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Cholesterol Drug Scare Shenanigans

Posted on September 4, 2008 | Comments Off

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September 04, 2008, FoxNews.com

Why is the editor of the New England Journal of Medicine encouraging a cancer scare over the cholesterol-lowering drug Vytorin? Is he overcompensating for past bad behavior?

Prescribed for millions of patients, Vytorin is a single pill that combines the cholesterol-lowering medicines Zocor and Zetia. Its popularity declined in early 2008 after several studies questioned whether Vytorin produced any health benefit and a panel of cardiologists recommended that the drug be used only as a last resort.

Then, in July, a Norwegian researcher reported that, in a clinical trial known as SEAS, 102 patients taking Vytorin developed cancer, compared with 67 patients taking a placebo — a statistically significant result indicating that chance could be ruled out with some degree of confidence as the cause.

Drug companies Merck and Schering-Plough, the makers of Zocor and Zetia, respectively, subsequently commissioned famed epidemiologist Richard Peto of Oxford University to evaluate the SEAS results. Those findings were published this week on the Web site of the New England Journal of Medicine.

Based on his review of SEAS and two other ongoing Vytorin trials (called SHARP and IMPROVE-IT), Peto concluded that the trials provided no credible link between Vytorin and cancer risk, although follow-up would be needed to make a more reliable determination.

Peto based his conclusion on the fact that in the SEAS trial, there were no statistically significant increases in any specific type of cancer; the statistically significant result occurred only by adding all cancers together. Moreover, for the three specific cancers with reported risks closest to attaining statistical significance in the SEAS trial — skin, stomach and prostate — the results were precisely the opposite of what occurred in the SHARP and IMPROVE-IT trials. That is, in those trials, placebo patients had higher rates of cancer at those sites than did Vytorin users.

Additionally, Peto found no increase in risk of cancer over time in the three trials — generally, cancer risk increases with increasing exposure to a cancer-causing substance. This observation, he acknowledged, will also require more follow-up, since the patients in the trials have been followed for only a few years.

Although more Vytorin users than placebo patients died from cancer in all three trials, the result was only statistically significant in the SEAS trial. But Peto dismissed the SEAS result, since it was what had generated all the controversy in the first place and so couldn't be used to verify the validity of a link between Vytorin and cancer. More telling than overall cancer deaths, however, was the lack of a statistically significant excess number of deaths from any specific type of cancer.

Though the available data don't absolutely prove that Vytorin doesn't increase cancer risk, there seems to be no good reason to think that it does — unless you're the editor of the New England Journal of Medicine.

In an editorial accompanying the Peto analysis, editor Jeffrey Drazen wrote that, "Although the Oxford group may ultimately prove to be correct, it is appropriate to raise a note of caution." Without providing any back-up scientific data, Drazen then speculated that since Vytorin works by interfering with the gastrointestinal absorption of cholesterol, it might also interfere with the absorption of other unnamed molecular entities that "could conceivably affect the growth of cancer cells." Drazen also was unwilling to cede that higher cancer death rate of Zetia patients was simply due to chance "until further data are in."

But the main reason that Drazen is simply wrong about keeping the Vytorin cancer scare on life support is that there's no evidence whatsoever that the drug is associated with any specific form of cancer at any specific site.

For example, excessive smoking is associated with lung cancer, and occupational asbestos exposure is associated with mesothelioma. But given a specific route of exposure, no potential carcinogen is known to cause cancer at multiple sites on a random or haphazard basis. Aggregating different cancers into a catch-all "all cancer" category simply lacks demonstrable biological plausibility.

Drazen's insistence on waiting for more data on cancer deaths is similarly nonsensical. Vytorin would first need to be associated with an increased risk of a death from a specific form of cancer — a notion clearly contradicted by the data so far.

None of this should be controversial or new to Drazen. So what's up with him?

Prior to becoming editor of the New England Journal of Medicine, Drazen had close ties with many drug companies — and once got into trouble because of them.

In March 1999, the Food and Drug Administration found that Drazen made "false and misleading" statements about the safety and efficacy of the asthma drug levalbuterol made by Sepracor — a drug company that hired Drazen to review two studies on the drug and then to comment to a company interviewer. Needless to say, given this past, his NEJM appointment was somewhat controversial.

So since becoming editor, Drazen has seemingly gone out of his way to turn against the hand that once fed him. In a May 2005 Wall Street Journal article entitled, "Medical Editor Turns Activist On Drug Trials," former NEJM editor Marcia Angell said that, "[Drazen's] been converted. Through painful experience, Jeff is learning what these companies are about. He sees the ugly side that he hadn't seen

before — the bias that company-sponsored research contains, the suppression of results that they don't like, the spin of unfavorable results." Dr. Angell would apparently have us believe that Sepracor forced or tricked Drazen into saying "false and misleading" things about their drug.

So now it seems that instead of pro-drug company bias and spin, Drazen now leans toward anti-drug company bias and spin. Imagine if Drazen were just to stick to science in the first place. He wouldn't have to worry about shifting alliances to atone for his mistakes.

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