THERAPEUTICS INITIATIVE Evidence Based Drug Therapy

COX-2 inhibitors update:
Do journal publications tell the full story?

The COX-2 inhibitor story has evolved over a relatively short period of time, beginning with news of a 'breakthrough' class of drugs and evolving into concerns about cardiovascular toxicity.[1] The story has potential implications for physicians and patients far beyond this class of drugs. In Canada, the account began in early 1999 when celecoxib (Celebrex®) became available for prescription.

What is the presumptive therapeutic advantage of COX-2 selective NSAIDs?

The COX-2 inhibitors have been successfully marketed based on the presumption that the main mechanism by which non-selective NSAIDs cause gastrointestinal (GI) ulcers is inhibition of COX-1. Based on this hypothesis, drugs that selectively inhibit COX-2 enzymes will have similar anti-inflammatory activity with less GI toxicity. Short-term RCTs, in which all patients underwent endoscopy, showed fewer cumulative gastroduodenal erosions and ulcers with the COX-2 inhibitors (9-15%) than with non-selective NSAIDs (41-46%).[2,3] Regulatory authorities judged this surrogate outcome insufficient to prove that COX-2 selective inhibitors were better than non-selective NSAIDs in terms of the life-threatening complications of NSAIDs, ulcers complicated by GI bleeds, perforations and obstructions. Thus the monographs of celecoxib, rofecoxib (Vioxx®) and meloxicam (Mobicox)® include the same warnings of the risk of GI toxicity as all other NSAIDs.

What was the objective of the CLASS and VIGOR comparative trials?

With the objective to demonstrate a reduced incidence of complicated ulcers with COX-2 inhibitors, the manufacturers of celecoxib and rofecoxib conducted two large RCTs, the CLASS and VIGOR trials, respectively. The major findings of these trials were published in JAMA[4] and N Engl J Med[5] in 2000. In February 2001, Therapeutics Letter #39 summarized the most important outcome data from the published reports. Shortly after circulation of Letter #39, the FDA published on their website a complete review of the same CLASS and VIGOR trials[6-8], leading to a different interpretation of the overall safety of this class of drugs.[9]

Table. Patients with one or more Serious Adverse Event (FDA data)

Outcome	CLASS trials*					VIGOR trial				
	Celecoxib %	Other NSAIDs %	RR (95% CI)	ARR ARI %	NNT NNH 9 mo	Rofecoxib %	Naproxen %	RR (95% CI)	ARR ARI %	NNT NNH 9 mo
Mortality	0.48	0.43	1.12 (0.58 - 2.14)	NS	NS	0.54	0.37	1.46 (0.76 - 2.81)	NS	NS
Complicated ulcers	0.50	0.60	0.83 (0.46 -1.5)	NS	NS	0.40	0.92	0.43 (0.24 - 0.78)	0.52	192
Other serious adverse events	5.8	4.8	1.22 (1.01-1.47)	**1.0**	**100**	8.4	6.5	1.28 (1.10 -1.50)	**1.9**	**53**
Total serious adverse events	6.8	5.8	1.17 (0.99 -1.39)	NS	NS	9.3	7.8	1.21 (1.04 - 1.40)	**1.5**	**67**

* Because the two trials comparing celecoxib with ibuprofen and diclofenac are of different duration, and the FDA data provide only the combined celecoxib data, the trials cannot be reported separately. **NS** = Not statistically Significant. **RR** = Relative Risk. **CI** = Confidence Interval. **ARR** = Absolute Risk Reduction. **NNT** = Number Needed to Treat to prevent one event. **ARI** = Absolute Risk Increase. **NNH** = Number Needed to treat to cause one Harmful event.

Mailing Address: Therapeutics Initiative
The University of British Columbia
Department of Pharmacology & Therapeutics
2176 Health Sciences Mall
Vancouver, BC Canada V6T 1Z3

Tel.: (604) 822•0700
Fax: (604) 822•0701
E-mail: info@ti.ubc.ca
Web: www.ti.ubc.ca
(all Therapeutics Letters, Course Information)

What do the FDA data tell us?

The FDA data reveal that the CLASS study as published in JAMA, and summarized in Letter #39, reported only the first six months of data from two trials of longer duration. One of the trials was a 15-month trial comparing celecoxib with ibuprofen and the other was a 12-month trial comparing celecoxib with diclofenac. Both the six-month and full trial data are provided in the FDA review.[6,7] The published VIGOR trial duration and GI outcome data are the same as that found on the FDA website, but the FDA report is more complete and provides overall serious adverse event data.[8]

As pointed out in Letter #42, total serious adverse events (SAEs) provide essential information about both harm and benefit. SAEs include death, hospitalization or extension of hospitalization and any life-threatening event or serious disability. In the case of NSAIDs, complicated ulcers represent one of the SAEs.

The Table presents the percentage of total patients who had one or more SAE and a breakdown of those events into mortality, complicated ulcers and other SAEs.

Why do COX-2 inhibitors increase serious adverse events?

The reason for the increased incidence of serious adverse events with the COX-2 selective inhibitors can not be completely answered from the available FDA data. SAEs are more completely reported in the FDA VIGOR report than the FDA CLASS report. Myocardial infarction (RR 4.9 [1.7-14.3], ARI 0.4%, NNH 250) and adjudicated thrombotic cardiovascular events (RR 2.38 [1.39-4.00], ARI 0.6%, NNH 167) are increased with rofecoxib as compared to naproxen.[1,8] The reason why COX-2 inhibitors might increase thrombosis is discussed by Mukherjee et al.[1]

However, none of the reported individual or combined outcomes explain the overall 1.0-1.9% absolute risk increase of other serious adverse events associated with either celecoxib or rofecoxib.

Before making a claim of a safety benefit over a comparator, the total % SAEs should be less than that observed with the comparator. For example, rofecoxib as compared to naproxen reduced complicated ulcers (ARR 0.5%) leading to a claim of a safety benefit, but the magnitude of this benefit is outweighed by the harm associated with rofecoxib in terms of other SAEs (ARI 1.9%).

What about less serious outcomes?

In the VIGOR trial, symptomatic ulcers were reduced with rofecoxib as compared to naproxen, and withdrawals due to adverse events were the same in both groups (see Table, Letter #39). The complete data for symptomatic ulcers in the CLASS trial are as follows: 0.65% of patients treated with celecoxib and 1.0% of patients on other NSAIDs had symptomatic ulcers (RR 0.63 [0.39-1.03]). Interpretation of this trend is complicated by the fact that fewer patients in the celecoxib group (3.4%) underwent endoscopies as compared to patients treated with the other NSAIDs (4.9%; RR 0.70 [0.57-0.87]). The decrease in withdrawals due to adverse events with celecoxib at 6 months[4] (Letter #39) was also seen in the full trial: 22.4% of celecoxib patients and 24.6% of patients on other NSAIDs withdrew due to adverse events (RR 0.91 [0.84-0.98], ARR 2.4%, NNT = 42). This finding predominantly reflects a higher incidence of withdrawals due to GI symptoms and increase in hepatic enzymes in patients treated with diclofenac.

Conclusion:

- Based on FDA data from the CLASS and VIGOR studies, **COX-2 selective inhibitors are associated with an increased incidence of serious adverse events as compared to non-selective NSAIDs.**
- Published versions of the CLASS and VIGOR trials focused on GI events and failed to report other serious adverse events fully.
- **In the interests of public safety, serious adverse event rates from all trials must be published.**

This Letter contains an assessment and synthesis of publications up to November 2001. We attempt to maintain the accuracy of the information in the Therapeutics Letter by extensive literature searches and verification by both the authors and the editorial board. In addition this Therapeutics Letter was submitted for review to 120 experts and primary care physicians in order to correct any inaccuracies and to ensure that the information is concise and relevant to clinicians.

References:

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