Abstract

Celecoxib is the first COX-2-specific inhibitor approved for relief of the signs and symptoms of osteoarthritis (OA) and rheumatoid arthritis (RA), as well as for treatment of familial adenomatous polyposis. For both OA and RA, celecoxib has been shown to be significantly superior in efficacy to placebo and similar in efficacy to traditional non-steroidal anti-inflammatory drugs. Its advantage, however, is its gastrointestinal (GI) safety. Randomized clinical trials as well as long-term outcomes studies have demonstrated that the GI safety profile of celecoxib is superior to that of traditional NSAIDs and similar to that of placebo. Additionally, the renal and cardiovascular safety of celecoxib has also become apparent, as well as its efficacy, tolerability and safety in the elderly population.

KEY WORDS: Celecoxib, COX-2 inhibitors, NSAIDs, Osteoarthritis, Rheumatoid arthritis, Gastrointestinal safety.

The prostaglandins are a group of related compounds that are important mediators of a wide variety of physiological processes, including renal function, gastroprotection, reproduction, platelet function and immunomodulation. Prostaglandins are derived primarily from arachidonic acid via the cyclooxygenase (COX) pathway. In 1971, John Vane proposed that aspirin and the aspirin-like drugs, known as non-steroidal anti-inflammatory drugs (NSAIDs), inhibit the conversion of arachidonic acid into prostaglandins by inhibiting COX [1]. His work also suggested that this inhibition of COX not only results in the anti-inflammatory activity of these drugs, but also contributes to their toxicity [1]. However, the apparent inconsistencies in the regulation of COX in physiological processes led to the suggestion by Seibert et al. that there may be multiple COX pools [2]. The possibility of multiple COX pools was investigated further by Needleman and colleagues at Searle (Skokie, IL), who also suggested the concept of differential inhibition of COX as a means of maintaining anti-inflammatory efficacy while preventing toxicity [3]. These concepts were ultimately confirmed by the discovery in several independent laboratories of a second COX isoform, COX-2 [4–6]. In contrast to the constitutively expressed COX-1, which has several physiological functions, COX-2 is up-regulated during inflammation [7, 8], and its involvement has been demonstrated in the treatment of both arthritis [9, 10] and cancer [11]. The differences in expression and function between COX-1 and COX-2 validated the approach taken by Needleman’s group [3], and provided the basis for the aggressive research and development of drugs that would be specific for inhibition of COX-2 [12].

Celecoxib (Celebrex®) was the first of the new COX-2-specific inhibitors to reach the market, and it is the only one that has been approved for the treatment of the signs and symptoms of both osteoarthritis (OA) and rheumatoid arthritis (RA). Additionally, it is the only COX-2-specific inhibitor that has demonstrated efficacy and been approved for the treatment of familial adenomatous polyposis (FAP).

This review summarizes the efficacy and safety data that have been obtained in clinical trials, and focuses on some of the more recent findings that have emerged regarding COX-2 inhibition.

Mechanism of action of celecoxib

The discovery that there are two isoforms of COX, COX-1 and COX-2, provided insight into the mechanism of action and toxicity of the NSAIDs. Much has been learned about these isoenzymes since their discovery. COX-1 is primarily a constitutively expressed enzyme with important roles in gastrointestinal (GI) mucosal protection, platelet aggregation and renal function, while COX-2, in contrast, is an enzyme that is primarily up-regulated in response to tissue damage during inflammation [13, 14]. Many of the traditional NSAIDs inhibit both isoforms in a non-specific manner, thereby demonstrating both efficacy and toxicity. Although there is an ~60% homology in the amino acid structure between the two COX isoforms, the shape of the binding site in COX-2 theoretically permits compounds with a pronounced side chain to access the COX-2 binding site, which would not be accessible to the COX-1 binding site [15]. This was the goal for the targeted development of specific COX-2 inhibitors that would provide the same efficacy as NSAIDs while maintaining a COX-1-sparing effect that would enhance the safety profile.

In vitro assays confirm that celecoxib is a potent inhibitor of the COX-2 enzyme and COX-2-mediated
prostaglandin synthesis. *In vivo* studies demonstrated anti-inflammatory efficacy in several animal models and a good GI safety profile, lending further support to its mechanism of action. Although *in vitro* data and animal models do not necessarily predict therapeutic relevance in humans, the studies summarized in this review confirm that COX-2-specific inhibition with celecoxib is a viable approach to reducing the GI toxicity previously associated with traditional NSAIDs while providing the efficacy associated with high doses of these drugs.

**Human pharmacokinetics of celecoxib**

Mean maximum plasma concentrations (Cₘₐₓ) of celecoxib are reached 2 h after oral ingestion [16], and both Cₘₐₓ and the area under the time–concentration curve (AUC) are linear within the therapeutic dose range. The absolute bioavailability of celecoxib has not yet been determined. With multiple dosing, steady state is achieved within 5 days. Celecoxib can be administered without regard to the timing of meals, although a high-fat diet has been shown to increase the AUC and time to Cₘₐₓ.

As with many traditional NSAIDs, celecoxib is highly protein bound (>97%). It has a large volume of distribution within the tissues (~400 l).

The mean elimination half-life (t₁/₂) of celecoxib is 11.5 h [16], and the apparent clearance is 30 l/h. Less than 3% is excreted as unchanged compound in the urine and faeces [16]. Metabolism occurs in the liver, primarily via the cytochrome P₄₅₀ 2C₉ system, but P₄₅₀ 3A₄ also has a minor role [17]. Metabolic transformation occurs by hydroxylation and oxidation to an inactive carboxylic acid metabolite that is the primary metabolite of celecoxib [16]. Glucuronidation of this metabolite does occur, but only accounts for a small percentage of excreted product [16]. Excretion is primarily by the faecal route (57%), although ~27% is excreted in the urine [16].

Currently available data suggest that there are no interactions with many of the commonly prescribed drugs, including methotrexate [18], warfarin [19], phenytoin, glyburide or tolbutamide. Concomitant administration of celecoxib with lithium produced a 17% increase in the AUC of lithium [20]. Such a decrease in renal lithium clearance also occurs with traditional NSAIDs [21–23]. A drug interaction study with fluconazole and ketoconazole demonstrated that only fluconazole affects celecoxib pharmacokinetics; significant increases (P < 0.001) in the Cₘₐₓ and AUC of celecoxib (68 and 134%, respectively) were observed with concomitant fluconazole administration [24]. This is consistent with the role of cytochrome P₄₅₀ 2C₉ rather than 3A₄ as the primary mechanism of biotransformation.

**Celecoxib efficacy in OA**

The efficacy and safety of celecoxib for the treatment of OA were evaluated in a 12-week, randomized, double-blind, placebo-controlled trial using naproxen as comparator [25]. Twice-daily doses of celecoxib 50, 100 and 200 mg were compared with naproxen 500 mg BID in 1003 patients with OA of the knee. In patients already taking NSAIDs, disease flare after washout was required and needed to meet specific minimum criteria to establish flare. Patient evaluation was performed at baseline and at 2, 6 and 12 weeks, or early withdrawal. Standard efficacy assessments included, but were not limited to, patient’s assessment of pain (visual analogue scale), patient’s global assessment (Likert scale), and the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index. The WOMAC Index, which is a validated tool for OA of the knee and hip, evaluates pain, joint stiffness and physical function as separate components that are also combined into a composite score [26]. This tool was also used to evaluate the functional status of the patients [27]. In addition, the American Pain Society Patient Outcome Questionnaire was used to evaluate and compare each of the agents.

In these patients, the 50-mg dose of celecoxib demonstrated suboptimal efficacy, but all doses demonstrated significantly greater improvement than placebo (P ≤ 0.05) for treatment of the signs and symptoms of OA at 12 weeks, with most endpoints demonstrating significantly better scores than placebo at 2 and 6 weeks [25]. Significant improvements were observed in the functional status of patients who were taking celecoxib compared with those taking placebo [27]. The efficacy of the 100- and 200-mg doses of celecoxib was similar to naproxen for all endpoints [25, 27]. Comparably, results were observed in a trial evaluating the efficacy of celecoxib for OA of the hip [28]. This 12-week trial used the same doses as in the above study and obtained similar results; twice-daily 100- and 200-mg doses of celecoxib were significantly (P < 0.05) better than placebo at 2, 6 and 12 weeks, with comparable efficacy to naproxen for all endpoints.

Two studies of 6 weeks duration demonstrated that there is no difference in efficacy for the treatment of OA of the knee between celecoxib doses of 200 mg given once daily and celecoxib 100 mg given twice daily. Both doses of celecoxib were significantly better than placebo (P ≤ 0.05) at both the 2- and 6-week assessments. Figure 1 shows the reduction from baseline for patient’s assessment of pain in these two double-blind, placebo-controlled, parallel group studies. Similar results were obtained for the other endpoints of this study, including the WOMAC Index [29].

**Celecoxib efficacy in RA**

The efficacy and safety of celecoxib vs naproxen in patients with RA were evaluated in a placebo-controlled trial with a design similar to the above OA trials [30]. The OA and RA trials differed mainly according to the doses of celecoxib used. For RA, twice-daily doses of 100, 200 and 400 mg were evaluated vs naproxen 500 mg BID. Patient assessments using the standard criteria of the American College of Rheumatology (ACR) responder index, the ACR-20, were made at baseline (after NSAID
washout and demonstrated flare in patients previously taking NSAIDs), and at 2, 6 and 12 weeks, or early termination. At 12 weeks, the percentage of patients improving according to the ACR-20 was significantly greater (P < 0.05) in all active groups compared with placebo (Fig. 2), but there was no significant difference between celecoxib and naproxen, although celecoxib was numerically superior at all doses. For the patient's assessment of disease status, the percentage of patients improving in the celecoxib arms was also significantly superior to placebo, and the celecoxib 200-mg dose proved to be significantly superior to naproxen (Fig. 2). For none of the endpoints did the 400-mg dose demonstrate any appreciable increase in efficacy compared with the 200-mg dose.

In an international study, celecoxib 200 mg BID was evaluated in a head-to-head comparison against slow-release (SR) diclofenac 75 mg BID for the long-term management of stable RA [31]. During the course of the 24-week trial, celecoxib demonstrated sustained efficacy that was similar to diclofenac.

GI tolerability and safety of celecoxib in clinical trials

GI tolerability and safety were evaluated in all clinical trials.

Data pooled from several studies of celecoxib at doses of 100–200 mg BID or 200 mg QD (n = 4146) show no significant difference between celecoxib and placebo (n = 1864) in the incidence of nuisance symptoms such as abdominal pain, diarrhoea, dyspepsia, flatulence and nausea [20]. Furthermore, the incidence of these side-effects was lower than with the comparator NSAIDs ibuprofen (n = 387), diclofenac (n = 345) and naproxen (n = 1366). Although the occurrence of these nuisance symptoms is not correlated with the occurrence of more serious GI events [32–35], they are one of the primary causes of patient withdrawal from clinical trials, and stopping or switching NSAIDs during clinical use [35, 36].

In addition, several trials of 12-week–6 months duration utilized endoscopy to determine the incidence of gastroduodenal ulcers during treatment with celecoxib compared with the traditional NSAIDs naproxen, diclofenac and ibuprofen. In one 6-month trial in RA patients, the percentage of patients with a gastro-duodenal ulcer at final endoscopy (6 months or early withdrawal) was significantly lower in the celecoxib 200-mg BID group (4%) than in the diclofenac 75-mg SR BID group (15%; P < 0.001) [31]. However, since endoscopy was only performed at termination, the patients' ulcer status at entry was unknown.

In 12-week endoscopy studies that compared twice-daily celecoxib at doses of 50, 100, 200 and 400 mg with naproxen 500 mg BID in OA and RA patients [20, 37], all celecoxib groups had a significantly lower incidence of ulcers than the naproxen groups. In the OA trial (n = 1108), the incidence of gastroduodenal ulcers was 3.4, 3.1, 5.9 and 16.2% for celecoxib 50 mg BID, 100 mg BID, 200 mg BID and naproxen 500 mg BID, respectively. The incidence of gastroduodenal ulcers in the RA patients was 4.0, 2.7, 4.1 and 17.6% for celecoxib 100 mg BID, 200 mg BID, 400 mg BID and naproxen 500 mg BID, respectively.

In a 12-week serial endoscopy study in which endoscopy was performed at baseline, 4, 8 and 12 weeks, celecoxib 200 mg BID had a significantly lower cumulative incidence of ulcers than ibuprofen 800 mg TID (7 vs 23.3%; P < 0.001). In this study, the cumulative incidence of ulcers was also lower in the celecoxib group compared with diclofenac 75 mg BID (9.7%); however, this difference was not statistically significant.

Although the findings of these studies show that celecoxib is associated with fewer endoscopic ulcers than other NSAIDs, these data do not determine whether celecoxib use results in fewer serious GI events, such as perforation or bleeding.

A post-marketing surveillance analysis based on data from MedWatch reports confirms the upper GI safety profile of celecoxib that was observed in clinical trials.
This analysis calculates that the incidence of serious GI bleeds among users of celecoxib is 0.0015 per 100 patient-years. This is 50- to 100-fold lower than with traditional NSAIDs, although events in this account may be under-reported.

Long-term outcome studies of celecoxib

The Celecoxib Long-term Arthritis Safety Study (CLASS) was designed to confirm and extend the safety and tolerability of celecoxib that had been demonstrated in the clinical trials programme. CLASS was prospectively designed and consisted of two trials lasting 1 yr, each trial with two double-blinded, parallel groups: celecoxib 400 mg BID vs diclofenac 75 mg BID, and celecoxib 400 mg BID vs ibuprofen 800 mg TID. These supratherapeutic doses of celecoxib were four times the recommended therapeutic dose for OA and twice that for RA. More than 8000 patients (72% with OA, 28% with RA) were enrolled, 2000 in each treatment arm. Primary endpoints of the study were perforations, obstructions and bleeding (POBs), but all ulcer complications required endoscopic or X-ray confirmation of an ulcer or large erosion, and patients were subsequently withdrawn from the trial upon such confirmation.

Although the major results of these trials will be presented elsewhere (the report of the CLASS study has recently been published [39] and should be referred to for more detailed results), the following provides a brief summary of the 6-month pooled data. At 6 months, the pooled data show that patients taking celecoxib had fewer POBs than those taking the other NSAIDs (Fig. 3A). When the incidence of POBs was combined with the incidence of symptomatic ulcers, celecoxib demonstrated a significant reduction in these events compared with the other NSAIDs. Subgroup analysis of patients who were not taking aspirin (~80% of the study population) demonstrated that, among these patients, those taking celecoxib had a significantly lower incidence of POBs, as well as POBs plus symptomatic ulcers (Fig. 3B).

Other important data were generated from this trial. There was a significantly lower incidence of GI blood loss among the patients taking celecoxib, as well as increased GI tolerability, compared with diclofenac and ibuprofen use. Since NSAIDs have been shown to increase the permeability of the GI mucosa, which can lead to increased blood loss, anaemia can develop even in the absence of a bleed [40].

In addition to evaluating GI safety, this trial also recorded the incidence of cardiovascular and cerebrovascular events, which are discussed briefly in the following section.

Special issues: renal and cardiovascular safety, and use of celecoxib in the elderly

In addition to effects on the GI system, NSAIDs have been demonstrated to affect renal and cardiovascular function, presumably via a pressor effect due to inhibition of vasodilatory prostaglandins such as prostacyclin [41]. These effects are especially important in older patients, who may already be at risk for cardiovascular events and who may also have some degree of renal impairment.

Since COX-2 is constitutively expressed in the kidney and contributes to renal haemodynamics [42, 43], the renal safety of COX-2 inhibition has also been raised as an issue [44].

Although it has been suggested that celecoxib does cause sodium and potassium retention in salt-depleted, healthy male subjects [45], data from several studies show a favourable renal safety profile for celecoxib, even in the elderly population.

Data from the CLASS trial demonstrate that the incidence of renal adverse events does not increase with COX-2-specific inhibition with use of celecoxib at supratherapeutic doses. In fact, the incidence of hypertension, generalized oedema and peripheral oedema was significantly lower in the celecoxib group compared with the ibuprofen group (2.0 vs 3.0%, 0.5 vs 1.0% and 3.7 vs 5.3%, respectively; \( P \leq 0.05 \)). In addition, data from both the CLASS trial and a study performed in healthy elderly

![Fig. 3. Six-month ulcer complication and symptomatic ulcer rate in the CLASS trial. (A) All patients. (B) Patients not taking aspirin.](image)
patients (≥65 yr of age) [46] show that celecoxib has less of an effect on renal function than either diclofenac or ibuprofen (Fig. 4). With respect to cardiovascular implications of NSAID use, it has been known for some time that an increase in blood pressure is associated with NSAID use, and that NSAIDs can attenuate the effect of some anti-hypertensive medications, especially diuretics [47, 48]. A study by Heerdink previously demonstrated that the blood-pressure-lowering effect of diuretics is ablated by concomitant NSAID administration, resulting in an increased risk for congestive heart failure in the elderly [49]. With the recent article by Page and Henry [50] that confirmed an increased risk of congestive heart failure in patients taking NSAIDs, and the demonstration that COX-2 is the primary source of systemic prostacyclin [41] (a potent vasodilator that is involved in blood pressure regulation), the potential effects of COX-2 inhibitors on cardiovascular function have become an important issue.

Data obtained from the long-term outcomes study (CLASS trial) comparing supratherapeutic doses of celecoxib with diclofenac and ibuprofen showed no significant difference in the incidence of myocardial infarction, vascular events or cardiovascular deaths between the comparators (Table 1); 40% of the patients in this trial had a prior history of cardiovascular disease. However, there was a significant reduction in cerebrovascular events in the celecoxib group compared with the ibuprofen group ($P < 0.05$). Although it could be argued that aspirin may have had a protective effect, when the data are analysed for aspirin non-users, the incidence of cardiovascular and cerebrovascular events again shows no difference between patients taking celecoxib and comparator NSAIDs.

In addition to the above issues of impaired renal function and cardiovascular events examined in the CLASS study, which are both of increased risk in the elderly, there are also questions of potential differences in efficacy and GI safety in the elderly compared with younger patients. Subgroup analysis of patients <65 and ≥65 yr of age in North American clinical trials showed that celecoxib was equally effective in patients in both age groups. While younger patients had slightly better tolerability to celecoxib, there were no significant differences either between celecoxib and placebo groups or between the younger and older populations taking celecoxib. In a similar subgroup analysis of patients in active-controlled trials, there was no reduction in tolerability in the older population compared with the younger population. In fact, for most of the adverse events, the incidence was lower in the older than in the younger population, and, for all events except diarrhoea, celecoxib was consistently lower than the comparator NSAIDs (Table 2). Diarrhoea in the elderly population was slightly higher in the celecoxib group than in the comparator NSAID groups. In 12-week, placebo-controlled trials for which endoscopy

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**Table 1. Incidence of cardiovascular and cerebrovascular adverse events in the 13-month CLASS study**

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>Celecoxib, 400 mg BID ($n = 3995$)</th>
<th>Diclofenac, 75 mg BID ($n = 1999$)</th>
<th>Ibuprofen, 800 mg BID ($n = 1988$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2315 pt-y</td>
<td>1077 pt-y</td>
<td>1118 pt-y</td>
</tr>
<tr>
<td>Any myocardial event</td>
<td>1.7</td>
<td>1.1</td>
<td>1.3</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.5</td>
<td>0.3</td>
<td>0.5</td>
</tr>
<tr>
<td>Any vascular event</td>
<td>1.4</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Cerebrovascular event</td>
<td>0.2*</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Cardiovascular deaths</td>
<td>0.3</td>
<td>0.4</td>
<td>0.5</td>
</tr>
</tbody>
</table>

* $P < 0.05$ vs ibuprofen.
* pt-y, patient-years.
data are available, the pooled results again demonstrate that there is no apparent difference between the two age groups, with the incidence of endoscopic ulcers in both age groups not statistically different from the placebo groups (Fig. 5).

Celecoxib in patients with FAP

FAP is a devastating condition in which hundreds to thousands of adenomatous colorectal polyps form and usually result in cancer. FAP is a rare, hereditary disease that is linked to a defect in the APC tumour suppressor gene and is usually treated through surgical intervention. Animal models have shown that COX-2 is expressed in this condition [51]. Celecoxib has recently received approval for treatment of FAP based on an important study [52] that demonstrated a mean reduction in colorectal polyps of 28% with celecoxib 400 mg BID, significantly greater than the 4.5% reduction observed with placebo ($P < 0.005$). More than 50% of the patients in this trial achieved a reduction in polyps of at least 25%. While these results are important and promising, it should be noted that this trial did not have a cancer or surgical endpoint.

Table 2. Gastrointestinal (GI) tolerability of celecoxib by age group in active-control North American arthritis trials

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Celecoxib ($n=1893$)</th>
<th>NSAIDs ($n=1361$)</th>
<th>Celecoxib ($n=997$)</th>
<th>NSAIDs ($n=737$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;65 yr</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>5.4 (3.5)</td>
<td>7.6 (3.7)</td>
<td>4.0 (3.8)</td>
<td>9.2 (3.9)</td>
</tr>
<tr>
<td>Constipation</td>
<td>1.8 (2.1)</td>
<td>4.0 (2.3)</td>
<td>2.1 (2.4)</td>
<td>4.1 (2.5)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5.9 (6.2)</td>
<td>6.2 (6.7)</td>
<td>6.7 (7.8)</td>
<td>5.8 (7.4)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>10.5 (11.9)</td>
<td>11.9 (12.2)</td>
<td>8.9 (12.2)</td>
<td>12.2 (12.9)</td>
</tr>
<tr>
<td>Flatulence</td>
<td>2.5 (3.7)</td>
<td>3.7 (4.1)</td>
<td>1.8 (3.5)</td>
<td>3.5 (3.9)</td>
</tr>
<tr>
<td>Nausea</td>
<td>3.6 (4.8)</td>
<td>4.8 (4.0)</td>
<td>4.0 (7.2)</td>
<td>7.2 (7.8)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1.3 (1.6)</td>
<td>1.6 (1.4)</td>
<td>1.4 (1.6)</td>
<td>1.6 (1.2)</td>
</tr>
<tr>
<td>≥65 yr</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any GI event</td>
<td>27.4 (35.0)</td>
<td>35.0 (40.0)</td>
<td>28.2 (36.1)</td>
<td>36.1 (42.1)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>5.4 (4.0)</td>
<td>7.6 (4.0)</td>
<td>4.0 (4.0)</td>
<td>9.2 (4.0)</td>
</tr>
<tr>
<td>Constipation</td>
<td>1.8 (2.1)</td>
<td>4.0 (2.3)</td>
<td>2.1 (2.4)</td>
<td>4.1 (2.5)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5.9 (6.2)</td>
<td>6.2 (6.7)</td>
<td>6.7 (7.8)</td>
<td>5.8 (7.4)</td>
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<tr>
<td>Flatulence</td>
<td>2.5 (3.7)</td>
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<td>3.5 (3.9)</td>
</tr>
<tr>
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<td>3.6 (4.8)</td>
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<td>4.0 (7.2)</td>
<td>7.2 (7.8)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1.3 (1.6)</td>
<td>1.6 (1.4)</td>
<td>1.4 (1.6)</td>
<td>1.6 (1.2)</td>
</tr>
</tbody>
</table>

FIG. 5. Subgroup analysis of ulcer incidence in older and younger patients. Data are pooled from 12-week, placebo-controlled trials. *Significantly different from naproxen.

Conclusion

Celecoxib, a specific inhibitor of COX-2, has been approved for the treatment of the signs and symptoms of OA and RA. In placebo- and active-controlled clinical trials, it has been demonstrated to be significantly superior in efficacy to placebo and similar in efficacy to traditional NSAIDs. However, the advantage of celecoxib is in its improved GI safety. Clinical trials and long-term outcomes studies have demonstrated that celecoxib has GI tolerability that is superior to that of traditional NSAIDs and similar to that of placebo. In addition to improved tolerability, the use of celecoxib not only results in a lower incidence of endoscopic ulcers, which has been used as a surrogate endpoint in clinical trials, but also demonstrates in outcomes studies that the reduced rate of ulceration does translate into a reduction in ulcer-related complications.

Celecoxib not only represents an important breakthrough in the use of NSAIDs, but also validates the concept of differential inhibition of the COX isoforms that was first proposed as a means of retaining efficacy while reducing toxicity.

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