What Happened to the Coxibs on the Way to the Cardiologist?

David S. Alberts,1 John D. Potter,2 Maria Elena Martinez,1 Lisa M. Hess,1 Alison Stopeck,1 and Peter Lance1

1Arizona Cancer Center, University of Arizona, Tucson, Arizona and 2Fred Hutchinson Cancer Research Center, Seattle, Washington

By the time this editorial is printed, there will already have been hundreds of thousands of words written about the withdrawal of rofecoxib from the commercial market and the placement by Food and Drug Administration on “clinical hold” of all celecoxib colorectal adenoma prevention studies (1). The extremely promising role for rofecoxib and celecoxib, as well as other selective cyclooxygenase-2 (COX-2) inhibitors in cancer prevention, was here one day and almost literally gone the next. This turn of events is not only a major setback for two of the largest pharmaceutical companies but also is likely to have an extraordinarily dampening effect on chemopreventive agent development by the pharmaceutical industry for years to come.

So what went wrong in the phase I, II, and III and postmarketing surveillance of the selective COX-2 inhibitors? Certainly, outstanding science was responsible for the identification of the COX-2 molecular target, the synthesis of coxibs that hit and tightly bind to the target, and a series of well-designed early- and late-phase clinical trials of the coxibs in arthritis and cancer patients (2, 3).

Early in their development, there were concerns expressed by pharmacologists and biochemists that long-term selective inhibition of COX-2 might have effects both on coagulation and cardiovascular toxicity (4). Endothelial prostacyclin inhibits platelet aggregation, causes vasodilation, and prevents the proliferation of vascular smooth muscle cells, in contrast to thromboxane, the major COX-1 product of platelets, which causes platelet aggregation, vasoconstriction, and vascular proliferation (5). COX-2 is the dominant source of prostacyclin (6). The combination of reduced prostacyclin synthesis and uninhibited thromboxane synthesis in patients on long-term coxibs has been proposed as the likely explanation for coxib-related cardiovascular toxicity (7, 8). This imbalance is avoided with aspirin, a nonselective nonsteroidal anti-inflammatory drug, which inhibits thromboxane as well as prostacyclin synthesis. The net effect and magnitude of COX-2 inhibition has been difficult to establish in animal models in vitro or in clinical trials attesting to the complexity of the interactions involved in vascular pathophysiology.

It is also possible that it is the prolonged plasma concentrations of the coxibs that are responsible for their dangerous cardiovascular consequences. It may not be a coincidence that rofecoxib, which has a very prolonged plasma half-life of 17 hours, was the first coxib to express its cardiovascular toxicities, despite its once-a-day dosing schedule. It is possible that celecoxib with its shorter plasma half-life of 8 to 12 hours would not have shown as much toxicity, if dosed only once daily. A safety, phase IIa trial of celecoxib with and without selenium in normal, healthy volunteers using a once-daily dosing schedule of 400 mg (9) revealed extremely low plasma celecoxib concentrations at 12 and 24 hours post-dosing.3

Of course, post-marketing surveillance of both rofecoxib and celecoxib failed to uncover the cardiovascular toxicities. It was in the 3- to 5-year placebo-controlled colorectal adenoma prevention trials that an imbalance of cardiovascular/stroke events associated with rofecoxib and celecoxib was revealed. Of possible relevance, the twice-daily dosing schedule (both 400 and 800 mg/d) of the shorter half-life drug, celecoxib, was associated with a statistically significant increase in cardiovascular events in the Adenoma Prevention with Celecoxib Trial, which had a planned 3- to 5-year intervention period, whereas no risk has been identified thus far in the once-daily dose of 400 mg/d in the Prevention of Spontaneous Adenomatous Polyps Trial over the same period of intervention (10). To date, only studies with a twice-daily dosing schedules of celecoxib have shown an excess of cardiotoxicity (10, 11).

So, what did we learn from this chemoprevention drug development experience? First, investigators must understand and respect the pharmacology underlying drug discovery. Concerns about potential mechanisms of adverse events must be examined in-depth throughout the early and later phases of the drug approval process. This seems to be a lesson we need to learn over and over. The pharmacokinetics and metabolism of the drug must be studied in relation to different dosing schedules (e.g., once-daily versus twice-daily dosing) and potential toxicities, both acute and chronic. Second, we do not use cancer chemotherapeutic drugs as single agents because we know from experience (and understand the biology) that high-dose single agents induce selective survival, clonal outgrowth, and, ultimately, recurrence. It is plausible that there is a similar effect with high doses of a single chemopreventive agent, such as β-carotene (12), an effect that seems to be much less of an issue with the low-dose, multiple agent dietary interventions. With the coxibs, chemopreventive efficacy is demonstrable, but at the cost of elevating cardiovascular toxicity, probably as a consequence of prolonged plasma half-life (e.g., rofecoxib) or twice-daily dosing (e.g., celecoxib in the Adenoma Prevention with Celecoxib Trial at relatively high doses). At some point, we may conclude that low- to moderate-dose multiple agent regimens in the prevention arena may serve us best.

Third, placebo-controlled, phase II chemoprevention trials must extend well beyond 3 to 6 months to at least 1 to 2 years if we are to obtain essential long-term safety data. Fourth, serious thought should be given to the development of a few vanguard locations for large, national phase III trials to minimize risk of long-term chemopreventive agents due to toxicity. The coxibs, as well as previous experience with presumably safe chemopreventive agents, teach us that we must recognize the potential for toxicity and that this must not be overshadowed by beneficial effects. Once the
vanguard participants have progressed beyond 1 to 2 years without evidence of excess events in the intervention groups, then the much larger efficacy-testing participant population can be accrued.

Fifth, as discussed increasingly over the past few years, post-marketing surveillance, especially of drugs reaching large, relatively healthy populations, must be improved dramatically. The short-term, 6-month phase III arthritis trials were of inadequate length to reveal the potential for toxicity observed when coxib dosing was continuous for several years. In this setting, it is essential that well-designed, placebo-controlled, post-marketing trials be done with orally dosed drugs that are destined to reach large, healthy populations for the purpose of keeping them that way.

Finally, as Hawk and Viner (13) eloquently discussed in a recent editorial in this journal, we must remember “the critical role that risk-benefit assessments play in agent development for cancer prevention.” Although safety of new medications is of paramount importance, a sense of proportion is also vital for the rational evaluation of the balance between risks and benefits of long-term therapies to prevent fatal diseases. Despite close consideration of the real, but modest, cardiovascular toxicity of the coxibs, we have heard little of the contrast with the equally real and greater gastrointestinal toxicity of nonselective COX inhibitors, a source of extensive morbidity and mortality (14-16). Furthermore, we all await the final unblinding of the end-point colonoscopy data for the rofecoxib and celecoxib colorectal adenoma prevention trials. Certainly, if the coxib interventions are associated with a consistently large reduction in adenoma recurrence, especially a reduction in large adenomas, then the benefits for celecoxib may far outweigh the risks, at least for a selected population of patients with a history of high-risk adenomas.

Unfortunately, and perhaps largely because of this last problem of selective inattention, the lessons learned may fall on deaf ears. The pharmaceutical industry is likely to turn its attention and resources away from chemopreventive-agent drug development as a result of these discouraging events; we would encourage them not to do so.

References
What Happened to the Coxibs on the Way to the Cardiologist?

David S. Alberts, John D. Potter, Maria Elena Martinez, et al.


Updated version
Access the most recent version of this article at:
http://cebp.aacrjournals.org/content/14/3/555

Cited articles
This article cites 13 articles, 6 of which you can access for free at:
http://cebp.aacrjournals.org/content/14/3/555.full#ref-list-1

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.