Clinical experience with cyclooxygenase-2 inhibitors

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Abstract
Rheumatoid arthritis (RA) and osteoarthritis (OA) are chronic conditions requiring long-term therapy for pain relief. Currently prescribed non-steroidal anti-inflammatory drugs (NSAIDs) provide symptomatic efficacy, but are frequently associated with gastrointestinal (GI) toxicities such as dyspepsia and ulcereations. In a small but significant number of cases, complications including perforations and massive bleeding develop and these may be fatal. A desirable therapeutic strategy would maintain efficacy while minimizing gastric intolerance. Two potential approaches have been suggested: (i) administration of NSAIDs in combination with gastroprotective compounds; or (ii) administration of potentially safer anti-inflammatory compounds which act via selective inhibition of cyclooxygenase-2 (COX-2). The selective COX-2 inhibitors rofecoxib and celecoxib consistently demonstrate efficacy comparable to conventional NSAIDs in patients with RA and OA, but have a significantly reduced propensity to cause GI toxicity. In many cases, the gastric effects of therapeutically active doses of COX-2 inhibitors are indistinguishable from placebo. The safety benefits of COX-2 inhibitors given alone appear similar to combined therapy with conventional NSAIDs and gastroprotective agents. Findings warrant the consideration of COX-2 inhibitors as first-line therapy in patients requiring long-term pain relief.

KEY WORDS: Cyclooxygenase-2-inhibitors, Osteoarthritis, Gastropathy, Pain, Rheumatoid, Arthritis, NSAIDs, Long-term-treatment.

Introduction
Patients with rheumatoid arthritis (RA) or osteoarthritis (OA) are commonly treated with non-steroidal anti-inflammatory drugs (NSAIDs) over extended periods in order to obtain symptomatic relief. Although these drugs are efficacious, their long-term use is compromised by significant gastrointestinal (GI) toxicity [1–5]. NSAID-related GI adverse events may be broadly classified into three categories: (i) ‘nuisance symptoms’ such as dyspepsia and nausea; (ii) mucosal lesions visible endoscopically or radiographically; and (iii) serious GI complications such as perforated ulcers and major bleeding [5]. Most patients taking acute aspirin or conventional NSAIDs rapidly develop mucosal conditions manifested as erosions and petechiae; although these conditions often disappear with long-term drug use, some individuals develop potentially life threatening complications including upper GI bleeding, perforation and gastric outlet obstruction. It is estimated that ~1–2% of patients taking NSAIDs for 1 yr experience such complications [6–10] and 15–30% of patients exhibit endoscopic ulceration [10–12]. In addition, at least 25% of patients experience dyspepsia as a result of conventional NSAID therapy; most patients with stomach pain do not develop lesions, but many stop taking the drug because of the pain [10]. It is of particular concern that many patients developing serious GI complications are asymptomatic prior to hospitalization. A large multicentre prospective observational study involving 1921 patients with RA taking NSAIDs reported that 81% of patients hospitalized with serious GI complications had no prior GI adverse event or significant symptoms, making it difficult for clinicians to identify patients at risk and indicating that any strategy for prophylaxis of serious GI complications cannot rely on the presence of non-threatening gastric toxicities [13].

The annual percentages of NSAID-related GI complications assume great importance given the large number of patients taking these drugs over extended periods of time; it is estimated that there are 13 million NSAID users in the USA, including 8 million with OA, and patients with chronic arthritis often take these medications for >30 yr [5]. An NSAID-attributable risk of ~1.3% per yr for occurrence of a GI episode requiring hospitalization in RA patients would equate to an ~1 in 3 chance of such an event occurring over the entire course of the disease [6]. In the USA, it has been conservatively estimated that there are potentially 107 000 annual hospitalizations for NSAID-related GI complications and 16 500 annual NSAID-related deaths among patients.
with definite or probable RA or OA, a figure almost as high as the combined number of deaths due to asthma, cervical cancer and malignant melanoma [14]. It has been calculated that if NSAID-related mortality were tabulated separately in US National Vital Statistics reports, it would be the fifteenth most common cause of death in the country [5]. In the UK, it has been estimated that 12,000 ulcer complications and 1200 deaths per yr may be attributable to the use of NSAIDs, with significant financial as well as medical costs [1].

Strategies to minimize the GI toxicity associated with conventional NSAIDs

There are two potential strategies to minimize GI toxicity in patients requiring long-term anti-inflammatory therapy. The first is to co-administer conventional NSAIDs with gastroprotective agents, including proton pump inhibitors or prostaglandin analogues, in order to treat or prevent the emergence of NSAID-associated GI toxicity. The second is to prescribe potentially safer anti-inflammatory compounds which act via selective inhibition of cyclooxygenase-2 (COX-2), e.g. rofecoxib (VIOXX, Merck & Co., Inc.) or celecoxib (Celebrex, Pharmacia).

* Coadministration of gastroprotective compounds with NSAIDs

Proton pump inhibitors and prostaglandins are effective in the prevention and treatment of NSAID-induced GI toxicity [4, 8, 15–19]. Proton pump inhibitors such as omeprazole protect the gastroduodenal mucosa by suppressing acid secretion, while prostaglandins such as misoprostol act by replacing cytoprotective mucosal prostaglandins depleted by NSAIDs [19]. Although such compounds are effective, it is also apparent that some patients are not fully protected and a number of initial responders with healed ulcers subsequently relapse. A large trial in 8843 older RA patients demonstrated that misoprostol reduced serious NSAID-induced upper GI complaints by 40% compared with placebo and the number of symptomatic ulcers was reduced by 57% [8]. A study comparing the efficacy of omeprazole and misoprostol in 935 NSAID users with pre-existing ulceration demonstrated healing efficacy rates of 76 and 71%, respectively, but gastric ulcers recurred in 13 and 10% of cases after 6 months of maintenance therapy [19]. In addition, prostaglandin analogues may themselves be poorly tolerated and have been associated with adverse effects including diarrhoea and abdominal pain [4, 8, 19]. Also, a recent study demonstrated that patients given proton pump inhibitors in combination with metabolically competing drugs, including diclofenac, ibuprofen, warfarin and phenyoit, were overall nine times more likely to experience adverse events compared with those given competing drugs alone [20].

The cost of prescribing gastroprotective drugs is significant. Data from Spain demonstrate that the cost to the Spanish National Health Service arising from NSAID-induced gastroenteropathy in the year 2000 approached €600 million; importantly, most of this was spent in the prevention of side effects (€451 million), with only a relatively small proportion spent on actual treatment of complications (€60 million) (results using updated data from [21]). It is now estimated that 50% of individuals are receiving cytoprotective prophylaxis, greatly increasing the cost and burden of NSAIDs. In 1998, it was estimated that the national health system in Spain spent close to €20 000 to prevent a single bleeding episode, compared with €1868 to treat an individual bleeding episode [21].

**Rationale for the use of selective COX-2 inhibitors**

Cyclooxygenase-1 (COX-1) is primarily an enzyme constitutively expressed in many tissues where it has important roles in the production of prostaglandins essential for normal homeostatic processes, including GI mucosal protection, whereas COX-2 is an inducible enzyme found at low concentrations in healthy tissues, but which is up-regulated in response to tissue damage during inflammation [22, 23]. Conventional NSAIDs, such as naproxen, ibuprofen and diclofenac, inhibit both COX-1 and COX-2, and therefore produce anti-inflammatory effects at the expense of toxicity in areas where COX-1 is normally expressed [24, 25]. Compounds such as rofecoxib and celecoxib are selective COX-2 inhibitors which are expected to have similar anti-inflammatory properties to non-selective NSAIDs (by virtue of their COX-2 inhibitory properties), but a reduced propensity to induce GI toxicity (by virtue of their COX-1 sparing properties). This hypothesis has been examined in a number of clinical studies and the findings are considered below.

**Clinical efficacy of selective COX-2 inhibitors compared with conventional non-selective NSAIDs**

Table 1 summarizes the clinical efficacy of COX-2 inhibitors compared with non-selective NSAIDs in randomized, double-blind trials on patients with RA or OA. Available studies consistently demonstrate that rofecoxib and celecoxib are very effective in the treatment of these conditions, with efficacy superior to placebo and comparable to currently prescribed non-selective NSAIDs such as ibuprofen, diclofenac, nabumetone and naproxen. In a typical study on 809 OA patients reporting pain experienced while walking on a flat surface [26], rofecoxib 12.5 or 25 mg once daily for 6 weeks provided analgesia comparable to ibuprofen 800 mg tid (a dose twice the daily average used in the UK and over three times the daily average used in France). Rofecoxib also showed efficacy comparable to a high dose of diclofenac in a longer-term study on OA patients treated continuously for 1 yr [27]. In a placebo-controlled study on 272 elderly OA patients (age ≥ 80 yr), rofecoxib 12.5 and 25 mg once daily was as effective as a high dose of nabumetone (500 mg tid) in terms of global assessment of disease status over a 6-week treatment period (data on file, Merck & Co., Inc.); the dose of nabumetone used in
this study exceeded the average daily dose used in most European countries. Rofecoxib was actually significantly more effective than nabumetone given at 1000 mg/day in a large study on 1042 OA patients; 55% of patients given rofecoxib 12.5 mg/day showed good or excellent responses after 6 weeks, compared with 47.9% with nabumetone and 26.8% with placebo [28]. A trial on celecoxib also suggested improved activity relative to the comparator NSAID in RA patients; both celecoxib and naproxen significantly improved signs and symptoms of the disease, but only the COX-2 inhibitor significantly improved patient and physician global assessments [29].

**Gastric tolerability of selective COX-2 inhibitors compared with non-selective NSAIDs**

Table 2 summarizes the findings of randomized, double-blind trials investigating the GI toxicity of selective COX-2 inhibitors. Rofecoxib and celecoxib are significantly and consistently less toxic to the GI tract when compared with conventional non-selective NSAIDs such as ibuprofen, naproxen and diclofenac. One of the first studies carried out using rofecoxib 250 mg/day (at least 10 times the dose regularly used in OA patients) demonstrated that the incidence of erosions or ulcers after 7 days of treatment was not significantly different from placebo (mucosal scores ≥ 2 in 8.0 and 12.2% of subjects taking placebo and rofecoxib, respectively), whereas 70.6% of subjects taking ibuprofen and 94.1% taking aspirin had erosions or ulcers [36]. In the same study, the incidence of gastric ulcers was 0% with placebo and rofecoxib, 9.8% with ibuprofen and 17.6% with aspirin. Similar findings were evident in a pair of trials in OA patients, where the incidence of GI ulceration was low in patients taking placebo or rofecoxib at 2–4 times the therapeutically effective dose, but significantly elevated in patients taking ibuprofen [37, 38]. Combined data from these trials showed that for placebo, rofecoxib 25 mg/day, rofecoxib 50 mg/day and ibuprofen 2.4 g/day the cumulative incidences of gastric or duodenal ulcers (≥3 mm) were, respectively, 7.34, 4.69, 8.07 and 28.47% after 3 months (intention-to-treat life-table analysis), rising to 46.36% with ibuprofen and 9.74% with the lower dose of rofecoxib after 6 months [37, 39]. The 25 mg/day dose of rofecoxib corresponded to the highest dose recommended for OA patients, but was indistinguishable from placebo in terms of ulceration rates [37]. Calculations based on endoscopically observed ulcer incidences for rofecoxib 25 mg/day and ibuprofen 800 mg tid at 6 months indicated that only 2.8 patients would need to be treated

<table>
<thead>
<tr>
<th>No. of patients enrolled</th>
<th>Disease treated</th>
<th>Therapy duration</th>
<th>COX-2 inhibitor</th>
<th>Control NSAID</th>
<th>Main efficacy findings</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>809 OA</td>
<td>6 weeks</td>
<td>ROF 12.5 or 25 mg/day</td>
<td>Ibuprofen 800 mg tid</td>
<td>Both doses of ROF comparable to ibuprofen; significant improvements in measures of pain on walking, disease status and self-assessment of response compared with placebo</td>
<td>[26]</td>
<td></td>
</tr>
<tr>
<td>784 OA</td>
<td>1 yr</td>
<td>ROF 12.5 or 25 mg/day</td>
<td>Diclofenac 50 mg tid</td>
<td>Both doses of ROF comparable to diclofenac for measures of pain on walking, disease status and self-assessment of response compared with placebo</td>
<td>[27]</td>
<td></td>
</tr>
<tr>
<td>736 OA</td>
<td>6 weeks</td>
<td>ROF 12.5 or 25 mg/day</td>
<td>Ibuprofen 800 mg tid</td>
<td>Comparable significant efficacy for both doses of ROF and ibuprofen for measures of pain on walking, disease status and self-assessment of response compared with placebo</td>
<td>[30]</td>
<td></td>
</tr>
<tr>
<td>1042 OA</td>
<td>6 weeks</td>
<td>ROF 12.5 mg/day</td>
<td>Nabumetone 1000 mg/day</td>
<td>ROF and nabumetone superior to placebo in terms of patients showing good or excellent responses. ROF significantly superior to nabumetone</td>
<td>[28]</td>
<td></td>
</tr>
<tr>
<td>5556 OA</td>
<td>12 weeks</td>
<td>ROF 25 mg/day</td>
<td>Naproxen 500 mg bid</td>
<td>No significant differences between drugs for patient global assessment of disease status, AUSCAN OA indices or discontinuation for lack of efficacy</td>
<td>[31]</td>
<td></td>
</tr>
<tr>
<td>8076 RA</td>
<td>1 yr</td>
<td>ROF 50 mg/day</td>
<td>Naproxen 500 mg bid</td>
<td>Both drugs similarly efficacious. Low discontinuation rates for lack of efficacy for both drugs</td>
<td>[32]</td>
<td></td>
</tr>
<tr>
<td>13 194 OA</td>
<td>12 weeks</td>
<td>CEL 200 or 400 mg/day</td>
<td>Diclofenac 100 mg/day</td>
<td>No significant differences between either dose of CEL or diclofenac measured by arthritis pain and night pain</td>
<td>[33]</td>
<td></td>
</tr>
<tr>
<td>1003 OA</td>
<td>12 weeks</td>
<td>CEL 50, 100 or 200 mg bid</td>
<td>Naproxen 500 mg bid</td>
<td>CEL 100 and 200 mg bid comparable to naproxen, with significant improvements in signs and symptoms of OA. CEL 50 mg bid less active than higher doses, but significantly more effective than placebo</td>
<td>[34]</td>
<td></td>
</tr>
<tr>
<td>1149 RA</td>
<td>12 weeks</td>
<td>CEL 100, 200 or 400 mg bid</td>
<td>Naproxen 500 mg bid</td>
<td>All doses of CEL and naproxen significantly improved signs and symptoms of RA. CEL, but not naproxen, significantly improved patient and physician global assessments</td>
<td>[29]</td>
<td></td>
</tr>
<tr>
<td>655 RA</td>
<td>24 weeks</td>
<td>CEL 200 mg bid</td>
<td>Diclofenac SR 75 mg bid</td>
<td>Both drugs similarly efficacious in the management of pain and inflammation</td>
<td>[35]</td>
<td></td>
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</table>
with this dose of rofecoxib rather than ibuprofen in order to avert the development of such an endoscopic ulcer in one patient [38].

Studies on celecoxib reinforce these findings, with a similar low incidence of gastroduodenal ulcers associated with placebo (4%) and celecoxib 400 mg bid (6%) in contrast to the higher levels seen with naproxen (26%) [29]. An earlier study demonstrated that healthy subjects given up to 200 mg celecoxib bid for 1 week experienced no gastric ulcers, whereas 19% given naproxen had at least one gastric ulcer [40]; in the same study, gastric erosions and/or ulcers were present in 9–13% of subjects given celecoxib or placebo, in contrast to 72% in naproxen-treated subjects.

The recently completed VIGOR study (VIOXX GI Outcomes Research) provided rigorous testing of the GI safety of rofecoxib [32]. Eight thousand and seventy-six patients with RA were randomized to receive a standard dose of naproxen or a relatively high dose of rofecoxib (50 mg/day; twice the maximum dose recommended for chronic use). During a median follow-up period of 9 months, the confirmed incidence of upper GI toxicity was significantly lower with rofecoxib than with naproxen (2.1 and 4.5 per 100 patient-yr, respectively; relative risk 0.5, 95% CI 0.3–0.6). When focusing on complicated events including perforation, obstruction and major upper GI bleeding, the incidence rates were 0.6 and 1.4 per 100 patient-yr for rofecoxib and naproxen, respectively (relative risk 0.4, 95% CI 0.2–0.8). This means that only 41 patients would need to be treated with rofecoxib rather than naproxen in order to avert one clinical upper GI event in a 1-yr period. Importantly, there was an 88% reduced risk of developing clinical upper GI events with rofecoxib compared with naproxen in a sub-group of very low risk patients (age <65 yr, no steroid use, no prior upper GI events and no Helicobacter pylori infection) [41]. The findings from the VIGOR trial translate into clear benefits for health resources in terms of less hospitalization for upper GI events, decreases in the use of GI co-therapy and fewer endoscopic procedures. In this trial, the rate of cardiovascular adverse events was similar for both compounds except in the case of myocardial infarction. The rate of myocardial infarction was significantly lower in the naproxen group.

### Table 2. Gastrointestinal toxicity of rofecoxib (ROF) and celecoxib (CEL) compared with non-selective NSAIDs in randomized, double-blind trials

<table>
<thead>
<tr>
<th>No. of subjects enrolled</th>
<th>Treatment duration</th>
<th>COX-2 inhibitor</th>
<th>Control NSAID</th>
<th>Main findings</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>170 healthy subjects</td>
<td>1 week</td>
<td>ROF 250 mg/day</td>
<td>Ibuprofen 800 mg tid or aspirin 650 mg qds</td>
<td>Significantly less gastrointestinal mucosal damage with ROF than with ibuprofen or aspirin. Effects of ROF on gastric mucosa not significantly different to placebo.</td>
<td>[36]</td>
</tr>
<tr>
<td>775 OA patients</td>
<td>24 weeks</td>
<td>ROF 25 or 50 mg/day</td>
<td>Ibuprofen 800 mg tid</td>
<td>Ulcers and erosions significantly less common with ROF than with ibuprofen. ROF caused significantly less gastroduodenal ulceration than ibuprofen. Uter rates with ROF comparable to placebo.</td>
<td>[37]</td>
</tr>
<tr>
<td>742 OA patients</td>
<td>24 weeks</td>
<td>ROF 25 or 50 mg/day</td>
<td>Ibuprofen 800 mg tid</td>
<td>Fecal blood loss similar for placebo and both doses of ROF, but higher with ibuprofen.</td>
<td>[38]</td>
</tr>
<tr>
<td>67 healthy subjects</td>
<td>28 days</td>
<td>ROF 25 or 50 mg/day</td>
<td>Ibuprofen 800 mg tid</td>
<td>Significantly fewer clinically important upper GI events with ROF compared with naproxen.</td>
<td>[39]</td>
</tr>
<tr>
<td>8076 RA patients</td>
<td>1 yr</td>
<td>ROF 50 mg/day</td>
<td>Naproxen 500 mg bid</td>
<td>Incidence of gastroduodenal ulcers not significantly different between placebo and any dose of CEL; incidence with naproxen significantly higher compared with placebo or CEL.</td>
<td>[32, 41]</td>
</tr>
<tr>
<td>5556 OA patients</td>
<td>12 weeks</td>
<td>ROF 25 mg/day</td>
<td>Naproxen 500 mg bid</td>
<td>Incidence of symptomatic ulcers + ulcer complications with ROF compared with placebo.</td>
<td>[31]</td>
</tr>
<tr>
<td>1149 RA patients</td>
<td>12 weeks</td>
<td>CEL 100, 200 or 400 mg bid</td>
<td>Naproxen 500 mg bid</td>
<td>Incidence of symptomatic gastroduodenal ulcer complications generally comparable for CEL, naproxen and placebo.</td>
<td>[30]</td>
</tr>
<tr>
<td>8059 OA or RA patients</td>
<td>6 months</td>
<td>CEL 400 mg bid</td>
<td>Ibuprofen 800 mg tid or diclofenec 75 mg bid</td>
<td>Incidence of symptomatic gastrointestinal tract complaints generally comparable for CEL, naproxen and placebo.</td>
<td>[35]</td>
</tr>
<tr>
<td>13 274 OA patients</td>
<td>12 weeks</td>
<td>CEL 200 or 400 mg/day</td>
<td>Naproxen 1000 mg/day or diclofenec 100 mg/day</td>
<td>Significantly fewer ulcer complications and symptomatic upper GI ulcerations with CEL compared with conventional NSAIDs.</td>
<td>[47–49]</td>
</tr>
<tr>
<td>128 healthy subjects</td>
<td>1 week</td>
<td>CEL 100 or 200 mg bid</td>
<td>Naproxen 500 mg bid</td>
<td>Incidence of symptomatic gastroduodenal ulcer complications generally comparable for CEL, naproxen and placebo.</td>
<td>[40]</td>
</tr>
<tr>
<td>1003 OA patients</td>
<td>12 weeks</td>
<td>CEL 50, 100 or 200 mg bid</td>
<td>Naproxen 500 mg bid</td>
<td>No gastric ulcers with placebo or CEL, but significant ulceration with naproxen.</td>
<td>[34]</td>
</tr>
<tr>
<td>655 RA patients</td>
<td>24 weeks</td>
<td>CEL 200 mg bid</td>
<td>Diclofenac SR 75 mg bid</td>
<td>Incidence of gastroduodenal ulcers and withdrawal rates due to gastrointestinal toxicity significantly higher with diclofenac compared with CEL.</td>
<td>[42]</td>
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</table>
but only in those patients who were found to meet the criteria for low-dose aspirin prophylaxis but were not using this treatment. Hence, it has been postulated that naproxen has a coronary protective effect because of its thromboxane and platelet aggregation inhibitory properties, while rofecoxib does not provide this protection [32]. However, further research is needed to clarify this.

The findings of the recent ‘Advantage’ trial are noteworthy as the 5556 OA patients enrolled were permitted to take low-dose aspirin in addition to rofecoxib or naproxen for 3 months [31]. Rofecoxib again showed significantly superior GI tolerability and was associated with a significantly lower requirement for concomitant GI medication compared with the conventional NSAID. The cumulative incidence of discontinuations due to GI toxicity was 8.1% with naproxen and 5.9% with rofecoxib. The CLASS study (Celecoxib Long-term Arthritis Safety Study) also demonstrated a lower incidence of GI toxicity with a selective COX-2 inhibitor compared with conventional NSAIDs in a patient population permitted to take concomitant aspirin [42]. The annualized incidence of upper GI ulcer complications and symptomatic ulcers for the entire study population was 2.08% with celecoxib (given at doses greater than those indicated clinically) and 3.54% with standard doses of NSAIDs (relative risk 0.59, 95% CI 0.38–0.94). The decrease in upper GI toxicity with celecoxib was observed in patients not taking concomitant aspirin; the annualized incidence of upper GI ulcer complications plus symptomatic ulcers in this sub-group was 1.40% with celecoxib and 2.91% with NSAIDs (relative risk 0.48, 95% CI 0.28–0.89).

Superior GI tolerance of COX-2 inhibitors has further been demonstrated in studies using pooled data from clinical trials. Pooled analysis of eight phase 2b/3 rofecoxib OA trials demonstrated that the incidence of PUBs (upper GI perforations, symptomatic gastroduodenal ulcers and upper GI tract bleeding) over 12 months was significantly lower for rofecoxib compared with NSAIDs, with a cumulative risk over this period of 1.3 vs 1.8%, respectively [7]. Pooled analysis of multicentre clinical trials involving a total of 11 008 patients with OA or RA demonstrated an 8-fold lower incidence of upper GI ulcer complications with celecoxib compared with non-selective NSAIDs; the incidence of ulcer complications was similar in patients given placebo or celecoxib (>85% of whom were receiving maximally therapeutic or supratherapeutic doses, i.e. 100 mg bid or higher) [9]. Data based on MedWatch reports to the FDA comprising >340 000 patient-years’ experience with celecoxib in the actual population suggested a remarkably safe GI toxicity profile, with an incidence of serious GI bleeding of 0.0015 per 100 patient-yr; for allowing for likely underreporting, it was estimated that even if only 1% of serious bleeds were reported, the incidence was no different from the background rate of serious bleeds in the general population (0.19 per 100 patient-yr) [43].

It is important that any long-term therapeutic strategy for pain relief in patients with a previous history of ulcer complications should have a low risk of causing recurrence. Current data indicate that, in this respect, monotherapy with a selective COX-2 inhibitor is a safe and effective alternative to combined therapy with conventional NSAIDs and a proton pump inhibitor. A recent randomized placebo-controlled trial on 130 chronic NSAID users with healed H. pylori negative ulcers showed recurrent bleeding within 6 months in 5.6% of patients receiving celecoxib 200 mg bid and in 12.9% of patients receiving diclofenac + omeprazole (P = n.s.) [44]. A further randomized study on 115 high-risk patients with healed H. pylori negative NSAID-induced peptic ulcer bleeding also demonstrated that celecoxib monotherapy and the combination of naproxen plus lansoprazole had similar high efficacies in reducing the risk of recurrent ulcer complications; in an intention-to-treat analysis, 2/57 patients taking combination treatment and 2/58 given the COX-2 inhibitor experienced ulcer complications [45]. These findings are important as they demonstrate that even in high-risk patients requiring long-term anti-inflammatory therapy, treatment with a single drug is as effective as the combination of a more toxic compound given with a gastroprotective agent.

Conclusions

Results from a variety of clinical studies utilizing experimental and real-life paradigms consistently demonstrate a significantly improved GI safety profile for selective COX-2 inhibitors compared with commonly prescribed non-selective NSAIDs. The findings are particularly convincing as these safety benefits are maintained when using doses of COX-2 inhibitors higher than those clinically recommended. Furthermore, recent data suggest that COX-2 inhibitors have GI safety profiles similar to those of conventional NSAIDs combined with cytoprotective compounds, with the convenience of requiring only a single tablet. The drugs are effective for the treatment of patients with RA or OA and efficacy is comparable to high doses of non-selective NSAIDs. Available data strongly suggest that selective COX-2 inhibitors are strong candidates for the first-line treatment of patients requiring long-term pain relief.

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Clinical experience with cyclooxygenase-2 inhibitors

21

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