

Surrogate End Points and FDA Approval

A Tale of 2 Lipid-Altering Drugs

Bruce M. Psaty, MD, PhD

Thomas Lumley, PhD

RISK FACTORS SUCH AS HIGH BLOOD PRESSURE, elevated low-density lipoprotein (LDL) cholesterol levels, and high blood glucose levels are strongly, consistently, and directly associated with the risk of major cardiovascular events, including myocardial infarction, stroke, and heart failure. Over the last several decades, the development and widespread use of drugs to reduce the level of these risk factors have been a mainstay of cardiovascular disease prevention efforts.

For new drugs designed to treat these conditions, the US Food and Drug Administration (FDA) generally uses their treatment effects on the level of the risk factor to evaluate them for approval. Risk-factor levels serve as surrogate end points for the outcomes of primary interest—the incidence of cardiovascular disease. According to the FDA guidance on lipid-lowering therapy, “The objective of lipid-altering therapy is not merely to alter serum lipids but to diminish the morbidity and mortality from cardiovascular disease and/or pancreatitis that is associated with abnormal serum lipid levels.” Because the “ability to extrapolate the value of any particular lipid-altering drug in accomplishing either of these objectives is limited . . . lipid altering agents should be shown to have a relatively low incidence of adverse effects prior to approval for marketing.”¹

The primary advantage of the use of surrogate end points is the ability to evaluate drugs more quickly and in smaller trials than would be required for the demonstration of a reduction in the risk of major cardiovascular events. At the time of approval, however, information remains incomplete about uncommon risks and about the actual health benefits of drugs evaluated on the basis of surrogate end points. Drug effects on LDL cholesterol levels, for instance, are unlikely to provide useful information about off-target adverse effects such as rhabdomyolysis or about health benefits that involve other mechanisms. The public health advantages of rapid approval for drugs that turn out to be safe and effective need to be balanced against harms that might occur when drugs approved on the basis of surrogate end points turn out later either to have significant safety problems or to lack efficacy. Recent experience with 2 lipid-altering drugs, ezetimibe and torcetrapib, provides new evi-

dence about surrogate end point approaches to the drug approval process.

Ezetimibe

In October 2002, ezetimibe, a drug that inhibits the absorption of cholesterol by the small intestine, was approved for the treatment of hypercholesterolemia on the basis of its ability to reduce levels of LDL cholesterol. The FDA guidance on lipid-altering agents suggests that the “. . . demonstration of at least a 15% reduction from baseline in LDL cholesterol, in the absence of unfavorable alterations in other lipid parameters, is generally required for drug approval.”¹ The phase 3 trials of ezetimibe, summarized in the product label, were successful. In two 12-week trials that randomized 892 and 827 patients with hypercholesterolemia to placebo or active treatment,^{2,3} ezetimibe was associated with 16.5% and 16.9% greater reduction in LDL cholesterol levels than placebo. Additional trials showed that ezetimibe was more effective than placebo in reducing LDL cholesterol levels in patients who were already taking statins⁴ and in patients who simultaneously initiated statin and ezetimibe therapies.⁵ Except for a slightly higher frequency of mild elevations of hepatic enzyme levels in several studies,^{2,4} the frequency of adverse events did not generally differ significantly between ezetimibe and placebo, and serious adverse events were uncommon.

With expert marketing of ezetimibe alone and of the combination of ezetimibe and simvastatin in commercials highlighting the diet plus family history theme, sales of ezetimibe or the combination reached \$5 billion in 2007.⁶ Clinical trials evaluating the association between ezetimibe and the progression of atherosclerosis or the risk of cardiovascular events, however, have been slow to appear.

In January 2008, the sponsor disseminated a press release reporting the results of the ENHANCE trial.⁷ In the 2-year trial that randomized 720 patients, ezetimibe plus simvastatin was associated with a more pronounced reduction in LDL cholesterol levels than simvastatin alone (58% vs 41%; $P < .01$). For the primary end point of change in mean ca-

Author Affiliations: Cardiovascular Health Research Unit, Departments of Medicine, Epidemiology, Health Services (Dr Psaty) and Biostatistics (Dr Lumley), University of Washington; and Center for Health Studies, Group Health (Dr Psaty), Seattle, Washington.

Corresponding Author: Bruce M. Psaty, MD, PhD, Cardiovascular Health Research Unit, 1730 Minor Ave, Ste 1360, Seattle, WA 98101 (psaty@u.washington.edu).

rotid intima media thickness (IMT) measured at 3 sites, there was no significant difference ($P = .29$). Indeed, progression of carotid IMT was slightly but not significantly more rapid among patients randomized to ezetimibe plus simvastatin (0.1111 mm vs 0.0058 mm for simvastatin alone). According to the press release,⁷ adverse events were uncommon in both randomized study groups of the trial, and there were too few cardiovascular events to evaluate the association of treatment with health benefits.

As a measure of subclinical disease, carotid IMT, like lipid levels, is a surrogate end point. Biologically, measures of subclinical atherosclerosis are “closer” than lipid levels to measures of health benefits such as cardiovascular events. The scientific expectation is that the effects on lipids, on atherosclerosis, and on cardiovascular events should generally move in the same direction. But wall thickness is not the only determinant of risk,⁸ so it is theoretically possible that effects on IMT and clinical events could differ. A large, long-term trial in high-risk patients with acute coronary syndrome will eventually evaluate ezetimibe on the primary end point of major cardiovascular events, but this trial was started in January 2006, and the estimated completion date will not be until January 2011.

Torcetrapib

High-density lipoprotein (HDL) cholesterol level, a marker of reverse cholesterol transport, is inversely associated with cardiovascular risk, even in older adults.⁹ Although LDL levels rather than HDL levels have been the traditional targets of lipid-alerting therapies,¹ new drugs targeting HDL such as torcetrapib, an inhibitor of cholesteryl ester transfer protein, have been under development. In an early report involving 19 patients, torcetrapib taken at 120 mg per day was associated with large increases in plasma HDL cholesterol levels, 61% in individuals who were also treated with atorvastatin and 46% in those who were not.¹⁰ In two 8-week studies of 162 and 174 patients with below-average HDL cholesterol levels, torcetrapib dose was directly and strongly related to increases in HDL cholesterol levels.^{11,12}

Torcetrapib was also evaluated in several phase 3 trials of atherosclerosis progression. Despite large differences in HDL cholesterol levels between patients treated with torcetrapib and placebo, progression of coronary atherosclerosis and carotid atherosclerosis did not differ between treatments in moderate-sized trials that enrolled 752 to 1188 patients.^{13,14} In these trials, systolic blood pressure was significantly higher in the groups that had received torcetrapib.

In the ILLUMINATE trial,¹⁵ 15 057 patients with high cardiovascular risk were randomized to receive torcetrapib plus atorvastatin or atorvastatin alone. Among patients who received torcetrapib for 3 months, mean levels of HDL cholesterol were 28.4 mg/dL higher and mean levels of LDL cholesterol were 19.7 mg/dL lower than among individuals who had received placebo. Systolic blood pressure was also higher

by 4 mm Hg among patients who had received torcetrapib. After a median follow-up of 550 days, the trial was stopped early because of an increase in the risk of the primary end point, major cardiovascular events (hazard ratio, 1.25; 95% confidence interval, 1.09-1.44), and because of an increase in total mortality (hazard ratio, 1.58; 95% confidence interval, 1.14-2.19). In view of these results, the manufacturer halted the development of torcetrapib in December 2006.

Comment

The differences in histories of ezetimibe and torcetrapib, both drugs designed to alter lipid levels and prevent cardiovascular events, are striking. Ezetimibe was approved and marketed aggressively. The randomized clinical trials evaluating its effects on atherosclerosis and clinical events have been slow to be reported or started. Torcetrapib was never approved. A large, long-term randomized trial evaluating its association with major cardiovascular events was well under way before approval.

Of the 2 approaches, torcetrapib was clearly the more successful. If torcetrapib had been approved solely on the basis of its ability to increase HDL cholesterol levels, the drug might have been marketed for many years before the increase in cardiovascular events was detected. In the ILLUMINATE trial,¹⁵ torcetrapib was associated with an extra 12 cardiovascular events and an extra 3 deaths per 1000 person-years of use. This difference would be completely undetectable in voluntary reports of adverse events, and it would have been difficult to detect convincingly even in the best-designed observational study. The reliable detection of risks of this size requires large, long-term clinical trials such as ILLUMINATE.¹⁵

Risks of the magnitude seen in ILLUMINATE are nonetheless exceedingly large from the point of view of public health. In 1999-2000, the National Health and Nutrition Examination Survey data suggested that almost 1 in 10 US adults aged 20 years or older was taking a lipid-lowering medication.¹⁶ Drugs that increase HDL levels are likely to acquire a huge market soon after approval. Torcetrapib, had it been approved, might have been associated with an estimated 12 000 extra cardiovascular events and 3000 extra deaths per million person-years of use. Although the sponsor sustained short-term economic loss from the demise of torcetrapib, the approach used by the sponsor in its serious high-quality evaluation not only deserves praise, but may have spared the company the potential cost, litigation, and embarrassment that would likely have occurred if an approved drug later turned out to be unsafe and had to be withdrawn. Conversely, if torcetrapib had been safe and effective, the sponsor would have had sound scientific data for promoting its use early in the process.

The lack of experience in evaluating drugs that increase HDL cholesterol levels suggested the advisability of phase 3 trials that used the prevention of atherosclerosis progres-

sion, and not simply the reduction in HDL cholesterol levels, as a primary end point (personal communication, Steven Nissen, MD [Cardiovascular Medicine, Cleveland Clinic, Cleveland, Ohio], February 20, 2008). The increase in systolic blood pressure may also have suggested the need for a more complete preapproval evaluation. Nonetheless, this method of evaluation, which includes starting a large, long-term trial before drug approval, is an important development.

This course is not the one followed for ezetimibe; 3 years separated the date of approval from the start of the large cardiovascular outcome trial. The absence of evidence of a benefit on carotid IMT does not exclude the possibility of a benefit in terms of clinical cardiovascular events. But more than 5 years after its approval, information is still lacking about whether ezetimibe may “diminish the morbidity and mortality from cardiovascular disease.” If the effects of ezetimibe on cardiovascular events are as null as the reported effects on carotid IMT, thousands of patients may have been receiving a therapy that is less effective than either a statin or, for those already taking a statin, an increase in the statin dose. The substitution of an ineffective drug for an effective drug is another and costly form of harm.

After reports of an increase in the risk of myocardial infarction associated with rosiglitazone¹⁷ and an advisory committee hearing, the FDA is considering a new approach: “For new antidiabetic drugs, a reasonable approach might be to approve new entities on the basis of improved glycemic control and to ensure that well-designed, long-term studies comparing the new treatment with established therapy, with cardiovascular outcomes as endpoints of interest, are conducted in a timely manner after approval.”¹⁸ The same life cycle approach recommended by the Institute of Medicine is also important for drugs used for the treatment of high levels of lipids, elevated blood pressure, and obesity.

For drugs used to treat cardiovascular risk factors, the FDA needs to work with the sponsor, as it wisely did for the approval of torcetrapib, so that large, long-term trials evaluating new drugs that will be used by millions of US individuals start early, evaluate the reduction in cardiovascular disease incidence, and are completed soon after drug approval.¹⁹ In a recent Commentary, Greenland and Lloyd-Jones advocated the conduct of industry-sponsored trials that “meaningfully add to the evidence base to make clinical decision.”²⁰ Because most observational studies, especially those conducted only with administrative data from large electronic medical record databases, will not be adequate to detect benefits or risks of the magnitude observed in ILLUMINATE,¹⁵ the FDA may on occasion need to use its new authority to insist on the conduct of large long-term clinical trials of public health importance.²¹

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