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ORIGINAL ARTICLE

The hepatic safety and tolerability of the cyclooxygenase-2 selective NSAID celecoxib: pooled analysis of 41 randomized controlled trials

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ABSTRACT

Objective: To assess the hepatic safety and tolerability of celecoxib versus placebo and three commonly prescribed nonselective nonsteroidal anti-inflammatory drugs (NSAIDs).

Research design and methods: This was a retrospective, pooled analysis of a 41-study dataset involving patients with osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, chronic low back pain, and Alzheimer's disease. Criteria for selection of studies were:

(1) Randomized, parallel-group design and planned treatment duration of ≥2 weeks
(2) ≥1 placebo or NSAID comparator
(3) ≥1 arm with celecoxib at total daily dose of ≥200 mg
(4) Data available as of October 31, 2004

Data were pooled by treatment and subject from the safety analysis population of included studies. Treatment-emergent hepatobiliary adverse events (AEs) were compared for celecoxib <200 mg/day (943 patients), 200 mg/day (12 008 patients), 400 mg/day (7380 patients), and 800 mg/day (4602 patients); placebo (4057 patients); diclofenac 100–150 mg/day (7639 patients); naproxen 1000 mg/day (2953 patients); and ibuprofen 2400 mg/day (2484 patients). Hepatobiliary laboratory abnormalities were also analyzed.

Results: There were no cases of liver failure, treatment-related liver transplant, or treatment-related hepatobiliary death. Incidence of serious hepatic AEs was low, with 13 (0.05%) serious hepatic AEs among 24 933 celecoxib-treated patients, and 16 (0.21%) among 7639 diclofenac-treated patients. No patients receiving celecoxib or any nonselective NSAID met criteria for Hy's rule (alanine aminotransferase [ALT] ≥3 × upper limit of normal [ULN] with bilirubin ≥2 × ULN). The incidence of notable (≥5 × ULN) and severe (≥10 × ULN) ALT elevations was similar for all treatment groups except diclofenac. Significantly fewer hepatobiliary AEs were reported for celecoxib (any dose; 1.11%) than for diclofenac (vs. 4.24%, $p < 0.0001$); for ibuprofen (vs. 1.53%, $p = 0.06$) and placebo (vs. 0.89%, $p = 0.21$) the incidence of AEs was comparable to celecoxib.

Limitations: A number of limitations should be considered when evaluating the results: findings were limited by the quality and reporting of the studies selected; difficulty in estimating the incidence of AEs due to the low frequency of events; acetaminophen not included as an active comparator.

Conclusions: In this pooled analysis, the incidence of hepatic AEs in patients treated with celecoxib was similar to that for both placebo-treated patients and patients treated with ibuprofen or naproxen, but lower than for diclofenac.

Introduction

Along with acetaminophen, nonselective and cyclooxygenase-2 (COX-2) selective nonsteroidal anti-inflammatory drugs (NSAIDs) are, for many patients, the mainstay of initial pharmacotherapy for arthritis and musculoskeletal conditions. Among the most commonly used medicines worldwide, the most frequently prescribed nonselective NSAIDs include ibuprofen (total daily dose 1200–3200 mg), diclofenac (total daily dose 100–200 mg), and naproxen (total daily dose 500–1000 mg). Celecoxib, a COX-2 selective NSAID, is also widely used and is recommended at daily dose ranges from 200 to 400 mg[1].

Asymptomatic elevations of serum aminotransferases are not uncommon in patients taking NSAIDs or acetaminophen; however, unlike with acetaminophen, serious hepatotoxicity is a rare complication of NSAID therapy[2]. Although epidemiologic data suggest only a modest increase in the risk of serious hepatotoxicity in patients receiving NSAIDs, clinical manifestations of serious hepatic injuries associated with their use may include hepatitis, jaundice, liver failure requiring transplantation, and ultimately death.

Although not statistically significant, in a systematic review of population-based epidemiologic studies, the comparative risk of clinically significant hepatotoxicity (defined as liver injury resulting in hospitalization) in current versus past NSAID users was estimated to range from 1.2 to 1.7[3]. The incidence of hepatotoxicity resulting in hospitalization ranged from 3.1 to 23.4 per 100 000 patient-years of current NSAID use; furthermore, no NSAID-associated deaths from liver injury were reported in more than 396 000 patient-years of cumulative exposure[3].

Although the risk of liver injury is low, NSAID-related hepatotoxicity is of clinical and economic importance because of the widespread availability and very high levels of prescribing and consumption of NSAIDs[4]. In the United States, drug-related hepatotoxicity is the most common cause of acute liver failure, and the most common adverse event (AE) leading to drug nonapproval and postmarketing withdrawal. The nonselective NSAIDs bromfenac, ibufenac, and benoxaprofen have been withdrawn following cases of clinically significant hepatotoxicity (including some deaths)[5,6]. Nearly all nonselective NSAIDs have been associated with hepatic injury in either case reports or epidemiologic studies, with diclofenac and sulindac more commonly implicated than others[7–9]. Hepatotoxicity has also been reported in patients receiving naproxen[10] and ibuprofen[11]. Idiosyncratic reactions, caused by patient-specific hypersensitivity or metabolic aberrations that result in a build-up of toxic metabolites, appear to underlie many cases of NSAID-related hepatotoxicity[12–15].

The COX-2 preferential NSAID nimesulide, and the newer COX-2 selective NSAIDs, have also been associated with rare cases of hepatotoxicity[2,16–22]. However, in an analysis of 31 studies from the clinical trial program for celecoxib (14 controlled clinical arthritis trials, one long-term, open-label trial, 11 clinical analgesia trials, and five phase 1 pharmacology trials), hepatic AEs were no more frequent with celecoxib (25–400 mg BID) than with placebo after use for up to 2 years[23].

Recently, postmarketing reports emerged describing liver problems in patients taking the COX-2 selective NSAID lumiracoxib, usually with doses >100 mg/day. Up until mid-November 2007, 74 cases of serious liver problems were identified, including at least three transplants and two deaths[24,25]. These reports prompted the withdrawal of lumiracoxib from several countries and its nonapproval in the United States. In Europe, changes in prescribing and monitoring recommendations were imposed.

Continuing concern over the potential for NSAID therapy to cause liver damage prompted an extensive analysis of an expanded database for celecoxib. The objective of this study was to assess the hepatic safety profile of celecoxib compared with placebo and three commonly prescribed nonselective NSAIDs, through pooled analysis of clinical trial data in patients with osteoarthritis (OA), rheumatoid arthritis (RA), ankylosing spondylitis, chronic low back pain, and Alzheimer's disease.

Patients and methods

Selection of studies

Data were pooled from the same group of randomized clinical trials of celecoxib as used in the 2005 US Food and Drug Administration Advisory Committee briefing on the cardiovascular safety of celecoxib and valdecoxib[26]. The dataset included 41 clinical trials (involving 44 308 patients) that met the following criteria: randomized, parallel-group studies in the Pfizer Corporate Clinical Trials Registry; at least one treatment group receiving celecoxib at a dose of ≥200 mg/day; at least one placebo or NSAID comparator (nonselective NSAID or rofecoxib) group; a planned duration of ≥2 weeks; and study completed, study report finalized by October 31, 2004.

Of the 41 studies included, 21 studies were more than 12 weeks in duration; 33 studies were carried out in patients with OA and/or RA (duration 2 weeks to 15 months), two in ankylosing spondylitis (6 and 12 weeks), four in chronic low back pain (4–12 weeks),

and two in Alzheimer's disease (52 and 70 weeks). Across the safety analysis populations of the 41 studies, a total of 24 933 patients received celecoxib 50–800 mg/day (with 943 [3.8%] patients receiving celecoxib <200 mg/day, 12 008 [48.2%] receiving 200 mg/day, 7380 [29.6%] receiving 400 mg/day, and 4602 [18.5%] receiving 800 mg/day). In addition, 4057 patients received placebo, and 15 674 patients received an active comparator. The latter included 13 990 patients who were treated with a nonselective NSAID: diclofenac 100–150 mg/day (7639 patients; 54.6%), naproxen 1000 mg/day (2953 patients; 21.1%), ibuprofen 2400 mg/day (2484 patients; 17.8%), loxoprofen 180 mg/day (824 patients; 5.9%), and ketoprofen 200 mg/day (90 patients; 0.6%). In addition, 1328 patients were treated with rofecoxib 25 mg/day and 356 patients with acetaminophen 4000 mg/day. The current analysis focused on the comparison of celecoxib with placebo and with the commonly used nonselective NSAIDs diclofenac, naproxen, and ibuprofen. Patient exposure to loxoprofen, ketoprofen, acetaminophen, and rofecoxib, was too limited for meaningful analysis; with the exception of one 12-week study involving rofecoxib, all trials in the dataset involving these NSAIDs were short-term studies of 4–6 weeks' duration.

Overall, 21 studies had a duration of 12 weeks or longer, with three of these at least 1 year in duration. Of the remaining studies, 14 were for 6 weeks, five were for 4 weeks, and one was for 2 weeks. For celecoxib versus placebo comparisons, 76% of planned patient exposure to celecoxib was ≥3 months and 22% was ≥1 year; in total, 7462 patients were exposed to celecoxib ≥200 mg/day for 1268 patient-years compared with 4057 exposed to placebo for 585 patient-years. For celecoxib versus nonselective NSAID comparisons, 97% of planned patient exposure was for ≥3 months and 48% was ≥1 year; 19 773 patients were treated with celecoxib ≥200 mg/day for 5651 patient-years compared with 13 990 treated with nonselective NSAIDs for 4386 patient-years. Total exposure to celecoxib 200 mg/day, 400 mg/day, and 800 mg/day was 2190, 1732, and 2408 patient-years, respectively; total exposure to diclofenac, ibuprofen, and naproxen was 2618, 1201, and 498 patient-years, respectively.

Assessments for hepatic end points

Events identified for this analysis were those reported from patient-level data from 41 clinical studies as treatment-emergent hepatobiliary AEs (any undesirable experiences associated with the use of the treatment medication, regardless of its cause); treatment-emergent hepatobiliary serious AEs (an AE that results in death or persistent or significant disability/incapacity, is life-threatening, is a congenital anomaly/birth defect, or requires hospitalization or prolonging of existing hospitalization and related laboratory parameters); and related laboratory parameters. Events included all investigator-reported events (as per the World Health Organization Adverse Reactions Terminology [WHOART] dictionary [1998]) of any hepatic or biliary-related categories occurring up until 28 days after the last dose of study drug. Analysis of hepatic-only AEs was also performed, excluding all biliary events and all clinical laboratory abnormalities reported by the investigators as AEs. Deaths potentially related to hepatic cause were also identified; all deaths were reviewed by two clinicians (GC, HM), including review of narratives from the clinical study reports to agree cause of death.

All hepatobiliary laboratory abnormalities were identified from the laboratory parameters dataset. Percentages of patients with aspartate aminotransferase (AST) or alanine aminotransferase (ALT) increases to predetermined levels at any posttreatment laboratory test were analyzed for each treatment group. Particularly, analysis was conducted for: 'Hy's rule' for clinical significance (ALT ≥ 3 × upper limit of normal [ULN] with bilirubin ≥2 × ULN; regarded as an indicator of drug-induced hepatic toxicity[27]); notable transaminase elevations, ≥5 × ULN (regarded as clinically significant); and severe transaminase elevations ≥10 × ULN.

Statistical methods

Baseline demographic information, including age, sex, indication under study, and aspirin use was summarized by treatment group for all subjects enrolled in the 41 studies. Comparisons were primarily based on incidence of hepatic AEs, laboratory abnormalities, and time to discontinuation due to hepatic AEs, using data from the safety populations of the included studies. For the time to discontinuation all data up to the actual treatment duration was included in the analysis; a treatment arm of shorter duration was considered as 'censored' in the survival analysis, starting from the corresponding final visit.

All tests of significance and confidence intervals (CIs) for statistical comparisons, where provided, were two-sided with 0.05 alpha level, and no adjustments to type I error were made for multiple comparisons. Serious hepatic AEs were analyzed separately. For analysis and comparison of incidence rates, the total number of subjects and the number of events were presented across all 41 studies by treatment. The χ^2-test was used to analyze differences in incidence rates between treatment groups, and 95% CIs and *p*-values for statistical tests of the hypothesis that risk

difference = 0.0 were calculated. Kaplan–Meier curves were used to present time to discontinuation due to hepatic AEs, with log-rank tests to compare treatments.

Annualized event rates across the 41 studies were calculated by dividing the numbers of patients with events by the total exposure to study medication and multiplying by 1000 to arrive at numbers of events per 1000 patient-years of exposure. For increases in ALT and AST that were recorded as AEs, events were coded to the respective WHOART preferred terms and converted to annualized event rates as above.

Results

Population characteristics

Baseline demographic characteristics were generally balanced across integrated treatment groups (Table 1). Mean patient age ranged from 58–61 years across treatment groups. Approximately two-thirds of patients in each group were women. Most patients were enrolled in studies for OA/RA.

Serious hepatic AEs

Severe liver toxicity such as liver failure or drug-related liver transplant was not observed in celecoxib- or non-selective NSAID-treated patients from this dataset. Of four deaths that were considered likely or possibly related to hepatobiliary causes (cholelithiasis with subsequent sepsis, celecoxib group; carcinoma of the gallbladder, celecoxib group; gangrenous gallbladder with postoperative complications, naproxen group; bile duct carcinoma, diclofenac group), none was considered by the reporting investigators to be related to treatment. No patients receiving celecoxib at any dose met the criteria for Hy's rule (ALT $\geq 3 \times$ ULN with bilirubin $\geq 2 \times$ ULN).

Serious hepatobiliary AEs are shown in Table 2. Hepatic laboratory abnormalities and biliary-related AEs, regardless of causality, accounted for most cases. Symptomatic liver disease was rarely reported. Across the dataset, there was only one case of jaundice, in a patient treated with diclofenac ($N = 7639$). In total there were six cases of hepatitis, one in the celecoxib 400 mg/day treatment group ($N = 7380$), one in the celecoxib 800 mg/day treatment group ($N = 4602$), and four in the diclofenac group ($N = 7639$).

Laboratory parameters

Across all studies, only one patient, receiving placebo ($N = 4057$), met Hy's rule criteria (Table 3). Percentages of patients experiencing ALT $\geq 5 \times$ ULN or $\geq 10 \times$ ULN were very small (Table 3). Relative to placebo, celecoxib-treated patients had a similar risk of developing ALT $\geq 5 \times$ ULN (odds ratio, 1.26; 95% CI, 0.29–5.49) and ALT $\geq 10 \times$ ULN (odds ratio, 0.84; 95% CI, 0.10–7.17). Relative to diclofenac, fewer celecoxib-treated patients developed ALT $\geq 5 \times$ ULN (odds ratio, 0.06; 95% CI, 0.03–0.10) and ALT $\geq 10 \times$ ULN (odds ratio, 0.05; 95% CI, 0.02–0.12). The percentage of patients on ibuprofen and naproxen with ALT $> 5 \times$ ULN (0.08% and 0.04 %, respectively) or ALT $> 10 \times$ ULN (0% and 0%, respectively) was also similar to both placebo and celecoxib (Table 3).

Table 1. *Baseline patient characteristics (41 studies in chronic indications)*

Characteristic	Placebo $N = 4057$	Celecoxib (any dose) $N = 24\,933$	Combined nonselective NSAIDs* $N = 13\,990$
Age (years)			
Mean	58.3	60.8	60.0
≥65, *n* (%)	1447 (35.7)	10 452 (41.9)	5357 (38.3)
≥75, *n* (%)	424 (10.5)	3255 (13.1)	1582 (11.3)
Sex, %			
Male/female	35.7/64.3	30.1/69.9	30.0/70.0
Indication, *n* (%)			
OA/RA	3040 (74.9)	22 915 (91.9)	13 303 (95.1)
Chronic low back pain	632 (15.6)	1333 (5.3)	440 (3.1)
Ankylosing spondylitis	232 (5.7)	377 (1.5)	247 (1.8)
Alzheimer's disease	153 (3.8)	308 (1.2)	0 (0.0)
Aspirin use, *n* (%)	530 (13.1)	3167 (12.7)	1635 (11.7)

*Naproxen, diclofenac, ibuprofen, ketoprofen, and loxoprofen (combined totals)
OA, osteoarthritis; RA, rheumatoid arthritis

Table 2. *Serious hepatobiliary adverse events (AEs): number (%) of patients*

Category AE (WHOART)	Placebo $N=4057$	Celecoxib* any dose $N=24\,933$	Celecoxib 200 mg/day $n=12\,008$	Celecoxib 400 mg/day $n=7380$	Celecoxib 800 mg/day $n=4602$	Diclofenac 100–150 mg/day $N=7639$	Ibuprofen 2400 mg/day $N=2484$	Naproxen 1000 mg/day $N=2953$
Serious hepatic laboratory AEs								
Hepatic function abnormal	0	4 (0.02)	1 (0.01)	3 (0.04)	0	5 (0.07)	0	0
ALT increased	0	2 (0.01)	1 (0.01)	1 (0.01)	0	3 (0.04)	0	0
AST increased	0	2 (0.01)	1 (0.01)	1 (0.01)	0	3 (0.04)	0	0
Serious hepatic AEs (nonbiliary)								
Hepatic cirrhosis	0	1 (0.004)	0	0	1 (0.02)	0	0	0
Hepatitis	0	2 (0.01)	0	1 (0.01)	1 (0.02)	4 (0.05)	0	0
Hepatitis cholestatic	0	1 (0.004)	0	0	1 (0.02)	0	0	0
Hepatocellular damage	0	1 (0.004)	1 (0.01)	0	0	0	0	0
Jaundice	0	0	0	0	0	1 (0.01)	0	0
Serious, biliary-related AEs								
Biliary pain	0	0	0	0	0	1 (0.01)	0	0
Cholecystitis	1 (0.03)	9 (0.04)	5 (0.04)	0	4 (0.09)	2 (0.03)	2 (0.08)	0
Cholelithiasis	0	5 (0.02)	2 (0.02)	1 (0.01)	2 (0.04)	5 (0.07)	4 (0.16)	0
Gallbladder disorder	1 (0.03)	0	0	0	0	0	0	2 (0.07)

*In this dataset, there were no serious hepatobiliary events in celecoxib <200 mg/day ($n=943$) group
WHOART, World Health Organization Adverse Reactions Terminology; ALT, alanine transaminase; AST, aspartate transaminase

Table 3. *Laboratory abnormalities (postbaseline maximum value)*

Parameter	Placebo	Celecoxib (any dose)	Celecoxib <200 mg/day	Celecoxib 200 mg/day	Celecoxib 400 mg/day	Celecoxib 800 mg/day	Diclofenac 100–150 mg/day	Ibuprofen 2400 mg/day	Naproxen 1000 mg/day
ALT increase									
≥3 × ULN with bilirubin*	1/3183	0/13 448	0/928	0/5123	0/2909	0/4488	0/3083	0/2421	0/1870
≥2 × ULN, *n/N* (%)	(0.03)								
≥5 × ULN, *n/N* (%)	2/3865 (0.05)	15/23 073 (0.07)	0/928	6/10 567 (0.06)	4/7084 (0.06)	5/4494 (0.11)	78/7054 (1.11)	2/2424 (0.08)	1/2729 (0.04)
Odds ratio relative to placebo (95% CI)	–	1.26 (0.29–5.49)	–	1.10 (0.22–5.44)	1.09 (0.20–5.96)	2.15 (0.42–11.10)	21.60 (5.30–87.94)	–	–
Odds ratio relative to diclofenac (95% CI)	–	0.06 (0.03–0.10)	–	0.05 (0.02–0.12)	0.05 (0.02–0.14)	0.10 (0.04–0.25)	–	–	–
≥10 × ULN, *n/N* (%)	1/3865 (0.03)	5/23 073 (0.02)	0/928	1/10 567 (0.01)	1/7084 (0.01)	3/4494 (0.07)	34/7054 (0.48)	0/2424	0/2729
Odds ratio relative to placebo (95% CI)	–	0.84 (0.10–7.17)	–	0.37 (0.02–5.85)	0.55 (0.03–8.72)	2.58 (0.27–24.92)	18.72 (2.56–136.80)	–	–
Odds ratio relative to diclofenac (95% CI)	–	0.05 (0.02–0.12)	–	0.02 (0.003–0.14)	0.03 (0.004–0.21)	0.14 (0.04–0.45)	–	–	–

*Patients who did not have bilirubin laboratory test on same day were excluded
ALT, alanine transaminase; ULN, upper limit of the normal range; *n*, number of patients experiencing event; CI, confidence interval

There were no clinically meaningful differences in the percentage of patients with raised alkaline phosphatase or hypoalbuminemia in celecoxib- and placebo-treated patients.

Incidence of hepatobiliary AEs adjusted for duration of exposure

When all hepatobiliary AEs were considered together, there was no significant difference in incidence when comparing celecoxib- ($n = 276/24\,933$; 1.11%, all doses combined) to the ibuprofen- ($n = 38/2484$; 1.53%, $p = 0.06$), or placebo- treatment groups ($n = 36/4057$; 0.89%, $p = 0.21$). Although fewer hepatobiliary AEs were reported with naproxen (0.68%, $p = 0.03$) compared to celecoxib, the statistical significance was marginal (Table 4). After exclusion of laboratory and biliary AEs, the incidence of hepatic-only AEs was 13/24 933 (0.05%) for celecoxib (all doses); there were no cases of hepatic-only AEs in the placebo group (Table 4). However, the small number of events reported here does not allow any meaningful comparison.

After adjusting for duration of exposure, the incidence rates for both laboratory- and hepatic-related AEs following treatment with celecoxib (200–800 mg/day) were similar to or lower than for placebo, and lower than for diclofenac (Table 4). The hepatobiliary AE rate per 1000 patient-years, excluding laboratory AEs, was 7.8 for celecoxib 200 mg/day versus 6.9 for placebo, 10.3 for diclofenac, 5.8 for ibuprofen, and 10.0 for naproxen. There was no evidence of increased event rates with increasing celecoxib dose up to 800 mg/day (Table 4).

Time to discontinuation due to hepatic AEs

The estimated cumulative function for time to withdrawal caused by hepatic AEs is shown in Figure 1 for celecoxib and diclofenac. Although the withdrawal rate of patients on diclofenac was <1% over the first 90 days, the separation in the withdrawal rates was noticed early after the onset of treatment (within the first 3 weeks). Statistical comparisons using the log-rank test demonstrated that time to discontinuation for celecoxib (all doses) was not significantly different from that for ibuprofen and naproxen ($p = 0.88$ and $p = 0.66$, respectively), and significantly longer than for diclofenac ($p < 0.0001$).

Discussion

The authors have presented data pooled from 41 randomized clinical studies on hepatobiliary AEs and laboratory abnormalities arising during treatment with placebo, celecoxib, and nonselective NSAIDs (naproxen, diclofenac, and ibuprofen, at commonly used therapeutic doses). Various doses of celecoxib were analyzed, including the most commonly used arthritis doses of 200 mg/day and 400 mg/day, and up to 800 mg/day, respectively. The incidence of serious hepatic events was low, with no cases of severe liver toxicity, liver failure, or drug-related liver transplant in patients treated with celecoxib or nonselective NSAIDs. Most hepatobiliary AEs were characterized by the investigators as mild-to-moderate in nature and commonly presented as elevations in hepatic aminotransferases (data not shown). The incidence of hepatobiliary AEs (including laboratory abnormalities) with celecoxib was generally similar to, or lower than, that noted for placebo or nonselective NSAID comparators, other than for a significantly greater incidence of all hepatobiliary AEs versus naproxen (result unadjusted for duration of exposure). There was a trend toward higher incidence with diclofenac, particularly of the laboratory-related AEs of elevated ALT and AST, and of abnormal hepatic function (data not shown). The incidence of notable ($>5 \times$ ULN) and severe ($>10 \times$ ULN) increases in ALT was markedly greater for diclofenac than for any other treatment group.

Overall, the results of this analysis are consistent with those of previous hepatic safety analyses by Maddrey *et al.*[23] and Rostom *et al.*[28] in which celecoxib therapy was associated with an incidence of hepatic AEs similar to that of placebo and a range of nonselective NSAIDs excluding diclofenac, and also with the results of large individual celecoxib studies. In the Celecoxib Long-term Arthritis Safety Study (CLASS), one of the 41 studies included in this analysis, there was a significantly greater incidence of ALT and AST elevations in patients receiving diclofenac 150 mg/day than in those treated with a supratherapeutic dose of celecoxib (800 mg/day) or with ibuprofen (2400 mg/day). Overall, 97% of all ALT and AST abnormalities in CLASS occurred in the diclofenac-treatment group[29]. Two long-term placebo-controlled studies involving celecoxib, the Prevention of Sporadic Colorectal Adenomas With Celecoxib (APC) study and the Prevention of Colorectal Sporadic Adenomatous Polyps (PreSAP) study, were not included in our analysis because they fell outside the cut-off date for study completion[30,31]. However, unpublished data from a pooled analyses of 3588 patients, 77% of whom had completed 3 years of treatment, showed a greater incidence of hepatobiliary AEs and serious AEs in placebo-treated patients (hepatobiliary AEs 2.8%; hepatobiliary serious AEs 1%) than in celecoxib-treated patients (400 mg/day; hepatobiliary AEs 1.8%; hepatobiliary

Table 4. *Hepatobiliary and hepatic adverse events (AEs): results unadjusted and adjusted for duration of exposure*

Parameter	Placebo $N=4057$	Celecoxib (any dose) $N=24\,933$	Celecoxib <200 mg/day $n=943$	Celecoxib 200 mg/day $n=12\,008$	Celecoxib 400 mg/day $n=7380$	Celecoxib 800 mg/day $n=4602$	Diclofenac 100–150 mg/day $N=7639$	Ibuprofen 2400 mg/day $N=2484$	Naproxen 1000 mg/day $N=2953$
Total exposure (patient-years)*	584	–	–	2190	1732	2409	2618	1201	498
All hepatobiliary AEs,† *n* (%)	36 (0.89)	276 (1.11)	6 (0.64)	125 (1.04)	68 (0.92)	77 (1.67)	324 (4.24)	38 (1.53)	20 (0.68)
p-value versus celecoxib (any dose)	0.21	–	–	–	–	–	<0.0001	0.06	0.03
Hepatic AEs excluding laboratory and biliary AEs,‡ *n* (%)	0 (0)	13 (0.05)	0 (0)	3 (0.02)	3 (0.04)	7 (0.15)	11 (0.14)	2 (0.08)	0 (0)
p-value versus celecoxib (any dose)	0.15	–	–	–	–	–	0.01	0.56	0.21
Hepatobiliary AE event rate, excluding laboratory AEs, per 1000 patient-years§ (number of patients with events)	6.9 (4)	–	–	7.8 (17)	4.0 (7)	5.8 (14)	10.3 (27)	5.8 (7)	10.0 (5)
ALT increases reported as AEs, event rate per 1000 patient-years§ (number of patients with events)	27.4 (16)	–	–	27.9 (61)	19.6 (34)	17.8 (43)	77.5 (203)	20.0 (24)	16.1 (8)

*Estimated as the sum of the maximum possible exposures for individual studies, which were calculated as the planned study duration (days) multiplied by the number of patients and divided by the number of weeks or months in a year; not calculated for celecoxib (any dose) and celecoxib <200 mg/day

†All terms analysis

‡Excludes all laboratory-related AEs (bilirubinemia, hepatic function abnormal, AST increased, ALT increased, albumin/globulin ratio abnormal, bilirubinuria, bilirubin decreased, increased gamma-glutamyl) and all biliary system-related terms (biliary pain, cholecystitis, cholelithiasis, gallbladder disorder)

§Number of patients with events divided by total exposure and multiplied by 1000, to give number of patients with events per 1000 patient-years

Includes data up to 28 days after last dose of study drug; subjects with multiple AEs are only counted once; *p*-value from χ^2-test

n, number of patients experiencing event; AST, aspartate transaminase; ALT, alanine transaminase

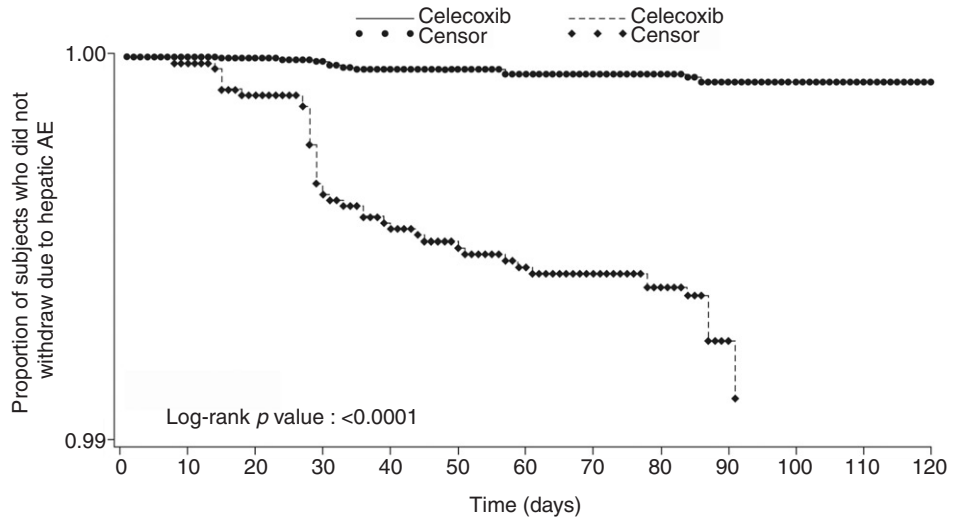

Figure 1. *Time to withdrawal due to hepatic adverse events (AEs): estimated cumulative function between celecoxib (any dose; data taken from all 41 studies in pooled analyses) and diclofenac. Log-rank test with censoring rules applied*

serious AEs 0.4%); consistent with our findings that serious hepatobiliary AEs were rarely reported in patients receiving celecoxib.

In the analysis there was no strong evidence of a dose relationship between celecoxib and hepatobiliary AEs. In the analysis unadjusted for time of exposure, slightly higher rates of hepatobiliary AEs, and serious AEs, were noted with the highest dosage of 800 mg/day compared with the lower doses. However, the celecoxib 800 mg/day treatment arm was weighted toward a longer exposure time characterized by the CLASS trial (median treatment duration 9 months, with 2320 patient-years of exposure to celecoxib 800 mg), which may lead to biased comparisons. The annualized event rates show no increase in events with increasing celecoxib dose up to 800 mg/day. Objective evaluation of ALT and AST increases could not rule out the possibility that mild elevations ($<3 \times$ ULN) are somewhat more likely in patients treated with celecoxib 800 mg/day compared with those treated with placebo or with celecoxib at lower doses (data not shown). Annualized event rates were not calculated for mild and notable increases in ALT and AST for methodological reasons. However, celecoxib 800 mg/day is a supratherapeutic dose for arthritis patients, twice the maximum approved dose for the treatment of RA and four times that for OA in the United States. The percentages of celecoxib 800 mg/day treated patients with AST or ALT elevations were similar to those observed with ibuprofen, and less than those observed with diclofenac, at approved therapeutic doses.

Compared with diclofenac, the incidence of significant increases in ALT or AST with celecoxib treatment at commonly used doses was very low. Odds ratios for notable ($>5 \times$ ULN) or severe ($>10 \times$ ULN) ALT elevations for celecoxib 400 mg/day relative to placebo were 1.09 (0.20–5.96) and 0.55 (0.03–8.72), respectively, compared with 21.60 (5.30–87.94) and 18.72 (2.56–136.80) for diclofenac relative to placebo. In addition, more serious hepatobiliary and hepatic events were reported in patients receiving diclofenac than in those receiving celecoxib. Diclofenac has previously been associated with rare cases of serious liver injury and, consistent with its widespread use, is among the most frequent causes of drug-related idiosyncratic hepatotoxicity[32,33]. The mechanisms of diclofenac-induced liver injury have not yet been fully defined, but are probably influenced by a combination of factors related to drug metabolism, metabolite formation and clearance, and host response[15]. It is possible that the hepatotoxicity of diclofenac and lumiracoxib, which share a very close structural resemblance, is mediated by analogous reactive intermediates[34].

Although no single study has been designed to evaluate the hepatic safety and tolerability of celecoxib to date, the current study represents the most extensive analysis of the hepatic safety profile of celecoxib. Because of the highly controlled setting of randomized clinical trials, our results are unlikely to be affected by the underreporting of AEs, which can be a significant issue in epidemiologic studies. However, because of the low frequency of events, even with pooled data forming a relatively large dataset it is difficult to draw precise estimates of incidence from clinical trial settings, particularly for serious events. Another issue inherent to the retrospective pooled analysis design is that findings are limited by the quality and reporting of the studies selected. For example, our results cannot necessarily be extrapolated beyond the eligibility criteria, treatment duration and the chronic disease populations involved in the included studies, such as to those with a

preexisting liver condition or abnormal liver biochemistry. However, to specifically design and power a single study to evaluate these events would involve both a significant undertaking and a very large population of subjects.

Another limitation is that although acetaminophen was a comparator in two of the celecoxib studies, our analysis did not include it as an active comparator, despite the fact that acetaminophen is a known hepatotoxic agent (and the most common cause of acute liver failure). The two acetaminophen studies were excluded from our meta-analysis because they were inadequate in size and duration of use, and safety findings were more difficult to interpret due to a cross-over trial design. However, acetaminophen would have been taken concurrently with study medication by some patients in other treatment groups, making our analysis conservative: despite permitted use of acetaminophen as rescue medication, the observed incidence of hepatotoxicity was low. Despite the known methodologic drawbacks described above, and which are common to pooled analyses of clinical trial data, the findings reported here are consistent with current epidemiologic data.

Conclusion

In this analysis of data from 41 randomized controlled trials, the incidence of investigator-reported hepatic AEs and hepatic laboratory abnormalities following treatment with celecoxib was similar to that of placebo and three commonly prescribed nonselective NSAIDs, but lower than for diclofenac. The results are consistent with data from pivotal individual clinical trials, and are in line with current prescribing recommendations for no dosage adjustments necessary in patients with mild hepatic impairment; in patients with moderate impairment, celecoxib should be introduced at the lowest recommended dose. The benefit/risk associated with the use of celecoxib as currently labeled remains favorable.

Transparency

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Declaration of financial/other relationships
P.S., B.S., G.C., C. L. and H.M. are full time employees of Pfizer Inc.

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