Vioxx shows some long-term cardiac effects

In 2000, John Baron, M.D., had high hopes for Vioxx, and he wasn’t alone. The drug was helping to ease the pain of millions of patients worldwide, without causing the gastrointestinal problems associated with aspirin. When Merck, Vioxx’s manufacturer, asked Baron to help lead a clinical trial testing the drug’s effectiveness for colon-cancer prevention, he was excited. “Here were drugs almost without side effects, so it seemed, and with potential cancer-protective properties,” he recalls thinking. “But, well, that’s not what happened.”

In the study—the Adenomatous Polyp Prevention on Vioxx (APPROVe) trial—the drug did, indeed, show signs of protecting patients from adenomas, benign growths that can progress to cancer. Unfortunately, it also doubled the risk of cardiovascular problems, such as heart attacks and strokes. When this became clear, in September 2004, the trial’s safety and data monitoring committee let Baron know; he informed Merck, and within a week Vioxx was off the market.

Trial: Over the next few years, Baron and his collaborators analyzed the data from the trial and wrote two papers on the drug’s apparent cardiovascular risks and chemopreventive effects. In a third paper, recently published in the Lancet, Baron discussed a follow-up effort intended to discover if the heightened risk of cardiovascular problems continued even after patients stopped taking Vioxx.

Risks: The APPROVe subjects were contacted and asked if they’d had a heart attack or stroke in the year after going off Vioxx. The results were broadly similar to those of the earlier studies, though the overall relative risks were somewhat smaller. Baron says that the number of people in the study and the number who suffered death or disease were too low to draw definitive conclusions. The risk in the year after going off Vioxx “was not statistically significant but was elevated,” he says. “Probably . . . there is an increased risk but . . . the study was too small to see it conclusively.”

Baron’s analysis also revealed that pre-existing cardiovascular risk factors—such as hypertension, smoking, or being overweight—seemed to raise the cardiovascular risk from taking Vioxx. Baron says that he is “marginally confident” about the conclusion but cautions that he can’t be certain of this link.

Questions have been raised recently about when Merck first knew about the risks of Vioxx. According to the New York Times, lawsuits against the firm have stated that “scientists at Merck were worried about Vioxx’s potential cardiovascular risks as early as 1997.” Still, for a time, the drug appeared to have real benefits.

Baron, who has stayed out of the legal turmoil that followed the revelations of 2004, says it can be difficult to come to definitive conclusions about the risks and benefits of a treatment. “You have to weigh the merits of one kind of endpoint against the harms of another,” he says. “And that’s not easy.”

Amos Esty