

Evidence Behind the Ezetimibe/Simvastatin Controversies

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Ezetimibe (Zetia®, Merck) was approved by the FDA in October 2002 followed by an approval in July 2004, of the combination of ezetimibe and simvastatin in a single tablet (Vytorin®, Merck).¹ Approval of both products was based on the cholesterol lowering effect, not cardiovascular events. To date, there is still a lack of outcomes data with either product. Despite the lack of data, ezetimibe and ezetimibe/simvastatin have been prescribed to almost three million people worldwide and last year, sales accounted for just over \$5 million dollars.^{2,3} Almost one year ago, news began to break questioning the efficacy of ezetimibe/simvastatin and more recently some are questioning the safety of ezetimibe/simvastatin.

INDICATIONS

Ezetimibe/simvastatin is indicated for lowering total cholesterol, low density lipoprotein cholesterol (LDL), ApoB, triglycerides and non-high high density lipoprotein (HDL) cholesterol as well as to increase HDL in patients with primary (heterozygous familial and nonfamilial) hyperlipidemia or mixed hyperlipidemia.⁴ It is also approved as an adjunct with other lipid lowering therapies for lowering total cholesterol and LDL in homozygous familial hyperlipidemia.

CLINICAL EFFICACY

Results from the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) study were released January 14, 2008, in a press release from Merck/Schering Plough stating that based on the primary endpoint of the study, there was no significant difference between ezetimibe/simvastatin and simvastatin alone.^{5,6}

The ENHANCE study was a prospective, double-blind, multicenter study with patients aged 30-75 years who had heterozygous familial hypercholesterolemia (HeFH).⁷ Patients were ran-

domized to simvastatin 80 mg plus placebo or simvastatin 80 mg plus ezetimibe 10 mg. Patient's LDL level had to be greater than or equal to 210 mg/dL. The 24 month double blind portion of the study followed a screening phase and a six week single-blind placebo run in phase. Carotid intima media thickness (CIMT) was assessed with ultrasound at baseline, 6, 12, 18 and 24 months with replicate scans done within one week of the baseline and 24 month scans. The primary outcome was the change from baseline in the mean CIMT. Secondary outcomes included the proportion of patients with regression in the mean CIMT, the proportion of patients with new plaques of more than 1.3 mm, as well as lipid levels.

A total of 720 patients were randomized with 642 patients included in the efficacy analysis. Patients in the ezetimibe/simvastatin group had higher body mass index (27.4 ± 4.6 vs 26.7 ± 4.4 , $p=0.047$), a higher rate of hypertension ($p=0.09$) and a lower rate of previous myocardial infarctions ($p=0.06$). Prior use of statins was reported by approximately 80% of patients in each group. The results in table 1 show that changes in cholesterol levels in the combination therapy group were greater than in the monotherapy group but the difference in change from baseline in carotid IMT between groups was not significant. Other intima media thickening measures, proportion of patients with regression or with new plaque formation, were also not significantly different between groups.

Seven patients in the simvastatin group had cardiovascular events (cardiovascular related death 1, nonfatal myocardial infarction 2, nonfatal stroke 1, coronary revascularization 5) compared to 10 patients in the ezetimibe/simvastatin group (cardiovascular related death 2, nonfatal myocardial infarction 3, nonfatal stroke, and coronary revascularization 6).

There are several limitations to the ENHANCE study including the study population, the lack of a minimum CIMT for study entry, the methodologies used for imaging, possibly the study duration and the sample size. The study included only

TABLE 1. CHANGES FROM BASELINE AT 24 MONTHS

	Simvastatin	Simvastatin/ezetimibe	p-value
Mean intima media thickness of carotid artery (mm)	0.0058±0.0037	0.0111±0.0038	0.29
Total cholesterol (%)	-31.9±0.8	-45.3±0.8	<0.01
LDL (%)	-39.1±0.9	-55.6±0.9	<0.01
HDL (%)	7.8±0.9	10.2±1.0	0.05

HeFH patients, who are not the typical dyslipidemia patients, given that HeFH affects 0.2% of the population.⁸ Additionally, 80% of patients were already being treated with statins.⁷ There were editorials and summary comments from the expert panel suggesting some potential concerns with the imaging methodologies, including inconsistent measurements, use of outdated imaging methodologies, missing data and biologically implausible readings.⁹⁻¹¹ The estimated sample size of 650 was based on detecting a difference of 0.05 mm in CIMT assuming a standard deviation of 0.20 mm.⁷ Two editorialists and the statistician on the expert panel suggest that the standard deviation was about 0.06 mm.^{10,11} If this is true, an effect size of 0.01 mm could result in a statistically significant result.¹¹ The authors response was that the study was underpowered to detect a significant difference in the range of 0.06 mm to 0.11 mm but could measure significant differences of 0.15 mm.¹²

The results of the study confirm the cholesterol lowering effects of ezetimibe/simvastatin but given the limitations of the study the effect of the addition of ezetimibe to simvastatin on atherosclerosis progression in the high risk population of patients with HeFH remains unanswered.

The effect of ezetimibe/simvastatin 10 mg/40 mg on LDL cholesterol in patients with aortic stenosis (SEAS) has also just been completed and results published online ahead of print.¹³ The SEAS study was a prospective, double-blind, placebo controlled multicenter study in patients with asymptomatic, mild to moderate aortic valve stenosis who otherwise did not have an indication for cholesterol lowering therapy. Patients were to be followed for at least four years. The primary endpoint of the study was a composite of cardiovascular events associated with aortic valve disease and atherosclerotic disease. Secondary endpoints were the individual components of the primary endpoint.

The study included 1873 patients. There were 333 patients with a cardiovascular event in the ezetimibe/simvastatin group compared with 355 patients in the placebo group (hazard ratio 0.96, 95% CI 0.83 to 1.12, $p=0.59$). There was no significant difference between the groups for the aortic disease event endpoint (308 vs 325, hazard ratio 0.97; 95% CI 0.83 to 1.14, $p=0.73$). There was a significant difference between groups for the ischemic cardiovascular events with 148 (15.7%) patients in the ezetimibe/simvastatin group having an ischemic event compared with 187 (20.1%) patients in the placebo group (HR 0.78; 95% CI 0.63 to 0.97; $p=0.02$). The therapy was generally well tolerated; however, in the safety analysis, 93 (9.9%) patients in the ezetimibe/simvastatin group versus 65 (7%) patients in the placebo group had a cancer ($p=0.03$). There were also more cancer deaths in the ezetimibe/simvastatin group (39 (4.1%) versus 23 (2.5%) $p=0.05$; $p=0.06$ with Yates' continuity correction).

The cancers were not a particular type nor did the number of events increase with more prolonged treatment.

This study demonstrated that the combination therapy did not have a significant effect on the composite endpoint of cardiovascular events; however, LDL was lowered and there were significantly fewer ischemic events in the treatment group. While there were numerically more cancer related deaths in the ezetimibe/simvastatin group, the confidence interval around the hazard ratio includes 1 with a corrected p value that exceeds 0.05; therefore, it is possible that there is not a difference between the groups. The unexpected outcome of more cancers and cancer related deaths needs further investigation.

Investigators have recently completed an analysis on interim data from two large currently ongoing ezetimibe/simvastatin studies, SHARP (Study of Heart and Renal Protection) and IMPROVE-IT (Improved Reduction of Outcomes Vytarin Efficacy – International Trial) for a combined total of 20,617 patients.¹⁴ Patients in the SHARP trial have chronic kidney disease and are receiving either ezetimibe 10 mg/simvastatin 20 mg or placebo and at the time of the interim analysis have a mean follow-up period of 2.7 years. The IMPROVE-IT study is in patients with acute coronary syndrome and they are receiving ezetimibe 10 mg/simvastatin 40 mg or simvastatin 40 mg. The mean follow-up period in IMPROVE-IT is one year. The results of their analysis are summarized in table 2, showing that the increased incidence of cancer seen in the SEAS has not been seen thus far in the SHARP and IMPROVE-IT studies. There is a slightly greater risk of cancer related deaths in the treatment groups, but this is not statistically significant.

UTILIZATION

These controversies raised by the ENHANCE and SEAS studies have caused great concern, and may affect the care of a very large number of patients. Jackevicius et al conducted an analysis of IMS Health claims data to assess the prescribing practices and expenditures of ezetimibe and ezetimibe/simvastatin in the United States and Canada.¹⁵ The objective was to compare the trends between the two countries. Utilization of ezetimibe and ezetimibe/simvastatin was higher in the US than in Canada. In the US, the use of ezetimibe increased by an average of 27,200 prescriptions per month and ezetimibe/simvastatin use increased by an average of 61,000 prescriptions per month. At baseline (2002), there were 3927 monthly lipid lowering agent prescriptions per 100,000 people which increased to 6,827 prescriptions per 100,000 people in 2006. The number of statin prescriptions per 100,000 people in 2002 and 2006 were 3,423 and 5,509, respectively, which was a decrease from 86.5% to 80.8% of prescriptions.

TABLE 2. ANALYSIS OF CANCER EVENTS IN SEAS, SHARP AND IMPROVE-IT

Cancer events	Active	Control	
SEAS	101 (37 fatal)	65 (20 fatal)	$p=0.006$ (uncorrected)
SHARP & IMPROVE-IT	313 (97 fatal)	326 (72 fatal)	Risk ratio 0.96, 95% CI 0.82 to 1.12

ECONOMIC CONSIDERATIONS

The average wholesale prices per tablet of ezetimibe 10 mg and ezetimibe/simvastatin are \$3.53 and \$3.60, respectively. Costs of medications that may be used as alternatives to ezetimibe or the combination include Niaspan (\$2.39-\$4.20/capsule); cholestyramine powder (\$0.10-0.15/gm), fenofibrates (\$0.60 to almost \$3 depending on the dose and product) or statins with more potent LDL lowering than simvastatin such as atorvastatin (\$3.18-\$4.54) or rosuvastatin (\$3.97).

FACTS TO CONSIDER

The ENHANCE study was a single, surrogate marker endpoint study which was not designed to evaluate cardiovascular outcomes. The study showed that the addition of ezetimibe to simvastatin did not result in greater reduction in carotid intima thickening compared to simvastatin alone. The LDL lowering of the combination ezetimibe/simvastatin was confirmed in the study. Patients included in the study had heterozygous familial hyperlipidemia, not the typical dyslipidemia patient seen in practice and most of the patients had already been treated with a statin prior to study participation.

The increased incidences of cancer and cancer related deaths in patients receiving the combination of ezetimibe/simvastatin in the SEAS study were low and reportedly could have occurred by chance. When the interim data from two larger studies were evaluated to see if the incidences of cancer and cancer related deaths were greater with ezetimibe/simvastatin there did not appear to be a difference. The patients in this study had mild to moderate aortic stenosis with no other indication for cholesterol lowering therapy and the mean follow up of the patients in the interim data analysis is only up to about two years.

WHAT TO TELL YOUR PATIENTS

Should patients stop taking their ezetimibe/simvastatin?

No, the study that some might think calls into question the benefits of adding ezetimibe to simvastatin, perhaps even questioning the benefit of lowering cholesterol, did not measure important outcomes like preventing heart attacks or strokes. We still do not know the extent of the benefit of ezetimibe, except that it lowers cholesterol. Lowering cholesterol is still important for reducing patient's risks for heart attacks and strokes.

The information that raised concerns about ezetimibe/simvastatin possibly causing cancer was from a single study and was not enough to conclusively say that there is an increased risk of cancer. Investigators have looked at the number of patients developing cancer in two larger studies that are currently being done with ezetimibe/simvastatin and they have not found that significantly more patients taking the combination have developed cancer. Additional research is needed to confidently answer this question.

Is there an increased risk of cancer and cancer related deaths with ezetimibe/simvastatin?

More research needs to be done to answer this question. As stated above, the information that raised concerns about ezetimibe/simvastatin possibly causing cancer was from a single study and was not enough to conclusively say that there is an increased

risk of cancer and cancer related deaths. Investigators have looked at the number of patients developing cancer in two larger studies that are currently being done with ezetimibe/simvastatin and they have not found that significantly more patients taking the combination have developed cancer.

What alternatives to ezetimibe/simvastatin are there?

Patients should discuss their cholesterol levels with their physicians to determine this. The list of options may include increasing the simvastatin dose, changing to a more potent statin, adding bile acid sequestrants, fenofibrates, or FDA approved prescription niacin products.

Where can they get more information?

Patients can be referred to the FDA Consumer Health Information document, "Making Sense of Vytorin Concerns."¹⁶ ●

REFERENCES

1. Food and Drug Administration Center for Drug Evaluation and Research. Electronic Orange Book. Available at: <http://www.fda.gov/cder/ob/default.htm>. Accessed on: July 30, 2008.
2. Berenson A. Trial intensifies concerns about safety of Vytorin. Available at: <http://www.nytimes.com/2008/07/22/business/22drug.html>. Accessed on: September 8, 2008.
3. Schering-Plough. Schering-Plough Fact Sheet. Available at: http://www.schering-plough.com/schering_plough/news/fact_sheet.jsp. Accessed on: September 8, 2008.
4. Vytorin (ezetimibe/simvastatin). [package insert]. Merck/ Schering Plough. North Wales, PA. July 2008.
5. American College of Cardiology. ACC statement on ENHANCE trial. Available at: <http://www.acc.org/enhance.htm>. Accessed on: July 22, 2008.
6. American Heart Association. Statement from the American Heart Association on ENHANCE study results. Available at: http://www.americanheart.org/print_presenter.jhtml?identifier=3053094. Accessed on: July 22, 2008.
7. Kastelein JJP, Akdim F, Stroes ESG et al. Simvastatin with or without ezetimibe in familial hypercholesterolemia. *N Engl J Med* 2008; 358:1431-1443.
8. MERCK/Schering-Plough Pharmaceuticals. Merck/Schering-Plough Pharmaceuticals comments on results of the ENHANCE study: study presented at American College of Cardiology scientific sessions and published in on-line version of *The New England Journal of Medicine*. Available at: http://www.msppharma.com/msppharma/documents/press_release/enhance_clinical_trial_03-30-08.pdf. Accessed on: July 22, 2008.
9. Blake JA. Simvastatin with or without ezetimibe in familial hypercholesterolemia. *N Engl J Med* 2008; 359:530-531 (editorial).
10. Diamond GA, Kaul S. Simvastatin with or without ezetimibe in familial hypercholesterolemia. *N Engl J Med* 2008; 359:530 (editorial).
11. Strony J. ENHANCE experts panel meeting summary. Available at: http://s.wsj.net/public-resources/documents/WSJ_ENHANCE_review.pdf. Accessed on: July 22, 2008.
12. Akdim F, Groot ED, Kastelein JJ. Simvastatin with or without ezetimibe in familial hypercholesterolemia. *N Engl J Med* 2008; 359:532 (authors reply).
13. Rossebo AB, Pedersen TR, Boman K et al. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. *N Engl J Med* 2008. Available at: <http://content.nejm.org/cgi/reprint/NEJMoa0804602v1.pdf>. Accessed: September 4, 2008.
14. Peto R, Emberson J, Landray M et al. Analyses of cancer data from three ezetimibe trials. *N Engl J Med* 2008. Available at: <http://content.nejm.org/cgi/reprint/NEJMsa0806603v1.pdf>. Accessed: September 4, 2008.
15. Jackevicius CA, Tu JV, Ross JS, Ko DT, Krumholz HM. Use of ezetimibe in the United States and Canada. *N Engl J Med* 2008; 358:1819-1828.
16. Food and Drug Administration Center for Drug Evaluation and Research. Making sense of Vytorin concerns. Available at: <http://www.fda.gov/consumer/updates/vytorin071808.pdf>. Accessed on: September 12, 2008.

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JPSW CORRECTION

The 2007 Wisconsin Pharmacist Compensation Survey published in the September/October *JPSW* inadvertently left out Brian Kaske as one of the article's authors. The correct authors are David H. Kreling, PhD, Brian Kaske and David A. Mott, PhD. We apologize for the omission.