Gastrointestinal Tolerability of the Selective Cyclooxygenase-2 (COX-2) Inhibitor Rofecoxib Compared With Nonselective COX-1 and COX-2 Inhibitors in Osteoarthritis

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Background: Most nonsteroidal anti-inflammatory drugs (NSAIDs) are nonselective cyclooxygenase (COX-1 and COX-2) inhibitors and are associated with a variety of upper gastrointestinal (GI) tract symptoms. The roles of COX-1 and COX-2 in the pathogenesis of these symptoms are unclear. To test whether COX-2 inhibition with rofecoxib would have greater GI tolerability than nonselective COX-1 and COX-2 inhibition, we compared the incidences of (1) treatment discontinuations for GI adverse events (AEs) and (2) prespecified dyspeptic-type GI AEs among patients with osteoarthritis treated with rofecoxib vs NSAIDs.

Methods: A prespecified, combined analysis of investigator-reported GI AEs in all 8 double-blind, randomized, phase 2b/3 osteoarthritis trials of rofecoxib was conducted. Patients included men and women with osteoarthritis (N=5435); there was no upper age limit for entry. Treatments tested included rofecoxib, 12.5, 25, or 50 mg (combined), vs ibuprofen, diclofenac, or nabumetone (combined). Primary outcomes were the time (by survival analysis) to (1) treatment discontinuation due to GI AEs and (2) first reported dyspeptic-type GI AE. Between-treatment comparisons were made by log-rank test.

Results: The number of treatment discontinuations caused by GI AEs during 12 months was significantly lower (P=.02) with rofecoxib vs NSAIDs (8.2 vs 12.0 per 100 patient-years; relative risk, 0.70; 95% confidence interval, 0.52-0.94). The incidence of prespecified dyspeptic-type GI AEs during the first 6 months was significantly lower (P=.02) with rofecoxib vs NSAIDs (69.3 vs 85.2 per 100 patient-years; relative risk, 0.85; 95% confidence interval, 0.74-0.97). However, the difference between treatments in dyspeptic-type GI AEs was attenuated after 6 months.

Conclusion: Rofecoxib was associated with a lower incidence of treatment discontinuations due to GI AEs over 12 months and a lower incidence of dyspeptic-type GI AEs over 6 months than treatment with nonselective COX inhibitors, or NSAIDs.

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Two isoforms of cyclooxygenase (COX), COX-1 and COX-2, catalyze human prostaglandin synthesis. Almost all currently available nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit both COX isoforms. COX-1 is constitutively expressed and generates prostaglandins believed to be involved in gastrointestinal (GI) mucosal protection, whereas COX-2 is induced at sites of inflammation throughout the body and generates prostaglandins that mediate inflammation and pain. Therefore, the anti-inflammatory effects of NSAIDs appear to be mediated via inhibition of COX-2, whereas the deleterious effects on the GI mucosa, which represent a significant source of morbidity and mortality, are believed to occur primarily via inhibition of COX-1. In addition, NSAIDs have been associated with a variety of upper GI tract symptoms, which may lead to switching NSAIDs, the use of concomitant medications for symptom relief, or discontinuation of NSAID therapy. Upper GI tract symptoms associated with NSAID use have generally not correlated well with mucosal damage or clinical events, and the roles of COX-1 and COX-2 in the pathogenesis of these symptoms are unclear.

Rofecoxib (VIOXX) selectively inhibits COX-2; at doses of up to 375 mg/d for 12 days and up to 1000 mg in single doses, it had no effect on COX-1 isoenzyme activity. In vitro and in vivo studies of rofecoxib showed no significant effect on prostaglandin synthesis in...
PATIENTS AND METHODS

The plan to conduct a combined analysis of all 8 phase 2b/3 osteoarthritis trials and blinded extensions with rofecoxib (Table 1)22,23,25-28 was prespecified. All studies were double-blind and randomized. All patients gave signed informed consent, and an institutional review board approved each study.

Patients were followed up in each study until (1) final evaluation after completion of study therapy, (2) final evaluation after early discontinuation for any reason (including development of an AE, lack of treatment efficacy, withdrawal of consent, etc.), (3) loss to follow-up, or (4) death. Early discontinuations were based on investigator clinical judgment and patient preference; investigators recorded the reason for discontinuation. In all the studies, a final patient contact and evaluation was scheduled for 14 days following completion or discontinuation.

Investigators were instructed to report all laboratory and clinical AEs that occurred during treatment and within 14 days of discontinuation of use of the study drug. The AEs were coded blind to treatment using a standard automated dictionary that classified them into broader categories grouped by body system. The AEs of interest for this study were those classified as belonging to the “GI system,” with the exception of those coded as “abdominal pain,” because the dictionary structure classified these under “body as a whole.” A subset of GI system AE terms typical of upper GI tract symptoms associated with NSAIDs29-31 was prespecified as dyspeptic-type GI AEs; this included acid reflux, dyspepsia, epigastric discomfort, heartburn, nausea, or vomiting.

Assessment of discontinuation due to GI AEs was based on early discontinuations due to any AE with a code that mapped to the GI system. The analyses did not include patients from the 2 endoscopic surveillance studies who discontinued treatment because of gastroduodenal ulcers or erosions found at scheduled endoscopy; these events were treated as study end points rather than as AEs. Counting these events would have inflated treatment differences in favor of rofecoxib because these trials showed a 75% reduction in endoscopic ulcers with rofecoxib compared with ibuprofen. AN additional post hoc analysis was done comparing discontinuation due to dyspeptic-type GI AEs and discontinuation due to the combination of GI or abdominal pain AEs.

Assessment of the incidence of dyspeptic-type GI AEs was based on investigator reports of eligible AEs. Additional post hoc analyses were done comparing the cumulative incidence of GI AEs and the combination of GI or abdominal pain AEs.

All analyses were based on all patients treated in the 8 trials, with prespecified exceptions as follows. Patients from the placebo and 5-mg rofecoxib groups of protocol 029 (Table 1) were switched by design after 6 weeks to diclofenac, 12.5-mg rofecoxib, or 25-mg rofecoxib, in a blinded extension phase. Similarly, patients from the placebo group of protocol 058 were switched after 6 weeks to nabumetone, 12.5-mg rofecoxib, or 25-mg rofecoxib, in a blinded extension phase. To avoid double counting patients in the analyses, it was prespecified that the data from patients randomized to placebo or 5-mg rofecoxib in the 6-week placebo-controlled phase of both studies would be excluded from analyses, whereas the data in these patients’ extension phase would be included. However, 117 such patients (2.1% of the total population) from studies 029 and 058 did not enter the extensions and were subsequently not included in the analysis.

Summary statistics included counts of events per 100 patient-years of treatment. Survival analyses of the time to discontinuation due to GI AEs and to first dyspeptic-type GI AE were used for between-treatment comparisons. The log-rank test was the primary method to compare the survival curves between groups. The Cox proportional hazards model was used to estimate the overall relative risk (RR) and 95% confidence intervals (CIs) of rofecoxib vs NSAIDs. The proportional hazards assumption of the model was tested at each time point. Analyses using type of protocol as a stratification factor (stratified log-rank test and stratified Cox proportional hazards model) were also conducted. Results of these were consistent with those of unstratified analyses; therefore, only results of unstratified analyses are presented. Results are reported at 6 and 12 months.

Comparisons between rofecoxib and NSAIDs and between NSAIDs and placebo were prespecified. Comparisons of rofecoxib with placebo are presented for completeness only; no hypotheses for rofecoxib vs placebo were prespecified. All comparisons to placebo restricted the analyses to the 4 placebo-controlled protocols without treatment switching (033/040 and 044/045, Table 1). The maximum duration of placebo treatment in these 4 studies was 4 months.

RESULTS

A total of 5435 patients were included in the analysis. Of these patients, 514 were treated with placebo, 3357 with rofecoxib (1209, 1603, and 545 received 12.5, 25, and 50 mg, combined treatment groups) than in the NSAID group (ibuprofen, diclofenac, and nabumetone, combined treatment groups). Two analogous prespecified hypotheses were that the rates of these end points would be higher for NSAIDs than for placebo.
mg 3 times daily; 590 received diclofenac, 50 mg 3 times daily; and 127 received nabumetone, 1500 mg once daily).

BASELINE CHARACTERISTICS

There were no clinically meaningful differences in baseline characteristics between groups (Table 2). Mean age overall was 63.3 years (range, 38-94 years), 44.7% were 65 years or older, and 72.9% were female. Most patients (90.3%) had previously used NSAIDs for their osteoarthritis. Approximately 10% of the patients in each group had a history of GI ulceration or bleeding.

DISCONTINUATIONS

Overall, 67.9% of patients completed their respective studies (74.5%, 69.3%, and 62.9% for placebo, rofecoxib, and NSAIDs, respectively). Fewer patients discontinued treatment for any cause from the placebo (25.5%) and rofecoxib (30.7%) groups than from the NSAID group (37.1%). Discontinuations due to any clinical AE were 4.7%, 9.4%, and 10.7% in the placebo, rofecoxib, and NSAID groups, respectively. Discontinuations due to lack of efficacy were 8.8% in the placebo and rofecoxib groups and 7.2% in the NSAID group.

The cumulative incidence of discontinuation due to GI AEs during 12 months was significantly lower (P = .02) with rofecoxib than with NSAIDs (Figure 1). The rates per 100 patient-years were 8.20 vs 12.03 for rofecoxib and NSAIDs, respectively (Table 3); the RR during 12 months was 0.70 (95% CI, 0.52-0.94). The difference between rofecoxib and NSAIDs was apparent as early as 6 weeks and remained consistent through 12 months. The results of post hoc analyses of discontinuation due to dyspeptic-type GI AEs and the combination of GI or abdominal pain AEs were consistent with the above results at both 6 and 12 months (Table 3).

In analyses confined to placebo-controlled protocols, the rates of discontinuations due to GI AEs throughout 4 months were 7.16 for placebo, 14.71 for rofecoxib, and 24.50 per 100 patient-years for NSAIDs. The RR throughout 4 months for NSAIDs vs placebo was 3.17 (95% CI, 1.46-6.91), while that for rofecoxib vs placebo was 2.03 (95% CI, 0.96-4.32).

DYSPEPTIC-TYPE GI ADVERSE EVENTS

The cumulative incidence of dyspeptic-type GI AEs was significantly lower with rofecoxib than NSAIDs up to 6 months (P = .02), after which the incidence rates converged (Figure 2). The difference in incidence curves was of borderline statistical significance throughout 12 months (P = .07). The rates per 100 patient-years were 69.29 vs 85.20 throughout 6 months and 54.51 and 63.56 throughout 12 months for rofecoxib and NSAIDs, respectively (Table 3). The RR was 0.85 (95% CI, 0.74-0.97) during 6 months and 0.88 (95% CI, 0.78-1.01) during 12 months. The Cox model assumption that the hazard ratio between treatments is constant over time was satisfied at time points up to 6 months but not at 12 months. The results of analyses of GI AEs and the combination of GI or abdominal pain AEs were consistent with the above results at both 6 and 12 months (Table 3).

In analyses confined to placebo-controlled protocols, the rates of dyspeptic-type GI AEs per 100 patient-years over 4 months were 79.76 for placebo, 115.67 for rofecoxib, and 152.01 for NSAIDs. The RR over 4 months for NSAIDs vs placebo was 1.63 (95% CI, 1.25-2.13), while that for rofecoxib vs placebo was 1.39 (95% CI, 1.09-1.78).
Symptoms referable to the GI tract are common among patients taking NSAIDs. Although their pathogenesis is not well understood, they may lead to clinical evaluations, use of concomitant gastroprotective agents, decreased adherence, or discontinuation of therapy. The roles of COX-1 and COX-2 inhibition in the genesis of NSAID-associated upper GI tract symptoms are not clear.

This study compared the GI tolerability of rofecoxib, an anti-inflammatory agent that selectively inhibits COX-2, to a group of nonselective NSAIDs by assessing the incidence of treatment discontinuation due to GI AEs and the incidence of a subset of upper GI tract dyspeptic-type AEs typical of NSAIDs. The results of the pre-specified and exploratory analyses indicate that rofecoxib had greater GI tolerability than the comparator NSAIDs by these measures. The results of analyses confined to studies containing placebo demonstrated that the rates of discontinuation due to GI AEs and dyspeptic-type GI AEs were significantly lower for placebo than

Table 2. Baseline Patient Group Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 514)</th>
<th>Rofecoxib (n = 3357)</th>
<th>NSAIDs (n = 1564)</th>
<th>Total (N = 5435)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (range), y</td>
<td>61.9 (40-87)</td>
<td>63.3 (38-94)</td>
<td>64.0 (38-92)</td>
<td>63.3 (38-94)</td>
</tr>
<tr>
<td>Female, %</td>
<td>74.1</td>
<td>72.8</td>
<td>72.9</td>
<td>72.9</td>
</tr>
<tr>
<td>Race, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>76.5</td>
<td>80.6</td>
<td>80.9</td>
<td>80.3</td>
</tr>
<tr>
<td>Hispanic</td>
<td>15.8</td>
<td>12.3</td>
<td>12.9</td>
<td>12.8</td>
</tr>
<tr>
<td>Black</td>
<td>5.5</td>
<td>5.5</td>
<td>4.6</td>
<td>5.2</td>
</tr>
<tr>
<td>Other</td>
<td>2.2</td>
<td>1.6</td>
<td>1.6</td>
<td>1.7</td>
</tr>
<tr>
<td>Smoker, %</td>
<td>47.3</td>
<td>43.9</td>
<td>44.0</td>
<td>44.3</td>
</tr>
<tr>
<td>History of PUB, %</td>
<td>9.7</td>
<td>10.3</td>
<td>10.0</td>
<td>10.1</td>
</tr>
<tr>
<td>Positive Helicobacter pylori infection, %</td>
<td>44.5</td>
<td>43.2</td>
<td>42.0</td>
<td>42.9</td>
</tr>
<tr>
<td>Prior osteoarthritis therapy, %</td>
<td>11.2</td>
<td>9.6</td>
<td>9.6</td>
<td>9.7</td>
</tr>
</tbody>
</table>

*NSAIDs indicates nonsteroidal anti-inflammatory drugs; PUB, gastrointestinal perforation, ulcer, or bleeding.
†Total sample size was 4864. Protocol 029 was excluded because gastrointestinal history data were not collected.
‡Total sample size was 1517 for protocols 044/045 only; infection based on positive histopathologic results.
§Total sample size was 3022 for protocols 033/040 and 034/035 only.

Table 3. Rates per 100 Patient-Years and Relative Risk Estimates (Rofecoxib vs NSAIDs) for Discontinuations and Adverse Events During 6 and 12 Months

<table>
<thead>
<tr>
<th></th>
<th>Rate per 100 Patient-Years</th>
<th>Relative Risk (95% CI)†</th>
<th>P‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinuation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Due to GI AEs</td>
<td>10.42</td>
<td>15.84</td>
<td>0.68 (0.50-0.92)</td>
</tr>
<tr>
<td>12 mo</td>
<td>8.20</td>
<td>12.03</td>
<td>0.70 (0.52-0.94)</td>
</tr>
<tr>
<td>Due to dyspeptic-type GI AEs</td>
<td>5.41</td>
<td>8.85</td>
<td>0.64 (0.42-0.97)</td>
</tr>
<tr>
<td>12 mo</td>
<td>4.20</td>
<td>6.34</td>
<td>0.69 (0.46-1.03)</td>
</tr>
<tr>
<td>Due to GI or abdominal pain AEs</td>
<td>11.93</td>
<td>18.40</td>
<td>0.67 (0.50-0.89)</td>
</tr>
<tr>
<td>12 mo</td>
<td>9.32</td>
<td>13.98</td>
<td>0.69 (0.52-0.90)</td>
</tr>
<tr>
<td>Adverse Events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspeptic-type GI AEs</td>
<td>69.29</td>
<td>85.20</td>
<td>0.85 (0.74-0.97)</td>
</tr>
<tr>
<td>12 mo§</td>
<td>54.51</td>
<td>63.56</td>
<td>0.88 (0.78-1.01)</td>
</tr>
<tr>
<td>GI AEs</td>
<td>69.29</td>
<td>85.20</td>
<td>0.85 (0.74-0.97)</td>
</tr>
<tr>
<td>12 mo§</td>
<td>54.51</td>
<td>63.56</td>
<td>0.88 (0.78-1.01)</td>
</tr>
<tr>
<td>GI or abdominal pain AEs</td>
<td>154.61</td>
<td>190.87</td>
<td>0.85 (0.77-0.93)</td>
</tr>
<tr>
<td>12 mo§</td>
<td>122.50</td>
<td>148.44</td>
<td>0.86 (0.78-0.95)</td>
</tr>
</tbody>
</table>

*NSAIDs indicates nonsteroidal anti-inflammatory drugs; CI, confidence interval; GI, gastrointestinal; and AEs, adverse events.
†From the Cox proportional hazards model up to this time point.
‡From the log-rank test for the comparison of cumulative incidence curves up to this time point.
§The Cox model assumption of proportional hazards not satisfied up to this time point.
NSAIDs, whereas the rates of these measures among patients treated with rofecoxib were between those of placebo and NSAIDs.

The difference in the cumulative incidence of dyspeptic-type GI AEs between rofecoxib and NSAIDs became smaller after 6 months and was not detected at 12 months. This may have been due to greater variability at later time points due to the multifactorial nature of the symptoms being assessed (eg, due to diet or illness) or due to the reduced sample size beyond 6 months. Another possible explanation for the results at 12 months is that the population at risk changed with time in the NSAID group. The incidence of discontinuation due to all GI AEs was significantly greater in the NSAID group. Therefore, the pool of patients at risk for dyspeptic-type GI AEs was reduced in the NSAID group, and discontinuation of these patients would introduce bias against rofecoxib if they were at increased risk for dyspeptic-type GI AEs compared with those who remained.

The analysis had limitations. First, the inclusion of studies with scheduled endoscopies mandated in their protocols may have caused a bias in favor of NSAIDs. Patients in these studies systematically discontinued treatment when they developed endoscopically evident gastroduodenal erosions or ulcers (3 mm in diameter), and a much higher rate of endoscopically detected ulceration was observed in the ibuprofen group than in the rofecoxib group. If these patients who discontinued treatment had excess potential to develop symptoms, then the observed incidence of clinical AEs may have been reduced for the NSAIDs group, resulting in a biased estimate of the RR of the various end points. Second, because of differences in study designs (Table 1), comparisons among doses of rofecoxib and individual NSAIDs were not possible because of confounding by type of protocol.

The analysis also had a number of strengths. It was designed prospectively and included a broad range of patients with a common indication from all phase 2b/3 osteoarthritis trials of rofecoxib. Doses of NSAID comparators for the included studies were chosen to be within the clinical range for treatment of osteoarthritis. The range of rofecoxib doses (average dose, 24.7 mg/d) were at and above the clinical dose range for osteoarthritis; rofecoxib, 12.5 and 25 mg once daily, has been demonstrated to be statistically equivalent to ibuprofen, 800 mg 3 times daily, and diclofenac, 150 mg 3 times daily, in the treatment of osteoarthritis. The analytic methods took account of the varying lengths of the included studies. Analyses stratified by type of protocol demonstrated that differences in study design did not confound the assessments performed in this study.

These results suggest that the use of ancillary health care resources could potentially be lessened by treatment of patients with osteoarthritis with rofecoxib as opposed to nonselective COX-1 and COX-2 inhibitors. Results of analyses on the use of concomitant gastroprotective agents and the need for diagnostic GI procedures in the combined phase 2b/3 rofecoxib trials in osteoarthritis will soon be available, as will the results of a health economic model to assess the GI-related health economic implications of rofecoxib in the treatment of osteoarthritis. The true impact of these potential advantages on the management of patients with osteoarthritis will ultimately need to be demonstrated in clinical practice. However, because of the likely propensity for clinicians to initially reserve the use of rofecoxib for patients with a history of NSAID intolerance or at high risk of serious upper GI tract complications with NSAIDs, it may require a number of years of experience with rofecoxib before such advantages are observed.

This analysis shows that in randomized clinical trials of patients with osteoarthritis, selective COX-2 inhibition with rofecoxib was associated with a significantly lower incidence of early treatment discontinuations due to GI AEs and with a lower incidence of upper GI tract symptoms relative to the comparator NSAIDs. These results suggest that inhibition of COX-1 may be at least partially responsible for the upper GI tract symptoms associated with NSAIDs and that selective COX-2 inhibition may result in greater GI tolerability than nonselective COX-1 and COX-2 inhibition.

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