Treating Hypercholesterolemia: Looking Forward

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Summary: Despite important advances in the management of hypercholesterolemia in recent decades, many patients with lipid disorders remain unidentified or undertreated and so continue to have unfavorable levels of low-density lipoprotein (LDL) cholesterol and an increased risk for coronary events. The statins—which inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in cholesterol biosynthesis—have proved to be the most powerful pharmacologic agents for lowering serum lipids, and newer statins offer even greater efficacy than the agents introduced 10 to 15 years ago. Studies have shown that rosuvastatin, in late-stage development, is a very potent agent for the treatment of primary hypercholesterolemia, and that relatively low doses decrease LDL cholesterol levels to a greater extent than do similar doses of pravastatin, simvastatin, or atorvastatin as evaluated in separate clinical trials. Pitavastatin, in phase II trials, also has promise as a more potent drug than currently available statins. Because neither of these drugs has been approved for use in the United States, clinical trial results should be considered preliminary. In the future, agents that combine the actions of statins and nicotinic acid may achieve still greater LDL cholesterol reductions. Drugs that lower lipids via mechanisms other than inhibition of HMG-CoA reductase also offer promise. The newest addition to the roster of lipid-regulating agents is ezetimibe, a cholesterol absorption inhibitor that has been approved for use either alone or in combination with a statin. Agents in development include bile acid transport inhibitors and inhibitors of acyl CoA:cholesterol acyltransferase. More research will be needed to determine the full clinical potential of such approaches to the management of hypercholesterolemia.

Key words: hypercholesterolemia, lipoprotein, low-density lipoprotein cholesterol, coronary disease, hydroxymethylglutaryl-CoA reductase inhibitors, investigational drugs

Introduction

In the past 20 years, public and professional education initiatives such as the National Cholesterol Education Program (NCEP) have increased awareness of hypercholesterolemia as a risk factor for cardiovascular disease. At the same time, treatment advances have placed the goal of significant serum-cholesterol reduction within reach for a large proportion of the at-risk population. Nevertheless, clinical practice lags behind therapeutic progress: improvement in the identification, treatment, and follow-up of individuals with hypercholesterolemia is needed if the nation is to realize the full potential of newer, more potent lipid-lowering agents, particularly as drugs that act through novel mechanisms move through the clinical development process.

Hypercholesterolemia: Defining the Challenge

Guidelines for detecting, evaluating, and treating high cholesterol, from both the NCEP Adult Treatment Panel II (ATP II) and Adult Treatment Panel III (ATP III), call for periodic cholesterol screening.^{1, 2} Elevated levels of low-density lipoprotein (LDL) cholesterol are the primary indication for initiating therapy aimed at reducing the risk for coronary heart disease (CHD). Evidence suggests, however, that many patients who are clearly at risk for CHD are not undergoing periodic cholesterol screening. An observational study examining 10-year data on the measurement of cholesterol levels among patients hospitalized for acute myocardial infarction (MI) in the Worcester, Massachusetts, area found a marked increase in rates of cholesterol measurement between 1986 (<60% screened) and 1991 (approximately 90% screened).³ Thereafter, however, the trend was reversed, with serum cholesterol measurements reported for less than 25% of hospitalized patients with MI, and complete lipid profiles (LDL and high-density lipoprotein [HDL] cholesterol and triglycerides) reported for only 15%, in 1997 (Fig. 1). A multivariate analysis showed

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Fig. 1 Annual percentage of patients hospitalized with myocardial infarction and undergoing total cholesterol screening, 1986–1997, in the Worcester, Mass., Heart Attack Study. Reprinted from Ref. No. 3 with permission.

that men and patients with an initial Q-wave MI were more likely to have their cholesterol levels measured during the index hospitalization. The likelihood of cholesterol screening declined with older age (1986–1988) and was significantly reduced in patients with a history of diabetes or hypertension.

In the same observational study, 0.4% of post-MI patients received prescriptions for lipid-lowering drugs in 1986. The rate remained relatively low until 1997, when it rose to 10.7%. Data from 1997 showed that patients who had their cholesterol levels measured were four times more likely to receive prescriptions for lipid-lowering therapy than patients whose lipid levels were not checked. Nonetheless, only 36.6% of patients found to have total cholesterol levels ≥ 6.2 mmol/l (≥ 240 mg/dl) received lipid-lowering therapy in 1997.

Studies examining physician practice and prescribing patterns for patients with varying degrees of risk document the undertreatment of hyperlipidemia and the need to improve physician adherence to evaluation and treatment guidelines in community-based and hospital settings. For example, in the Merck-funded Quality Assurance Program, a retrospective chart audit of 48,586 adult outpatients with coronary artery disease (CAD), found that only 44% had LDL cholesterol testing within 1 year of their last visit, only 39% were taking lipid-lowering medications, and only 25% were able to attain an LDL cholesterol level of ≤ 2.6 mmol/l (≤ 100 mg/dl), the goal for high-risk patients as established by NCEP ATP II⁴ (the goal established by NCEP ATP III is < 2.6 mmol/l [< 100 mg/dl]).² The chart audit also revealed that patients between the ages of 55 and 64 were more likely to receive a prescription for lipid-lowering therapy than patients > 65 , and that women < 65 years of age were less likely to receive a prescription than men < 65 years.

The Lipid Treatment Assessment Project (L-TAP), which studied 4,888 adult patients with dyslipidemia who had been receiving the same lipid-lowering therapy for at least 3 months, found that 38% of patients achieved ATP II target levels for LDL cholesterol.⁵ However, the study also found that achievement of goal was higher in the low-risk patients and lower in the high-risk patients: 68% in patients at low risk (fewer than two major risk factors for CHD and no evidence of CHD), 37% in patients at high risk (two or more

major risk factors but no evidence of CHD), and 18% in patients with CHD.

Practice and prescribing data from the National Registry of Myocardial Infarction 3 have shown that only 31.7% of 138,001 patients discharged from the hospital after an acute MI received a prescription for lipid-lowering medication as part of the discharge regimen.⁶ In this large prospective observational study, patients between 65 and 74 years of age were less likely to receive a prescription for lipid-lowering therapy than those younger than 55. Patients with a history of hypertension and those undergoing coronary artery bypass graft surgery were also less likely to receive a prescription.

Further evidence of the inadequate control of hypercholesterolemia even in high-risk patients comes from a recent analysis of data from the Third National Health and Nutrition Examination Survey. Of 417 survivors of MI, stroke, or both, whose LDL cholesterol levels were measured, fewer than half met the target levels established by the NCEP ATP III (Fig. 2).⁷ A total of 57% of these patients had levels > 3.36 mmol/l (> 130 mg/dl).

Meeting the Challenge

Current Efficacy of Statins

The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, or statins, are the most potent pharmacologic agents available for reducing elevated levels of LDL cholesterol.² By inhibiting the activity of HMG-CoA reductase, the statins limit cholesterol biosynthesis in the liver and extrahepatic cells. This also leads to upregulation of LDL receptors, which promotes the clearance of LDL cholesterol from plasma. The net result is a substantial reduction in LDL cholesterol levels.

Six major studies of simvastatin, lovastatin, and pravastatin have confirmed that statin therapy significantly reduces CHD-

Fig. 2 Low-density lipoprotein cholesterol (LDL-C) levels in 417 survivors of myocardial infarction, stroke, or both in the Third National Health and Nutrition Examination Survey. The white and gray bars signify levels below and above the cut-point that defines adequate control. Reprinted from Ref. No. 7 with permission.

associated risk in both primary and secondary prevention.⁸⁻¹³ These studies have shown that statins can lower LDL levels by 20 to 36%, decrease the incidence of nonfatal MI or CHD death by 27 to 34%, and reduce the need for interventional coronary procedures (angioplasty or coronary artery bypass graft surgery) by 20 to 37%. The risk for stroke may also be lowered by up to 31%. The most recent of these six trials, the Heart Protection Study (HPS), examined the effect of cholesterol-lowering therapy with simvastatin in the largest number ($n = 20,536$) and the widest range of high-risk individuals studied to date. The trial, which focused on groups for whom sufficient data had been lacking, included patients with diabetes or noncoronary occlusive arterial disease, but without CAD; women; the elderly; and those with below-average LDL cholesterol concentrations for Western societies. Results indicate that lowering LDL cholesterol by 39 mg/dl produced a proportional risk reduction of about 25% in patients with baseline levels < 116 mg/dl and in those with higher baseline levels. This supports the hypothesis that current guidelines may inadvertently result in undertreatment of high-risk patients who present with LDL cholesterol levels that are below or close to recommended targets.¹³

The HPS also found a significant decrease in the primary end point of all-cause mortality, based chiefly on a highly significant 18% reduction in the coronary death rate (also a primary end point) and a marginally significant reduction of 16% in other vascular deaths. There were highly significant reductions in the secondary end points of nonfatal MI or coronary death (-27%), nonfatal or fatal stroke (-25%), and coronary or noncoronary revascularization (-24%), with an overall 24% reduction in the occurrence of any major vascular event. Risk reductions were similar in each major subcategory of participant studied. Overall, results of the HPS demonstrate the importance of treating high risk, not just high cholesterol. The recently published Prospective Study of Pravastatin in the Elderly at Risk (PROSPER), which enrolled 5,804 men and women aged 70 to 82 years, found that pravastatin 40 mg/d significantly reduced the risk for a composite primary end point event (CHD death, nonfatal MI, or fatal/nonfatal stroke) by 15% and for CHD death or nonfatal MI by 19%, compared with placebo. However, there was no significant treatment effect on the incidence of stroke. Because only 266 patients suffered a stroke, one possible explanation for this outcome may be a lack of statistical power.^{14, 15}

The statins also produce moderate increases (5 to 15%) in HDL cholesterol.² Although the mechanisms responsible for this effect remain uncertain, they may involve apolipoprotein (apo)A-I, the major apolipoprotein of HDL. Researchers have suggested that statins may induce apoA-I messenger RNA by activating peroxisome proliferator-activated receptor- α , a nuclear transcription factor that binds to a peroxisome proliferator response element mapped to the apoA-I promoter A site.¹⁶ Because the addition of mevalonate can reverse this mechanism, it is thought that the effects of statins on apoA-I gene expression are a downstream effect of HMG-CoA reductase inhibition.¹⁶

Safety of Statins

The major safety concerns with statins have involved skeletal muscle function and liver toxicity. However, large-scale analyses attest to the highly favorable safety profiles of these drugs. In the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) of 6,605 participants randomized to lovastatin or placebo, serious drug-related adverse events and treatment discontinuations were similar for both treatment groups.⁸ Patients receiving lovastatin and placebo showed no significant differences in the incidence of creatine kinase elevations (> 10 times ULN), rhabdomyolysis, or treatment discontinuation because of myalgia. There were no cases of myopathy (i.e., muscle symptoms plus creatine kinase > 10 times ULN). Although any increase in alanine aminotransferase levels occurred significantly more often with lovastatin than with placebo (3.3 vs. 2.1%; $p = 0.003$), the incidence of consecutive liver enzyme elevations > 3 times ULN was rare and similar for both treatment groups. Mortality and incidence of fatal and nonfatal cancer were similar with lovastatin and placebo.

In the HPS, there was no significant excess in the number of simvastatin-treated patients with elevated alanine aminotransferase concentrations (> 4 times ULN) compared with those receiving placebo, and no significant difference between the groups in the number of patients who discontinued treatment because of elevated liver enzymes (48 [0.5%] in the simvastatin group vs. 35 [0.3%] in the placebo group).¹³ In addition, there was no significant difference between the treatment groups with regard to reports of unexplained muscle pain or weakness (32.9% among those receiving simvastatin, 33.2% among those receiving placebo on at least one occasion) and no significant difference in the number of patients who discontinued treatment because of muscle symptoms (49 in the simvastatin group vs. 50 in the placebo group). Rhabdomyolysis (creatinine kinase > 40 times ULN) developed in five patients in the simvastatin group and three in the placebo group, but none died.

The Prospective Pravastatin Pooling (PPP) Project, which analyzed data from three large-scale trials involving $> 19,000$ patients and $> 112,000$ patient-years, likewise found no significant differences in the occurrence of side effects with pravastatin therapy versus placebo.^{17, 18} Included in the PPP Project were one primary-prevention trial (West of Scotland Coronary Prevention Study) and two secondary-prevention trials (Cholesterol and Recurrent Events, Long-Term Intervention with Pravastatin in Ischemic Disease). In this combined analysis, the pravastatin and placebo groups did not differ in the proportion of noncardiovascular deaths and in the number of noncardiovascular serious adverse events, including musculoskeletal and hepatobiliary events, over an average of 5 to 6 years. The reduction in total mortality with pravastatin occurred largely because of the significant decrease in cardiovascular events. Similarly, pooled data from 44 studies involving 4,271 patients have shown that atorvastatin was safe and well tolerated, with less than 2% of statin patients withdrawing from the studies because of drug-attributable adverse

events. In addition, only 0.7% of patients had confirmed liver transaminase elevations > 3 times ULN, and no patients had proven drug-induced myopathy.¹⁹

Recently, four patients enrolled in a clinical trial were able to identify blinded statin therapy based on reproducible muscle symptoms.²⁰ Despite normal creatine kinase levels, the patients were found to have biopsy-confirmed myopathy. Pathologists reading the biopsies were not blinded to the patients' treatment status. Three of the subjects also had 3-methylglutaconic aciduria. These data suggest that creatine kinase levels may not be an adequate test for statin-associated myopathy. Therefore, physicians should closely monitor patients reporting muscle pain, decreased exercise tolerance, weakness, or other symptoms compatible with myopathy and determine whether the symptoms resolve when therapy is discontinued. In PROSPER, the incidence of skeletal muscle and hepatic adverse events was similar with pravastatin and placebo, with no reported cases of rhabdomyolysis. Although the rate of new cancers was 25% higher in the pravastatin group, the authors interpret this in the context of meta-analyses of prior statin trials, which showed no increased risk for cancer with long-term statin use. Moreover, the HPS, which enrolled a large number of elderly subjects, found no excess incidence of cancer with statin treatment. The investigators attribute the PROSPER result to chance, perhaps driven in part by the enrollment of individuals with occult cancers.^{14, 15, 21}

Because some epidemiologic studies have found an inverse association between serum cholesterol levels and hemorrhagic stroke, there has been concern that reducing cholesterol concentrations with drug therapy may increase the risk for intracranial hemorrhage.^{22, 23} However, neither the PPP Project nor the HPS found that pravastatin had any effect on the incidence of hemorrhagic stroke.^{13, 24}

FIG. 3 Changes from baseline in lipid fractions after 52 weeks of therapy with rosuvastatin versus atorvastatin. Reprinted from Ref. No. 28 with permission.

Statins in Development

Rosuvastatin and pitavastatin are two HMG-CoA reductase inhibitors now in development. Rosuvastatin has been submitted to the Food and Drug Administration, but it is not approved at this time.

Six double-blind studies of 6 to 52 weeks' duration have shown that rosuvastatin at relatively low doses is a very potent agent for the treatment of primary hypercholesterolemia. Four of the studies, each one involving approximately 400 to 500 subjects, compared rosuvastatin with atorvastatin, simvastatin, or pravastatin. In the six studies, rosuvastatin at doses of 5 mg and 10 mg reduced LDL cholesterol levels by 39 to 53%, with one of the studies reporting a reduction of 47% with 5 mg at 52 weeks (Fig. 3). All but one of the reductions, an outcome achieved with rosuvastatin 5 mg, were statistically significant versus either placebo or the comparator drug.²⁵⁻²⁹ Based on the results of separate clinical trials, atorvastatin reduces LDL cholesterol levels by 39 to 60%, simvastatin produces reductions of 26 to 47%, and pravastatin reduces LDL cholesterol by 22 to 37%, when administered at approved doses ranging from low (5 mg or 10 mg) to high (80 mg).³⁰⁻³² In two of the comparative studies cited above, the proportion of rosuvastatin patients who achieved ATP II goals for LDL cholesterol ranged from 71 to 87%, compared with 53 to 73% of patients taking pravastatin, simvastatin, or atorvastatin. Post hoc analyses following release of the ATP III guidelines show that target levels were reached by 64 to 84% of patients treated with rosuvastatin, compared with 48 to 72% in the pravastatin, simvastatin, and atorvastatin groups.^{25, 26} In the other two comparative studies, ATP II goals were achieved by 62 to 97% of rosuvastatin-treated patients with CHD, peripheral vascular disease, or diabetes versus 6 to 61% of patients taking pravastatin, simvastatin, or atorvastatin.^{27, 28}

Because rosuvastatin has not been approved, the starting dose is unknown. Therefore, the results of studies at different doses must be considered very preliminary.

Pitavastatin (NK-104), an investigational agent now in phase II trials, has been evaluated for periods of 8 to 104 weeks in two small studies conducted in patients with heterozygous familial hypercholesterolemia (HeFH). Results indicate that doses of 2 mg to 4 mg significantly reduced LDL cholesterol levels by 40 to 48% from baseline.^{33, 34} In a 12-week double-blind dose-finding study, pitavastatin 1 mg to 4 mg produced significant LDL cholesterol reductions of 34 to 47% in 273 patients with hyperlipidemia.³⁵ A comparative study of the same duration in 240 subjects with primary hypercholesterolemia found that pitavastatin 2 mg decreased LDL cholesterol levels by 38%, which was significantly greater than the reduction with pravastatin, the comparator drug.³⁶ As with rosuvastatin, the results of these studies should be considered preliminary, because pitavastatin is not approved and the starting dose is unknown.

Future statin-based agents may employ a dual mechanism to regulate serum cholesterol levels. Recent structural analyses indicate that statins leave the nicotinamide-binding site of HMG-CoA reductase unoccupied.³⁷ Conceivably, therefore,

the covalent attachment of a nicotinamide-like moiety to a statin might result in even greater potency.

On the Horizon: New Approaches to Lipid Lowering

Lipid metabolism involves many complex processes that may be potential targets for pharmacologic intervention aimed at regulating various dyslipidemias. At present, several novel agents for the reduction of LDL cholesterol are being investigated (Table I). With all investigational agents, the results of clinical trials must be considered preliminary, because the starting doses are unknown.

Recently, ezetimibe became the first agent in a new class of cholesterol absorption inhibitors to receive approval in the United States. As an adjunct to diet, ezetimibe was approved for use either alone or in combination with a statin to reduce total cholesterol, LDL cholesterol, and apoB in patients with primary hypercholesterolemia. Other indications include the lowering of total and LDL cholesterol levels in homozygous familial hypercholesterolemia (HoFH) and the treatment of homozygous sitosterolemia. For all indications, the recommended dose is 10 mg/day.³⁸

Ezetimibe selectively inhibits the absorption of dietary and biliary cholesterol at the brush border of the intestine.^{39,40} Both ezetimibe and its pharmacologically active glucuronide conjugate undergo enterohepatic recycling, which repeatedly delivers drug back to the intestine. No significant effect on major drug-metabolizing enzymes has been identified. Therefore, the potential for interaction with substrates of cytochrome P-450 enzymes is low.³⁹

Two phase III studies published as abstracts indicate that combination therapy with ezetimibe and a statin improves cholesterol lowering, with a safety profile similar to that of statin therapy alone. In 628 patients with primary hypercholesterolemia, a 12-week study compared ezetimibe 10 mg;

atorvastatin 10, 20, 40, or 80 mg either alone or with ezetimibe 10 mg; and placebo. For the primary endpoint, ezetimibe plus atorvastatin (pooled doses) significantly reduced LDL cholesterol by 54.5% from baseline, compared with -42.4% for atorvastatin alone (pooled doses).⁴¹ Ezetimibe alone reduced LDL cholesterol levels by 18.4%. A similarly designed study (n = 668) found that ezetimibe plus simvastatin (pooled doses) produced a 49.9% decrease in LDL cholesterol, which exceeded the reductions with simvastatin alone (-36.1%, pooled doses) (p < 0.01). Ezetimibe 10 mg decreased LDL cholesterol levels by 18.1%.⁴²

In 50 patients with HoFH, ezetimibe 10 mg plus a statin (atorvastatin or simvastatin) 40 or 80 mg reduced LDL cholesterol levels by 20.7% from baseline after 12 weeks of treatment following a lead-in period with open-label statin therapy (40 mg), versus a reduction of 6.7% with statin 80 mg alone. Ezetimibe plus statin 80 mg decreased LDL cholesterol by 27.5% from baseline following open-label statin therapy, compared with -7.0% in patients randomized to statin 80 mg alone. Figure 4 depicts mean percentage reductions in LDL cholesterol over time in the ezetimibe plus statin 80 patients. All between-group treatment effects were statistically significant, with no clinically meaningful differences in adverse effects.⁴⁰

In a small (n = 32) randomized evaluator-blind study, published as a poster abstract, ezetimibe 10 mg administered with fenofibrate 200 mg was found to reduce levels of LDL cholesterol by 36.3% from baseline, compared with -22.3, -13.5, and -10.1% for ezetimibe, fenofibrate, and placebo, respectively (p ≤ 0.03 for either drug alone or placebo).⁴³ Ezetimibe plus fenofibrate also reduced levels of LDL-III (small dense LDL) by 37%, a significantly greater decrease (p ≤ 0.05) than the results seen either with fenofibrate (+8%), ezetimibe (-8%), or placebo (+6%).

Another class of agents, the bile acid transport inhibitors, specifically inhibits the intestinal epithelial uptake of bile acids, which may affect cholesterol metabolism. These agents

TABLE I Agents in development for reducing low-density lipoprotein cholesterol

Mechanism of action/agent	Developmental phase	Results to date
Bile acid transport inhibition		
S-8921	Phase I	↓ Serum cholesterol and ↓ appearance of severe stenosis (preclinical) ^{45,46}
ACAT inhibition		
Avasimibe	Phase III	↓ Triglycerides, ↓ VLDL-C, ↓ cholesterol and ↓ atherosclerotic lesion progression ^{48,49}
TS-962	Preclinical	Possible suppression of arterial foam cell formation in early atherosclerosis ⁵⁰
F-12511	Phase I	Used with atorvastatin, ↓ cholesterol and ↓ apoB-100 greater than with each agent alone; potential plaque- stabilizing effects ⁵¹
HMG-CoA reductase inhibition		
Rosuvastatin	Phase III	↓ LDL-C 34–65% ²⁹
Pitavastatin	Phase II	↓ LDL-C 38–49% ^{34,35}

Abbreviations: ACAT = acyl CoA:cholesterol acyltransferase; apo = apolipoprotein; HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A; LDL-C = low-density lipoprotein cholesterol; VLDL-C = very-low-density lipoprotein cholesterol.

Fig. 4 Mean percentage reduction in low-density lipoprotein cholesterol over time for 50 patients with homozygous familial hypercholesterolemia receiving ezetimibe 10 mg/day plus statin (atorvastatin or simvastatin) 80 mg/day versus statin 80 mg/day alone. Reprinted from Ref. No. 40 with permission.

are likely to be more effective in lowering cholesterol levels than older bile acid-absorbing resins, which work through competitive, rather than specific, inhibition.⁴⁴ S-8921, a bile acid transport inhibitor that entered phase I clinical trials in 2000, has been shown in preclinical studies to reduce serum cholesterol levels via mechanisms that may involve increased fecal excretion of bile acids and increased hepatic LDL receptor expression.^{45,46} Animal data also indicate a decrease in the appearance of severe stenosis with S-8921.⁴⁶ Like cholesterol absorption inhibitors such as ezetimibe, the bile acid transport inhibitors could potentially be used with statin therapy to improve cholesterol lowering.⁴⁴

Three more experimental agents are members of a class known as acyl CoA:cholesterol acyltransferase (ACAT) inhibitors.⁴⁴ ACAT is an enzyme that esterifies cholesterol in the arterial wall and appears to be largely responsible for the generation of monocyte-macrophage foam cells in the presence of excess cholesterol. Inhibition of arterial wall ACAT may limit macrophage accumulation and reduce the expression of matrix metalloproteinases, the matrix-degrading enzymes that contribute to plaque rupture.⁴⁷ One ACAT inhibitor, avasimibe, has been found to reduce intracellular cholesteryl ester levels and to decrease atherosclerotic lesion area in rabbits.⁴⁷ Avasimibe is now in phase III clinical trials.

In an 8-week double-blind placebo-controlled trial ($n = 130$), avasimibe at doses of 50, 125, 250, and 500 mg/day significantly decreased triglyceride and very-low-density lipoprotein (VLDL) cholesterol levels in patients with combined hyperlipidemia and low levels of HDL cholesterol. The reductions in triglycerides and VLDL cholesterol ranged from 16 to 23% and from 20 to 30%, respectively; however, these results appear to be independent of dose, which suggests that hepatic ACAT may be maximally inhibited with 50 mg avasimibe. Alternatively, ACAT inhibition may increase with higher doses of the drug, but further decreases in lipid levels may be

blunted by a compensatory response. There were no statistically significant changes from baseline in total cholesterol, LDL cholesterol, or HDL cholesterol. The incidence of adverse events was similar with avasimibe and placebo (11 vs. 8%), with no clinically significant changes in laboratory values among patients receiving avasimibe.⁴⁸

Although clinical trials have consistently shown that statins can decrease the incidence of coronary events by up to one third, there is a need for pharmacologic interventions able to provide additional cardiovascular protection in patients with coronary atherosclerosis. By inhibiting ACAT in the arterial wall, avasimibe may slow the development of atherosclerosis by several possible mechanisms.⁴⁹ The Avasimibe and Progression of Coronary Lesions Assessed by Intravascular UltraSound (A-PLUS) trial, now in progress, is designed to test the hypothesis that avasimibe 50, 250, or 750 mg will inhibit the progression of atherosclerosis when administered with lipid-lowering therapy as needed to reach a target LDL cholesterol level ≤ 125 mg/dL.⁴⁹ Participants in this 2-year, 28-center study must have at least one lesion with stenosis of 20 to 50% diameter in a coronary artery of ≥ 2.5 mm. The primary end point is the change in plaque volume in a 30-mm segment of the coronary artery assessed by three-dimensional intravascular ultrasound.

Another ACAT inhibitor, TS-962, was shown to suppress the formation of arterial foam cells in hamsters fed a high-fat diet.⁵⁰ A third compound, F-12511, has potential lipid-lowering effects; F-12511 and atorvastatin appear to have synergistic hypocholesterolemic effects in rabbits.⁵¹

Conclusion

Despite clinical evidence that the statins significantly reduce LDL cholesterol and CHD-related risk, hyperlipidemia is still undertreated. The problem of undertreatment has two components: insufficient adherence to current guidelines and the inadequate response of some patients to currently available agents. The former issue requires the development of new compliance strategies for patients and physicians. Regarding the latter, although statins—which inhibit HMG-CoA reductase—are highly effective in reducing cardiovascular risk by up to one third, interventions are needed to prevent the remaining two thirds of events that still occur. Advances in statin therapy and the development of new agents aimed at modifying other mechanisms involved in lipid metabolism may help close the treatment gap and extend CHD risk reduction to a larger segment of the population.

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