes from baseline were not significantly different between treatment groups.

Secondary arthritis assessments

Secondary arthritis assessments also confirm that the two treatments were equally effective in managing RA pain and inflammation (Table 2). Least squares means analyses for the four assessments show that between-group differences in the change from baseline were not significant. In the patient's assessment of pain (VAS), the reduction from baseline to week 24 was similar in both treatment groups, 6.6 mm for celecoxib and 8.6 mm for diclofenac. The absolute decrease in duration of morning stiffness from baseline to week 24 was greater in the diclofenac group, 13.9 minutes versus 2.9 minutes for the celecoxib group, but the duration of morning stiffness was significantly higher in the diclofenac group at baseline. There was no difference in the mean score on the MHAQ functional disability index for the two treatment groups, either at baseline or week 24. The C-reactive protein values, a serologic marker for inflammation, did not change substantially in either treatment group during the course of the trial. No significant differences were found between treatment groups except at weeks 4 and 8, when the mean level of C-reactive protein was significantly lower in the celecoxib group ($P\leq.05$).

Table 2: Arthritis assessments at week 24*

Primary assessments	Celecoxib (n=326)		Diclofenac (n=329)	
	Baseline	Week 24	Baseline	Week 24
Physician's global assessment [†]	2.9 ±0.72	2.6 ±0.80	3.0 ±0.76	2.6 ±0.84
Patient's global assessment [†]	3.0 ±0.78	2.7 ±0.92	3.1 ±0.83	2.8 ±0.89
Number of tender/painful joints	20.3 ±14.35	14.5 ±14.11	21.7 ±14.35	16.4 ±14.72
Number of swollen joints	14.9 ±10.18	10.7 ±10.07	14.3 ±9.87	10.4 ±10.00
Secondary assessments	Baseline	Week 24	Baseline	Week 24
Pain–VAS [‡]	47.4 ±21.50	40.8 ±25.54	51.7 ±21.61	43.1 ±25.18
Duration of morning stiffness (min)	70.0 ±71.77	67.0 ±140.62	98.4 ±158.35	84.5 ±189.52
MHAQ [§] functional disability index	1.2 ±0.67	1.1 ±0.71	1.2 ±0.63	1.1 ±0.68
C-reactive protein (µg/L)	15097.0 ±23068.63	17430.0 ±22887.21	18367.0 ±26436.50	20490.1 ±26963.85

*Mean ± standard deviation.

[†]Visual Analogue Scale.

[§]Modified Health Assessment Questionnaire.

Eighty (25%) patients in the celecoxib group and 73 (22%) patients in the diclofenac group were classified as improved on the ACR-20 responder index at week 24; significant differences between treatment groups in the distribution of ACR-20 responses were not detected at any time point. The time to withdrawal and the number of patients withdrawn for lack of arthritis efficacy were similar in each treatment group; 26 (8%) withdrew from the celecoxib group and 22 (7%) from the diclofenac group.

Safety and tolerability

Based on UGI endoscopic examinations, treatment-emergent adverse events, physical examinations, and clinical laboratory results, the safety and tolerability of therapy was better with celecoxib than with diclofenac.

Endoscopically-determined GI safety

Celecoxib was clearly superior to diclofenac in GI safety. Significantly more ulcers were detected in patients receiving diclofenac than in patients receiving celecoxib, when analysed for all gastroduodenal ulcers (Figure 2a, Table 3), or when analysed by ulcer location (Figure 2b, Table 3). Similarly, significantly more ulcers and/or mucosal erosions were detected in the stomach and in the duodenum of patients receiving diclofenac than were detected at the corresponding site in patients receiving celecoxib (Figure 2c, Table 3). While more ulcers were detected in *H pylori*-positive than *H pylori*-negative patients in either treatment group, differences within each treatment group were not statistically significant (Table 3). Similarly, there was no significant effect of corticosteroid use on the number of ulcers that were detected in either treatment group (Table 3).

Table 3: Gastrointestinal ulcer incidence and risk factors

	Celecoxib (n=212)	Diclofenac (n=218)	P-value
Patients with a detected ulcer			
Gastroduodenal	8 (4%)	33 (15%)	<.001
Gastric	5 (2%)	24 (11%)	.002
Duodenal	4 (2%)	15 (7%)	.003
Patients with detected erosion and/or ulcer			
Gastric	38 (18%)	74 (34%)	<.001
Duodenal	11 (5%)	23 (11%)	.009
Ulcer incidence by <i>H pylori</i> status*			
Positive serology	7/93 (7.5%)	19/87 (21.8%)	†
Negative serology	1/97 (1.0%)	10/100 (10%)	†
Ulcer incidence by concomitant corticosteroid use‡			
Corticosteroid use	2/80 (2.5%)	12/102 (11.8%)	†
No corticosteroid use	6/132 (4.5%)	21/116 (18.1%)	†

*Among patients with known *H pylori* status only.

†Differences within treatment group were not statistically significant.

‡Among patients receiving concomitant corticosteroid therapy only.

Figure 2a. GI Safety

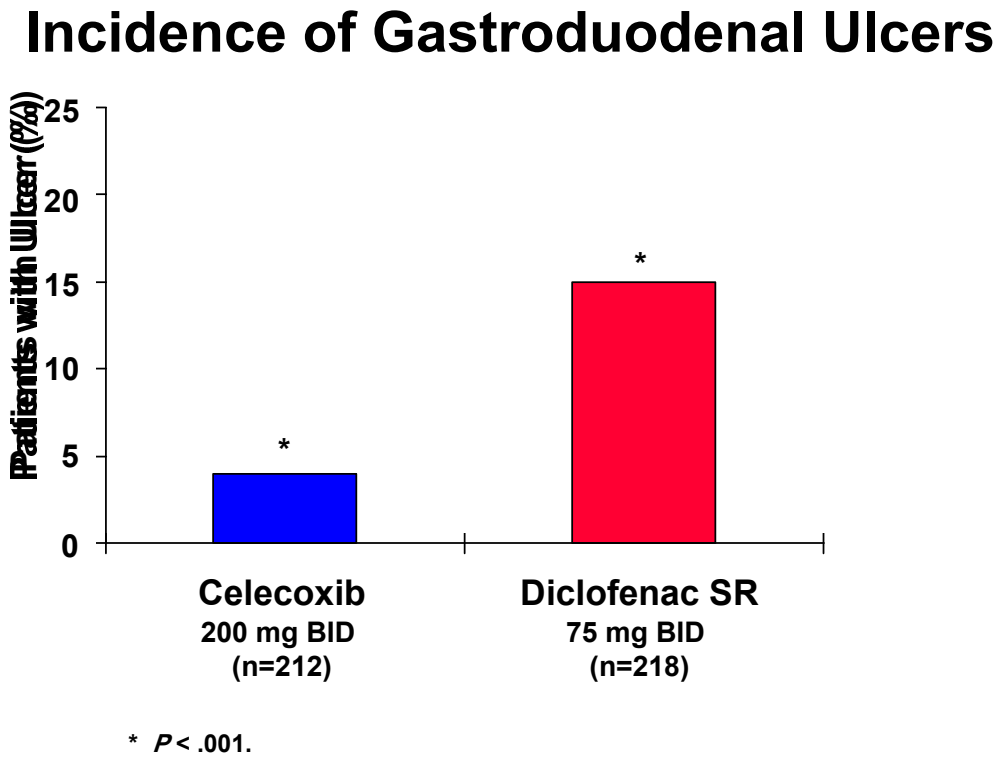


Figure 2b. GI Safety

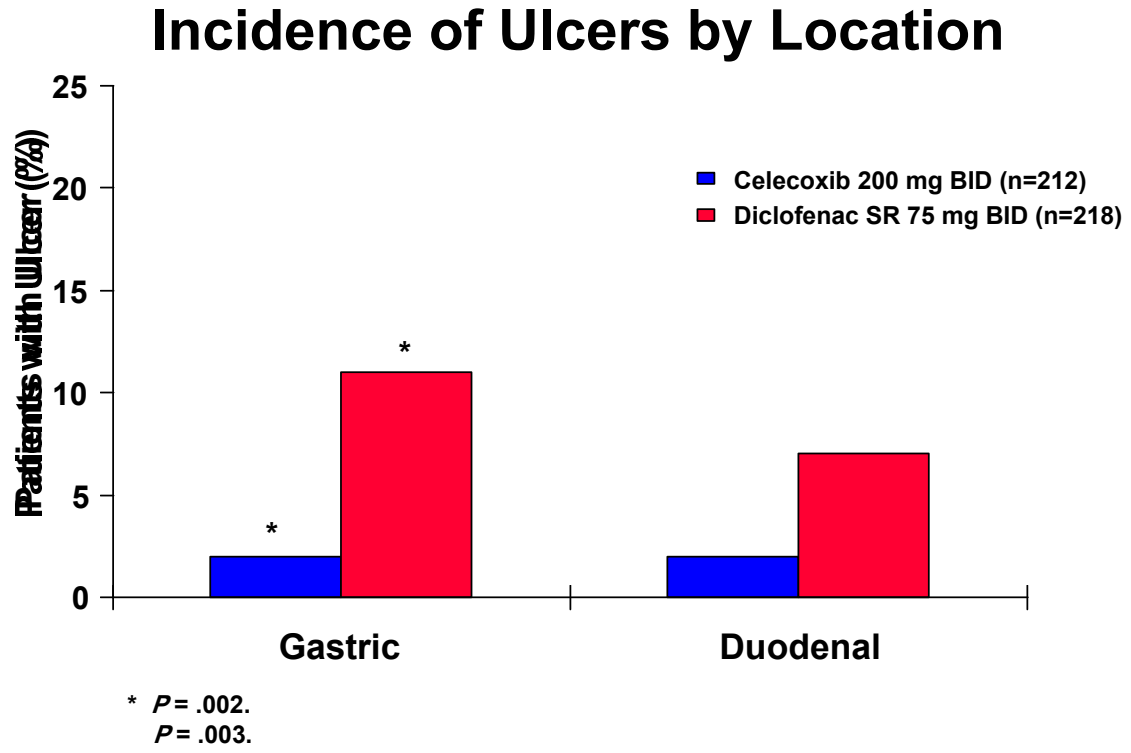
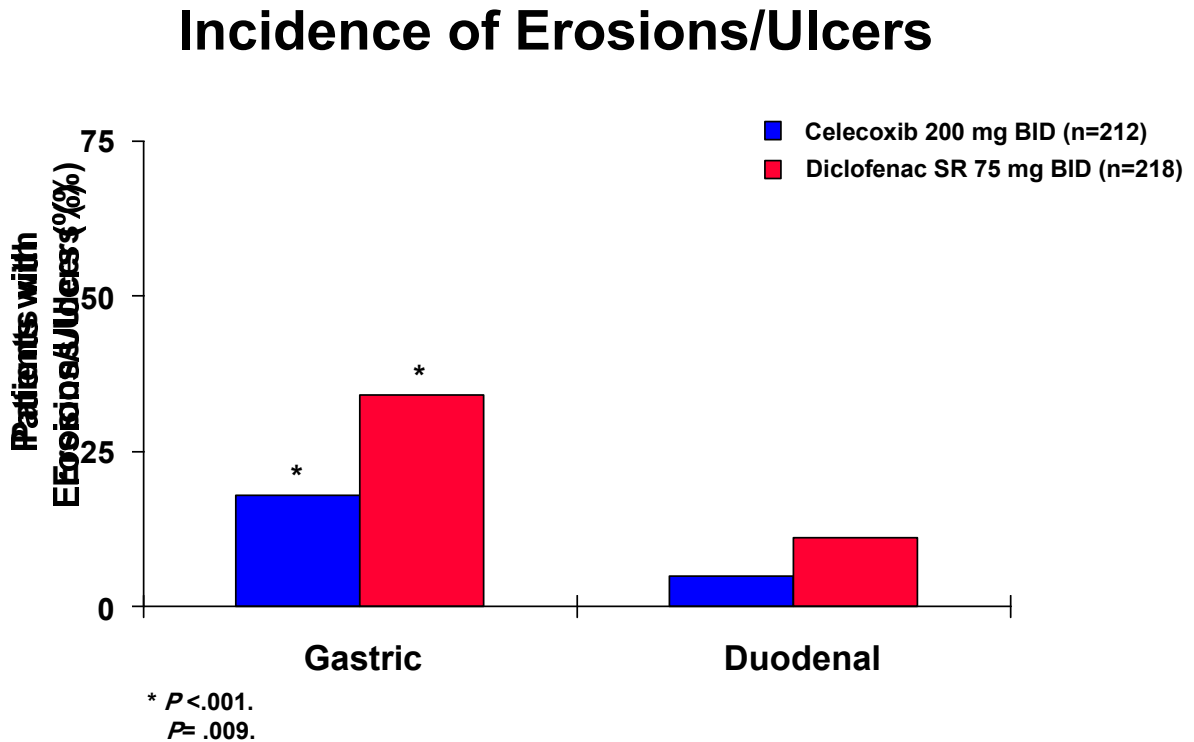


Figure 2c. GI Safety



GI tolerability

GI-related adverse events, mostly mild to moderate in severity, were reported by 159 (48%) patients in the diclofenac group and 118 (36%) patients in the celecoxib group. The percent incidence of all GI adverse events was higher in the diclofenac group, except for three events, where the incidence was very low, but slightly higher in the celecoxib group: tooth disorder (2%), hiatal hernia (1%), and hematemesis (1%).

Five serious GI-related adverse events occurred, all experienced by patients treated with diclofenac. These included two clinically significant GI bleeding events, one associated with multiple erosions, requiring a transfusion of four units of blood; and the other associated with a gastric ulcer, resulting in anaemia. The other serious GI events involved two cases of gastritis and one case of intestinal stenosis.

The incidence of withdrawal for a GI-related adverse event was nearly three times higher among diclofenac-treated patients — 51 (16%) from the diclofenac group and 18 patients (6%) from the celecoxib group ($P<.001$).

Overall tolerability

An adverse event, for the most part mild to moderate, was reported by 239 patients (73%) in the diclofenac group and 222 patients (68%) in the celecoxib group. The most frequently reported adverse events in either treatment group were: diarrhoea, abdominal pain, dyspepsia, headache, upper respiratory tract infection, nausea, fatigue and vomiting (Table 4). Sixty-four (19%) patients treated with diclofenac withdrew as a result of an adverse event, nearly twice as many as the 34 (10%) patients treated with celecoxib ($P=.001$). The time to withdrawal for any adverse event was significantly earlier for patients in the diclofenac group ($P=.001$).

Throughout the study, changes from mean baseline values for liver function enzymes (alkaline phosphatase, SGOT [AST], and SGPT [ALT]) were significantly elevated ($P\leq.05$) in the diclofenac-treated group. In the celecoxib-treated group, mean values for liver function enzymes stayed the same or declined slightly.

Table 4: Most frequently-reported adverse events*

	Celecoxib (n=326)	Diclofenac (n=329)
Diarrhoea	39 (12%)	46 (14%)
Abdominal pain	36 (11%)	68 (21%)
Dyspepsia	32 (10%)	42 (13%)
Headache	30 (9%)	19 (6%)
Upper respiratory tract infection	19 (6%)	30 (9%)
Nausea	15 (5%)	27 (8%)
Fatigue	11 (3%)	16 (5%)
Vomiting	6 (2%)	17 (5%)

*≥5% incidence in either treatment group.

Discussion

The results of this study show that long-term management of RA with celecoxib 200 mg BID delivers sustained anti-inflammatory and analgesic activity equal to that with diclofenac SR 75 mg BID, but with better GI safety and overall tolerability. The nearly four-fold lower incidence of gastroduodenal ulcer in the celecoxib group provides strong evidence of its GI safety. Furthermore, significantly fewer patients in the celecoxib group withdrew from the study due to any treatment-emergent adverse event.

Together, these clinical results provide additional support for the hypothesis that a specific COX-2 inhibitor can have anti-inflammatory and analgesic properties with improved GI safety and tolerability.^{11,12}

The design of this clinical trial reflects the typical clinical practice environment in several ways. The study population is representative of the general population of patients with RA, since patients with a history of GI complications, such as ulcer or haemorrhage, were not excluded. Screening of study candidates for active GI disease was based on clinical evaluation only — no UGI endoscopic examination was conducted prior to study entry. Diclofenac SR, an NSAID widely prescribed for its favourable GI safety profile,

was chosen as the comparator, at the dosage commonly employed for RA management. Unlike the previous study comparing celecoxib with naproxen, patients were not required to experience an arthritis flare before receiving treatment or before establishing baseline values. Never-the-less, the percent of patients experiencing improvement by ACR-20 criteria — 25% in the celecoxib-treated group and 22% in the diclofenac-treated group — was considerable.

A prior, random survey of GI injury determined by endoscopic examination reported a 24% point prevalence of gastroduodenal ulcer in 1,826 patients on NSAID therapy.²¹ An unpublished observation from this study found the incidence of gastroduodenal ulcer among the 461 patients on diclofenac therapy was 17.8% (personal communication, G.S. Geis), similar to the 15% incidence of gastroduodenal ulcer detected in the diclofenac group in this study. On the other hand, the 4% incidence of gastroduodenal ulcer detected in the celecoxib group in this study is the same as that reported in the prior comparative studies of celecoxib, in patients treated with either placebo or celecoxib 100 mg, 200 mg, or 400 mg BID for 12 weeks.²⁰

In the celecoxib group in this study, the number of ulcers detected in the stomach was as low as those detected in the duodenum. However, more gastric ulcers than duodenal ulcers were detected in the diclofenac group. While an increased vulnerability of the stomach to NSAID therapy has been reported in other studies of NSAID-induced GI ulcers³³ and upper GI bleeding or perforation,³⁴ the question of whether therapy with NSAIDs induces more gastric ulcers than duodenal ulcers remains to be resolved.

Within both treatment groups, patients who had *H pylori*-positive serology had more ulcers than those with negative serology, but the difference was not significant. This finding supports the results of the prior comparative study of celecoxib in patients with RA, which also did not find that *H pylori* status was a risk factor in NSAID-induced ulcers.²⁰ At baseline, significantly more patients in the diclofenac group were receiving corticosteroids, but we did not find any relationship between corticosteroid use and ulcer incidence in either treatment group. An association between corticosteroid use and ulcer incidence was not found in the prior comparative study of celecoxib either,²⁰

although an older meta-analysis of NSAID-induced ulcers reported concomitant corticosteroid use was a risk factor.³

This long-term study reinforces and extends the findings of earlier comparative celecoxib studies: celecoxib is as effective as naproxen or diclofenac, with greater upper GI tract safety and overall tolerability. Celecoxib, the first member of the new class of specific COX-2 inhibitors, possesses the full activity of existing non-steroidal agents for pain and inflammation, with greater GI safety and tolerability.

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