

## The withdrawal of rofecoxib<sup>†</sup>

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In recent years, critics of epidemiology have charged that epidemiology is unreliable when stacked up against 'hard' sciences<sup>1</sup> and that pharmacoepidemiology in particular pales in comparison with randomized trials.<sup>2,3</sup> The recent withdrawal of rofecoxib should be viewed as an opportunity to analyze possible gaps in the system of drug approval and pharmacovigilance. In the case of rofecoxib, the voluntary removal was preceded by an array of instances where pharmacoepidemiology data does not appear to have been acted on. The rofecoxib episode indicates that the findings from well-conducted non-experimental epidemiology cannot be dismissed as unreliable, and that pharmacoepidemiology must be more tightly integrated into the regulatory process. We cannot depend on the hope that data from randomized trials will eventually corroborate the results of pharmacoepidemiologic research. The main lesson of rofecoxib's withdrawal is that the trial data, which appeared for reasons unrelated to the concerns generated by the pharmacoepidemiologic results, should not have been needed to take action.

### BACKGROUND

Merck voluntarily withdrew rofecoxib (Vioxx<sup>®</sup>), a cyclo-oxygenase-2 (COX-2) inhibitor, on a global basis on September 30th, 2004.<sup>4</sup> Public statements by Merck indicate that it made the decision to withdraw rofecoxib after the safety monitoring board of

the APPROVe (Adenomatous Polyp Prevention on VIOXX) trial found an increased risk of cardiovascular events in patients treated with 25 mg daily of rofecoxib compared to placebo.<sup>4</sup> Merck had launched rofecoxib in the U.S.A. in May 1999. In 2001, Merck's spending on direct to consumer advertising of the drug was the highest in industry at \$161 million.<sup>5</sup> By April 2001, rofecoxib, along with the other approved COX-2 at that time, celecoxib, accounted for 38% of all NSAID prescriptions according to a study conducted in Alabama.<sup>6</sup> In a recently published study, over 65% of all new NSAID prescriptions were COX-2.<sup>7</sup> Rofecoxib was an important drug for Merck, as it sold \$2.5 billion in 2003, or 11% of the company's revenue.<sup>8</sup> Following the news of rofecoxib's withdrawal Merck's stock plummeted 27%, reducing Merck's market capitalization by \$25 billion.<sup>‡</sup>

Following the publication of the results of the Vioxx Gastrointestinal Outcomes Research (VIGOR) trial in 2000,<sup>9</sup> the cardiovascular safety profile of rofecoxib was the subject of a continuous controversy. VIGOR was a clinical trial comparing the gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis (RA). It included a total of 8076 patients with RA randomly assigned to receive either rofecoxib (50 mg daily) or naproxen (1000 mg daily). After a mean follow-up period of 9 months, the investigators observed 35 cardiovascular (CV) events<sup>§</sup> in the rofecoxib group and 18 in the naproxen group (relative risk [RR], 1.9; 95%CI, 1.1–3.4). There were five times more cases of MI in the rofecoxib group

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<sup>‡</sup>This figure is higher than the 2000 GDP of 74 countries ([http://www.nationmaster.com/graph-B/eco\\_gdp\\_ppp](http://www.nationmaster.com/graph-B/eco_gdp_ppp)).

<sup>§</sup>Defined as death linked to cardiovascular disease (CVD), myocardial infarction (MI), or cerebrovascular accident (CVA).

( $n=20$ ) than in the naproxen group ( $n=4$ ); RR 5; 95%CI, 1.7–14.6. Aside from chance and bias, the key causal explanations for these findings were: naproxen decreased the risk of CV events; rofecoxib increased the risk of CV events, or a combination of these. The hypothesis pointing to a causal role of rofecoxib had two independent components. The first component was the theory that selective inhibition of COX-2 would lead to an unopposed secretion of thromboxane A<sub>2</sub> (TXA<sub>2</sub>) and a decreased secretion of prostacyclin (PGI<sub>2</sub>)<sup>10–12</sup> and could induce a thrombotic effect and vasoconstriction. The second component was based on the differences in systolic blood pressure (SBP) between the two treatment groups observed in VIGOR. SBP is an independent risk factor in the development of CVD, including coronary heart disease (CHD), CVA, and congestive heart failure (CHF).<sup>13–15</sup> The mean SBP among patients taking rofecoxib was 133.2 or 4.6 mmHg higher than the mean baseline measurement. In contrast, the mean SBP among those taking naproxen was 129.8 or 1 mmHg higher than baseline. Thus the difference between the two treatment groups was 3.6 mmHg after an average 9 months of follow-up.

The VIGOR authors attributed the twofold increase in risk of CV events to the fact that many of the cases were not taking prophylactic aspirin and to naproxen's 'cardioprotective' effect, defined as the prevention of thromboembolic events such as MI and most strokes. A subsequent series of articles supported naproxen's cardioprotection.<sup>16–18</sup> In fact, the editor of the journal that published these articles concluded that "... there is no evidence that the use of COX-2 increases... the risk of myocardial infarction. The results of VIGOR... are readily explainable by the beneficial effect of naproxen...".<sup>19</sup>

Following the publication of VIGOR, several pharmacoepidemiology studies were performed. Ray *et al.* reported that the use of rofecoxib at doses >25 mg daily in new users was associated with an increased risk of MI (RR 1.93; 95%CI, 1.09–3.43)<sup>20</sup> compared to non-users. The risk was slightly lower among all users and not elevated among users of other NSAID or COX-2 including rofecoxib at doses ≤25 mg daily. Solomon *et al.* published<sup>21</sup> a study in which rofecoxib use was associated with an increased risk compared with non-users of NSAID and celecoxib. Finally, an additional study was recently presented at the 20th International Conference on Pharmacoepidemiology and Risk Management (ICPE) in Bordeaux, France.<sup>22</sup> This study showed a small increased risk of MI at doses ≤25 mg daily (OR 1.29; 95%CI, 0.93–1.79) and a larger increase at doses >25 mg daily (OR 3.15;

95%CI, 1.14–8.75). On the other hand, other epidemiologic studies<sup>23–25</sup> and the pooled analyses of rofecoxib trials did not show an increased risk in CV events, compared with non-naproxen NSAID.<sup>26,27</sup> Approximately 1 month after the results of the last study by Graham *et al.*<sup>22</sup> were presented at ICPE the Safety Monitoring Board for APPROVe recommended stopping the trial based on a twofold increased risk of CV events (15 cases per 1000 patients over 3 years on rofecoxib vs. 7.5 cases per 1000 patients over 3 years on placebo). Almost immediately Merck announced the withdrawal of the drug because the results were 'statistically significant and indicated there is an issue'.<sup>8</sup>

### LESSONS FROM THE WITHDRAWAL

Given the magnitude of this withdrawal, it is justifiable to analyze what lessons the interested parties—regulators, pharmaceutical companies and researchers—can learn from this episode in order to avoid similar mistakes in the future. Here are some suggestions:

#### *A complete and detached look at the available data*

An integral part of the scientific method is self-criticism, including an evaluation of all possible hypotheses that may explain a given set of results. Although looking back and criticizing the work of others is always easy, when evaluating the results of VIGOR, all potential explanations for the results may not have been accorded comparable weight. The explanation that naproxen was cardioprotective, for example, should have received greater scrutiny given that other studies showed that naproxen was not cardioprotective.<sup>28–30</sup> In a recent review of observational studies, the pooled RR for naproxen was 0.88 (95%CI, 0.80–0.95)<sup>31</sup> supporting some cardioprotective effect for naproxen. However, unless we were to accept that naproxen was better than aspirin in the prevention of MI, the effect reported in some of these studies was biologically implausible and would not explain the fivefold increase in the risk of MI seen in VIGOR. In secondary prevention trials, aspirin decreases the risk of CVD by approximately 25%.<sup>32</sup> In primary prevention trials, aspirin reduced the risk of all CV events by 15% and MI by 30%,<sup>33,34</sup> results that translate to a RR of 0.85 (95%CI, 0.78–0.94). The OR reported in the studies that supported the cardioprotection of naproxen were as low as 0.61–0.65.<sup>16,17</sup> Despite this implausibility, the reports of naproxen's cardioprotective effect were rapidly

accepted by many in the scientific community.<sup>19</sup> Even those that would not accept naproxen's cardioprotection as a sufficient justification for the VIGOR results were ready to accept some degree of cardioprotection 'combined with chance' as an explanation.<sup>35</sup>

### *Look at the big picture*

The authors of VIGOR dismissed the role of blood pressure by noting that there was only one patient with both hypertension and MI. While the difference of 3.6 mmHg in SBP between the two treatment arms in VIGOR could not account for the difference in MI observed in the trial, its importance at a population level was perhaps underestimated.<sup>36</sup> There is evidence that blood pressure is directly related to CHD and vascular mortality without evidence of a threshold down to 115/75 mmHg.<sup>37,38</sup> The presence or absence of hypertension, diagnosed using a threshold (generally 140/90 mmHg), may not have been sensitive enough to study the possible effect of the differences in SBP between the two groups of patients. Singh *et al.*<sup>39</sup> modeled the effect that a 3 mmHg change in SBP would have in the U.S. RA population based on the National Health and Nutrition Examination Survey (NHANES III).<sup>40</sup> When a mean population increase of 3 mmHg of SBP over 1 year was applied to adults diagnosed with RA in the NHANES III, a 5% increase in the risk of CV events was predicted by the Framingham Risk Equation. Singh *et al.* applied an increase of 3 mmHg to a U.S. cohort of 5.7 million patients with RA over a year and estimated that 3874 CV events were attributable to this SBP increase. In addition, CHF is much more closely related to SBP than other CVD<sup>15</sup> and it is considered the most important public health issue in CV medicine.<sup>41</sup> Non-selective NSAIDs have been shown to trigger CHF<sup>42</sup> and be the cause 19% of hospital admissions for CHF.<sup>43</sup> We need much more research on the population effect of SBP increases induced by NSAID and COX-2.

### *A vindication of pharmacoepidemiology studies, strong pharmacovigilance and risk management*

When faced with a series of pharmacoepidemiologic studies showing an increased risk of CV events with rofecoxib Merck discounted their results because they were obtained from observational studies<sup>44,45</sup> and were 'not as strong as clinical trials like those performed prior to FDA approval'.<sup>46</sup> This dismissal of pharmacoepidemiology studies and over-reliance on clinical trial data was not unique to Merck. In some

corridors of the FDA, there is still a tendency to disregard any research that does not come from a randomized trial and is buttressed by a test of statistical significance. Rofecoxib's product information (PI) was changed in 2002 to describe the results of VIGOR (published in 2000).<sup>47</sup> No mention of the results of any pharmacoepidemiology studies, including of that conducted and sponsored by FDA, was included in the PI, even though data were available. In Europe, rofecoxib and other COX-2 were taken to arbitration (article 31) by France and Germany. The outcome of the arbitration was recently made public<sup>48</sup> and also seems to have ignored the results of pharmacoepidemiologic studies in what a former member of the CPMP described as a decision 'based on politics, not technical matters'.

In the case of rofecoxib, pharmacoepidemiology studies were necessary in view of the substantial differences between the patients included in VIGOR and those taking the drug in practice. For instance, the patients included in VIGOR only had RA, while the drug was approved for use in patients with RA, osteoarthritis (OA) and acute pain, including migraine and dysmenorrhea.<sup>47</sup> In addition, patients included in VIGOR received 50 mg of rofecoxib daily, while the most frequently used dose in clinical practice was 25 mg per day. Finally, the patients included in VIGOR had better CV profiles than those included in RA populations in the U.S.A., such as the patients with RA included in NHANES III<sup>39</sup> and others.<sup>49</sup> Since pharmacoepidemiology studies were needed, it is reasonable to expect that the results from properly conducted studies are translated into regulatory actions, including label changes. The existence of apparently contradictory results among pharmacoepidemiology studies should not be used as an excuse for not including their data in the PI, since this is done routinely with information from clinical trials. For instance, the data regarding CV events in VIGOR is included in the U.S. PI followed by a statement that other clinical trials did not show such effect.<sup>47</sup>

Even so, one can question whether withdrawing rofecoxib was the right decision, especially if the decision was taken because of the results from APPROVe. Allegedly the increased risk in CV events was only apparent after 18 months of continuous treatment.<sup>8</sup> This is an important point to take into consideration, since the continuous use of any NSAID or COX-2 for 18 months for pain or arthritis is uncommon. In a study by Moride *et al.* the median duration of therapy for rofecoxib was 23 days.<sup>50</sup> There seems to be little doubt that maintaining the 50 mg

daily dose was not justifiable in the presence of alternative therapies with similar effectiveness and no known CV risk. Appropriate risk minimization strategies could have perhaps been developed to avoid the use of the 50 mg daily dose and ensure that the 25 mg daily dose was restricted to selected patients. Probably, patients with acute pain or OA who were at risk for gastrointestinal bleeding, but did not have CV risk factors, could have taken 25 mg of rofecoxib daily for a short period of time without substantially increasing their risk of developing CV events. An individual's response to pain is idiosyncratic and some patients respond better to some drugs than others. Among the patients who receive the 111 million prescriptions that are written for NSAID worldwide<sup>51</sup> it is easy to imagine that there are some that have and would continue to benefit from rofecoxib. Perhaps translating the results of good pharmacoepidemiology studies that were already available in 2002<sup>20</sup> into adequate labeling changes and risk minimization strategies, could have prevented this result.

Although the decision to withdraw the drug may be debatable, the side effects in question were sudden death, MI and stroke which are by far the principal causes of death in the industrialized world. Members of FDA were quoted to have been "...concerned and aware of the potential for cardiovascular effects for the last few years".<sup>52</sup> If VIGOR is considered the first signal and the results were published in 2000, it may be legitimate to expect faster action—not necessarily a withdrawal—by regulatory agencies worldwide.

## CONCLUSION

Drug safety and pharmacovigilance is a discipline that should use data and information from different sources. This example of diminished scientific self-criticism and over reliance on clinical trial data may have put some patients at unnecessary risk of a fatal event and denied other patients a useful low-dose medication. Some will argue that rofecoxib was over-used or even misused,<sup>53</sup> but unquestionably some patients benefited from it. Let us hope that one result of this episode will be a willingness to treat pharmacoepidemiologic data critically, to be sure, but also with appropriate respect, and to ensure that good data from any source receive prompt translation into prudent regulatory actions and risk-minimization strategies.

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