See also page 115

Translated from ***Rev Prescrire*** **April 2005 ; 25 (260): 281**

COX-2 INHIBITORS: STILL NO DECISIVE ACTION

● **Evidence that the Cox-2 inhibitors have severe cardiovascular adverse effects continues to accumulate, including an increase in overall mortality in several trials of rofecoxib.**

● **Yet regulatory agencies on both sides of the Atlantic have so far only taken half-measures, issuing new contraindications and warnings that complicate matters for prescribers (but not for the companies concerned), and leave patients exposed to significant dangers.**

The clinical evaluation of Cox-2 inhibitors continued to evolve in February 2005.

Rofecoxib: excess overall mortality. We now know a little more about what happened in the Merck-funded APPROVe trial of colorectal polyp prevention with rofecoxib. This trial, comparing rofecoxib 25 mg/day with placebo for three years, enrolled 2586 patients in 29 countries (including France) (1,2). The patients, whose average age was 59 years, had had a polyp removed less than three months before entering the trial; 35% of them had hypertension, 22% were smokers and 9% were diabetic.

The overall mortality rate has not been reported, and neither has the possible preventive effect of rofecoxib on colorectal polyp formation. Ten cardiovascular deaths occurred in each group (about 2.6 per 1000 patient-years). The incidence of thrombotic events was 15 per 1000 patient-years with rofecoxib and 7.8 per 1000 patient-years in the placebo group (p=0.008 at three years). The incidence of heart failure was about 7 per 1000 patient-years with rofecoxib (starting in the first year), compared to about 2 per 1000 patient-years on placebo (values read from a graph; p=0.004 at three years).

In two placebo-controlled trials of rofecoxib 25 mg/day in Alzheimer's disease, the overall mortality rate was higher with rofecoxib (41/1069, versus 23/1074 on placebo (p<0.03, our calculation). The overall mortality rate was also higher with rofecoxib than with naproxen in the VIGOR trial (1,3).

Celecoxib: a confirmed risk of thrombosis and heart failure. A similar placebo-controlled trial (the APC study) funded by Pfizer and the US National Cancer Institute, compared celecoxib 400 mg/day with celecoxib 800 mg/day in 2035 patients similar to those enrolled in the APPROVe trial (4). After about three years the overall mortality rate was 9 per 1000 on placebo and celecoxib 400 mg, compared with 13 per 1000 with celecoxib 800 mg; the respective incidence rates of death due to cardiovascular events or heart failure were 3.4, 7.8 and 11.4 per 1000 (p=0.01). The possible impact of celecoxib on polyp prevention has not been reported.

European agency: class effect and modified Summary of Product Characteristics (SPCs). In February 2005 the French regulatory agency followed the lead of the European Medicines Evaluation Agency (EMEA) by modifying the SPCs for Cox-2 inhibitors, pending a data review to be completed in April 2005 (5,6). Neither agency presented any new data, but both concluded that the increased risk of cardiovascular adverse effects was a class effect of Cox-2 inhibitors.

According to the new SPCs, Cox-2 inhibitors are contraindicated in patients with ischaemic heart disease or a history of stroke; etoricoxib is contraindicated in patients with uncontrolled arterial hypertension; a warning has been added for patients with cardiovascular risk factors; and, in general, the lowest effective dose should be used for the shortest possible period in order to avoid cardiovascular adverse effects.

FDA: biased committees. In February 2005, two FDA committees concluded that celecoxib, valdecoxib and rofecoxib had increased risks of cardiovascular adverse effects (7,8). Yet they recommended that the three drugs be allowed to remain on the market, voting 31 for and 1 against maintaining celecoxib, 17 for and 15 against maintaining rofecoxib, and 17 for and 13 against maintaining valdecoxib (two abstentions). The committees recommended that further warnings be added to the SPCs.

However, according to an enquiry conducted by the New York Times, no fewer than 10 out of the 32 committee members had previously worked for the companies concerned (8). Without these members' votes the committees would have recommended the market withdrawal of valdecoxib and rofecoxib.

No decision had been announced by the FDA as of 3 March 2005.

Profit over health. The EMEA appears to stand by its statement, released in April 2004, expressing the view that: " available data indicated that significant and consistent gastrointestinal benefit of COX-2 inhibitors compared with conventional NSAIDs has not been demonstrated" (2).

In summary, by leaving Cox-2 inhibitors on the market, regulatory agencies on both sides of the Atlantic show they are more sensitive to the concerns of drug companies than to patients' safety. Patients remain exposed to a documented risk of adverse effects from drugs that have no proven therapeutic advantages, while prescribers are left wasting their time picking through the debris.

In France, the approved price of celecoxib has still not been reduced.

Watch this space.

©Prescrire Editorial Staff

Selected references from Prescrire's literature search.

1- Bresalier RS et al. "Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial" *N Engl J Med* 2005; **352**. Website http://www.nejm.org searched on 3 March 2005.
2- See page 115.
3- US Food and Drug Administration "Review of NDA21042/s030 (update of cardiovascular thrombotic events in Alzheimer's studies 078 and 091)". Website http://www.fda.gov searched on 3 March 2005.
4- Solomon SD et al. "Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention" *N Engl J* Med 2005; **352**. Website http://www.nejm.org searched on 3 March 2005.
5- Afssaps "Sécurité d'emploi des coxibs: nouvelles contre-indications et mises en garde concernant le risque cardiovasculaire" 17 February 2005. Website http://afssaps.sante.fr searched on 21 February 2005.
6- European Medicines Agency "Public statement. European medicines agency announces regulatory action on COX-2 inhibitors" 17 February 2005. Website http://www.emea.eu.int searched on 21 February 2005.
7- "Committees issue preliminary recommendations to FDA following review of COX-II inhibitors" 24 February 2005. Website http://www.druginfozone.nhs.uk searched on 24 February 2005.
8- Harris G and Berenson A "10 voters on panel backing pain pills had industry ties" New York Times 25 February 2005. Website http://www.ahrp.org searched on 3 March 2005.

LAST MINUTE !

The FDA finally decided in early April 2005 that valdecoxib must be withdrawn from the market due to its unfavourable risk-benefit balance (serious skin reactions and cardiovascular toxicity). The EMEA followed the lead [To be continued].