Upper gastrointestinal tolerability of celecoxib compared with diclofenac in the treatment of osteoarthritis and rheumatoid arthritis

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Abstract

Objective

To compare the upper gastrointestinal (UGI) tolerability of celecoxib (a cyclooxygenase-2 specific inhibitor) and diclofenac using data from three randomised, double-blind clinical trials in osteoarthritis (OA) and rheumatoid arthritis (RA).

Methods

Patients in two OA studies received either celecoxib 100 mg BID (n = 545), diclofenac 50 mg BID or TID (n = 540), or placebo (n = 200) for 6 weeks. In the RA study, patients received celecoxib 200 mg BID (n = 326) or diclofenac 75 mg BID (n = 329) for 24 weeks. The cumulative incidence of abdominal pain, dyspepsia, nausea or any of these events (UGI tolerability composite endpoint) after the first 6 weeks was estimated using time-to-event analysis.

Results

In the pooled OA trials, the cumulative incidence of the composite endpoint was significantly higher with diclofenac (17.6%; 95% CI: 14.4 - 20.9%) than celecoxib (11.1%; 95% CI: 8.4 - 13.8%; p = 0.002) and comparable with placebo (13.3%; 95% CI: 8.1 - 18.4%; p = 0.157). In the RA trial, the cumulative incidence of the UGI tolerability composite endpoint was also significantly higher with diclofenac (20.7%; 95% CI: 16.3 - 25.1%) than celecoxib (15.9%; 95% CI: 11.9 - 20.0%; p = 0.013). Celecoxib was also better tolerated than diclofenac in this trial in terms of the cumulative incidences of abdominal pain (p = 0.031) and dyspepsia (p = 0.062). The results of the UGI tolerability composite endpoint analysis were confirmed using the Cox proportional hazards model to control for other predictors of UGI adverse events.

Conclusion

The UGI tolerability of therapeutic dosages of celecoxib was significantly better than diclofenac in patients with RA or OA.

Key words

Upper gastrointestinal tract, tolerability, arthritis, celecoxib.

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Introduction

The gastrointestinal (GI) side effects associated with the use of non-steroidal anti-inflammatory medications have been widely discussed in the epidemiological and clinical literature (1-7). The majority of attention paid to this topic, however, has focused on the severe side effects associated with NSAIDs including gastro-duodenal ulceration, GI bleeding, and perforations (3-6, 8). Patients with arthritis taking regular NSAIDs are admitted to hospital as a result of a GI adverse event at a rate of approximately 0.73% to 1.9% per patient-year (2,6,9-11). In contrast, arthritis patients not treated with NSAIDs are admitted with GI adverse events only approximately 0.27% to 0.29% per patient-year (10-12). In addition, NSAIDs are more commonly associated with an increased risk of self-reported upper GI (UGI) symptoms. UGI symptoms are reported in approximately 30% of patients treated with NSAIDs in randomised controlled trials (13). The relative risks of UGI symptoms range from 1.16-fold to 1.85-fold (14, 15) for NSAIDs compared with placebo; abdominal pain, dyspepsia, and nausea are the most commonly reported symptoms (11-15).

The development of UGI symptoms often limits the use of NSAIDs in a large percentage of patients. In one study, nearly 13% of patients treated with NSAIDs without concomitant medications withdrew over a 6-month period due to symptoms of abdominal pain, dyspepsia, or nausea (11). Furthermore, observational data suggest that 10% to 20% of patients will switch NSAID therapies within 4 months. Side effects are the second most commonly cited reason for changing to another NSAID after lack of efficacy (16). UGI tolerability problems associated with conventional NSAIDs also complicate patient management by the physician. Some physicians undertake endoscopy or radiology to investigate for underlying gastroduodenal ulceration prior to initiating treatment in patients at high risk (17, 18). For patients who experience UGI symptoms and remain on NSAID therapy, anti-ulcer medications are often used either to reduce UGI symptoms, or as prophylaxis against serious GI events (17, 18).

A medication that minimises the problems of UGI intolerability and the risks of serious GI toxicity, while offering efficacy comparable to existing therapies, may provide significant advantages over existing therapies. This report presents an analysis of the comparative UGI tolerability of celecoxib (a cyclo-oxygenase 2 (COX-2) inhibitor) 200-400 mg per day and the conventional NSAID diclofenac (100-150 mg per day) based on data from three randomised, controlled clinical trials.

Methods

Study design

This report offers a pooled statistical analysis of three double-blind arthritis trials involving celecoxib and diclofenac. Celecoxib is a highly selective inhibitor of COX-2 (19). In randomised clinical trials, celecoxib has demonstrated efficacy comparable to that of conventional NSAIDs, yet with significant reductions in endoscopic ulcers and clinically significant GI events. (15, 20-24). The three studies reported here were chosen for this analysis because their study design was relatively similar. All three contained parallel celecoxib and diclofenac treatment arms; were conducted as multicentre, randomised, double-blind group studies; and administered dosages within their therapeutic ranges. The CLASS trial was not included in the analysis because its study results were unavailable at the time of this analysis (25).

Study 1 was conducted in the United States in patients with OA of the knee over a treatment period of 6 weeks. Patients were randomized to celecoxib 100 mg BID, diclofenac 50 mg TID, or placebo. The results of this trial have been reported elsewhere (20).

Study 2 was an international study that enrolled patients primarily from European countries; no patients were from the US. This trial was conducted in patients with OA of the knee or hip over a treatment period of 6 weeks. Patients were randomised to either celecoxib 100 mg BID or diclofenac 50 mg BID.

Study 3 was an international study that enrolled patients primarily from European countries. No patients were from the US. This trial was conducted in patients with RA over a treatment period of 24 weeks to compare the effects of celecoxib 200 mg BID and diclofenac SR 75 mg BID. This trial has been reported elsewhere (23).

In both the OA trials, a total of 1,285 patients (598 in Study 1 and 687 in Study 2) were randomised and received at least one dose of study medication. Patients were adults with OA of the knee (Study 1) or the hip and/or knee (Study 2) for at least 6 months and diagnosed according to the American College of Rheumatology criteria (26-28). At baseline, patients were also required to have symptomatic disease and a Functional Capacity Classification of I, II, or III (I = complete functional capacity with the ability to carry on all usual duties without handicaps; II = functional capacity adequate to conduct normal activities despite the handicap of discomfort or limited mobility of one or more joints; III = functional capacity adequate to perform only few or none of the duties of usual occupation or self-care) (29).

In the RA trial, 655 patients were randomised and received at least one dose of study medication. All had adult-onset RA for at least 6 months, diagnosed according to the criteria of the American Rheumatism Association (30). Additionally, all were required to have a Functional Capacity Classification of I, II, or III at baseline. Criteria for exclusion from participation included recent treatment with disease-modifying drugs, oral corticosteroids (unless at stable doses for at least 12 weeks) or corticosteroid injections. During the study, the use of additional NSAIDs (including low dose aspirin), chronic analgesia, or anti-ulcer agents was discouraged.

In all three studies, additional exclusion criteria were the presence of any other rheumatic condition, acute trauma of the joints under examination, peptic ulceration, GI bleeding, inflammatory bowel disease, renal or hepatic failure, a significant coagulation defect, and malignancy.

The three studies differed in entry criteria with respect to the arthritis status at baseline. In Study 1, patients were required to meet pre-defined criteria for an OA flare, which have been described elsewhere (20). The criteria for entry into Study 2 were less stringent than the pre-defined OA flare criteria. OA patients in Study 2 were required simply to have a Patients' Global Assessment score of 'fair', 'poor', or 'very poor'. Criteria for global arthritis assessments or 'flare' were not defined in the RA trial (Study 3). These trial design differences are notable, because in a previous UGI tolerability analysis involving naproxen, patient functional status (a measure related to global assessments and arthritis flare criteria) was a marginally significant ($p = 0.07$) predictor of UGI symptoms (15).

Outcome event definition

At the study visits, investigators or their assigned study personnel were instructed to question patients for signs and symptoms by asking: "Since your last visit, have you experienced or do you currently have any symptoms that are not associated with your arthritis ?" Signs or symptoms associated with arthritis were specifically excluded because they were captured within the arthritis efficacy assessments. The investigator summarized signs and symptoms in the case report form. The investigator also recorded the start and stop date of the sign or symptom and its severity. Severity was graded by the investigator according to the following definitions: mild (causing no limitation of usual activities), moderate (causing some limitation of usual activities), and severe (causing inability to carry out usual activities).

The investigator description of the signs and symptoms were mapped to the World Health Organization Adverse Reaction Terminology (WHOART) list. Each sign or symptom, as recorded by the physician in the case report form, was mapped to three different hierarchical adverse event codes: a system organ class, a preferred term, and an included term. An automated system performed this task. Signs and symptoms which the automated system was unable to map were manually coded in a blinded fashion. While each event was mapped to three levels, the preferred term was the lowest level of dictionary term to which the data were reported.

Adverse events were recorded at the Week 2, 4, and 6 visits in the OA studies and the Week 4, 8, 12, 16, 20, and 24 visits in the RA study. The start and stop date of each UGI symptom reported by the patient, in addition to its severity, was recorded. The UGI adverse event preferred terms evaluated in this report were abdominal pain, nausea, and dyspepsia. These three UGI symptoms were the most common UGI adverse events reported in these trials (20, 23). The following describes the included terms within each preferred term: included terms for abdominal pain were abdominal pain, abdominal distress, abdominal pain upper, cramp abdominal, abdominal discomfort, abdominal pain lower; included terms for dyspepsia were acid indigestion, stomach upset, indigestion; and included terms for nausea were nausea and gagging.

Patients reporting at least one mild, moderate, or severe episode of dyspepsia, nausea, or abdominal pain during the first 6 weeks of treatment (including patients in the RA study) were defined as patients with dyspepsia, nausea, or abdominal pain. In addition, the number of patients who reported at least one of the above three common UGI symptoms was calculated (UGI tolerability composite endpoint). The RA analysis was censored after 6 weeks for 2 reasons. First, the large majority of incidents of abdominal pain, dyspepsia, or nausea (75%) occurred within the first 6 weeks of the 6-month trial in each treatment arm (75.0% for celecoxib; 74.6% for diclofenac). A second reason was that censoring at 6 weeks allows comparisons among the RA and OA trials within a consistent follow-up period.

Analytic approach

Interpretation of pooled results requires data from studies that are sufficiently similar (31). The study designs, as described above, were sufficiently similar

Table I. Distribution of demographic characteristics and arthritis conditions by study.

	Study One (US OA Trial) n = 598	Study Two (Inter. OA Trial) n = 687	Study Three (Inter. RA Trial) n = 655	p-value
Age, mean (sd)	61.7 (11.16)[a]	63.7 (10.09)[b]	55.2 (11.81)[c]	0.0001
Female gender (%)	65.2[a]	71.8[b]	73.4[b]	0.004
Caucasian ethnicity (%)	81.4[a]	95.6[b]	98.3[c]	0.001
Disease duration in years, mean (sd)	8.6 (8.6)[a]	6.9 (6.28)[b]	10.5 (8.45)[c]	0.0001
Patient global assessment (%)				
Very good	0	0	2.0	
Good	0.2	0.2	22.0	
Fair	18.1	52.3	50.4	
Poor	64.9	39.7	22.4	
Very poor	16.8	7.9	3.2	
History of GI ulcer (%)	7.9a	2.6[b]	8.4[a]	0.001
History of NSAID intolerance (%)	2.7a	2.3[a]	6.7[b]	0.001
Patients using concurrent:				
Corticosteroid(%)	9.5[a]	5.25[b]	48.7[c]	0.001
Low-dose aspirin use(%)	15.7[a]	8.3[b]	1.5[c]	0.001
Outcome events				
Dyspepsia (%)	6.4[a]	5.0[a]	9.9[b]	0.001
Nausea	2.8	4.1	4.6	0.26
Abdominal pain	4.7[a]	5.8[a]	10.2 [b]	0.001
UGI Tolerability Comp. Endpoint (any of above)	13.2[a]	13.8[a]	20.8 [b]	0.001

p-values are from ANOVA (for continuous variables) and Pearson's chi-square (for categorical variables).
Note: Variables which differ significantly ($p < 0.05$) are designated with different letters.
* Mutually exclusive and exhaustive categories

for all data to be pooled. In addition to evaluating study design, we evaluated the comparability of the study populations and outcome event results between trials, as evidence for pooling the studies. Next, we compared separately the clinical, demographic, and outcome results for the celecoxib groups and the two diclofenac groups (from the 2 OA trials). These groups were pooled, contingent on similarities of the study populations and the percentages of patients experiencing the outcome events.

Statistical methods

Clinical and demographic characteristics of study participants were compared using the Pearson's Chi-square test for categorical variables, withdrawal rates, one-way analysis of variance (ANOVA), and Student's t-tests for continuous variables.

Time-to-event analysis, using the Kaplan-Meier method, was used to estimate the 6-week cumulative incidences of dyspepsia, abdominal pain, nausea, and of any of these events (the UGI tolerability composite endpoint). Patients were uncensored at the date of their first reported UGI event. If no event occurred, patients were censored at the time of early withdrawal or at Week 6, whichever came first. Non-parametric log-rank tests were used to compare the different treatment groups (32).

The Cox proportional hazards model was used to investigate the effects of potential risk factors of UGI symptoms. Stepwise regression techniques were used to select the most important predictors (any one with statistical significance level ≤ 0.15). The final Cox proportional hazards model for the composite endpoint included all variables that showed a level of statistical significance of 0.15 in any one of four stepwise analyses for abdominal pain, dyspepsia, nausea, or the composite. Results from the final Cox model are reported in the Results section as 'adjusted' relative risks. All analyses were conducted using SAS software, Version 6.12 (SAS® Institute; Cary, NC, USA). All p values are 2-sided.

Results

Study pooling

Table I describes the clinical and demographic characteristics of patients in the individual trials. Compared with the OA populations, RA patients were significantly younger, had a significantly higher use of concomitant corticosteroids, had a significantly lower use of concomitant low-dose aspirin, and had a significantly higher history of GI intolerance to NSAIDs. The two OA trials were generally similar to one another; however, there were some notable exceptions, such as significant differences in the prevalence of patients with a history of GI ulcer. With respect to the outcome event, the percentage of RA patients experiencing the UGI tolerability composite endpoint (dyspepsia, abdominal pain, or nausea) was significantly higher than among OA patients. Therefore, due to meaningful differences in the RA and OA populations and in the reported crude UGI event results, analyses of the OA and RA trial data were performed separately.

Next, for the OA trials, we evaluated the appropriateness of pooling the two celecoxib 100 mg dosage groups and/or pooling the two diclofenac 50 mg BID and TID dosage groups. The two celecoxib treatment groups differed on five of nine of the baseline demographic and clinical variables reported in Table II. Celecoxib OA patients in the US trial (Study 1) had a higher history of NSAID intolerance ($p = 0.002$), were less likely to be Caucasian ($p = 0.001$), had a more severe self-reported arthritis condition ($p = 0.001$), and were more likely to use concomitant corticosteroids ($p = 0.018$) and low-dose aspirin ($p = 0.002$). Despite the baseline differences reported above, the percentages of patients in the two celecoxib treatment groups reporting the composite endpoint were nearly identical (10.6% vs. 10.7%; $p = 0.96$).

The comparability of the baseline characteristics of the diclofenac 50 mg BID and TID treatment groups was similar to that reported for the celecoxib treatment group comparison. Despite the differing dosages of diclofenac (50 mg BID and 50 mg TID), the incidence of

Table II. Homogeneity of celecoxib and diclofenac treatment groups within OA trials.

Variable	Celecoxib Treatment Groups (Study 1) n=199 100 mg BID	Celecoxib Treatment Groups (Study 2) n=346 100 mg BID	p-value	Diclofenac Treatment Groups (Study 1) n=199	Diclofenac Treatment Groups (Study 2) n=341 50 mg TID	p-value 50 mg BID
Age, mean (SD)	61.9 (11.3)	63.3 (10.5)	0.16	62.7 (11.05)	64.1 (10.1)	0.14
Female gender (%)	68.3	71.1	0.50	61.8	72.4	0.01
Caucasian ethnicity (%)	85.4	95.7	0.001	82.4	95.6	0.001
Disease duration in years, mean (SD)	8.5 (9.5)	7.3 (6.7)	0.09	8.5 (8.6)	6.6 (5.8)	0.001
History of GI ulcer (%)	8.5	2.6	0.002	6.0	2.6	0.049
History of NSAID intolerance (%)	4.0	2.6	0.36	2.0	2.1	0.97
Patient's global assessment (%)			0.001			0.001
Very good	--	--		--	--	
Good	--	--		0.5	0.3	
Fair	56.7	17.1		16.7	47.8	
Poor	35.6	64.8		66.7	44.o	
Very Poor	7.8	18.1		16.2	7.8	
Patients using concomitant (%)						
Corticosteroids	11.1	5.5	0.018	7.0	5.0	0.32
Low-dose aspirin	16.6	7.8	0.002	18.6	8.8	0.001
Outcome events						
Dyspepsia (%)	5.5	3.2	0.18	7.5	6.7	0.73
Nausea	2.0	3.2	0.42	3.5	5.0	0.43
Abdominal pain	3.5	4.9	0.45	7.0	6.7	0.90
UGI Tolerability Comp. Endpoint (any of above)	10.6	10.7	0.96	17.6	17.0	0.86
Study withdrawal* (%)						
Completed study	83.9	92.5	0.002	83.9	90.6	0.02
Withdrew due to lack of efficacy	9.1	1.2	0.001	5.0	0.9	0.002
Withdrew due to GI	1.0	2.0	0.37	5.0	3.8	0.50
Withdrew due to other	6.0	4.4	0.39	6.1	4.7	0.50

* Mutually exclusive and exhaustive categories
p-values are from t-tests (for continuous variables) and Pearson's chi-square (for categorical variables)

Table III. Treatment group comparisons of baseline demographic and arthritis characteristics, and risk factors for GI symptoms

Variable	Pooled OA Trials Celecoxib 100 mg BID n=545	Pooled OA Trials Diclofenac 50 mg BID/TID n=540	Pooled OA Trials Placebo n=200	p-value	RA Trial Celecoxib 200 mg BID 75 mg BID n=326	RA Trial Diclofenac n=329	p-value
Age, mean (SD)	62.8 (10.5)a	63.6 (10.5) a	60.4 (11.1) b	0.045	55.9 (11.8)	54.5 (11.8)	0.093
Female gender (%)	70.1	68.5	65.5	0.48	75.8	71.1	0.179
Caucasian ethnicity (%)	91.9 a	90.7 a	76.5 b	0.001	98.2	98.5	0.45
Disease duration in years, mean (SD)	7.7 (7.9)a,b	7.3 (6.9) a	8.8 (8.0) b	0.643	11.0 (9.1)	9.9 (7.7)	0.085
History of gastroduodenal ulcer (%)	4.8 a	3.9 a	9.0 b	0.017	8.6	8.2	0.89
History of NSAID intolerance (%)	3.1	2.0	2.0	0.46	6.8	6.7	1.0
Patient's global assessment (%)							
Very good	0	0	0	<0.001	2.5	1.5	0.30
Good	0	0.4	0		21.8	22.2	
Fair	42.2	36.4	20.6		53.4	47.4	
Poor	46.2	52.3	63.3		19.9	24.9	
Very Poor	11.6	11.0	16.1		2.5	4.0	
Patients using concomitant (%)							
Corticosteroids	7.5	5.7	10.5	0.081	44.8	52.6	0.046
Low-dose aspirin	11.0	12.4	12.0	0.77	1.5	1.5	0.99
Completed study (%)*	89.4 a	88.2 a	72.0 b	<0.001	92.0	93.3	0.53
Withdrew due to lack of efficacy	4.0 a	2.4 a	21.0 b	<0.001	8.0	6.7	0.53
Withdrew due to GI	1.7 a	4.3 b	2.0 a	0.026	3.1	10.0	<0.001
Withdrew due to other	4.9	5.1	5.0	0.98	7.3	9.5	0.34

Note: p-values are from t-tests and ANOVA (for continuous variables) and Pearson's chi-square (for categorical variables)
* Mutually exclusive and exhaustive categories

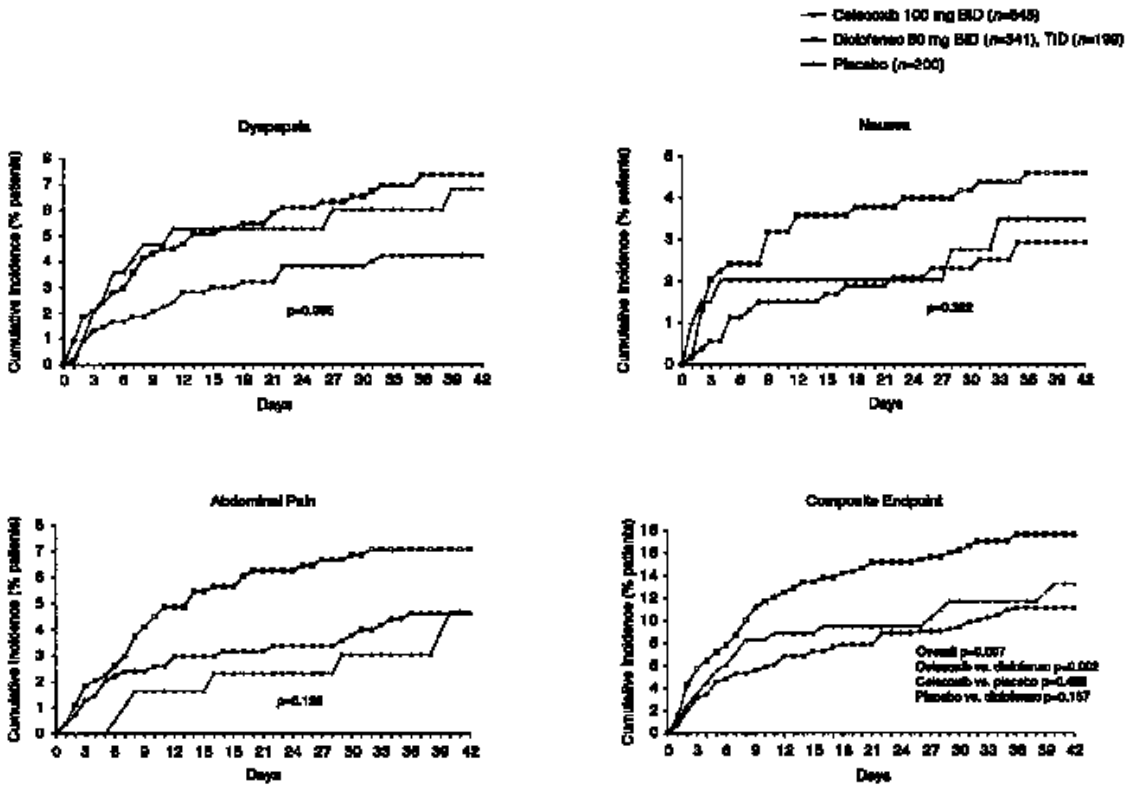

Fig. 1. Kaplan-Meier curves of the cumulative incidences of individual and UGI tolerability composite endpoint during 6 weeks treatment with celecoxib, diclofenac, or placebo in patients with OA.

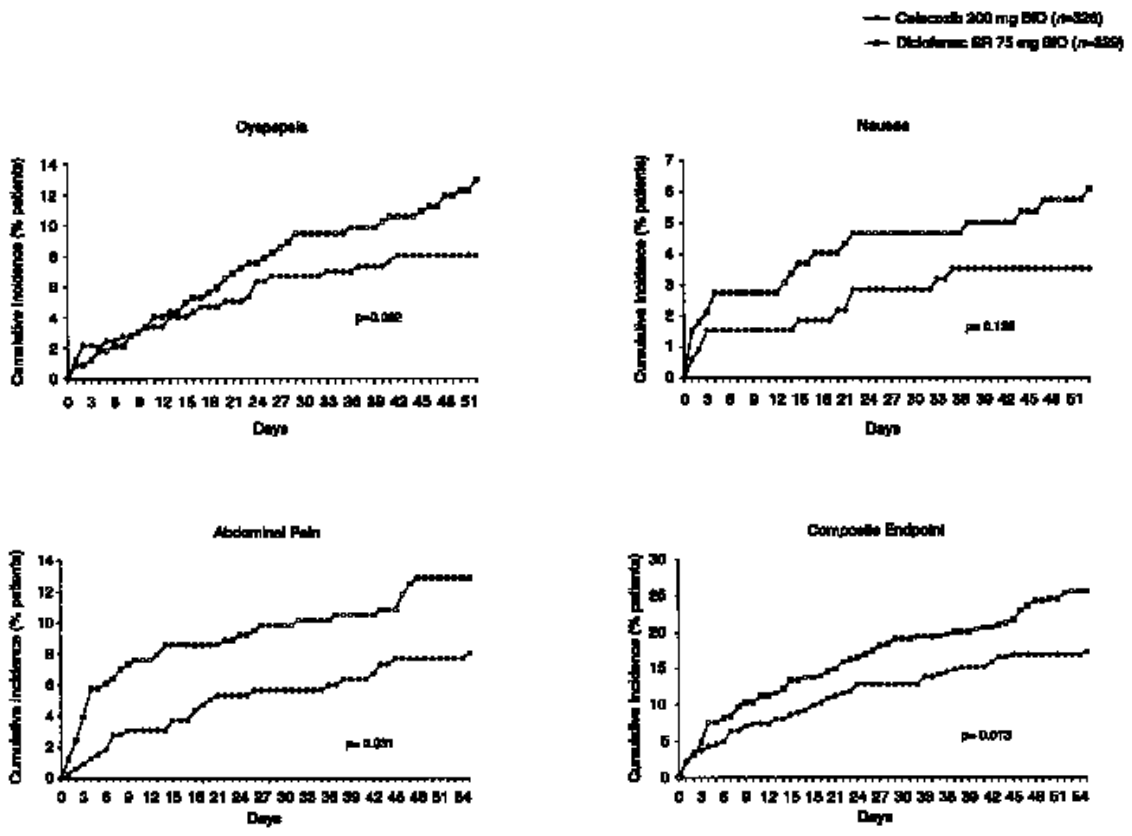

Fig. 2. Kaplan-Meier curves of the cumulative incidences of individual and UGI tolerability composite endpoint during the first 6 weeks treatment with celecoxib or diclofenac in patients with RA.

Table IV. Relative risk (RR) of the UGI tolerability composite endpoint over 6 weeks predicted by univariate risk factor analysis (Cox proportional hazards model).

		Pooled OA trials			RA trial		
Risk Factor		RR	95% CI	p-value	RR	95% CI	p-value
Treatment	Diclofenac	1.0	—	—	1.0	—	—
	Celecoxib	0.62	(0.46-0.84)	0.002	0.67	(0.49-0.90)	0.008
	Placebo	0.67	(0.44-1.00)	0.057	—	—	—
Age (years)	(50	1.0	—	—	1.0	—	—
	51-60	1.00	(0.64-1.60)	0.962	1.26	(0.85-1.86)	0.243
	61-70	0.94	(0.61-1.45)	0.786	1.30	(0.86-1.96)	0.220
	> 71	1.20	(0.75-1.94)	0.453	1.68	(1.03-2.75)	0.041
Gender	Male	1.0	—	—	1.0	—	—
	Female	1.20	(0.88-1.63)	0.258	1.04	(0.74-1.47)	0.806
Ethnicity	Non-Caucasian	1.0	—	—	1.0	—	—
	Caucasian	0.94	(0.59-1.48)	0.776	1.0	(1.0-1.02)	0.750
History of gastroduodenal ulcer	No	1.0	—	—	1.0	—	—
	Yes	1.11	(0.57-2.15)	0.766	1.88	(1.28-2.77)	0.003
History of NSAID intolerance	No	1.0	—	—	1.0	—	—
	Yes	1.64	(0.84-3.21)	0.163	2.39	(1.67-3.43)	0.001
Patients using concomitant							
Corticosteroids	No	1.0	—	—	1.0	—	—
	Yes	1.57	(1.02-2.41)	0.044	0.84	(0.63-1.14)	0.267
Low-dose aspirin	No	1.0	—	—	1.0	—	—
	Yes	1.38	(0.95-2.00)	0.097	—	*	*

*Statistic not calculated

the UGI tolerability composite endpoint was similar within the diclofenac arms (17.6% for TID; 17.0% for BID; p = 0.86). Based on the comparisons reported above, data from the celecoxib 100 mg arms were pooled into a single treatment group, as were data from the diclofenac treatment arms (50 mg BID and TID).

Incidences of UGI adverse events

The clinical and demographic characteristics of the pooled OA study population and the RA study population are reported in Table III. Within the RA trial, the two treatment groups were comparable on all baseline variables. Within the pooled OA data, the three treatment groups (celecoxib, diclofenac, placebo) were comparable with the exception of a lower age, higher history of gastroduodenal ulcer, and higher non-Caucasian ethnicity in the placebo group than in the active treatment arms.

A significantly higher percentage of diclofenac patients withdrew due to a GI adverse event (4.3%) compared to celecoxib (1.7%) or placebo patients (2.0%) ($p < 0.05$). A significantly higher percentage of placebo patients withdrew due to lack of efficacy (21.0%) compared with patients randomised to celecoxib (4.0%) or diclofenac (2.4%) ($p < 0.05$) (Table III).

Kaplan-Meier curves of the cumulative incidence of UGI adverse events over the first 6 weeks of all trials are illustrated in Figures 1 and 2. The overall p value (testing for differences among any of the three treatment groups) for the OA trials indicated no statistically significant differences ($p < 0.05$) with respect to the individual adverse event endpoints. The adjusted relative risks obtained from the Cox model for celecoxib compared with diclofenac were consistent for abdominal pain (RR = 0.64; 95% CI: 0.37-1.05; p = 0.07), dyspepsia (RR = 0.56; 95% CI: 0.33-0.95; p = 0.031) and nausea (RR = 0.62; 95% CI: 0.32-1.16; p = 0.13). Diclofenac was statistically significantly worse than celecoxib for the composite endpoint using non-parametric log-rank tests. The cumulative incidence of the composite endpoint at 6 weeks with diclofenac was 17.6% (95% CI: 14.4-20.9%) at 6-weeks compared with 11.1% (95% CI: 8.4-13.8%) for celecoxib (p = 0.0002) and 13.3% (95% CI: 8.1-18.4%) for placebo (p = 0.157).

In the RA trial, the incidence of each of the UGI events was also lower with the

Table V. Relative risk of the UGI tolerability composite endpoint over 6 weeks by treatment (final Cox's proportional hazards model).

Treatment	Pooled OA trials			RA trial		
	Relative Risk	95% CI	p-value	Relative Risk	95% CI	p-value
Diclofenac	1.0	—	—	1.0	—	—
Celecoxib	0.59	(0.43-0.82)	0.002	0.62	(0.44-0.88)	0.007
Placebo	0.70	(0.44-1.11)	0.128	NA	NA	NA

Note: final Cox models include treatment,history of NSAID intolerance, concomitant low-dose aspirin use, and corticosteroid use.

celecoxib 200 mg BID group than with the diclofenac SR 75 mg BID group during the first 6 weeks of treatment. This difference was statistically significant for abdominal pain ($p = 0.031$) and marginally significant for dyspepsia ($p = 0.062$) using non-parametric log-rank tests. The overall UGI tolerability of celecoxib was statistically significantly better than that of diclofenac: the 6-week cumulative incidence of the composite endpoint was 20.7% (95% CI: 16.3- 25.1%) for diclofenac compared with 15.9% (95% CI: 11.9-20.0%) for celecoxib ($p = 0.013$).

Risk factor analysis and final Cox model

Univariate analysis of predictors of UGI adverse events using the Cox proportional hazards model (Table IV) found that, in addition to the treatment effect, concomitant corticosteroid use was a significant predictor of any of the UGI adverse events in the pooled OA studies (RR 1.57; 95% CI 1.02-2.41; $p = 0.044$). This finding may be a spurious one, however, as corticosteroid use is likely to be a marker of concomitant disease. Concomitant low-dose aspirin use showed a trend towards being a predictor as well (RR 1.38; 95% CI 0.95-2.00; $p = 0.097$). In the RA trial, in addition to the treatment effect, the following were significant predictors of the UGI events: age (71 years (RR 1.68; 95% CI 1.03-2.75; $p = 0.041$); a history of a gastroduodenal ulcer (RR 1.88; 95% CI 1.28-2.77; $p = 0.003$); and a history of GI intolerance (RR 2.39; 95% CI 1.67-3.43; $p = 0.001$). The final model included the following variables found to be predictive of any of abdominal pain, dyspepsia, nausea, or the UGI tolerability composite endpoint during the stepwise regression process (as described in the Methods). In addition to treatment, these variables were a history of NSAID intolerance, low-dose aspirin use, and corticosteroid use. This analysis confirmed that celecoxib had a significantly lower effect on UGI symptoms compared with diclofenac under conditions wherein other predictors had been controlled (Table V), with little change in the adjusted relative risk values compared with the unadjusted values. The relative risk with celecoxib (RR = 0.59) was comparable to that reported among placebo patients (RR = 0.70; $p > 0.20$).

Discussion

The main finding of this analysis indicates that celecoxib has superior UGI tolerability compared with the conventional NSAID diclofenac in the treatment of OA or RA over a 6-week period. A limitation of this evaluation was the difference in the study designs, patient populations, and dosages of the 3 studies compared in this pooled analysis. The systematic approach to pooling described herein and the explicit presentation of data prior to pooling were steps taken to address this limitation. A second limitation was that adverse event data collected in this study and reported here were not identified as primary or secondary endpoints in these studies. Nevertheless, the magnitude of the relative risk of UGI events in the celecoxib versus the diclofenac group was comparable in the two disease groups (RR of 0.62 for the pooled OA studies and 0.67 for the RA study). Celecoxib demonstrated GI tolerability similar to placebo in the OA trials; the lack of a placebo arm in the RA trial precluded this comparison. The finding that only 1.7% to 3.1% of patients on celecoxib discontinued medication due to GI adverse events, compared with 4.3% to 10.1% of those on diclofenac (treatment group comparisons are $p < 0.05$ and $p < 0.001$, respectively), further supports the superior GI tolerability of celecoxib.

Results reported here for diclofenac are also consistent with those previously reported for naproxen (15). In a pooled analysis of five trials using a similar methodology, the risks associated with celecoxib were from 0.60- to 0.63-fold lower than those associated with naproxen (15). In this study the risks of celecoxib were 0.59-fold (95% CI: 0.43-0.82) and 0.62-fold (95% CI: 0.44-0.88) lower compared to that associated with diclofenac, suggesting a consistent effect of diclofenac and naproxen on UGI symptoms. Whether diclofenac is representative of all non-selective NSAIDs in terms of UGI tolerability remains to be determined. Diclofenac, however, is a relevant comparator based on its widespread use. In 1999 diclofenac was the most commonly prescribed NSAID in Europe and Latin American countries. It was the second most commonly prescribed NSAID in Asia, Australia, and Africa, although in the US diclofenac was prescribed less frequently than celecoxib, ibuprofen, and naproxen (33).

The aetiology of dyspepsia from NSAIDs is uncertain. Although it is often assumed that dyspepsia is associated with the inhibition of COX-1, there is a poor correlation between the presence of dyspepsia and gastric ulceration from NSAIDs and it is likely that mechanisms other than COX 1 inhibition are involved. In addition, silent ulceration is common, and therefore it cannot be assumed that the reduction in dyspepsia from celecoxib is associated with an improved safety profile. The potential reduction in ulcer complications from celecoxib has been addressed separately in the CLASS trial (25). This study demonstrated a reduction in symptomatic ulcers and ulcer complications from celecoxib in comparison with standard NSAIDs. However, the trend in reducing ulcer complications alone failed to reach statistical significance unless patients were excluded from the analysis who were also taking low dose aspirin. The implication of these findings is outside the scope of this discussion.

The treatment and prophylaxis of NSAID-associated GI side effects incurs significant economic costs. These costs have been enumerated in recent analyses of observational data in Italy (34),Canada (35), the UK (36), and the US (1) among others. Given the UGI tolerability of celecoxib and previous results demonstrating its superior GI safety profile compared with traditional NSAIDs, celecoxib has the potential to significantly reduce the costs associated with NSAID-induced GI side effects. Whether overall outcome may be influenced by treatment with better tolerated drugs such as celecoxib will need to be determined by naturalistic clinical trials.

In conclusion, this analysis of clinical

trials data provides evidence for a superior GI tolerability of therapeutic doses of celecoxib compared with conventional NSAIDs in the treatment of OA and RA, and suggests that celecoxib provides a valuable therapeutic alternative in the treatment of arthritis.

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