Trends-in-Medicine

July 2008

by Lynne Peterson and D. Woods

Quick Pulse

Trends-in-Medicine
Stephen Snyder, Publisher
2731 N.E. Pinecrest Lakes Blvd.
Jensen Beach, FL 34957
772-334-7409 Fax 772-334-0856
www.trends-in-medicine.com
TrendsInMedicine@aol.com

MORE CONTROVERSY FOR VYTORIN

A large European trial of Merck/Schering-Plough's cholesterol-lowering drug, Vytorin – a combination of 40 mg of Merck's Zocor (simvastatin) and 10 mg of Schering's Zetia (ezetimibe) – has shown disappointing results and possibly raised new questions about the drug. The randomized, placebo-controlled SEAS trial of 1,873 patients with mild-to-moderate, asymptomatic aortic stenosis was conducted at 173 sites in Norway, Sweden, Denmark, Finland, Germany, and the U.K. The trial:

- **Decreased LDL overall** at 8 weeks by 61% with Vytorin vs. no change with placebo, and the effect was sustained throughout the study. This was described as "substantially lower than what is seen in most trials with lipid-lowering regimens."
- **Missed the primary endpoint** of cardiovascular (CV) death, aortic valve replacement surgery, congestive heart failure (CHF) resulting in hospitalization from aortic stenosis (AS) progression, non-fatal myocardial infarction (MI), CABG, PCI, hospitalization for unstable angina, and non-hemorrhagic stroke.
- **Missed the secondary endpoint** relating to aortic stenosis – a composite of CV death, aortic valve replacement surgery, and CHF resulting in hospitalization from AS progression.
- **Significantly reduced the ischemia in the other secondary endpoint** – a 22% reduction (p=0.02) in the composite of CV death, non-fatal MI, CABG, PCI, hospitalization for unstable angina, and non-hemorrhagic stroke. The main component in the reduction was a reduction in the need for revascularization. Principal investigator Professor Terje Pedersen of Ulleval University Hospital in Oslo, Norway, said, "This finding was better than we hoped for…The most important component of the ischemic endpoint was CABG, and that was quite substantially lower. The rate was much lower in the treated group than the placebo group, and the surprising thing was that most of the bypass surgery was done in patients who had their valve replaced, so while the surgeon was opening the chest, he might choose to do bypass because it was convenient, but it was not necessary in a large percentage of patients treated with (Vytorin)."

SEAS was funded by Merck, but the data were analyzed by the investigators, who released the results at a press conference in London instead of waiting for presentation at a major medical conference or publication in a peer-reviewed medical journal because they "found it very difficult to maintain the secrecy of the results." The study was completed in March, when the last patient had been followed for four years. Researchers then continued to collect data for a few weeks and enter it into the database. On June 30, 2008, the data file was frozen, and data analysis began.

More than five million older Americans have some form of aortic stenosis, which involves partial blockage and calcification of the aortic valve, and the only treatment is surgery. Untreated, it can lead to heart failure or MI. Valve replacement, performed in patients with severe symptoms, is the second most frequent type of heart surgery. Some research shows that a high level of LDL is a risk factor for developing aortic stenosis, and lowering LDL may result in reducing rates of heart attacks, strokes, and other heart-related problems.

Since Pfizer's Lipitor (atorvastatin) previously showed no benefit on aortic stenosis, the lack of an effect on AS was not surprising. What was surprising – and what dominated the press conference discussion – was a marked increase in cancer in the SEAS patients taking Vytorin. Patients on Vytorin had a 50% higher incidence of cancer compared to placebo.

The SEAS researchers decided that releasing this data would confuse doctors and the public, so they sought additional expert input. Dr. Pedersen said, "We have done a number of analyses to find out whether this apparent increased risk of cancer was real or due to chance. We noted the previous histories of the patients, (and) we looked at prior cancers…We can say that the total cancer burden in a lifetime is the same… We felt that this was not enough to calm the nerves of the company or the public opinion…Therefore, we decided to contact the other studies that were going on using the same combination of drug."

After consultations with investigators in two other Vytorin trials – IMPROVE-IT, which is still enrolling, and SHARP, which is ongoing but fully enrolled – Sir Richard Peto, a well-known cancer biostatistician and epidemiologist at the University of Oxford, U.K., was asked to do an emergency analysis. Over the weekend before this announcement, Dr. Peto analyzed the data from all three trials – SEAS, SHARP, and IMPROVE-IT. He concluded that there was no evidence to support the risk seen in the SEAS data. He said that he saw no elevated cancer risk with Vytorin and no trend to an increased risk, "We should not be diverted by fears of cancer …There is no good evidence, no credible evidence, of an overall increase in cancer."

In IMPROVE-IT and SHARP combined, there were 313 cancers in the Vytorin arm vs. 326 in the control arm. With all three trials pooled, there was still no increased cancer risk with Vytorin (p=0.5). Dr. Peto said, "My expertise is the causes of cancer, and this isn't a pattern one would expect to see…There was a roughly 50% increase in cancer in just a few years…and it was a variety of cancers. Most causes are in one cancer, and it was more than play of chance…We were uncomfortable in handing over data that might be looked at without an appropriate epidemiologic view…So we told our investigators that we would do an independent analysis and report it to regulatory agencies around the world. We sent it to the regulators at the same time we sent it to the company, so the company has not had input…(The data) do not confirm the hypothesis that (Vytorin) is associated with an increased cancer risk. They do not…We can look over time at active vs. control in Years 1, 2, 3, and beyond, and if something were really causing cancer, you would expect the effect to get bigger over time…Actually you wouldn't expect it to increase, and we don't. If you had no effect, then you would expect the excess to be uniform over time, and it is."

According to Dr. Peto, the data from SHARP and IMPROVE-IT show that there is no increase in cancer risk over time, not in cancer incidence and not in death from cancer. He also said that trials of statins, with data out to five years, show no apparent effect on cancer risk. As for the SEAS data, he said, "We know that we don't have a sudden 50% increase in cancer within a few years. We know that…Some (patients) by chance got more and some got less, but it averaged out to nothing going on." He called the increase in prostate cancer "not remarkable, not even as remarkable as rolling 6s with dice."

SEAS Trial Results

Measurement	Vytorin	Placebo	p-value
LDL reduction at 8 weeks (from baseline of 140 mg/dL)	52 mg/dL (61%)	0	---
Primary endpoint: Composite of major cardiovascular events	333 patients	355 patients	Nss HR 0.96
Secondary endpoints			
Aortic valve disease events	308 patients	326 patients	Nss HR 0.97
Ischemic events	148 patients (15.7%)	187 patients (20.1%)	0.02
Adverse events			
Serious adverse events attributed to cancer	93 (9.9%)	65 (7.0%)	0.027
Cancer deaths	39 (4.1%)	23 (2.5%)	0.05
Rate of new cancers	106	67	---
Prostate cancer	23 patients	14 patients	---
Kidney cancer	25 patients	11 patients	---

Dr. Rory Collins, professor of medicine and epidemiology at the University of Oxford and chairman of the SHARP steering committee, said that the Data Monitoring Committee (DMC) which reviewed data from the three studies "completely endorses Professor Peto's conclusions that the analysis of SHARP and IMPROVE-IT do not support any increase in cancer… Its conclusion at the end of the meeting was that the committee was unanimous that there is no reason to modify the SHARP protocol."

Dr. Robert Califf of Duke University, a principal investigator for IMPROVE-IT, said, "While I agree …that we shouldn't be alarmed, I wouldn't want anyone to take away that we aren't looking carefully over time at the outcomes."

Dr. Steven Nissen of the Cleveland Clinic, a past president of the American College of Cardiology and a known critic of Vytorin, was even less willing to dismiss the cancer issue. He said in an interview, "This cancer issue can't be overlooked. You can't use data from incomplete experiments to try to refute other data. The companies are behind this all the way. Look at the number of cardiovascular events averted with Vytorin – 39 – but they stack up against 28 excess cancers and a significant increase in cancer mortality. It goes back to what I said after ENHANCE, (we should) only use drugs that have a clinically proven health benefit and that means statins for first-, second-, and third-line therapy, and reserve Vytorin for the last resort."

Reporters participating in the press conference tried to clarify the benefits of the drug. Dr. Pedersen responded, "I don't have the details with me."

Asked how the SEAS trial data relates to ENHANCE (which earlier this year found that Vytorin significantly reduced LDL vs. simvastatin alone but did not slow atherosclerosis when carotid intima media thickness was measured by ultrasound in patients with heterogeneous familiar hypercholesterolemia), Dr. Pedersen said, "ENHANCE used a surrogate endpoint which we didn't study at all…We studied the occurrence of clinical events, and I don't think that it is relevant to compare the two studies." Dr. Collins added, "With ENHANCE… there were patients looking at a surrogate outcome, the artery wall, to see if a further reduction in LDL produced any additional change in the artery wall because patients were all getting statins and then adding ezetimibe on the surrogate end-point that was not sensitive…I think ENHANCE was not a good study. It is not that the result was not good, but that the study wasn't good. It had little ability to test the clinical efficacy of (Vytorin) because it used a surrogate outcome that was not informative on clinical efficacy. SEAS had the benefit of combining a statin and ezetimibe and producing a big reduction in LDL. It is very difficult to have that with a statin alone. The combination allows you to get big reductions in LDL and that is…good news for these patients." Dr. Eugene Braunwald of Harvard Medical School, an IMPROVE-IT investigator, said, "I believe that ENHANCE was a flawed trial which really didn't provide any new information. I believe that the SEAS trial is the first clinical outcome trial that shows that the combination of ezetimibe and a statin improved clinical outcome, so I see that as a very encouraging finding. It was not compared to the statin alone, but that is what we are doing in the IMPROVE-IT trial."

A reporter commented, "Several panelists have challenged the validity of ENHANCE and its design, and it seems to me to be a different problem with the design of this study." A speaker responded, "If one looks at the previous trials of a statin alone vs. control…the bigger the LDL reduction, the bigger the reduction in MI, stroke, and revascularization. I think that reinforces the rationale in the SEAS and SHARP trials."

Asked whether the LDL lowering might be due simply to simvastatin and not ezetimibe, Dr. Califf said this is one reason that the IMPROVE-IT trial should be completed, "IMPROVE-IT is the only large trial looking at ezetimibe vs. placebo on top of a statin. We can't conclude that it was ezetimibe. It was the combination that had the results…The main point is that we do need to get the answers on the balance of risk to benefit with IMPROVE-IT and SHARP. I think that everyone can appreciate the complexity of bringing these massive datasets together and putting them in Dr. Peto's hands. Perhaps it is the way things should be done in the future on sharing across trials…We are left now with the need to go forward and get these trials completed."

In an odd piece of timing, the FDA press office emailed reporters a Consumer Update on Vytorin during the press conference. The Update – a Q&A with Dr. Robert Temple, director of the FDA's Office of Medical Policy in the Center for Drug Evaluation and Research (CDER) dated July 18, 2008 – dealt only with ENHANCE, not SEAS (**www.fda.gov/consumer/updates/vytorin071808.html**). Among the points in the Update were:

- "The (ENHANCE) results were disappointing, of course, but they do not give the answer about the value of ezetimibe. At this point we know that ezetimibe lowers cholesterol modestly (not nearly as much as a statin), but we do not have definitive evidence that it lowers the risk for cardiovascular disease. The answer to whether it does should come from a large (18,000-patient) outcome study (IMPROVE-IT) that will examine the effect of ezetimibe added to simvastatin on cardiovascular outcomes. That study is underway but will not be completed for several years (2012)."
- "It is not clear why the lower levels of LDL cholesterol in patients who took Vytorin did not lead to favorable changes in carotid artery wall thickness, compared to patients treated with simvastatin alone. FDA is now reviewing the final results from the ENHANCE study."
- "Although the study (ENHANCE) could perhaps lead to doubts about ezetimibe – noting again that its lack of effect was on a biomarker – it casts no doubt at all on the value of lowering cholesterol with a statin…There is no basis at all for questioning the cardiovascular benefits of statins in reducing the rate of death, heart attack, and stroke in people at risk from elevated LDL cholesterol. And we are worried that some people might suddenly stop taking their statins or other preventive medicines, such as antihypertensives, either because they misunderstood news reports or are affected by a more general sense of doubt."
- *On advice for consumers:* "People should not misunderstand ENHANCE and think it means that elevated LDL cholesterol need not be lowered…People should not stop taking Vytorin or any other drug containing a statin without their doctor's recommendation, even if they have concerns about the study. Patients can discuss with their

doctors whether they should take a larger statin dose or add ezetimibe to control LDL cholesterol adequately. The results with statins make it overwhelmingly clear that controlling LDL cholesterol is essential."

♦