

## Another Selective COX-2 Inhibitor: More Questions Than Answers?



In this issue of *The Journal*, Matsumoto, *et al* compare etoricoxib, a selective inhibitor of cyclooxygenase 2 (COX-2), with naproxen in patients with rheumatoid arthritis (RA)<sup>1</sup>. Etoricoxib is about 100 times more selective for COX-2 than COX-1, making it the most selective COX-2 inhibitor currently available<sup>2</sup>. Once-daily dosing is appropriate based on the long half-life of 22 hours. Rapid symptomatic responses are observed related to the short time to peak plasma concentration of about 1 hour<sup>3</sup>. The drug is available for prescription in the UK, Mexico, and South America for RA, osteoarthritis, and acute pain but has emerged at a time of increasing concern about cardiovascular safety of the selective COX-2 inhibitors (CSI).

The history of CSI has been controversial. The discovery of the COX-1 and COX-2 isoenzymes and the definition of their roles in the early 1990s led to the exciting proposition that inhibition of COX-2 but not COX-1 would reduce the substantial risk of serious upper gastrointestinal (GI) adverse effects seen with conventional nonsteroidal antiinflammatory drugs (NSAID) while maintaining antiinflammatory and analgesic efficacy. Early studies with celecoxib and rofecoxib supported this contention and revealed impressive reductions in the incidence of endoscopically evident peptic ulcers<sup>4</sup>. However, in order to make the important claim of greater GI safety than conventional NSAID, the US Food and Drug Administration (FDA) required not only properly powered, GI event-driven, randomized controlled studies but also doses of celecoxib and rofecoxib at least twice the highest doses recommended for chronic therapy. These discussions led to the CLASS and VIGOR studies, each with over 8000 patients<sup>5,6</sup>. The VIGOR study showed a significant reduction in the rate of clinically significant upper GI peptic ulcers and complications of the order of 50–60% in comparison to naproxen 1500 mg daily<sup>5</sup>, and this superiority is now reflected in the label. However, there has been controversy in relation to these studies: in regard to VIGOR because of the unexpected but significantly increased rate of cardiovascular thrombotic events with rofecoxib compared to naproxen and CLASS because of the apparent loss of GI safety benefit beyond a median of

6 months' treatment with celecoxib versus ibuprofen and diclofenac, and irregularities in the analysis and reporting of the findings<sup>7</sup>.

Other important safety concerns have emerged related to a physiological role for COX-2 in the kidney. It is now accepted that peripheral edema, renal impairment, and precipitation or worsening of cardiac failure and hypertension can occur with CSI just like NSAID, notably in those patients with risk factors for these conditions<sup>8</sup>.

Of most concern is the uncertainty regarding the cardiovascular safety of CSI. It has long been apparent that cardiovascular health depends upon prostacyclin production from the endothelium. Prostacyclin inhibits platelet aggregation and vasodilates arteries, countering the effects of platelet-derived thromboxane A<sub>2</sub>, a potent vasoconstrictor and stimulus for platelet aggregation. More recently it has become apparent that endothelial synthesis of prostacyclin is largely dependent on COX-2. Prostacyclin synthesis is critical in patients with atherosclerosis and situations of platelet activation in order to modulate the release and actions of thromboxane A<sub>2</sub><sup>9,10</sup>. Thus, in contrast to conventional NSAID, the failure of CSI to inhibit platelet COX-1 derived thromboxane A<sub>2</sub> would appear to enhance thrombotic cardiovascular risk.

In the VIGOR study the confirmed overall cardiovascular event rates for rofecoxib and naproxen were 1.8 and 0.6 per 100 patient-years of exposure, respectively, giving a significant relative risk reduction in the naproxen group of 0.42 (95% confidence interval 0.25–0.72)<sup>11</sup>. Most of this difference was accounted for by cardiac events, particularly myocardial infarctions. Controversy has continued whether the finding is due to chance, a higher risk with rofecoxib, a lower risk with naproxen, or a combination of these last 2 possibilities. Examination of the complete clinical trial database for rofecoxib in over 28,000 patients also with OA and Alzheimer's disease has led to the conclusion that rofecoxib does not differ from non-naproxen NSAID, but that chronic high dose naproxen might exhibit aspirin-like cardiovascular protection at least in RA<sup>11,12</sup>, the latter contention supported more recently in a number of epidemiological

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See A randomized, controlled, clinical trial of etoricoxib in the treatment of rheumatoid arthritis, *page 1623*

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studies<sup>13</sup>. However, the FDA has added a description of the cardiovascular findings in VIGOR to the label for rofecoxib along with a statement urging caution “in patients with a medical history of ischemic heart disease...”<sup>14</sup>.

Comparisons with celecoxib in the CLASS study are difficult because the comparator NSAID were different (namely ibuprofen and diclofenac), low dose aspirin was permitted and over 20% of individuals were taking it, and finally, about two-thirds of the patients had OA and only one-third RA. RA is increasingly recognized to pose a risk for cardiovascular disease of about 2-fold in its own right, related to the effect of chronic inflammation. However, one analysis of the CLASS data has not suggested a prothrombotic risk for celecoxib<sup>15</sup>, and in contrast to rofecoxib, the FDA has not required cautionary statements on the label. The celecoxib data might also suggest a unique protective effect of naproxen in contrast to ibuprofen and diclofenac.

How is etoricoxib placed in the light of the controversies discussed?

Matsumoto and colleagues have undertaken a well conducted, multicenter, randomized, double-blinded, controlled, 12 week comparison of etoricoxib 90 mg daily with naproxen 500 mg twice daily and placebo in 816 patients with RA whose disease flared upon withdrawal of chronic NSAID therapy<sup>1</sup>. As might be expected, etoricoxib and naproxen were superior to placebo in all 4 standard primary efficacy endpoints and both drugs were generally well tolerated without significant differences from placebo. Interestingly, there were 2 confirmed, adjudicated cardiovascular adverse events, both occurring in patients taking etoricoxib, a transient ischemic attack and a non-Q wave myocardial infarction. An unexpected result was that etoricoxib showed significant superiority to naproxen in all primary and most secondary endpoints. However, an identical study showed equivalent efficacy for etoricoxib and naproxen<sup>16</sup>. Interestingly, there were 3 confirmed cardiovascular thrombotic adverse events — angina pectoris and pulmonary embolus in 2 patients taking etoricoxib and thrombophlebitis in one patient taking placebo. There were important exclusions in the Matsumoto study that need to be kept in mind when extrapolating results to clinical practice. Patients with a history of “angina or congestive heart failure...and/or who had a history of myocardial infarction, coronary angioplasty, or coronary bypass within the past year and/or a history of stroke or transient ischemic attack within the past 2 years” were excluded. However, low dose aspirin up to 100 mg/day was allowed.

We now need large, event-driven, properly powered, randomized, controlled clinical trials of etoricoxib and other CSI using maximal clinically relevant doses versus conventional NSAID not only to prove GI but also cardiovascular safety. Given the prevalence of musculoskeletal and cardiovascular disease and the extensive use of NSAID and CSI, these types of studies are justified and necessary. Indeed, the

FDA has very recently requested that further clinical data on cardiovascular safety be submitted when the etoricoxib dossier is presented for registration.

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