Cyclooxygenase-2 Specific Inhibitors and Upper Gastrointestinal Tolerability in Patients with Osteoarthritis Receiving Concomitant Low Dose Aspirin: Pooled Analysis of 2 Trials

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ABSTRACT. ***Objective.*** To evaluate the relative gastrointestinal (GI) tolerability of celecoxib and rofecoxib in elderly hypertensive patients with osteoarthritis (OA) with or without coadministration of low dose aspirin (ASA) (≤ 325 mg daily).

Methods. Two independently conducted, multicenter, double blind, randomized controlled trials designed to evaluate GI tolerability, in addition to cardiorenal study endpoints, in patients randomized to celecoxib 200 mg once daily (qd; n = 960) or rofecoxib 25 mg qd (n = 942) were analyzed. GI tolerability was assessed using investigator-reported GI symptoms, prespecified as abdominal pain, dyspepsia, and nausea. The pooled incidences of the 3 reported GI symptoms, regardless of severity (mild and moderate to severe), and the incidences of mild or moderate to severe GI symptoms individually were evaluated.

Results. In the pooled population, the incidence of the 3 GI symptoms, regardless of severity, was not significantly different for patients receiving celecoxib or rofecoxib. In contrast, the aggregate incidence of moderate to severe GI symptoms for patients receiving rofecoxib (5.2%) was significantly greater than for those receiving celecoxib (3.2%; $p < 0.05$). Notably, the significant difference between the 2 arms was more pronounced in the population of patients receiving concomitant low dose ASA (rofecoxib 9.7% vs celecoxib 1.5%; $p < 0.001$). The incidence of moderate to severe GI symptoms was similar with rofecoxib (3.3%) and celecoxib (3.9%; $p = 0.564$) treatment in patients who did not receive low dose ASA.

Conclusion. While the GI tolerability was similar in the 2 arms of the entire pooled population, celecoxib 200 mg qd was associated with a significantly lower incidence of moderate to severe GI symptoms than rofecoxib 25 mg qd in patients receiving concomitant low dose ASA. (J Rheumatol 2005;32:111–7)

Key Indexing Terms:
GASTROINTESTINAL TOLERABILITY SYMPTOMS
COX-2 SPECIFIC INHIBITORS OSTEOARTHRITIS

Nonspecific nonsteroidal antiinflammatory drugs (NSAID) are among the most commonly prescribed drugs worldwide but are associated with significant gastrointestinal (GI) toxicity, which limits their clinical utility[1,2]. NSAID related GI toxicity ranges from clinically troublesome GI symptoms (e.g., abdominal pain, dyspepsia, and nausea) to endoscopic gastroduodenal mucosal lesions and serious upper GI ulcer complications (perforation, gastric outlet obstruction, and bleeding)[3].

Much of the epidemiological and clinical literature regarding NSAID associated toxicity has focused on these clinically significant serious upper GI/gastroduodenal ulcer complications[1-8]. However, much less attention has been devoted to evaluating the incidence and clinical effect of GI tolerability as determined by symptoms such as abdominal pain, dyspepsia, or nausea, which are among the most commonly reported symptoms in NSAID users[9-11]. It is noteworthy that these NSAID associated GI symptoms are reported to occur early — most commonly within the first 6 weeks of treatment — in contrast to the risk of NSAID associated ulcer complications, which remains constant over time of NSAID exposure[12-14].

GI tolerability is of concern in patients receiving both

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acute and chronic treatment with nonspecific NSAID, such as patients with osteoarthritis (OA) or rheumatoid arthritis (RA). In OA/RA trials of up to 3 months' duration, abdominal pain, dyspepsia, and nausea have been reported in 18–24% of NSAID users[12,13], and were severe enough to be associated with a 10% withdrawal rate[14]. Further, in a large-scale 6-month trial, 20% of RA patients receiving nonspecific NSAID withdrew due to GI intolerance[15].

The cyclooxygenase (COX)-2 specific inhibitors, including celecoxib and rofecoxib, have demonstrated improved GI tolerability compared with nonspecific NSAID in multiple OA/RA trials[12,16-18]. For example, the cumulative incidences of abdominal pain, dyspepsia, and nausea with celecoxib 100 mg twice a day (bid) were significantly lower than with diclofenac 75 mg bid in a pooled analysis of 3 OA and RA trials[12]. Moreover, and of greater clinical significance, the cumulative incidences of moderate to severe abdominal pain, dyspepsia, and nausea were significantly lower, even when adjusted for risk factors, with celecoxib 50–400 mg bid than with naproxen 500 mg bid treatment in an analysis of five 12-week OA/RA trials[16]. Further, in other OA/RA trials, withdrawal rates due to abdominal pain and dyspepsia (in celecoxib comparative trials) or dyspeptic-type GI events (in rofecoxib comparative trials) were significantly lower with a COX-2 specific inhibitor than for the nonspecific NSAID[17,18].

Low dose aspirin (ASA), when used alone for cardiovascular (CV) prophylaxis, increases the risk for serious upper GI ulcer complications and may further increase the rate when coadministered with a nonspecific NSAID[4,8,19-26]. It is also well recognized that ASA alone, and possibly when coadministered with NSAID or COX-2 specific inhibitors, is associated with an increased rate of reported GI symptoms. Therefore, independent of the clinical relevance of ASA associated upper GI ulcer complications (alone or in combination with NSAID or COX-2 specific inhibitors), evaluating the incidence of GI symptoms using celecoxib and other COX-2 specific inhibitors in OA/RA patients receiving low dose ASA would be of clinical interest. Therefore, independent of ulcer complications, this pooled analysis was specifically conducted to focus on and evaluate the relative incidence of GI symptoms in elderly hypertensive patients with OA using once daily (qd) dosages of celecoxib (200 mg) and rofecoxib (25 mg), with or without the coadministration of low dose ASA.

MATERIALS AND METHODS

Study design. To evaluate the relative GI tolerability of celecoxib and rofecoxib in the presence of concomitant low dose ASA use (≤ 325 mg daily), data were pooled from 2 independently conducted, multicenter, double blind, randomized controlled trials in OA patients. The 2 trials were of identical design and rationale, with comparable data collection and endpoints. In these trials, patients aged ≥ 65 years with OA of the hand, hip, or knee, who were also receiving treatment for hypertension, were enrolled at 208 study sites in the United States and Canada[27,28]. ASA use (≤ 325 mg daily) was permitted during each trial for antithrombotic CV prophylaxis. The study design for each trial was approved by the study site Institutional Review Board and each trial was conducted in accord with the Declaration of Helsinki. Patients gave their written informed consent prior to participation in the trials.

Each trial was designed to evaluate cardiorenal safety in addition to GI tolerability. The primary study endpoints were the incidences of clinically significant edema and destabilized systolic blood pressure (SBP), the results of which are reported elsewhere[27,28]. In total, 1902 patients received celecoxib 200 mg qd [Celebrex®, Pharmacia Corp., Peapack, NJ; n = 960, intent-to-treat (ITT)] or rofecoxib 25 mg once daily (Vioxx®, Merck, Whitehouse Station, NJ; n = 942, ITT) for 6 weeks between December 1999 and March 2001. In both trials, patients who had a history of esophageal, gastric, pyloric channel, or duodenal ulceration within 30 days prior to the first dose of study medication were excluded from the studies. Additionally, patients who had active GI disease and those using or requiring the use of antiulcer medications (e.g., antacids, H_2 receptor antagonists, proton pump inhibitors, prostaglandins) were also excluded from the studies.

In each trial, any adverse events (globally defined as any new symptom, sign, or occurrence, regardless of severity or causality) were reported by investigators, and standardized using World Health Organization (WHO) classification terms[27,28]. All reported events were also graded by the investigator as mild (causing no limitation of usual activities), moderate (causing some limitation of usual activities), or severe (causing inability to carry out usual activities). We prespecified our analysis to focus only on the subset of investigator-reported symptoms of abdominal pain, dyspepsia, and nausea.

Endpoints. The primary focus of this analysis was the aggregate incidence of moderate to severe abdominal pain, dyspepsia, and nausea, since these were felt to be the most clinically meaningful. This approach is consistent with that adopted by Bensen, *et al*[16]. Three cohorts were analyzed: all patients (ITT cohort), patients receiving low dose ASA (ASA users), and patients who did not receive low dose ASA (non-ASA users). The secondary analyses included the aggregate incidence of GI symptoms of mild severity, and the incidence of the individual GI symptoms of abdominal pain, dyspepsia, and nausea by severity (mild or moderate to severe). Further, an evaluation of patients withdrawn for GI adverse events was performed, in aggregate for mild and moderate to severe symptoms, and for the 3 individual events of abdominal pain, dyspepsia, and nausea separately. All analyses were performed stratified by ASA use.

Statistical analyses. Interpretation of pooled results requires data from trials that are sufficiently similar[29]. We examined the homogeneity of these trials with respect to population demographics, the primary cardiorenal (clinically significant hypertension) endpoint, and the incidence of abdominal pain, dyspepsia and nausea. The trials were pooled with a contingent on finding statistical homogeneity. Homogeneity of categorical variables was tested using the Mantel-Haenszel chi-square test, and for continuous variables, homogeneity of variance was tested using the Levene method. For both methods, populations were assumed to be homogeneous if p was greater than 0.05.

The primary analysis was the comparison of crude aggregate incidence rates for moderate to severe NSAID associated symptoms predefined as abdominal pain, dyspepsia, and nausea between patients treated with celecoxib and rofecoxib, stratified by concomitant use of low dose ASA. Comparisons of crude incidence rates for all investigator-reported GI symptoms (regardless of severity) within these treatment arms were included as a secondary analysis. All statistical comparisons were made using a 2-sided Fisher exact analysis. A significant p value (< 0.05) was designated for all assessments.

RESULTS

The first trial included 810 patients with OA, of which 411 received celecoxib 200 mg qd and 399 received rofecoxib

25 mg qd. In the second trial, which comprised 1092 OA patients, 549 patients received celecoxib 200 mg qd and 543 received rofecoxib 25 mg qd.

Trial pooling and baseline characteristics. The results of the homogeneity analyses presented in Table 1 confirm that the 2 trials were sufficiently similar to justify pooling. There was no significant difference between trials in the proportion of patients with cardiorenal outcomes (Table 1).

The pooled celecoxib (n = 960) and rofecoxib (n = 942) groups had similar baseline demographics, including age, sex, and CV clinical history (Table 2). The only significant difference between treatment groups in the pooled ITT cohort was the proportion of patients receiving treatment with angiotensin converting enzyme (ACE) inhibitors (44.9% celecoxib vs 39.1% rofecoxib; p = 0.01). Patients in the pooled ITT cohort had a mean age of 73 years, a mean duration of OA ranging from 11.7 to 12.1 years, and a mean duration of hypertension between 12.8 to 13.1 years (Table 2). In the pooled ITT cohort, the proportion of patients receiving concomitant low dose ASA for cardioprotection in the celecoxib treatment group (28.5%; n = 274) was similar to the rofecoxib group (29.6%; n = 279; Table 2).

GI symptoms. Figure 1 illustrates the incidence of all investigator-reported GI symptoms (abdominal pain, dyspepsia, and nausea) regardless of severity. The aggregate incidence of the 3 reported symptoms (including all grades of severity) was not significantly different for patients receiving celecoxib and rofecoxib in the 3 groups.

In contrast, the aggregate incidence of moderate to severe GI symptoms in the ITT cohort was significantly greater for patients receiving rofecoxib (5.2%) than for those receiving celecoxib (3.2%; p < 0.05), as shown in Figure 2. Notably, this significant difference in incidence of moderate to severe GI symptoms between rofecoxib and celecoxib was more pronounced in the population of patients receiving concomitant low dose ASA (9.7% vs 1.5%; p < 0.001). Unlike the results in the ASA-using population, the incidence of moderate to severe GI symptoms was similar with rofecoxib (3.3%) and celecoxib (3.9%; p = 0.564) treatment in the population of patients who did not receive low dose ASA (Figure 2).

Table 3 shows the incidence of individual symptoms broken out by severity and also by ASA use. The incidence of mild abdominal pain was similar with celecoxib and rofecoxib treatment in the ITT group (2.2% and 2.3%, respectively) and in the populations of low dose ASA users (3.7% and 3.2%, respectively) and non-users (1.6% and 2.0%, respectively). However, significantly more patients receiving rofecoxib experienced moderate to severe abdominal pain than with celecoxib treatment in the ITT cohort (2.2% vs 1.0%, respectively; p < 0.05) and particularly in the low dose ASA users (4.7% vs 0.7%, respectively; p < 0.01). In contrast, the incidence of moderate to severe abdominal pain was identical for non-ASA users receiving celecoxib or rofecoxib treatment (both 1.2%; Table 3). Regarding the incidences of mild or moderate to severe dyspepsia or nausea for all participating patients, there were no significant differences between the celecoxib and rofecoxib groups and the subpopulations of low dose ASA users and non-users (Table 3).

Table 4 reports the incidence of withdrawals attributed to the occurrence of one or more of the 3 GI symptoms. In the total population and in the population of non-ASA users, there were no significant differences between the celecoxib and rofecoxib treatment groups. However, in low dose ASA users, celecoxib treatment was associated with significantly fewer withdrawals compared with rofecoxib due to the occurrence of any one of the 3 GI symptoms, regardless of severity (0.7% vs 3.9%, respectively; p < 0.05). Not unexpectedly, in the group of patients with any one of the GI symptoms (abdominal pain, dyspepsia, or nausea) rated as moderate to severe, the rate of withdrawal with celecoxib was also significantly lower compared to rofecoxib (0.4% vs 3.2%; p < 0.05), with the majority of patients withdrawn experiencing moderate to severe symptoms. Concerning the specific symptoms, a greater percentage of patients treated with rofecoxib withdrew for abdominal pain (3.6% vs 0.7%; p < 0.05; Table 4). Further, there were no reported serious GI events such as perforation, obstructions, or bleeds.

Table 1. Results of testing for homogeneity in the study populations.

	p
Homogeneity of demographics	
Mean age, yrs	0.218
Sex, n (% female)	0.413
Mean duration of hypertension, yrs	0.871
Mean duration of OA, yrs	0.407
Mean systolic BP, mm Hg	0.469
Mean diastolic BP, mm Hg	0.443
Antihypertensive therapy	
Diuretics	0.312
ACE inhibitors	0.027
Calcium channel blockers	0.613
ß-blockers	0.973
Other	0.166
Homogeneity of upper GI safety and tolerability measures, (ITT cohort)	
All GI events*	0.146
Moderate to severe GI events	0.285
All abdominal pain, dyspepsia, and nausea	0.494
Moderate to severe abdominal pain, dyspepsia, and nausea	0.811
Homogeneity of clinically significant hypertension	
Clinically significant hypertension (primary endpoint)	0.147

* Mild, moderate, and severe adverse events.

DISCUSSION

In this pooled analysis, hypertensive OA patients receiving low dose ASA for cardioprotection experienced significant-

Table 2. Baseline demographics and patient characteristics: pooled ITT cohort (all patients).

	Celecoxib 200 mg qd, n = 960*	Rofecoxib 25 mg qd, n = 942*	p
Mean age, yrs	73.5	73.6	NS
Age range (%)			
< 65 yrs	0.1	0	NS
65–74 yrs	60.9	59.9	NS
> 74 yrs	39.0	40.1	NS
Sex (% female)	62.7	65.0	NS
Mean duration of hypertension, yrs	13.1	12.8	NS
Mean duration of OA, yrs	12.1	11.7	NS
Mean treated blood pressure, mm Hg	136.9/76.0	136.4/76.0	NS
Cardiovascular clinical history (%)			
Hypertension	100	100	NS
Angina	13.3	12.2	NS
Coronary artery disease	15	16.1	NS
Congestive heart failure	3.8	3.8	NS
Myocardial infarction	0.0	0.0	NS
Baseline low dose ASA use, n (%)	274 (28.5)	279 (29.6)	NS
Baseline antihypertensive medication (%)			
Diuretics	44.8	46	NS
ACE inhibitors	44.9	39.1	0.01
Calcium channel blockers	33.9	37	NS
ß-blockers	33.0	30.9	NS
Other	7.7	8.6	NS
Combination treatments	51.7	52.5	NS

* ITT cohort. NS: not statistically significant.

ly more moderate to severe GI symptoms (abdominal pain, dyspepsia, and/or nausea), and specifically abdominal pain, with rofecoxib 25 mg qd than with celecoxib 200 mg qd treatment. Celecoxib was also associated with a significantly lower incidence of withdrawals due to GI symptoms, moderate to severe GI symptoms, and moderate to severe abdominal pain than rofecoxib in low dose ASA users. These significant differences were not observed for the entire ITT cohort or among patients not receiving ASA.

GI intolerance remains one of the most common clinical factors limiting the use of nonspecific NSAID, including ASA, and may lead to an increased rate of healthcare utilization, the use of concomitant gastroprotective or acid-suppressive agents, and/or decreased adherence, or discontinuation of therapy[30]. ASA is associated with a GI tolerability profile typical of nonspecific NSAID and, at over-the-

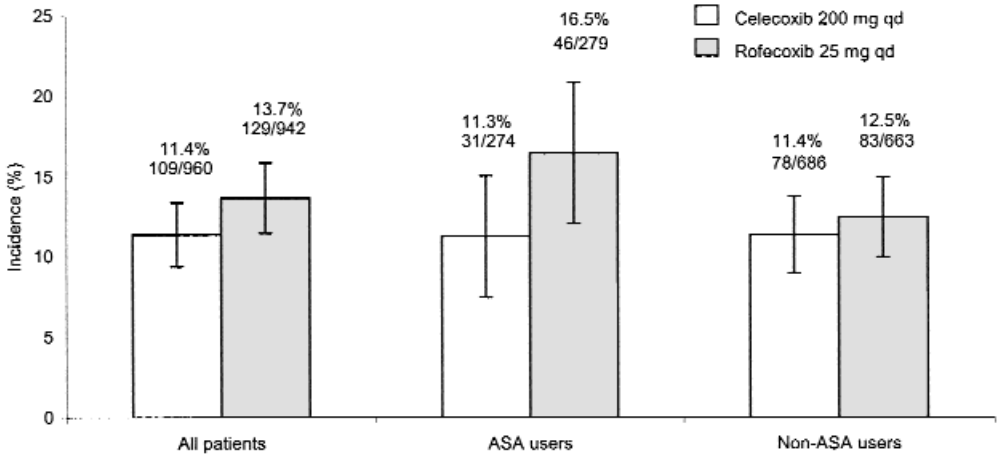

Figure 1. Pooled incidence of GI symptoms (mild and moderate to severe). Actual percentage incidences and the proportion of patients affected are given above each column. Bars above and below each column represent 95% confidence intervals.

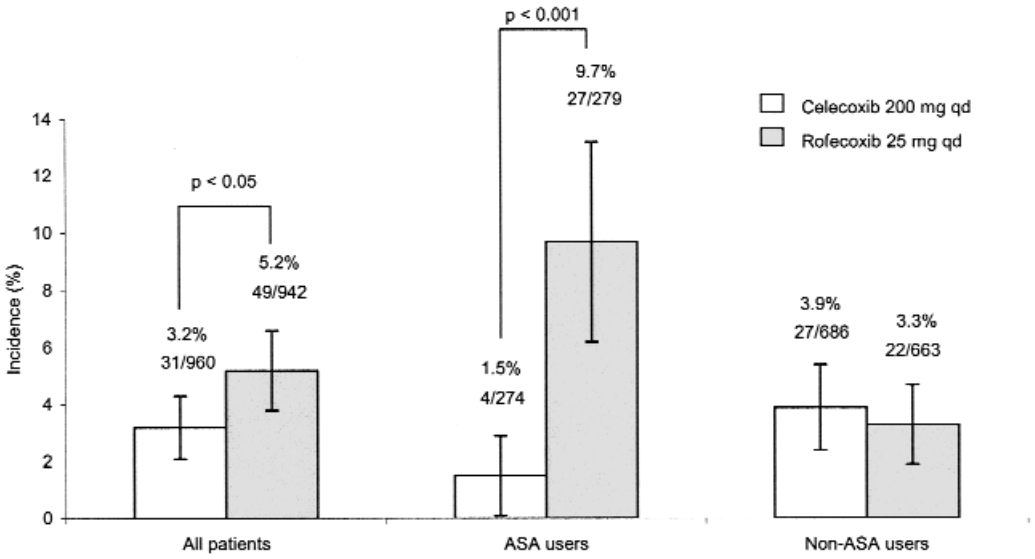

Figure 2. Pooled incidence of moderate to severe GI symptoms. Actual percentage incidences and the proportion of patients affected are given above each column. Bars above and below each column represent 95% confidence intervals.

counter doses (3000 mg daily), the incidence of GI symptoms (mainly abdominal pain, dyspepsia, nausea, and diarrhea) has been reported to be significantly higher with ASA than with ibuprofen 1200 mg daily (18.5% vs 11.5%)[31]. Even low dose ASA use for CV prophylaxis is associated with an increased risk for dyspepsia/GI symptoms and also serious upper GI ulcer complications. Notably, with regard to this analysis, the tolerability of low dose ASA is further

Table 3. GI symptoms: incidence of mild and moderate to severe abdominal pain, dyspepsia, and nausea.

	Celecoxib 200 mg qd, n = 960*	Rofecoxib 25 mg qd, n = 942*	p
Mild abdominal pain, proportion (%)			
All patients	21/960 (2.2)	22/942 (2.3)	0.878
ASA users	10/274 (3.7)	9/279 (3.2)	0.819
Non-ASA users	11/686 (1.6)	13/663 (2.0)	0.683
Moderate to severe abdominal pain, proportion (%)			
All patients	10/960 (1.0)	21/942 (2.2)	0.047
ASA users	2/274 (0.7)	13/279 (4.7)	0.007
Non-ASA users	8/686 (1.2)	8/663 (1.2)	1.000
Mild dyspepsia, proportion (%)			
All patients	44/960 (4.6)	47/942 (5.0)	0.747
ASA users	12/274 (4.4)	8/279 (2.9)	0.371
Non-ASA users	32/686 (4.7)	39/663 (5.9)	0.332
Moderate to severe dyspepsia, proportion (%)			
All patients	18/960 (1.9)	20/942 (2.1)	0.745
ASA users	2/274 (0.7)	9/279 (3.2)	0.063
Non-ASA users	16/686 (2.3)	10/663 (1.5)	0.324
Mild nausea, proportion (%)			
All patients	13/960 (1.4)	11/942 (1.2)	0.838
ASA users	5/274 (1.8)	2/279 (0.7)	0.282
Non-ASA users	8/686 (1.2)	9/663 (1.4)	0.811
Moderate to severe nausea, proportion (%)			
All patients	3/960 (0.3)	8/942 (0.9)	0.141
ASA users	0/274 (0.0)	5/279 (1.8)	0.061
Non-ASA users	3/686 (0.4)	4/663 (0.6)	0.722

* ITT cohort.

Table 4. Incidence of withdrawals due to GI symptoms and GI adverse events.

Event Causing Withdrawal	Low Dose ASA Users		Non-ASA Users		All Patients	
	Celecoxib 200 mg qd, n = 273	Rofecoxib 25 mg qd, n = 279	Celecoxib 200 mg qd, n = 687	Rofecoxib 25 mg qd, n = 663	Celecoxib 200 mg qd, n = 960	Rofecoxib 25 mg qd, n = 942
GI symptom, n (%)*						
All†	2 (0.7)††	11 (3.9)	11 (1.6)	7 (1.1)	13 (1.4)	18 (1.9)
Mild	1 (0.4)	2 (0.7)	3 (0.4)	2 (0.3)	4 (0.4)	4 (0.4)
Moderate to severe	1 (0.4)††	9 (3.2)	8 (1.2)	5 (0.8)	9 (0.9)	14 (1.5)
GI symptom, n (%)						
Abdominal pain	2 (0.7)††	10 (3.6)	5 (0.7)	4 (0.6)	7 (0.7)	14 (1.5)
Dyspepsia	0 (0.0)	3 (1.1)	7 (1.0)	2 (0.3)	7 (0.7)	5 (0.5)
Nausea	1 (0.4)	1 (0.4)	3 (0.4)	2 (0.3)	4 (0.4)	3 (0.3)

* Abdominal pain, dyspepsia, and/or nausea. † Patients are counted once in determining this total incidence. †† $p < 0.05$ vs rofecoxib.

exacerbated when concomitantly administered with another nonspecific NSAID[4,8,19-26].

Using investigator-reported adverse events, several clinical trials have established that the COX-2 specific inhibitors celecoxib and rofecoxib have improved GI tolerability compared with therapeutic dosages of nonspecific NSAID, including naproxen, ibuprofen, and diclofenac, in OA/RA trials of 6–12 weeks in duration[12,16-18,32]. In longer-term arthritis outcome trials, withdrawals due to GI symptoms were lower with celecoxib [Celecoxib Long-term Arthritis Safety Study (CLASS): 8.7% vs 10.7%] and rofecoxib [Vioxx Gastrointestinal Outcomes Research Study (VIGOR): 3.5% vs 4.9%] compared with the comparator nonspecific NSAID[33,34]. In addition, significantly fewer patients in CLASS experienced dyspepsia with celecoxib compared with ibuprofen or diclofenac treatment ($p < 0.05$)[33]. In general, GI symptoms such as abdominal pain, dyspepsia, and nausea do not correlate well with mucosal damage or serious upper GI ulcer complications, and the roles of COX-1 and COX-2 in the pathogenesis of these symptoms are unclear[18]. Although the decrease in dyspepsia observed in CLASS could be attributable to the COX-1-sparing properties of celecoxib, the rate was reduced from 16.1% with ibuprofen or diclofenac to only 14.4% with celecoxib treatment, indicating that other factors may contribute to the development of these GI symptoms[33].

The incidences of abdominal pain, dyspepsia, and nausea associated with celecoxib (200 or 400 mg daily) or nonspecific NSAID (naproxen or diclofenac) treatment have also been evaluated in patients receiving low dose ASA in a large clinical outcome trial[35]. Celecoxib was associated with a significantly lower incidence of moderate to severe abdominal pain, dyspepsia, and nausea than nonspecific NSAID in low dose ASA users (3.56% vs 8.38%; $p = 0.0028$; 57.5% risk reduction)[35].

There is a paucity of published clinical trials data directly comparing the relative GI tolerability of COX-2 specific inhibitors such as celecoxib and rofecoxib. Although CLASS and VIGOR demonstrated improved tolerability for celecoxib and rofecoxib relative to their comparator nonspecific NSAID, it is not possible to draw conclusions on the relative GI tolerability of these COX-2 specific inhibitors across trials for several reasons. CLASS and VIGOR used different nonspecific NSAID comparators[33,34], while patients receiving low dose ASA for CV prophylaxis were enrolled in CLASS but excluded from the VIGOR trial[33,34].

Our analysis represents the first head-to-head comparison of the GI tolerability of therapeutic dosages of celecoxib and rofecoxib in patients receiving low dose ASA. The differences in GI tolerability between celecoxib and rofecoxib in patients receiving concomitant low dose ASA are probably not attributable to their effects on the target enzyme, COX-2. These differences in GI tolerability may, instead, reflect differences in drug-drug interactions or in the molecular structure or properties of these drugs. Such a molecular hypothesis might also explain the published differences in hypertension and edema also observed between celecoxib and rofecoxib in the 2 trials utilized for our analysis[27,28].

Although their overall GI tolerability is similar, celecoxib 200 mg qd is associated with a significantly lower incidence of moderate to severe GI symptoms, and specifically abdominal pain, than a rofecoxib 25 mg qd regimen in patients receiving concomitant low dose ASA. Additional trials in high risk populations, such as patients receiving low dose ASA, would help to better evaluate the GI tolerability of COX-2 specific inhibitors and potential mechanisms for these differences. These findings provide physicians with important additional tolerability information on the effects of treatment for OA with a COX-2 specific inhibitor plus low dose ASA.

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