Research Review

PRODUCT REVIEW

Celebrex™ (celecoxib)

In this review:

About the Reviewers

Dr John Wyeth

MBChB, MD, FRACP, FRCP (London)

Gastroenterologist and Clinical Leader, Capital & Coast DHB, Clinical Senior Lecturer at Wellington Medical School where his interests include nutrition, irritable bowel syndrome, IBD and gut motility conditions.

Dr Peter Jones

B Med Sci, PhD, MB ChB, FRACP

Consultant Rheumatologist, Waikato DHB, Associate Professor, Faculty of Medical and Health Sciences, Auckland University. His interests are in pain management, new drugs for rheumatic disease, osteoporosis and genetics of gout.

About Research Review

Research Review is an independent medical publishing organisation producing electronic publications in a wide variety of specialist areas.

Product Reviews feature independent short summaries of major research affecting an individual medicine or technique. They include a background to the particular condition, a summary of the medicine and selected studies by a key NZ specialist with a comment on the relevance to NZ practice.

Research Review publications are intended for New Zealand medical professionals.

Rheumatoid arthritis and osteoarthritis

Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory, autoimmune disease that is thought to result from abnormal B-cell–T-cell interactions. A variety of factors, including genetic and environmental, have been linked to its development, progression and persistence. Its prevalence in Australasia is 2000 per 100,000, which is considerably higher than the relatively uniform prevalence seen in most countries.[1] It is more common in women than men, with the NZ 2006/07 NZ Health Survey reporting prevalences of 3.7% and 2.3% for women and men, respectively.[2] It typically emerges between the ages of 25 and 50 years, and is more likely to occur in smokers than nonsmokers. In addition to severe pain, swelling and stiffness in the joints that can impair everyday activities, RA can also result in tiredness, lack of energy, reduced appetite, interference with sleep and weight loss. Patients with RA also have an increased risk of heart disease.

Osteoarthritis (OA) can be primary or secondary to causes such as injury, inflammatory arthritis or crystal deposition. Several genetic polymorphisms have been associated with the disease itself and its outcomes, and risk factors include advancing age, obesity and trauma.[3,4] It is the most common form of arthritis in the elderly population, and there was a greater prevalence in NZ women than men in the NZ 2006/07 Health Survey (7.8% vs. 5.3%).[2] This survey also reported that >50% of NZ women aged ≥75 years had a diagnosis of arthritis, and arthritis has the highest prevalence in Europeans. Like patients with RA, those with OA experience significant impairment performing everyday tasks, particularly in those with OA affecting their hands.[5] Much of this impairment is attributable to both pain level and fear of (re)injury.

Current Treatment Approaches

As there are currently no curative therapies for RA and OA, treatment focuses on providing symptomatic relief, to enable as close to normal life as possible, and slowing disease progression.

Most current RA guidelines focus on pharmacological treatments that halt or slow disease progression, with DMARDs (particularly methotrexate) being first-line, and biologicals added after several months if response is inadequate.[6-10] The optional addition of short-term corticosteroids for symptoms is often recommended, due to their anti-inflammatory actions. OA guidelines typically include NSAIDs and cyclo-oxygenase-2 (COX-2) inhibitors for pain relief, along with other oral analgesics, intra-articular injections of corticosteroids or hyaluronans, and various topical agents.

Major guidelines include the 'standard' NSAID or COX-2 inhibitor at the lowest effective dose and the shortest duration possible for symptom control in both OA and RA, taking into account the patient's risk factors for associated adverse effects, and with the caveat of offering other analgesics (e.g. paracetamol [acetaminophen], codeine) to reduce the need for long-term treatment with NSAIDs/COX-2 inhibitors.[6,10] If NSAIDs/COX-2 inhibitors do not elicit a satisfactory response, then revision of disease control therapy (DMARDs/biologicals) is indicated. The guidelines also indicate that a concomitant proton-pump inhibitor (PPI) should be prescribed with an NSAID or COX-2 inhibitor. Special consideration also needs to be made for patients who require low-dose aspirin therapy.

About celecoxib

In NZ, celecoxib is currently approved by Medsafe for the management of pain and inflammation associated with OA, RA and ankylosing spondylitis, and also for acute pain and treatment in adults with primary dysmenorrhoea.[11] Additional indications approved in other countries include (general) acute pain, juvenile RA for patients aged ≥2 years and as an adjunct to usual care to reduce the number of polyps in familial adenomatous polyposis.[12] It is contraindicated in patients who have had a hypersensitivity or allergic-type reaction to the agent, other NSAIDs or sulphonamides, for perioperative pain associated with coronary artery bypass graft (CABG) surgery, unstable or significant established ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease, active peptic ulceration or gastrointestinal (GI) bleeding, severe renal impairment, severe hepatic impairment and congestive heart failure.

Celecoxib undergoes moderate absorption following oral administration, with a T_{max} of 2–3 hours; this is delayed by 1–2 hours following a high-fat meal, which also increases total absorption by 10–20%.[12,13] It is extensively protein bound, and has an apparent V_D of around 400L. It is primarily metabolised by CYP2C9, with a $T_{½}$ of 4–15 hours. It undergoes almost complete biotransformation prior to excretion in urine and faeces. Differences in drug disposition have been seen between races, and pharmacokinetic changes may be present in the elderly. Celecoxib steady-state AUC is increased by ~40% and 180% in patients with mild and moderate hepatic impairment, respectively. Celecoxib is known to interact with several drugs (warfarin, lithium, ACE inhibitors, ARBs, fluconazole, furosemide), but should be used with caution with any concomitant CYP2C9 inhibitor. Besides low-dose aspirin, it should not be administered with other NSAIDs, due to an increased risk of adverse reactions. Celecoxib also inhibits CYP2D6 *in vitro*, so the potential for *in vivo* interactions with drugs metabolised by this isoenzyme should be considered.

Celecoxib is available in NZ as 100mg and 200mg capsules only, marketed exclusively as Celebrex®, but it is also manufactured in 50mg and 400mg forms in other countries.[11,12]

Major GI and CV safety trials of celecoxib

Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study[14]

Authors: Silverstein FE et al

Summary: The Celecoxib Long-Term Arthritis Safety Study (CLASS) found that celecoxib administered at dosages greater than those clinically indicated resulted in lower incidences of symptomatic ulcers and ulcer complications than NSAIDs at standard dosages, with the greatest decrease in upper GI toxicity seen when aspirin was not being taken concomitantly.

Methods: Patients aged ≥18 years with OA or RA were randomised to receive celecoxib 400mg twice daily (n=3987), ibuprofen 800mg three times daily (n=1985) or diclofenac 75mg twice daily (n=1996) for 6 months; concomitant aspirin use for CV disease prophylaxis was allowed.

Results: Compared with NSAIDs, celecoxib was associated with a significantly lower annualised incidence of upper GI ulcer complications plus symptomatic ulcers (2.08% vs. 3.54%; relative risk 0.59 [95% CI 0.38, 0.94]); the annualised incidence of upper GI ulcer complications alone was nonsignificantly lower with celecoxib (0.76% vs. 1.45%; 0.53 [0.26, 1.11]). Among concomitant aspirin recipients, those assigned to celecoxib had similar annualised incidence rates to NSAID recipients for upper GI ulcer complications alone and combined with symptomatic ulcers. There were also fewer chronic GI blood loss, GI intolerance, hepatotoxic and renotoxic events among celecoxib recipients than NSAID recipients. The incidences of CV events did not differ between the two groups, irrespective of concomitant aspirin use.

Comment (PJ): The reporting of 6-month data as an annualised incidence has been heavily criticised, especially as the 12-month data did not show significant differences between the active comparator drugs. The study did not meet its primary endpoint, which was to show a lower rate of upper GI ulcer complications with celecoxib compared with other NSAIDs, but achieved significance for the composite endpoint including symptomatic ulcer. The study was not designed to show a difference in the subgroup analysis of aspirin users, and this result could be affected by bias. Despite these concerns, this paper is widely thought to establish a superior GI safety profile of celecoxib compared with NSAIDs.

Comment (JW): To paraphrase the authors, there was a higher than expected ulcer complication rate in the celecoxib group than predicted. This may reflect the high rates of *Helicobacter pylori* infection (38%) in the two study cohorts, whilst NZ rates are usually <30% in an adult population. The inclusion of aspirin users also had an effect on ulcer complications, with both treatment groups having similar complication rates if taking aspirin.

Celecoxib versus omeprazole and diclofenac in patients with osteoarthritis and rheumatoid arthritis (CONDOR)[15]

Authors: Chan FKL et al

Summary: The risk of entire GI tract clinical outcomes was found to be lower among patients with OA or RA who received a COX-2 selective NSAID than it was among patients who received a nonselective NSAID plus PPI in this RCT.

Methods: Study participants were: i) diagnosed with OA or RA; ii) *H. pylori* negative; iii) at increased GI risk; iv) aged ≥18 years with a history of duodenal ulceration or ≥60 years; and v) enrolled from 196 centres across 32 countries/territories. They were randomised to receive celecoxib 200mg twice daily (n=2238) or slow-release diclofenac 75mg twice daily plus omeprazole 20mg once daily (n=2246) for 6 months.

Results: In an intention-to-treat analysis, criteria for the primary endpoint (composite of clinically significant upper and lower GI events) were met by significantly fewer celecoxib recipients than diclofenac plus omeprazole recipients (0.9% vs. 3.8%; hazard ratio 4.3 [95% CI 2.6, 7.0; p<0.0001]). There was also a significantly lower withdrawal rate due to GI adverse events among celecoxib recipients compared with diclofenac plus omeprazole recipients (6% vs. 8%; p=0.0006).

Comment (PJ): This study did not show a difference between celecoxib and diclofenac for upper GI events, confirming the results of the CLASS study. Upper and lower GI events were inferred from falls in haemoglobin levels and subsequent workup and adjudication by a review committee. The site of bleeding could not be established in the majority of cases, so it is not known whether the bleeding was from the small or large bowel. It is therefore possible that the lower rate of presumed bleeding events with celecoxib is due to a lack of antiplatelet effect rather than a lack of mucosal injury.

Comment (JW): NSAID complications are not limited to the stomach, and injury can occur in the small and large intestines. The primary endpoints for this study attempted to assess this by using other markers of injury, e.g. drop in haemoglobin level. Ulcer complications were reduced in the celecoxib group compared with diclofenac and omeprazole. Full investigation of unexplained drops in haemoglobin did not occur in all subjects, so conclusions around this group are unclear.

Video capsule endoscopy to prospectively assess small bowel injury with celecoxib, naproxen plus omeprazole, and placebo[16]

Authors: Goldstein JL et al, on behalf of the investigators

Summary: Video capsule endoscopy (VCE) showed fewer small bowel mucosal breaks associated with celecoxib than with naproxen plus omeprazole.

Methods: Healthy subjects with normal VCE findings at baseline were randomised to receive celecoxib 200mg twice daily (n=120), naproxen 500mg twice daily plus omeprazole 20mg once daily (n=118) or placebo (n=118) for 2 weeks.

Results: The number of small bowel mucosal breaks per participant (primary endpoint) was significantly greater in naproxen plus omeprazole recipients compared with celecoxib and placebo recipients (2.99 vs. 0.32 and 0.11, respectively [p<0.001]), as was the proportion of participants with mucosal breaks (55% vs. 16% and 7%, respectively). While the magnitude of the difference between celecoxib and placebo was small, it was statistically significant (p=0.04). An incidental finding of the study was that a not insignificant proportion (13.8%) of screened subjects were ineligible due to small bowel lesions on baseline VCE.

Comment (PJ): This study appears to confirm clinical impressions that naproxen causes more problems with small bowel and lower GI bleeding than other NSAIDs. COX-2 selective inhibitors are thought to cause fewer problems with erosion and ulceration in the stomach than unselective inhibitors, in part because they do not affect the bicarbonate pump, a COX-1 dependent process that maintains the pH gradient across the stomach wall and protects the mucosa against attack by stomach acid. The mechanism by which COX-2 inhibitors would cause less small bowel erosion or ulceration than unselective NSAIDs is not known.

Comment (JW): Two important points are highlighted by this paper. Firstly, as we are better able to investigate the small intestine, we are finding more potentially pathogenic changes, raising the question of clinical significance of these lesions. More importantly, subjects taking celecoxib had significantly fewer prospectively identified lesions than the other active treatment group, with about a 4-fold difference in absolute numbers of patients with mucosal lesions between the two treatment groups. Another important point to remember is that celecoxib patients still had more mucosal lesions than the placebo group. Celecoxib reduces risk of mucosal lesions, but doesn't abolish the risk.

Major GI and CV safety systematic reviews and meta-analyses of celecoxib

Risk of cardiovascular events in patients receiving celecoxib: a meta-analysis of randomized clinical trials[17]

Authors: White WB et al

Summary: This meta-analysis showed that CV events were no more common with celecoxib than with nonselective NSAIDs or placebo.

Trial characteristics: There were 39 trials included in this meta-analysis, involving: i) 7462 patients who had received celecoxib 200–800 mg/day (1268 patient-years) versus 4057 placebo recipients (585 patient-years); and ii) 19,773 patients who had received celecoxib 200–800 mg/day (5651 patient-years) versus 13,990 nonselective NSAID recipients (diclofenac, ibuprofen, ketoprofen, loxoprofen and naproxen; 4386 patient-years).

Findings: The overall incidence rates for CV events were low, and did not differ significantly between celecoxib and placebo recipients or between celecoxib and nonselective NSAID recipients, irrespective of celecoxib dose, use of concomitant aspirin or the presence of CV risk factors.

Comment (PJ): Meta-analyses are used to glean information not forthcoming from smaller studies. While it is reassuring that CV event rates were similar between celecoxib and nonselective NSAIDs, none of the included trials were powered for CV endpoints, and none of the trials stratified patients according to baseline CV risk. Of more concern, the meta-analysis did not include data from the APC or PreSAP polyposis prevention studies, because these trials were blinded at the time of publication. Those studies showed a dose-related increase in thrombotic CV events with celecoxib compared with placebo, although the absolute rate of events was low and similar to those observed in the rofecoxib polyposis study. For similar reasons, data from ADAPT study in Alzheimer's disease were not included. The results of the prospectively randomised PRECISION study, which looked at CV outcomes, are awaited with interest.

Comment (JW): It is known that NSAID use is associated with an increased CV risk. Whether the risk is the same or different with use of COX-2 inhibitors is still unclear.

Tolerability and adverse events in clinical trials of celecoxib in osteoarthritis and rheumatoid arthritis: systematic review and meta-analysis of information from company clinical trial reports[18]

Authors: Moore RA et al

Summary: Celecoxib was found to be associated with less GI events than other NSAIDs in this systematic review and meta-analysis.

Trial characteristics: Company clinical trial reports of 31 RCTs investigating celecoxib 50–800 mg/day for ≥2 weeks in patients with OA or RA (n=39,605) were included.

Findings: Compared with placebo, celecoxib was associated with fewer discontinuations (any cause or lack of efficacy), fewer serious adverse events and less nausea, but more dyspepsia, diarrhoea, oedema, GI events and treatment-related events. Compared with other NSAIDs, celecoxib was associated with fewer symptomatic ulcers and bleeds, endoscopically detected ulcers and treatment-related or GI events (and discontinuations due to such events), as well as less vomiting, abdominal pain, dyspepsia and reduced haemoglobin/haematocrit. Compared with paracetamol, celecoxib was associated with fewer discontinuations (any cause, lack of efficacy or diarrhoea). Compared with rofecoxib, celecoxib was associated with less abdominal pain and oedema.

Comment (PJ): Company clinical trial reports contain more information than published papers, particularly regarding adverse events. Most of the trials reviewed lasted 12 weeks or more, and the main outcome was discontinuations (all cause, lack of efficacy, adverse events and GI adverse events). Celecoxib was clearly better tolerated than comparator NSAIDs (principally naproxen, diclofenac, ibuprofen), but discontinuations for lack of efficacy were higher despite the published reports showing equivalence of effect on pain outcomes. Celecoxib was also more likely to be continued than paracetamol 4000mg daily. These reports are reassuring regarding celecoxib being better tolerated than comparator NSAIDs.

Comment (JW): Patients will discontinue medication for many reasons, including adverse reactions. Not all adverse reactions are reported, so a surrogate marker for tolerability of a drug is discontinuation rates. This meta-analysis of company clinical trial reports supports celecoxib as being well tolerated with low discontinuation rates. Clinical practice outside of a clinical trial will differ, with different types of patients being treated or patients taking more concomitant medication, which may lead to other adverse events occurring.

The hepatic safety and tolerability of the cyclooxygenase-2 selective NSAID celecoxib: pooled analysis of 41 randomized controlled trials[19]

Authors: Soni P et al

Summary: The incidence of hepatic adverse events associated with the use of celecoxib was found to be similar to those associated with placebo, ibuprofen and naproxen, and lower than that associated with diclofenac, in this pooled analysis of 41 RCTs.

Trial characteristics: Trial inclusion criteria were: i) randomised, parallel-group design with a planned treatment duration of ≥2 weeks; ii) ≥1 placebo or NSAID comparator; iii) ≥1 arm of celecoxib ≥200 mg/day; and iv) data available as at October 31st 2004. Enrolled participants had OA, RA, ankylosing spondylitis, chronic low back pain or Alzheimer's disease.

Findings: The incidence of serious hepatic adverse events was 0.05% for celecoxib-treated patients (n=24,933), compared with 0.21% for diclofenac-treated patients (n=7639). Celecoxib at any dosage was associated with significantly fewer hepatobiliary adverse events than diclofenac (1.11% vs. 4.24% [p<0.0001]), while the incidence of such events with celecoxib was comparable with placebo and ibuprofen (0.89% [p=0.21] and 1.53% [p=0.06], respectively). No cases of liver failure, treatment-related liver transplant or treatment-related hepatobiliary death were reported.

Comment (PJ): Serious liver injury has been associated with almost all NSAIDs. The effect of diclofenac on liver aminotransferases is well known, and several NSAIDs and COX-2 inhibitors have been withdrawn due to hepatic toxicity concerns. This study used various definitions of serious hepatic injury, but the figures quoted in the abstract are an aggregated result. Overall, celecoxib was associated with a very low rate of hepatic events. The study was funded by Pfizer and the paper written by company employees.

Comment (JW): NSAID use is not uncommonly associated with reversible elevations in aminotransferases. This is confirmed in this paper, with similar findings observed in celecoxib use. Liver failure was not reported in this review, but if abnormal liver function tests are found in a patient on treatment, celecoxib should be withheld and monitoring of liver function continued until resolution occurs.

Summary of other evidence

A number of other studies support reduced GI toxicity with celecoxib.

- Two RCTs reported less GI toxicity with celecoxib 200 and 400 mg/daily for OA and ankylosing spondylitis than diclofenac and naproxen.[20,21]
- Superiority over diclofenac for upper GI events has also been reported with high-dose celecoxib (800 mg/day).[22]
- An analysis of UK prescription data has reported 23% and 44% relative reductions in symptomatic GI events and complicated upper GI conditions, respectively, compared with meloxicam.[23]

A 2008 systematic review found that, despite a great deal of variability in the data, COX-2 inhibitors were associated with superior GI tolerability overall, but as a class had a greater risk of MI than nonselective NSAIDs.[24] However, a review published in 2009 concluded that data available at that time on CV risk associated with celecoxib use were overall inconsistent, but did suggest a slightly increased risk (particularly at higher dosages) comparable with nonselective NSAIDs.[25] In addition, a more recently published, somewhat controversial network meta-analysis of 31 trials (n=116,429) also challenged the idea that CV risk is a class effect of COX-2 inhibitors, with celecoxib not significantly increasing the risk of any of the CV outcomes assessed or all-cause mortality.[26] Of note, this study received mainstream media attention in this country, and this, along with media coverage of other studies and market withdrawals, may result in some patients we see having concerns. Therefore, we need to be ready to present a balanced view of the risks and benefits associated with celecoxib use to our patients.

Conclusions

JW: From a gastroenterologist's viewpoint, NSAIDs are always viewed with caution because of their GI effects. There is good evidence that the risks of the most alarming GI complications, such as GI bleeding and ulceration, are reduced with use of COX-2-selective drugs compared with nonspecific NSAIDs. This reduced GI-risk profile is not at the expense of efficacy in treating arthritis pain. It is important to remember that use of either COX-2-selective drugs or nonspecific NSAIDs can result in dyspepsia without serious complications. When prescribing a COX-2 agent, as for any drug, there will always be a risk of an adverse event and good patient selection is the key.

PJ: Celecoxib is better tolerated for GI symptoms than comparator NSAIDs, likely improving its effectiveness. It is associated with less frequent upper and lower GI mucosal injury and bleeding events. While it is likely that there is some dose-related increase in CV events, the absolute rate of these is low and comparable with standard NSAIDs. There are fairly precise risk estimates that can be used to inform patient-physician consultations in balancing effective treatment of symptoms against potential GI and CV events.

Take-home messages

- All NSAIDs carry CV and GI risks
- COX-2 inhibitors have lower rates of GI bleeding and ulceration than nonselective NSAIDs
- Dose-related CV risk with celecoxib is likely
  - Comparable with other NSAIDs
  - Absolute risk is low
- Consider adverse event risks in all NSAID users
- Good risk estimates are available to inform treatment decisions

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