Clinical Pharmacology Update
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HMG-CoA reductase inhibitors

A new approach to the management of hypercholesterolemia

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Efforts to identify and treat individuals with elevated blood cholesterol levels have increased dramatically in recent years. The bile acid sequestrants (cholestyramine, colestipol) and nicotinic acid have been the mainstays of pharmacologic therapy for patients with phenotype(s) IIA and IIB hyperlipoproteinemia, but produce symptomatic side effects in a high percentage of patients. Clinical trials with a new class of cholesterol-lowering drugs, the HMG-CoA reductase inhibitors, have consistently demonstrated a dose-dependent reduction in total and low-density lipoprotein cholesterol levels of up to 30% and 40%, respectively. Symptomatic side effects requiring withdrawal of treatment have been uncommon, but the incidences of opacification of the ocular lens and hepatoxicity remain to be defined. Lovastatin is the first HMG-CoA reductase inhibitor commercially available in the United States. Its efficacy alone, and in combination with the bile acid sequestrants, is reviewed in this report.

Index terms: Antilipemic agents • Hyperlipoproteinemia, drug therapy

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Although a relationship between elevated blood cholesterol levels and increased coronary heart disease (CHD) incidence has been recognized for many years, concerted efforts to identify and aggressively treat individuals with "hypercholesterolemia" have emerged only recently.[1,2] The impetus for this effort is derived from epidemiologic studies and treatment trials. From an epidemiologic standpoint, six-year follow-up of the 361,662 middle-aged men screened for the Multiple Risk Factor Intervention Trial (MRFIT) demonstrated that the CHD risk associated with increasing blood cholesterol levels is continuous and graded (*Fig.* 1).[3] In MRFIT screenees, if the "baseline" risk of CHD is assumed to be present in men at the lowest cholesterol quintile (serum cholesterol levels ≤181 mg/dL), 50% of the excess CHD mortality is attributable to elevated blood cholesterol levels. Half of these excess deaths occurred in men with serum cholesterol levels above the 85th cholesterol percentile (serum cholesterol of 253 mg/dL or greater). Thus, blood cholesterol levels that had previously been assumed to be within the "normal" range are associated with an increased risk of premature CHD.

Evidence that treatment of hypercholesterolemia reduces the incidence of primary CHD was first presented in 1984, with publication of the

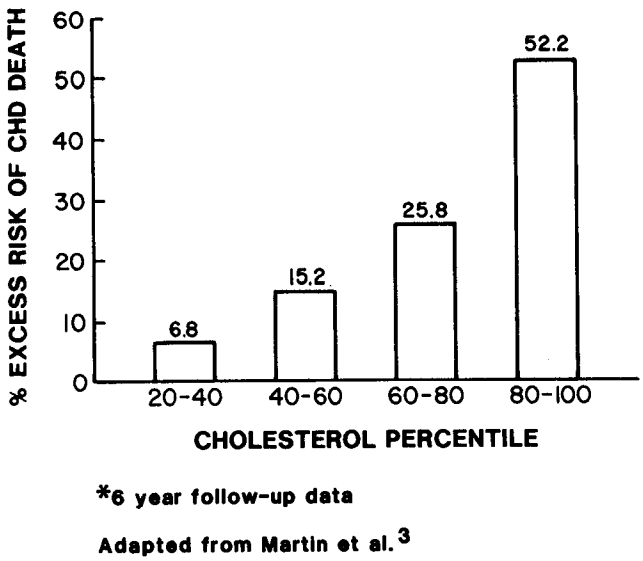

Fig. 1. Percentage excess risk of CHD death by cholesterol quintile in MRFIT screenees (six-year follow-up data). (Adapted from Martin et al.[5])

results of the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT).[4,5] This prospective, multicenter, randomized, double-blind clinical trial was designed to determine whether lowering elevated blood cholesterol levels in asymptomatic middle-aged men (N = 3,806) would reduce the incidence of coronary artery disease events; that is, to test the "lipid hypothesis." Participants with plasma cholesterol levels of 265 mg/dL (approximately the 90th percentile) or greater were randomized to cholestyramine resin (dose = 24 g/day) or a corresponding placebo and followed for seven to 10 years. All participants were offered a cholesterol-lowering diet before randomization.

The cholestyramine group had 8.5% and 12.6% greater reductions in total and low-density lipoprotein (LDL) cholesterol, respectively, than the placebo group.[4] This was associated with a 19% reduction in nonfatal myocardial infarction and a 24% reduction in fatal CHD incidence. For every 1% reduction in cholesterol level, there was approximately a 2% reduction in CHD risk in participants in the LRC-CPPT.[5]

Although it is not entirely justifiable to extrapolate the results of the LRC-CPPT to broader segments of the population (women, older and younger patients, individuals with lower blood cholesterol levels), it seems reasonable to suggest that pharmacologic intervention is reasonable in many individuals whose total and LDL cholesterol levels remain above the age-adjusted 75th percentile, despite attempts to reduce dietary intake of saturated fat and cholesterol. This is particularly true in individuals with associated cardiovascular risk factors. Previous recommendations from the National Institutes of Health Consensus Development panel advocated intensive treatment by dietary means for "moderate-risk" adults with blood cholesterol values between the 75th and 90th age-adjusted percentiles.[1] They also advocate that individuals with "high risk" blood cholesterol levels (values above the 90th age-adjusted percentile) also be treated intensively by dietary modification; if response to treatment is inadequate, appropriate pharmacologic therapy is recommended. Selected reference values for plasma total and LDL cholesterol in white men and women are provided in *Tables 1* and *2*.[6]

Current guidelines issued as part of the National Cholesterol Education Program (NCEP), sponsored by the National Heart, Lung, and Blood Institute of the National Institutes of Health, state that cholesterol levels below 200 mg/dL are "desirable" for all adults over age 20. Levels of 200-239 mg/dL are classified as "bor-

Table 1. Selected reference values for plasma total cholesterol and LDL in white men[5]

Age (yr)	Total cholesterol (mg/dL) percentiles			LDL cholesterol (mg/dL) percentiles		
	50	75	90	50	75	90
20–24	165	185	205	105	120	90
25–29	180	200	225	115	140	155
30–34	190	215	240	125	145	165
35–39	200	225	250	135	155	175
40–44	205	230	250	135	155	175
45–69	215	235	260	145	165	190
70+	205	230	250	145	165	180

Table 2. Selected reference values for plasma total and LDL cholesterol in white women[5]

Age (yr)	Total cholesterol (mg/dL) percentiles			LDL cholesterol (mg/dL) percentiles		
	50	75	90	50	75	90
20–24	170	190	215	105	120	140
25–34	175	195	220	110	125	145
35–39	185	205	230	120	140	160
40–44	195	215	235	125	145	165
45–49	205	225	250	130	150	175
50–54	220	240	265	140	160	185
54+	230	250	275	150	170	195

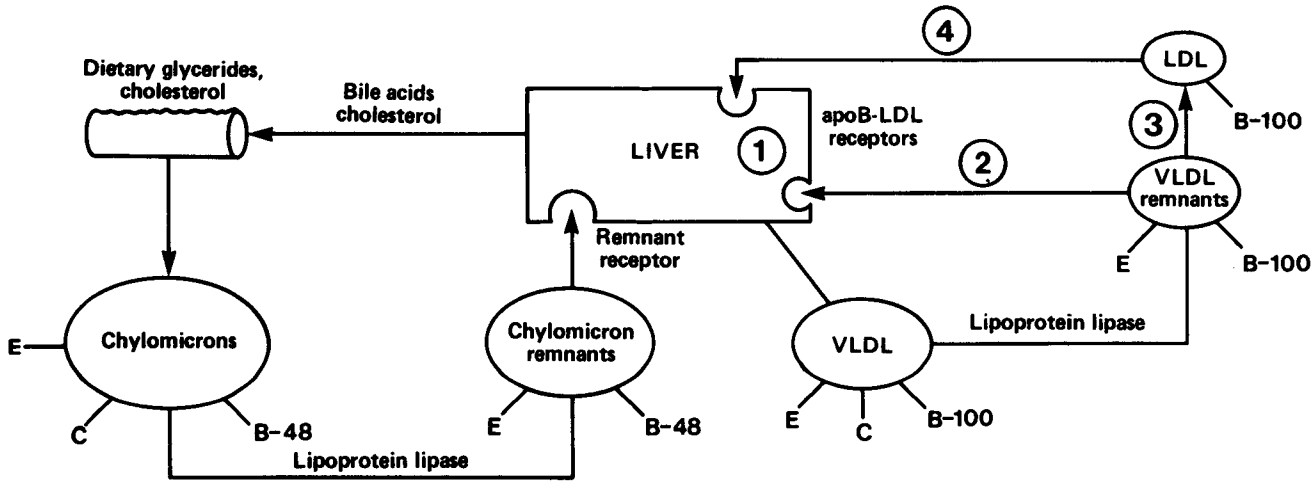

Fig. 2. The role of the liver in lipoprotein metabolism: it clears chylomicron remnants, synthesizes VLDL, clears VLDL remnants, and is responsible for clearance of LDL via a receptor-mediated process. 1) Synthesis of apoB-LDL receptors. 2) Receptor-mediated clearance of VLDL remnants. 3) Conversion of VLDL remnants to LDL. 4) Receptor-mediated clearance of LDL. (Adapted from Goldstein et al.[12])

derline-high," while levels of 240 mg/dL or greater are considered "high." Treatment decisions are to be based on LDL cholesterol levels and the presence of associated cardiovascular risk factors. The minimal goals of treatment are an LDL cholesterol level less than 160 mg/dL in patients who do not have CHD or two CHD risk factors. These risk factors include male sex, family history of premature CHD, cigarette smoking, hypertension, low HDL cholesterol, diabetes mellitus, definite cerebrovascular or peripheral vascular disease, or severe obesity. A minimal LDL cholesterol goal of less than 130 mg/dL has been established for patients with CHD or two risk factors. The panel's recommendation will be widely distributed to physicians early in 1988.[7]

At present, physicians are frequently reluctant to prescribe cholesterol-lowering agents for a number of very good reasons. The bile acid sequestrants (cholestyramine and colestipol) and nicotinic acid, which are the mainstays of treatment for individuals with types IIA and IIB hypercholesterolemia, frequently cause side effects. Gastrointestinal side effects, such as nausea, bloating, constipation, and flatulence, are the most frequent side effects of cholestyramine and colestipol.[4] Flushing occurs in most patients who receive the high doses of nicotinic acid that are required to reduce blood cholesterol levels. It is interesting to note that the total cholesterol levels in the cholestyramine-treated patients in the LRC-CPPT and the nicotinic acid-treated patients in the Coronary Drug Project were only reduced by about 10%, a problem partially related to poor adherence to treatment.[4,8] In addition, treatment of hypercholesterolemia with a bile acid sequestrant is quite costly. Thus, there is a great need for more effective and better-tolerated cholesterol-lowering drugs.

Recently, clinical trials testing the safety and efficacy of a new class of lipid-lowering drugs, which are competitive inhibitors of the enzyme 3-hydroxy-3 methylglutaryl CoA (HMG-CoA) reductase have been reported.[9–12] This enzyme catalyzes the rate-limiting step in endogenous cholesterol synthesis in the liver. Available information suggests that the HMG-CoA reductase inhibitors are well tolerated and quite effective in reducing elevated total and, particularly, LDL cholesterol levels. One of these agents, lovastatin (formerly called mevinolin), has been approved by the Food and Drug Administration (FDA) and is now available in the United States. Although other HMG-CoA reductase inhibitors are also being developed (pravastatin, simvastatin), this report focuses on published information from clinical trials using lovastatin.[9–12]

Metabolism of lipoproteins

To describe the mechanism of action of HMG-CoA reductase inhibitors, it is necessary to understand the mechanism(s) of lipid and lipoprotein metabolism. Goldstein and coworkers recently reviewed the metabolism of lipoproteins and described the central role of the liver in this process.[13] Dietary fats are transported from the

intestine to the blood via the lymphatics as chylomicrons containing apoproteins C, E, and B-48 (*Fig. 2*). Endothelial lipoprotein lipase hydrolyzes triglycerides from chylomicrons, forming chylomicron remnants that are rapidly removed by a receptor-mediated process in the liver. The liver synthesizes very-low-density lipoproteins (VLDL), which contain apoproteins B-100 (apoB), C, and E. Further hydrolysis of VLDL by lipoprotein lipase produces VLDL remnants, which are removed by the liver via a receptor-mediated process or converted into apoB-containing LDL (apoB-LDL). Approximately two thirds of apoB-LDLs are removed from the circulation via hepatic apoB-LDL receptors. Individuals with heterozygous familial hypercholesterolemia produce only approximately half the normal number of apoB-LDL receptors and tend to have LDL-cholesterol levels that are increased two-fold.

Role of HMG-CoA reductase

As previously stated, the conversion of HMG-CoA to mevalonic acid by HMG-CoA reductase is thought to be the rate-limiting step of endogenous cholesterol synthesis. When intracellular cholesterol levels fall (because of reduced intracellular cholesterol synthesis or increased conversion of intracellular cholesterol to bile acids), apoB-LDL receptor protein synthesis is stimulated.[13] Incorporation of functionally active apoB-LDL receptors into liver cell membranes augments removal of VLDL remnants and LDL from the circulation. In addition, production of LDL is reduced, since these cholesterol-rich lipoproteins are derived from VLDL remnants. In effect, when intracellular cholesterol levels are reduced, the liver maintains a critical intracellular cholesterol level by removing cholesterol-rich lipoproteins from the circulation. Thus, the liver plays a central role in the synthesis and catabolism of lipoproteins.

Classification of Hypercholesterolemia

A variety of classification schemes for types IIA and IIB hypercholesterolemia has appeared in the medical literature. A simplified approach divides hypercholesterolemia into two types: classic familial hypercholesterolemia (FH) and "nonfamilial" hypercholesterolemia. This classification is simple but ignores the fact that many patients with nonfamilial hypercholesterolemia probably have a range of genetic defects that contribute to their elevated blood cholesterol levels. Other investigators have used the term "primary moderate hypercholesterolemia" or "polygenic" hypercholesterolemia to describe these patients. It is felt that genetic as well as environmental factors (eg, diets high in saturated fats and cholesterol) contribute to the elevation in blood cholesterol levels observed in these patients. In contrast, patients with heterozygous FH have approximately a 50% reduction in functional apoB-LDL receptors due to the presence of a single-site mutation in the gene that encodes for synthesis of the apoB-LDL receptor.[13] Clinically, heterozygous FH is characterized by an autosomal dominant pattern of inheritance, severe hypercholesterolemia (total blood cholesterol blood levels typically above 350 mg/dL), tendinous xanthomas, and a very high incidence of premature CHD in patients and affected family members. It occurs in approximately one in 500 persons in the population.

Clinical trials with lovastatin

Effect of lovastatin in normocholesterolemics

Tobert and coworkers reported results of a placebo-controlled, double-blind, dose-finding study in 59 ambulatory normocholesterolemic volunteers.[14] Participants maintained their usual activities (and diets) during a two-week placebo run-in period and a four-week open-label treatment phase. Subjects were randomly assigned to placebo or lovastatin (6.25 mg, 12.5 mg, 25 mg, or 50 mg twice daily). Medication was taken before breakfast and with dinner. One group received a single evening dose of 25 mg lovastatin.

All doses reduced LDL-cholesterol levels significantly. There was no dose-response relationship across the twice daily dosing interval. This suggests that the 6.25-mg BID dose lies near the top of the dose-response curve in normal volunteers. The 25-mg evening lovastatin dose was not as effective as any of the BID dosing regimens. Total cholesterol reductions ranged from 23% to 27% and LDL cholesterol reductions from 35% to 45%, while high-density lipoprotein (HDL) and VLDL cholesterol levels did not change.

Lovastatin in nonfamilial hypercholesterolemia

The Lovastatin Study Group performed a randomized, double-blind, placebo-controlled, dose-finding study in 101 patients with nonfamilial

hypercholesterolemia.[15] These patients had a mean total serum cholesterol level of 303 mg/dL despite treatment with a lipid-lowering diet. After a four-week, single-blind placebo phase, patients were assigned to treatment with placebo or 5 mg to 40 mg lovastatin twice daily (with the morning and evening meal). Two groups received a single dose of 20 mg or 40 mg lovastatin with the evening meal.

A dose-response relationship was observed in the participants randomized to twice daily doses of 10 mg to 40 mg lovastatin (*Table 3*). Reductions in LDL cholesterol ranged from 24% to 39% in these patients. There was a tendency for VLDL cholesterol to fall; the change reached statistical significance at the 40-mg twice daily dose. HDL levels increased slightly, but these changes did not reach statistical significance. However, LDL/HDL ratios fell by 27% to 46% over the 10-mg to 40-mg twice daily dose range.

The patients receiving lovastatin 40 mg twice daily consistently had a favorable cholesterol-lowering response. A 20% or greater reduction of LDL cholesterol occurred in 97% of patients, and 51% had an LDL-cholesterol reduction of at least 40%. The LDL cholesterol never fell by more than 60%. Patients who received lovastatin 20 mg twice daily for 18 weeks had approximately a 30% reduction in LDL cholesterol. The cholesterol-lowering effect was apparent after two weeks and was maximal after four weeks. There was no reduction in efficacy over this 18-week period. The 30% reduction in LDL cholesterol with a 20-mg twice daily dose agrees with the data of Grundy and Vega,[11] who also performed LDL turnover studies in patients with primary moderate hypercholesterolemia. These investigators found that the fall in LDL levels could be explained more by a reduction in synthesis of apoB-LDL than by enhanced clearance of apoB-LDL from the circulation. This suggests that increased removal of VLDL remnants, which are the precursor for LDL cholesterol, is the major mechanism of the LDL cholesterol–lowering response in patients with nonfamilial hypercholesterolemia.

Table 3. Changes in lipids/lipoproteins during lovastatin treatment in patients with nonfamilial hypercholesterolemia (Adapted from Lovastatin Study Group II.[13])

	% Change by total daily lovastatin dose*			
Lipids/lipoproteins	10 mg	20 mg	40 mg	80 mg
Total cholesterol	−21	−18	−29	−32
LDL cholesterol	−25	−24	−34	−39
VLDL cholesterol	−23	−2	−31	−31
Triglycerides	−19	−15	−23	−27
HDL cholesterol	6	4	11	13

* Each dose given twice daily for six weeks (n = 19–21 per group).

Table 4. Changes in lipids/lipoproteins during lovastatin treatment in patients with heterozygous familial hypercholesterolemia (Adapted from Illingworth and Sexton.[15])

	% Change by total daily lovastatin dose*			
Lipids/lipoproteins	10 mg	20 mg	40 mg	80 mg
Total cholesterol	−17.1	−23.5	−30.4	−33.3
LDL-cholesterol	−19.8	−28.4	−35.0	−37.7
Triglycerides	−6.1	−11.0	−30.7	−34.3
HDL-cholesterol	−8.1	2.0	0	2.0

* Each dose administered twice daily for four weeks (n = 13).

Lovastatin in heterozygous familial hypercholesterolemia

As previously stated, heterozygous FH occurs in approximately one in 500 persons. These patients usually have severe hypercholesterolemia and virtually never have an adequate cholesterol-lowering response to diet. Pharmacologic therapy is usually indicated. At present, a bile acid sequestrant is administered alone or in combination with nicotinic acid. However, drug-related side effects often limit the efficacy of this therapy.

Illingworth and Sexton gave increasing doses of 5 mg, 10 mg, 20 mg, and 40 mg lovastatin twice daily (one month at each dose) to 13 patients with heterozygous FH (*Table 4*).[16] A dose-related reduction in LDL-cholesterol (from 19.8% on the 5-mg twice daily dose to 35% on the 20-mg twice daily dose) was observed. The response plateaued at the 20-mg twice daily dose; there was no statistically significant difference in the LDL-cholesterol reductions of the 20-mg and 40-mg twice daily doses (35% versus 37.7%, respectively). HDL-cholesterol levels did not change, but plasma triglycerides were reduced 30.7% and 34.3% at the highest doses.

Havel and coworkers reported the results of a dose-finding study with 5 mg to 40 mg lovastatin twice daily in patients with heterozygous familial hypercholesterolemia.[17] After six weeks of treatment, responses of lipids and lipoproteins to lo-

Table 5. Changes in lipids/lipoproteins during lovastatin treatment in patients with heterozygous familial hypercholesterolemia (Adapted from Havel et al.[16])

	% Change by total daily lovastatin dose*			
Lipids/lipoproteins	10 mg	20 mg	40 mg	80 mg
Total cholesterol	−15	−23	−27	−34
LDL cholesterol	−20	−29	−33	−42
Triglycerides	+5	−8	−17	−15
HDL cholesterol	18	8	12	8

* Each dose administered twice daily for six weeks (n = 19–20 per group).

vastatin treatment were dose related (*Table 5*). At the 40-mg twice daily dose, total serum cholesterol was reduced 34%, while LDL cholesterol levels fell by 42%. No loss of effect was noted after an additional 12 weeks of treatment. The percent reductions in total and LDL cholesterol levels were generally similar in this study and the Lovastatin Study Group's dose-finding study in patients with nonfamilial hypercholesterolemia.[15] Although this degree of total- and LDL-cholesterol reduction is obviously desirable, it is impor-

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Colestipol and lovastatin in hypercholesterolemics

Cholestyramine and colestipol are nonresorbable bile acid sequestrants (resins) that reduce reabsorption of bile acids from the intestinal lumen. Bile acids are synthesized from intracellular cholesterol in the liver. Bile acid sequestrants reduce LDL-cholesterol levels by increasing LDL-cholesterol clearance from the circulation.[18] Presumably, this is due to enhanced synthesis of apoB-LDL receptors (a consequence of intracellular cholesterol depletion). Thus, bile acid sequestrants and HMG-CoA reductase inhibitors both induce synthesis of apoB-LDL receptor proteins through intracellular cholesterol depletion, but through different mechanisms. Theoretically, the combination of intracellular cholesterol reduction through bile acid depletion with a bile acid sequestrant and reduced intracellular cholesterol synthesis with an HMG-CoA reductase inhibitor would be a particularly potent method to reduce elevated LDL-cholesterol levels.

Grundy and coworkers evaluated the effects of lovastatin and colestipol in eight patients with heterozygous FH.[19] Pretreatment total and LDL cholesterol levels were 367 ± 31 mg/dL and 321 ± 32 mg/dL, respectively. The patients were treated with lovastatin 20 mg twice daily and colestipol 10 g twice daily. Lipoprotein turnover studies were performed before and during drug treatment. Mean total- and LDL-cholesterol levels fell to 208 ± 18 mg/dL and 154 ± 19 mg/dL during combined drug therapy. Thus, combination therapy reduced total- and LDL-cholesterol levels by 43% and 52%, respectively. This was due to a 40% increase in the fractional catabolic rate of LDL cholesterol and a 26% decrease in its production rate. HDL-cholesterol levels increased from 27 ± 3 mg/dL to 35 ± 5 mg/dL (a 29% increase), while triglyceride levels did not change.

Illingworth studied 10 patients with heterozygous FH.[20] After five to nine weeks of treatment with lovastatin 40 mg twice daily, total and LDL cholesterol decreased by 33% and 38%, respectively. Addition of colestipol produced additional reductions in total- and LDL-cholesterol levels of 18% and 26%. Reductions in concentrations of LDL cholesterol ranged from 23% to 50% with lovastatin monotherapy; addition of colestipol caused further decreases of 13% to 35%. Combination therapy reduced LDL cholesterol 42% to 65% from pretreatment levels. Significant changes in triglyceride or HDL cholesterol levels were not observed.

Vega and Grundy studied the effects of colestipol (10 g twice daily) and lovastatin (20 mg twice daily) on plasma lipids and lipoproteins in 10 patients with primary moderate hypercholesterolemia.[21] Combined drug therapy reduced plasma total- and LDL-cholesterol levels by 36% and 48%, respectively. The reduction in LDL-

cholesterol levels, estimated from LDL turnover studies, was due to a 27% decrease in LDL-cholesterol production, a 20% increase in its fractional catabolic rate. HDL cholesterol increased by 17%. This magnitude of cholesterol reduction is greater than generally achieved through monotherapy with high doses of an HMG-CoA reductase inhibitor alone. Since the side effects of lovastatin and other HMG-CoA reductase inhibitors may be dose related, combination therapy seems reasonable when additional cholesterol-lowering therapy is indicated in patients receiving a moderate or high dose of lovastatin or another HMG-CoA reductase inhibitor.

Side effects

Lovastatin appears to be well tolerated. No serious adverse clinical or laboratory effects directly attributable to the drug were reported in the 101 patients with nonfamilial hypercholesterolemia during the Lovastatin Study Group trial.[14] No patient was withdrawn from the study due to an adverse clinical or laboratory event. The most commonly reported adverse effects considered possibly or probably drug related were gastrointestinal complaints, such as flatulence and diarrhea. They were mild to moderate in intensity and, in most cases, transient. No clear relationship between these gastrointestinal side effects and lovastatin dose was observed.

Of concern is the observation of new lens opacities at the conclusion of the study in 13 of the 101 patients with nonfamilial hypercholesterolemia.[14] It is of note, however, that none of these individuals experienced loss of measured visual acuity, and two patients with lens opacities observed at baseline had no lens opacities observed at the end of the study. In the study of lovastatin treatment in patients with familial hypercholesterolemia reported by Havel et al,[17] new lens opacities were noted in only two patients. Certainly, more information is required to assess the significance of these data. One of the problems in evaluating the effect of lovastatin on the eye is the multiplicity of terms ophthalmologists use to describe lens abnormalities. In addition, different ophthalmologists often examined patients before and during treatment in the early lovastatin trials. The new lens opacities described have been predominantly cortical and do not appear to progress rapidly or cause loss of vision within a year. Additional information about the ocular effects of long-term lovastatin therapy will be obtained during ongoing clinical trials that involve a large cohort of patients treated with varying doses of the drug.

Moderate dose-related increases in transaminases, particularly SGPT (ALT), have been observed in several lovastatin studies. In the Lovastatin Study Group trial in patients with nonfamilial hypercholesterolemia, three patients had an increase in SGPT to greater than twice the upper limit of the normal range.[14] It is uncertain whether these mild transaminase elevations were directly attributable to the drug, but elevations in liver enzymes have occurred after several months of treatment. It is of note that, during the first year of cholestyramine treatment in the LRC-CPPT, alkaline phosphatase and SGOT levels were higher in the cholestyramine-treated group than in the placebo group.[3] Thus, the role of lovastatin as a hepatotoxin requires further evaluation. Finally, the lovastatin package insert states that 0.5% of lovastatin-treated patients have developed myalgias associated with markedly elevated creatinine phosphokinase (CPK) levels and that one cardiac transplant recipient developed severe rhabdomyolysis and acute renal failure.

Discussion

The HMG-CoA reductase inhibitors are an exciting new class of cholesterol-lowering agents. These drugs appear to exert their effect by stimulating synthesis of apoB-LDL receptors. This enhances clearance of VLDL remnants. A reduction in endogenous LDL-cholesterol synthesis occurs.[13] Furthermore, clearance of LDL cholesterol is increased through induction of apoB-LDL receptors in the liver-cell membrane. The reductions in LDL-cholesterol levels in normocholesterolemic individuals, patients with "nonfamilial" hypercholesterolemia, and individuals with heterozygous familial hypercholesterolemia suggest that the level of intracellular cholesterol synthesis is an important determinant of blood LDL-cholesterol levels. Indeed, it is interesting that the percent reduction in total and LDL cholesterol levels is quite similar in normal volunteers, patients with nonfamilial hypercholesterolemia, and individuals with heterozygous familial hypercholesterolemia.

In more practical terms, the availability of potent and well-tolerated cholesterol-lowering agents will be a welcome addition to the thera-

peutic armamentarium for primary and secondary prevention of atherosclerotic vascular disease. However, more information is necessary to document the long-term safety of these drugs. The role of the HMG-CoA reductase inhibitors as ocular or hepatic toxins requires careful evaluation. Until we know more about long-term safety, it seems prudent to perform a detailed eye examination (including slit lamp examination of the lens) before treatment and at yearly intervals as recommended in the lovastatin package insert. In addition, serum transaminase (SGOT, SGPT) levels should probably be measured every four to six weeks.

The cost of one year of lovastatin treatment is usually over $1,500 when the cost of medication and follow-up for toxicity are considered. In addition, it should be recognized that there are currently no data that demonstrate the efficacy of lovastatin or the other HMG-CoA reductase inhibitors in primary or secondary prevention of atherosclerotic cardiovascular disease. These factors should be considered in this era of increasing enthusiasm for the pharmacologic treatment of hypercholesterolemia. The first step of treatment for patients with hypercholesterolemia is dietary modification, and there are patients who will have a beneficial cholesterol-lowering response. In addition, the bile acid sequestrants and nicotinic acid are still considered to be the first-line agents when drug treatment of hypercholesterolemia is indicated. In the future, data from treatment trials may provide clearer guidelines for use of an HMG-CoA reductase inhibitor to manage hypercholesterolemia.

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