Vioxx Withdrawal Alarms Cancer Prevention Researchers

Thanks to a colon cancer prevention study, millions of arthritis sufferers lost a favorite pain reliever. Is that good news or bad? Good news certainly for the patients who no longer face unreasonable risks for heart attack and stroke; bad news, potentially, if the Vioxx debacle drains the chemoprevention drug pipeline.

The study isn’t the first to reveal side effects of a promising chemoprevention agent, and it probably won’t be the last. Cancer researchers are eager to point out, however, that many approved drugs carry some risks and that the Vioxx case should not deter researchers and pharmaceutical companies from doing the long-term studies needed to show chemopreventive effects.

When Merck withdrew Vioxx (rofecoxib) from the market on September 30, concerns were for arthritis sufferers, the main users of the drug. But the study that showed the increased risk of heart attack and stroke among Vioxx users was a Merck-funded colon cancer chemoprevention trial. As the medical journal editorial pages ran condemnations of the U.S. Food and Drug Administration and the drug maker for ignoring early signs of trouble, the spotlight quickly widened to include the other COX-2 inhibitors.

Within days, Pfizer, maker of Celebrex (celecoxib) and Bextra (valdecoxib), announced that Bextra raised heart attack risk in heart bypass patients. So far, Celebrex’s safety has not been questioned. Celebrex is the most heavily studied COX-2 inhibitor in cancer chemoprevention and treatment trials.

There are nearly 50 ongoing National Cancer Institute–sponsored trials using celecoxib for cancer prevention or treatment, according to Ernest Hawk, M.D., of NCI’s Division of Cancer Prevention. The drug is being studied as a chemopreventive agent in cancers of the head and neck, colon and rectum, breast, lung, bladder, skin, and ovary. Hawk said NCI had been planning to use Vioxx in two cancer prevention trials, but, not surprisingly, those plans were aborted last month.

The furthest along and largest of NCI’s celecoxib trials is the Adenoma Prevention with Celecoxib (APC) trial, which is evaluating the safety and efficacy of celecoxib compared with placebo in patients with prior colorectal adenomas. Patients were enrolled regardless of cardiovascular risk, Hawk said, because the issue was not as well understood when the trial opened in 1999. “Following the reported cardiovascular safety concerns with rofecoxib, we added a cardiovascular expert to the independent data safety monitoring board.”

Patients on the celecoxib trials are worried. “Our patients read the newspaper and hear the newscasts,” said Raymond N. DuBois, M.D., Ph.D., of Vanderbilt University in Nashville. “They’re calling and asking if they should stay in the [polyp prevention] study. I can guarantee that if we were able to get any information that there was risk, we would’ve certainly stopped that trial,” said DuBois, a pioneer in COX-2 inhibitors and cancer.

Accrual is down in the National Surgical Adjuvant Breast and Bowel Project’s polyp prevention trial, according to D. Lawrence Wickerham, M.D., associate chair at NSABP. “Our responsibility is to get the facts out, and we’ve been doing that over the past 10 days,” he said. “In the case of Celebrex, we can document that [a lot] of information is out there about its cardiovascular effects, and the trials will go forward.”

A Familiar Road

Vioxx isn’t the first drug to show unforeseen risks when studied long-term. “Anytime you do large, long trials, there’s always a chance you’ll find something unexpected,” Hawk said.

In the Prostate Cancer Prevention Trial, finasteride reduced the risk of prostate cancer by 25%. The troubling news was that men who developed prostate cancer while on finasteride ended up with a more aggressive form of the disease. Researchers are still trying to figure out why.

Then there’s the famous case of beta-carotene supplements in smokers. The hypothesis was that the antioxidants beta-carotene and vitamin E would reduce risk for lung cancer and possibly other cancers. When the Alpha-Tocopherol, Beta-Carotene (ATBC) cancer prevention trial began in 1985, both vitamin E and beta-carotene were deemed completely safe, said Demetrius Albanes, M.D., senior investigator in NCI’s Division of Cancer Epidemiology and Genetics. Ironically, beta-carotene was thought to be the safer of the two, based on long-term studies in patients with erythropoietic porphyria, a genetic skin disease.

But in both the ATBC and CARET (Beta-Carotene and Retinol Efficacy Trial), lung cancer incidence and mortality were higher among beta-carotene users. “[These were] two randomized controlled trials … yet one can walk into most health food stores and still buy beta-carotene,” Hawk said. “I’m not sure if the label says ‘if you’re a smoker you should think twice about..."
to put somebody on a preventive agent

Risk Is Relative

“There is no such thing as a healthy person,” said Michael B. Sporn, M.D., in the Department of Pharmacology and Toxicology at Dartmouth Medical School. “We are all at some risk. The higher the risk, the more willing one is to put somebody on a preventive agent that might have some risk associated with it. The more information about chronic safety of a drug, the better off we are in terms of trying to use it in chemoprevention.”

Waun Ki Hong, M.D., at the University of Texas M. D. Anderson Cancer Center in Houston, takes this idea a step further. For some patients, the risk is very high; therefore, he regards some of today’s chemoprevention as early cancer treatment. Oral leukoplasia, for example, is an aggressive manifestation that can often lead to cancer. The question is how to treat those lesions that will in all likelihood progress to cancer. Hong is testing Celebrex in patients with these lesions, and in other precancerous conditions as well. He says he is also talking with the FDA and AstraZeneca about testing their lung cancer therapy drug, Iressa (gefitinib), an epidermal growth factor receptor (EGFR) inhibitor, as a lung cancer prevention agent in the near future.

Prevention researchers are already thinking about how to fill the chemoprevention pipeline. “Right now, most drugs being used for cancer prevention were initially developed for completely different purposes,” said DuBois. “Nobody has a large, well-funded program under way to develop primary cancer chemoprevention agents.” That needs to change, said Wickerham. “That’s a long-term activity, but it makes more sense. I’ve heard that several drug companies have begun exploring possibilities in that arena.”

Extending patent protection for drug makers to test their drugs as chemoprevention agents would help move drugs into the investigational pipeline, Wickerham added. Today, patents last 17 years. By the time an agent is tested and approved for one indication, then moved into chemoprevention for years of additional testing, the patent that ensures market share and future profit is close to expiring.

Different Strategies

Sporn said intermittent drug administration might reduce side effect risks. He has tested a rat model of breast cancer, giving a chemopreventive agent for one month, followed by several weeks without chemotherapy, then more treatment. “In light of the Vioxx result, which gives us a warning that a drug that is relatively safe over the short term may not be so safe when given chronically, intermittent administration needs to be looked at in chemoprevention,” Sporn said.

He is a fan of combination chemoprevention as well. Drug combination “is a very important path to follow,” agreed NCI’s Hawk. “Based on data in animal systems, it typically allows one to decrease the doses of the individual drugs, yet retain a more potent effect.” NCI has two combination chemoprevention clinical trials. The first combines sulindac and eflornithine for patients at moderate risk for colon cancer. The second is in individuals with familial adenomatous polyposis, comparing celecoxib alone to celecoxib plus eflornithine.

At least one of the pharmaceutical companies in the spotlight is still behind cancer prevention. “From Pfizer’s point of view, chemoprevention of cancer is something we still see as a very important area of research,” said Craig Eagle, M.D., Pfizer’s medical director of global oncology. “The challenge is finding drugs that do provide a degree of benefit without any problems.” Time will tell if others share his view.

“If drug companies steer clear of chemoprevention, I fear that this field will have to rely on nutritional compounds, dietary supplements, and other lifestyle alterations alone,” Hawk said. “[The Vioxx withdrawal] could have a cooling effect. It’s the last thing I want to see happen, given the opportunities to benefit people at significant risk for cancer.”

—Cori Vanchieri