Editorial

Forecasting Cholesterol Management—End of the Statin Gold Rush?

Upping the Ante

For the last 15 years or more, lowering the low-density lipoprotein (LDL) component of total serum cholesterol has been the principal focus in cholesterol management. Even more powerful HMG-CoA reductase inhibitors (statins) captured attention in their ability to lower LDL cholesterol (LDL-C). Simvastatin was approved by the U.S. Food and Drug Administration (FDA) 15 years ago, on December 23, 1991, with evidence of LDL-C lowering of an average 41% at the 40 mg daily dose and 47% at the maximum 80 mg daily dose.1 Lovastatin, the preceding leader in the statin market, approved by the FDA 4 years earlier, on August 13, 1987, reduced LDL-C by an average 30% at the 40 mg daily dose and by 40% when taken twice daily (80 mg daily dose).2,3 (Table 1).

The war to reduce LDL-C escalated 5 years later on December 17, 1996, when the FDA approved atorvastatin calcium. Efficacy in LDL-C lowering averaged 50% at the 40 mg daily dose of atorvastatin and 60% at the maximum 80 mg daily dose.4 Rather than pricing atorvastatin at a premium to simvastatin, the manufacturer of atorvastatin undercut the simvastatin price, introducing a product to the U.S. market that was superior in LDL-C-lowering capability and at lower cost. By 1999, atorvastatin had garnered 42% of the U.S. statin market by sales compared with 32% for simvastatin, and the gap grew even wider in 2000 when atorvastatin captured 46% of the total statin sales versus 31% for simvastatin. Measured by prescription volume, atorvastatin captured 55% of the statin market in 2003 versus 23% for simvastatin.5 Atorvastatin became the number 1 drug in the entire prescription drug market in the United States in 2002, with $5.20 billion in sales, 68% higher than the $3.10 billion in simvastatin sales that year and 55% higher than lansoprazole ($3.36 billion), the second-leading drug by sales in the United States.6

The worldwide market recall of cerivastatin on July 21, 2001, just 12 months after the maximum 8 mg dose was approved by the FDA, focused the attention of the public and health care professionals on the safety of the statin drug category.7 At the same time, however, the National Cholesterol Education Program (NCEP) and its Adult Treatment Panel (ATP) were working on their third set of guidelines. By late 2002, the publication of new ATP recommendations grabbed the spotlight away from the negative side of statins and focused the attention of the public and health care providers. By late 2002, the publication of new ATP recommendations grabbed the spotlight away from the negative side of statins

Cost-Effectiveness Analysis

Hay, writing in the January/February 2004 issue of JMCP, took issue with cost-effectiveness analyses that focus narrowly on direct drug cost to achieve each percentage point reduction in LDL-C.8 Hayes suggested that the relative cost-effectiveness of statins could be determined accurately only with consideration of adverse effects as well as reduction in clinical disease outcomes and LDL-C levels. He also cited the declining price of generic lovastatin in early 2004 and the anticipated price competition from other generic statins in coming years. From this basis, Hayes suggested that the $310 annual price premium (38%) for LDL-C reduction with atorvastatin 80 mg versus rosuvastatin 40 mg “could be a small premium to pay for atorvastatin’s proven safety record” and evidence of favorable effect on CHD patient outcomes. In hindsight, rosuvastatin apparently is not associated with the liver toxicity and rhabdomyolysis that occurred with cerivastatin, and the incidence of adverse effects appears to be no different for rosuvastatin than for the other statin drugs on the market.

Results of Large Clinical Trials Increase Demand

Large clinical trials published in the last 3 years have generally shown that more LDL-C reduction is better in the prevention of CHD events, a premise heavily marketed by makers of rosuvastatin.
statin and combination simvastatin/ezetimibe. The Pravastatin or Atorvastatin Evaluation and Infection Therapy Thrombolysis in Myocardial Infarction 22 Investigators (PROVE IT-TIMI 22) clinical trial results for patients with acute coronary syndrome (ACS) were first released at the meeting of the American College of Cardiology in New Orleans on March 8, 2004.16 After 2 years of therapy, pravastatin 40 mg per day was associated with a combined 26.3% incidence of death, myocardial infarction (MI), or worsening cardiac complications versus 22.4% with the highest (80 mg) dose of atorvastatin. A total of 3.2% of the ACS patients on pravastatin died versus 2.2% on atorvastatin, not statistically significant but interpreted as clinically significant by some. Debate ensued regarding whether the difference in outcomes was due to the lower average LDL-C achieved in atorvastatin patients (62 mg/dL versus 95 mg/dL for the pravastatin patients, both below the target of 100 mg/dL) or greater activity of atorvastatin against C-reactive protein (CRP), or perhaps some other unknown mechanism.

The 3.9% absolute difference between the combined primary outcome for atorvastatin versus pravastatin (26.3% vs. 22.4%) in PROVE IT-TIMI 22 translated into a 16% reduction in the hazard ratio (HR) in favor of atorvastatin (P = 0.005). The 3.9% absolute difference also translated into the need to treat 25.6 patients for 2 years with 80 mg atorvastatin per day to prevent 1 death, or nonfatal MI, or cardiac complication.17 Subsequent letters to the editor pointed out that the withdrawal rates in the PROVE IT-TIMI 22 trial were very high, 33.0% in the pravastatin 40 mg per day group at 2 years and 30.4% in the atorvastatin 80 mg per day group at 2 years.18 The authors of the PROVE IT-TIMI 22 study disclosed, in a response letter, that 738 of 2,054 patients started on pravastatin 40 mg per day discontinued therapy (35.9%) and 688 of 2,086 patients (33.0%) discontinued therapy with atorvastatin 80 mg per day; “myalgia or arthralgia” was the reason for discontinuation in 5.0% (37/738) of pravastatin patients and 4.1% (28/688) of atorvastatin patients.19 The sales of atorvastatin surged after the release of the results from the PROVE IT-TIMI 22 trial, with atorvastatin capturing 40% of the new prescriptions for statins.20

In the Treating to New Targets (TNT) study, cardiovascular outcomes in patients with clinically evident CHD and LDL-C levels of less than 130 mg per dl (3.4 mmol per liter) were tested for high-dose versus low-dose atorvastatin. Writing for the TNT investigators, LaRosa et al. found that a median 4.9 years of therapy with 80 mg of atorvastatin in secondary prevention was associated with an incidence of 8.7% (434 of 4,995 patients) in the primary cardiovascular end point (occurrence of a first major cardiovascular event, defined as death from CHD, nonfatal non-procedure-related MI, resuscitation after cardiac arrest, or fatal or nonfatal stroke).21 The incidence of the primary outcome was 10.9% (548 of 5,006 patients) for those who received 10 mg of atorvastatin per day. The 2.2% absolute difference represented a 22% relative reduction in risk (HR, 0.78; 95% confidence interval [CI], 0.69-0.89; P < 0.001). There was no difference, however, between the 2 treatment groups in overall mortality, and some observers pointed to the elevated liver enzymes in the high-dose group.22

Letters published subsequent to the TNT results highlighted the nonsignificant, higher rate of all-cause mortality in the higher-dose (80 mg) atorvastatin group,23 which differed from the results in PROVE IT-TIMI 22 in which high-dose statin therapy was associated with a reduction in risk of all-cause mortality. However, in the Aggrastat-to-Zocor (A-to-Z) clinical trial, 80 mg simvastatin per day was no different than 10 mg simvastatin per day in the incidence of all-cause mortality.24 Southern observed that the benefit of high-dose atorvastatin treatment may be attributable to the subgroup in TNT that had baseline LDL-C levels that were greater than 100 mg/dL, similar to the results in PROVE IT-TIMI 22, in which the benefit of intensive lipid-lowering was driven primarily by the subgroup (27% of the population) with a baseline LDL-C greater than 125 mg/dL.25

In the propitious-sounding REVERSAL (Reversal of Atherosclerosis with Aggressive Lipid Lowering) clinical trial, 654 patients with symptomatic coronary artery disease, a 20%
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or greater stenosis determined by angiography, and LDL-C levels between 125 mg/dL and 210 mg/dL were randomized to either pravastatin 40 mg or atorvastatin 80 mg per day.26 In the 502 patients (77.2%) who received both a baseline and follow-up intravenous ultrasound after 18 months of treatment, baseline LDL-C level (mean, 150.2 mg/dL [3.89 mmol/L] in both treatment groups) was reduced to 110 mg/dL (2.85 mmol/L) in the pravastatin 40 mg group and to 79 mg/dL (2.05 mmol/L) in the atorvastatin 80 mg group (P <0.001); adherence was not measured. The pravastatin group experienced an overall average 2.7% progression of coronary atherosclerosis (95% CI, 0.2%-4.7%; P=0.001) compared with baseline, while progression of coronary atherosclerosis did not occur in the atorvastatin group (-0.4%; 95% CI, -2.4% to 1.5%; P=0.98) compared with baseline. In 10 mm vessel subsegments with the greatest disease, both groups experienced atheroma regression. The investigators did not assess the effect on clinical outcomes, stating, “(I)t is statistically challenging to perform actively controlled statin trials using morbidity and mortality end points because the differences in event rates are likely to be small.”

Not to be outdone, the manufacturer of rosuvastatin sponsored the ASTEROID trial (A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden), the results of which were published in April 2006.13 Lacking a control group, the 24 months of treatment with maximum dose (40 mg) rosuvastatin was associated with regression of atherosclerosis while reducing LDL-C by 53.2%, from an average 130.4 mg/dL to 60.8 mg/dL (P <0.001) and increasing high-density lipoprotein cholesterol (HDL-C) by 14.7%, from 43.1 mg/dL to 49.0 mg/dL (P <0.001). Commentary around the release of the results of the ASTEROID trial in June 2006 included the proclamation: “The message of the ASTEROID trial can be simplified: if regression of disease is the desired outcome, then lower LDL-cholesterol is better.”27

Three Generic Statins but Cost per Outcome Remains High

Even if more LDL-C lowering is indeed better, independent of the statin effects on endothelial function and inflammatory mediators, direct drug cost can be high for the cardiovascular event reductions, not counting the costs from adverse effects. The direct drug cost became more favorable on April 20, 2006, when price competition increased with the market introduction of generic pravastatin. Two months later, an even larger market effect occurred when simvastatin became available by generic name, on June 24, 2006.28 These 2 drugs accounted for almost 40% of the total statin market in sales in the United States in 2005.29 Now, with generic simvastatin widely available in the United States in mid-2006, LDL-C reduction even at aggressive goals of nearly 50% is possible at much lower drug cost.

But even with a 50% reduction in the cost of simvastatin as it goes generic, the return on investment in avoidance of cardiovascular events can still be small. Based on the results of the Heart Protection Study (HPS),30 it would require treatment of 71.4 patients at risk of stroke for 5 years with simvastatin 40 mg per day to prevent 1 nonfatal stroke. At the time the HPS results were published in 2004, this amount of simvastatin had a cost of at least $520,000.31 By June 2006, the cost rose to $587,600 to prevent 1 nonfatal stroke.32 Even at a 50% price discount, the cost of generic simvastatin is nearly $300,000 to prevent 1 nonfatal stroke in patients at high risk of stroke.

Pravastatin fares no better in this value-for-money calculation in the prevention of 1 nonfatal stroke. The clinical trial that was used to obtain FDA approval of pravastatin for the stroke indication found an absolute difference in the primary outcome of 0.8% (number needed to treat=125) after an average 6 years of treatment with pravastatin 40 mg per day.33 In July 2006, with a 43% price discount for generic pravastatin compared with brand pravastatin, it would still cost $689,850 for generic pravastatin to prevent 1 nonfatal stroke in high-risk patients with a history of MI or unstable angina.

Therapeutic Alternatives to Statins

Nonstatin agents currently play a lower-profile role in cholesterol and cardiovascular risk management. Extended-release niacin elevates HDL-C by an average 20% when taken in a dose of 1,500 mg and by 22% at the 2,000 mg dose, taken at bedtime; however, high side-effect rates and the absence of evidence of improved overall mortality rates dampen enthusiasm for niacin. Likewise, ezetimibe has potential as adjunct or mono-therapy, but the lack of clinical end point outcomes data hinders widespread zeal for this agent. Omega fatty acids have shown conflicting data regarding mortality benefit in multiple meta-analyses; however, the most recent and comprehensive Cochrane Review combining primary and secondary prevention failed to demonstrate reductions in cardiovascular disease or mortality.34

Measures Other Than LDL-C

The roles of inflammation, in general, and CRP, in particular, warrant more investigation as possible predictors of the risk of adverse cardiovascular events, especially in subpopulations.35,36 Currently, the American College of Cardiology rates high-sensitivity (HS)-CRP as level-B evidence, with a recommendation rating of 2a (conflicting evidence but weight is in favor of efficacy). In particular for the patient group with intermediate 10-year Framingham risk scores, elevated HS-CRP >3.0 mg/dL may “help direct further evaluation and treatment.” Since direct treatment of CRP to lower scores <1.0 mg/dL has not been shown to affect outcomes, LDL-C is still the primary treatment measure for now.37

Spinning Statin Gold Into Platinum?

The end of the statin gold rush can be predicted from the areas of investment in research now favored by the pharmaceutical manufacturers. Evans and Kranson in their June 7, 2006, analysis...
of the pharmaceutical market for cholesterol drugs in the United States, proposed that drugs to elevate HDL-C would produce more sales and profits than would drugs to lower LDL-C. Part of the reasoning has to do with the price competition in the statin drug class, propelled by generic pravastatin to a small extent and generic simvastatin to a larger extent, and the increasing opportunity for MCOs to implement interventions in therapeutic selection. Second, the drugs that elevate HDL-C come from several classes, raising the odds that safe and effective patented compounds will ultimately reach the market. In the new race to elevate HDL-C, there is research with formulations of extended-release niacin to reduce the side effect of flushing, at least 2 cholesteryl ester transfer protein (CETP) inhibitors in clinical testing, and a combination of niacin, simvastatin, and a prostaglandin d2 antagonist (MRK 524b); Wall Street analysts include peroxisome proliferator-activated receptors (PPARs) and possibly rimonabant in the mix of products that might have potential market value in the shift in focus to HDL-C elevation.

Pharmaceutical companies pursuing the next atorvastatin-like blockbuster will probably not be dissuaded by the preliminary results of the phase 2 studies of torcetrapib, in which patients who received the 60 mg dose experienced an average 2 mm Hg increase in systolic blood pressure. Three of the phase 2 studies that measured 24-hour blood pressure found an average 2.7 mm increase in systolic pressure with torcetrapib. The magnitude and clinical significance of the elevation in systolic blood pressure observed in the phase 2 studies of torcetrapib will be delineated in the phase 3 clinical studies but, if deemed significant, will be examined to see whether the effect is specific to the molecule or generalizable to the CETP inhibitors as a class.

Based on data from the National Health and Nutrition Examination Survey (NHANES) III, and the present NCEP goals, Evans and Kranson estimated that 4% of patients need LDL-C reduction to <160 mg/dL, 7% to <130 mg/dL, 75% to <100 mg/dL, and 14% to <70 mg/dL. Based upon these aggressive LDL-C targets, simvastatin 40 mg is capable of reducing LDL-C to target goal in 76% of patients versus 93% for rosuvastatin 20 mg or 88% for atorvastatin 40 mg, the next to the highest dose of each of the 3 drugs (Figure 1). The combination of atorvastatin and torcetrapib, now in clinical trials, would move 95% of adherent patients to target LDL-C goal, as would MK-0524B: a combination of (1) Merck’s own extended-release niacin, (2) MK-0524 (a selective antagonist to nicotinic acid-induced vasodilation [flushing]), and (3) simvastatin. To assess the benefit of MK-0524B in the marketplace, U.S. clinical trial NCT00289900 is scheduled to start in July 2006. It is a 12-week phase 3 clinical trial sponsored by Merck comparing MK-0524B against atorvastatin, not atorvastatin + torcetrapib, which will be its likely market competitor. The manufacturer is also sponsoring U.S. clinical trial NCT00269217, a 7-treat-
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ment-arm study that pits MK-0524B against its own subcomponents (niacin, MK-0524, and simvastatin). To put the newer agents in perspective against older agents, the 36% HDL-C elevation estimated for MK-0524B (Figure 2) matches that reported by Whitney et al. for the complex, combined regimen of 2,500 mg per day (mean daily dose) of immediate-release niacin, 600 mg twice daily of gemfibrozil, and 2 to 16 gm per day (as tolerated) of cholestyramine.

While the manufacturer of the MK-0524B combination product selected atorvastatin as the active control, not atorvastatin + torcetrapib (its natural competitor), to test the LDL-C-lowering and HDL-C-elevating effects of MK-0524B, the manufacturer of combination atorvastatin + torcetrapib is not faultless. It has been criticized for manipulating the FDA clinical trial process to make certain that torcetrapib will not be available on the U.S. market except in combination with atorvastatin. Avorn pointedly criticized not only the manufacturer but also the FDA for subverting the antitrust laws intended to prevent such product “bundling.” In a subsequent letter exchange with the manufacturer, Avorn took the opportunity to draw attention to a separate statement from a senior executive that the manufacturer “does not intend to use the trials in this coercive way.”

Multiple CETP inhibitors are on the way. Evans et al. reported that Roche licensed JTT-705 from Japan Tobacco, and it is currently in clinical trials. The manufacturer of torcetrapib also has additional CETP agents. It recently stated that if elevated blood pressure does prove to be clinically important with torcetrapib, then it has other “back-up” CETPs. Importantly for managed care clinicians and administrators, the early lead in clinical testing of torcetrapib could be forfeited in regulatory review if Pfizer has to show that the blood pressure side effects do not outweigh the clinical value of partial coronary plaque reduction.

Taken together, the new search for gold in HDL-C elevation involves at least 9 products in phase 1 or phase 2 testing other than torcetrapib and the modified niacins. Evans et al. counted 4 different mechanisms of action, including the CETP inhibitor JTT-705. One of the MRK 524 compounds could be approved for the U.S. market as early as 2008.

To conclude, the long-awaited present opportunity for managed care clinicians and administrators to treat more patients with lower-cost generic statins and reduce antilipid-related drug costs will be undercut by the shift to manage new targets in addition to LDL-C reduction. The near future will see new veins in the gold mine of cholesterol agents, with platinum-sized profits for agents that elevate “good cholesterol” and treat mixed dyslipidemia; revenue for this new category should surpass statin profits within 5 years. We eagerly await outcomes data in the hope of establishing the cost-effectiveness of these new agents prior to their expected dominance in the marketplace.

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DISCLOSURES
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Percentage of Patients Above Goal LDL-C Who Can Achieve Both LDL-C Target and HDL-C Target of 40 or 60 mg per dL


HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol.

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