Editorial

Patient Empowerment: Rofecoxib Revisited

What have we learned directly from patients following the voluntary withdrawal of rofecoxib from the marketplace in September 2004? In this issue of *The Journal*, Hawker and colleagues[1] report results of a telephone survey of a community cohort of 1085 elderly patients (mean age 75.9 yrs) with knee or hip osteoarthritis, conducted 9 to 20 weeks following withdrawal of rofecoxib. When the 277 patients who had used rofecoxib were asked to rate the severity of their arthritis pain following cessation of rofecoxib, 74% reported it was "worse" or "much worse"; 18% would still take rofecoxib if it were available, and 75% would not use it again for fear of side effects. Most patients were unsure about the relative risk of heart attacks, but 67% of patients who expressed an opinion (about half the total cohort) felt that someone taking rofecoxib would have a risk of heart attack up to twice as great as that of a nonuser. Over 63% of respondents with an opinion estimated the absolute risk of heart attack or stroke with rofecoxib to be greater than 6%.

The Third Canadian Consensus Conference group, comprising health professionals and consumers, examined an evidence-based approach to prescribing nonsteroidal antiinflammatory drugs (NSAID) and made 8 recommendations[2]. The first of these, which concerned patient-physician communication, stated that "patients should be fully informed about information regarding the benefits and risks of their treatment options." The data from Hawker's study point out that patients are often misinformed by their physicians about the efficacy of coxibs, are more concerned with safety than efficacy, and often have misconceptions about the cardiovascular risks of rofecoxib. Nonetheless, many found that rofecoxib was effective for them, and a substantial minority would continue to use rofecoxib if it were available.

At both the joint meeting of the Arthritis Advisory Committee and the Risk Management Advisory Committee of the US Food and Drug Administration held in February 2005, as well as the Health Canada Expert Advisory Panel held in June 2005, patients' testimony about pain relief they obtained with rofecoxib was a cogent factor in convincing both regulatory agencies to consider reinstating rofecoxib[3,4].

What lessons did we learn when another commonly prescribed regimen — hormone replacement therapy (HRT) — was found to be associated with adverse effects? The Women's Health Initiative study was a randomized prospective controlled primary-prevention trial involving 16,608 healthy postmenopausal women (average age 63 yrs) that was designed to test the hypothesis that HRT has cardiovascular health benefits[5]. Patients received either conjugated equine estrogens plus medroxyprogesterone acetate or placebo. Coronary heart disease was the primary endpoint, and invasive breast cancer the primary adverse outcome. Although the planned duration of the trial was 8.5 years, it was discontinued prematurely (mean followup period 5.2 yrs) after the Data Safety Monitoring Board noted an excess of invasive breast cancer cases in the treatment group. There were also increases in the number of cases of coronary heart disease, stroke, and pulmonary embolism, and decreases in the number of colorectal cancer and fracture cases. However, the overall risk exceeded the benefits (the absolute excess number of events was 19 per 10,000 patient-years), despite decades of accumulated observational evidence suggesting that HRT helped to prevent chronic disease. Although media coverage of these results was widespread, the manufacturers of HRT therapies did not withdraw their products from the marketplace, as Merck did with rofecoxib. Instead, the drug labeling for HRT products was modified to reflect the new risks.

Fortunately, millions of postmenopausal women who suffered intolerable extremes of hot flushing, persistent drenching sweats, and mood swings were still able to obtain hormone replacement therapies. Everyone adapted to the new information — industry by making lower-dose HRT formulations available, and physicians and patients by being more prudent in the overall use of HRT. Symptomatic patients were empowered to demand HRT prescriptions

See The patient's perspective on the recall of Vioxx, *page 1082*

from reticent prescribers, and thus to improve their quality of life.

Regrettably, rofecoxib-responsive patients were denied options similar to those enjoyed by HRT users. Instead, the disproportionate and inappropriate hype in the medical community has amplified the rofecoxib debacle[6]. A recent editorial in *The New England Journal of Medicine* (NEJM)[7] further inflamed the situation by insinuating that critical information had been deliberately withheld from the initial publication of the VIGOR trial[8]. The academic authors and industry sponsors responded independently to this "expression of concern"[9,10]. The VIGOR trial protocol prespecified a cutoff date based on the primary outcome — the number of gastrointestinal ulcers. Cardiovascular (CV) events were not a prespecified analysis. Only late in the VIGOR study did the data safety monitoring board recommend adjudication and inclusion of the CV events. A cutoff date for CV events had to be set at the last minute. After this cutoff date had passed, 3 additional myocardial infarctions (MI) and one deep venous thrombosis were reported in the rofecoxib group, and one thrombotic stroke in the naproxen group. These additional complications were duly reported to the FDA as early as June 2000, and at the public FDA Arthritis Advisory Committee meetings in February 2001[11-13]. The net effect of the 3 additional MI on relative risk for CV events was a change from 4.25 to 5.00 for rofecoxib over naproxen — not a statistically significant difference. We agree with the academic authors who responded to the NEJM editorial that changing a prespecified endpoint after the data are unblinded is inappropriate and smacks of data manipulation[9]. Given that the additional MI were disclosed in the public domain (on an FDA posting) as early as February 2001, it would seem that the NEJM editorial reaffirming its "expression of concern"[14] is "much ado about nothing" — something of an overreaction, occurring as it does almost 5 years after the event (Table 1). In fact, emerging evidence suggests that all the coxibs and traditional NSAID (except perhaps naproxen) and also acetaminophen (in large doses) carry some increased cardiovascular risk[4,16], and it should be remembered that the authors of the VIGOR trial were the first to note this possible association[8].

Our patients with rheumatic illnesses need to be empowered to work with their physicians to select drugs that will enhance their quality of life. Many patients with intolerable postmenopausal symptoms still choose HRT despite possibly increased breast cancer risk. Many rofecoxib-responsive patients might have decided to continue rofecoxib despite the results of the APPROVe trial[15], had they been given a choice.

At the level of health policy decisions, physicians need to use their expertise and influence to advocate on behalf of their patients. At the clinical level, they need to improve patient-physician communication in order to empower patients to weigh their individual risks as accurately as they can, and then to choose the best therapies for themselves. Patient empowerment is long overdue.

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Table 1. The VIGOR study: sequence of events.

May 18, 2000	VIGOR manuscript submitted to *New England Journal of Medicine* (NEJM)[16]
June 29, 2000	US FDA documents increased cardiovascular risk of 0.5% and 0.1% for rofecoxib and naproxen, respectively[12]
November 23, 2000	NEJM publishes VIGOR study[8]
February 8, 2001	FDA Advisory Committee posts a review, noting 20 (not 17) myocardial infarctions in the VIGOR trial[11]
April 11, 2002	FDA mandates a label change to rofecoxib reflecting increased cardiovascular and stroke risk as well as gastrointestinal benefits[12]
September 30, 2004	Merck voluntarily pulls Vioxx off the market after the APPROVe trial noted a doubling of cardiovascular complications over placebo
November 21, 2005	Merck memorandum dated July 5, 2000, obtained by subpoena in the Vioxx litigation, suggests that 2 authors knew about the 3 additional myocardial infarctions 4.5 mo before VIGOR was published[17]
December 15, 2005	Open letter from Merck, explaining that prespecified cutoff dates were based on gastrointestinal outcome data[13]
December 29, 2005	NEJM editorial "Expression of concern" suggests that VIGOR data were manipulated[7]
March 16, 2006	Academic authors and industry respond independently to "Expression of concern"[9,10]
March 16, 2006	NEJM reaffirmas its "Expression of concern"[14]

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