REVIEW

Lovastatin: A New Hypolipidemic Agent A Review

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ABSTRACT

Hyperlipoproteinemia is one of the major risk factors in the development of atherosclerosis and premature coronary heart disease. Diet is the mainstay of therapy of hyperlipoproteinemia, while lipid lowering drugs are recommended for those patients with concentrations of atherogenic lipoproteins which exceed the 90th – 95th percentile for age. Unfortunately, diets that are palatable are not efficacious in lowering serum cholesterol levels. Pharmacotherapy with either a single agent or a combination of two drugs can efficaciously lower plasma lipoprotein levels. However, the majority of patients cannot tolerate these drugs since their use is associated with a number of unpleasant side effects.

Current research discovered a new class of therapuetic agents which have the advantage of added efficacy as well as a wider margin of safety. This new class of pharmacological agents is the 3-hydroxy-3- methylglutaryl coenzyme A (HMG CO A) reductase inhibitors. Several compounds belonging to this pharmacologic class have been investigated. Lovastatin formerly known as mevinolin is the only HMG CO A reductase inhibitor marketed.

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The purpose of this article is to review the pharmacology, the pharmacokinetics and the clinical efficacy of Lovastatin. Elevated serum Cholesterol levels and specifically Low-density-lipoprotein Level plays a fundamental role in the development of coronary heart disease and atherosclerosis [1,2,3,4, 5,6,7] . According to recent findings of the Lipid Research Clinic Primary Prevention Trial "the greater the LDL Cholesterol reduction with treatment, the greater the beneficial effect on Cardio-vascular disease progression". Therapy of hyperlipoproteinemia should always be initiated with diet. But, unfortunately, diets that most patients consider palatable reduce serum cholesterol by only 10 percent [4,5,8] . As outlined in the National Institutes of Health Consensus Conference on Cholesterol, "upto 10 percent of the American population should reduce its blood cholesterol concentrations by combined diet and drug intervention" [6].

A number of agents including the bile acid sequestrants (Cholestyramine and Colestipol), nicotinic acid, clofibrate, neomycin and probucol are effective in lowering serum cholesterol in patients with heterozygous familial hypercholesterolemia as well as other types of hypercholesterolemia when used either as single agents or in combination [1,2,17] . However, the majority of patients cannot tolerate these drugs either because they are bulky [13] and this is the case with the bile acid sequestrants or because of their other disturb-

ing side effects [1, 2, 17] . Lovastatin shares the efficacy of the former agents but differs in its wider margin of safety.

In order to understand the pharmacology of Lovastatin, the reader should review the cholesterol transport system.

Cholesterol Transport

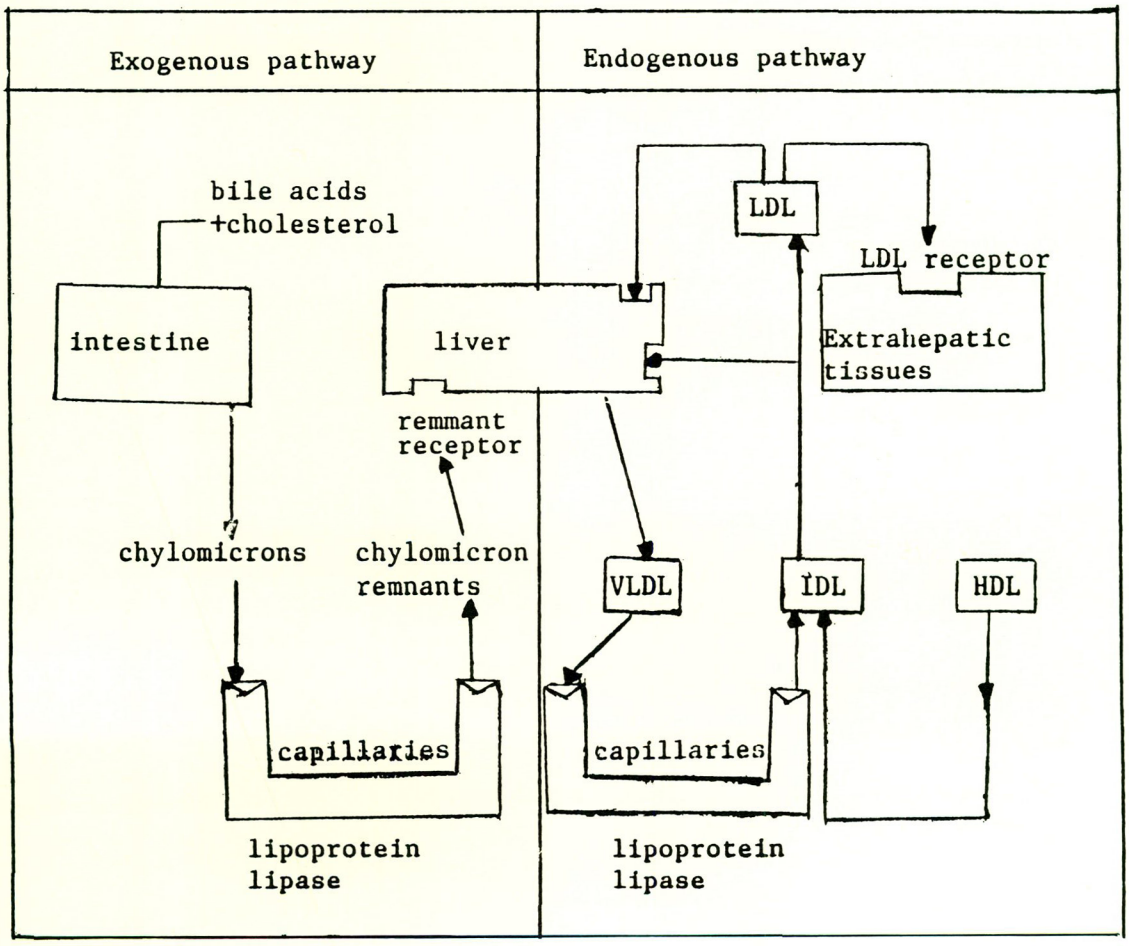
Cholesterol is an essential component of cell membranes and is necessary for hormone synthesis in the adrenal gland and gonades [12] . 60 – 80 percent of plasma cholesterol is synthesized by cells while the remaining 20 – 40 percent comes from diet [12] . The process of cholesterol synthesis is shown in figure (1). Cholesterol and triglycerides from the diet are incorporated into chylomicrons in the intestine and are transported from the intestine to lymphatics and plasma [12 , 13] .

Chylomicrons are triglyceride rich lipoproteins. Upon reaching the systemic circulation a large portion of the triglyceride is removed in the peripheral tissues by the enzyme lipoprotein lipase [13] . The remaining chylomicron particles are taken up by specific hepatic receptors [12,13] . The cholesterol deposited in the liver is degraded into bile acids and secreted into the intestine through enterohepatic circulation [12] . Some of the cholesterol combines with triglycerides from endogenous sources to form very-low-density lipoprotein (VLDL) in the liver; these particles are released into the circulation [12] . Hydrolysis of the triglyceride portion of VLDL is dependent on the enzyme lipoprotein lipase [12,13] .

Intravascular catabolism of VLDL particles leads to the formation of smaller lipoproteins known as Intermediate Density Lipoprotein

FIGURE 1

The Cholesterol Transport Pathways
Modified from reference 12



(IDL) [13]. LDL is the major lipoprotein that transports cholesterol in the plasma. In addition, LDL is the lipoprotein that is strongly associated with the occurrence of premature atherosclerosis and coronary heart disease [5,8]. LDL particles are removed from the plasma via LDL receptors found on both hepatic and extra-hepatic cells [12]. The liver, adrenal gland, and ovaries contain the largest number of LDL receptors and therefore, degrade approximately 75 percent of cholesterol [12]. The remaining 25 percent of cholesterol is degraded in peripheral cells [13]. The uptake of LDL by high affinity LDL receptors results in suppression of endogenous cholesterol synthesis, an increase in the rate of intra-cellular cholesterol esterification and a decrease in the number of high affinity LDL receptors found on the cell surface [12].

"The two types of hypercholesterolemia that reflect the importance of LDL receptors are heterozygous familial hypercholesterolemia and homozygous familial hypercholesterolemia". Both types of hypercholesterolemia are genetically determined. Patients with the first type of hypercholesterolemia have half the number of LDL receptors. As a consequence of reduced number of LDL receptors, the cholesterol levels in these patients is in the range of 7.75 – 13 mmol/L (299 – 502 mg/dl) or approximately 2.5 times the normal cholesterol levels. This group of patients are prone to develop premature atherosclerosis and coronary heart disease [2,7,12,13]. Patients with the second type of hypercholesterolemia have few or no functional high affinity LDL receptors [12,13]. Therefore, patients with this disorder present with a more severe clinical picture and plasma cholesterol in these patients is in the range of 18.10 – 25.86 mmol/L (700 – 1000 mg/dl). As a consequence of elevated plasma cholesterol levels, these patients develop atherosclerosis and coronary heart disease very early in life and often die before the age of 20 [5,12]. High Density Lipoprotein (HDL) represent the fourth class of lipoproteins. HDL particles are derived from direct hepatic secretion and during intravascular lipolysis of chylomicron particles [13]. "Clinical and epidemiological studies have shown an inverse correlation between plasma levels of HDL cholesterol and the development of atherosclerosis" [5,12,13]. High Density lipoprotein represent a major mechanism for removal of cholesterol from extrahepatic tissues and peripheral cells [5,12,13].

Pharmacology

Lovastatin is a fermentation product derived from Aspergillus terreus. It is rapidly converted in vivo to mevinolic acid, which is a potent inhibitor of 3-hydroxy-3-methylglutaryl – conenzyme A reductase [3]. This enzyme catalyzes the conversion of 3-hydroxy-3-methylglutaryl-coenzyme A to mevalonate which is the rate limiting step in cholesterol synthesis [3,4,12,13,14]. Inhibition of cholesterol synthesis in the liver results in a compensatory increase in hepatic high affinity low-density lipoprotein (LDL) receptors. As a consequence of this increase in the number of LDL receptors, the catabolism and elimination of low-density-lipoprotein will be enhanced [4,10,14,15]. At the same time there will be a decrease in the rate of synthesis of LDL [14,15]. The net effect on plasma lipoprotein is to lower low-density-lipoprotein concentrations which results in a decrease in total plasma cholesterol, while high-density-lipoprotein (HDL) concentration increase or remain the same [14].

Unlike HMG COA reductase inhibitors that inhibit late steps in cholesterol synthesis, Lovastatin inhibits early steps in cholesterol synthesis. Therefore, its use is not associated with toxicities that are related to accumulation of sterol intermediates [3,4].

Pharmacokinetics

Absorption of Lovastatin from the gastrointestinal tract is incomplete; approximately 30 percent of a dose is absorbed. The drug undergoes extensive first-pass metabolism in the liver and is primarily excreted in the bile [12,14]. Less than 10 percent of a dose is recovered in the urine [12]. The major active metabolite is a Beta-hydroxyacid, L-154,819. In humans, three other lactone hydroxyacid metabolites have been identified; all of which have HMG COA reductase activity [12]. Peak serum concentrations of the drug are reached two to four hours post ingestion. The elimination half life of the major active metabolite is one to two hours [12,14]. The bioavailability of Lovastatin increases by approximately 50 percent if it is

administered with food. For this reason, the manufacturer recommends that doses be taken with meals. Lovastatin and its major active metabolites are highly bound to plasma proteins. Lovastatin has not been evaluated in patients with hepatic or kidney diseases [12] .

Clinical Efficacy

Studies in Healthy volunteers

The safety and efficacy of Lovastatin was evaluated in a double blind, placebo controlled trial in 59 healthy men (serum cholestrol 3.88 – 7.76 mmol/L) in a multicenter trial. The mean reductions of total serum cholestrol and low-density-lipoprotein following Lovastatin doses of 6.25, 12.5, 25, or 50 mg for four weeks were 23 – 27 percent and 35-45 percent respectively. High-density-lipoprotein, very-low-density-lipoprotein and triglycerides were not significantly affected. The difference between the response to the smallest dose (6.25 mg) and the largest dose (50 mg) was not significant [3] .

Efficacy in Heterozygous Familial Hypercholesterolemia

Illingworth and Sexton evaluated the hypolipidemic effects of Lovastatin in 13 patients with heterozygous familial hyper-cholesterolemia. While these patients were maintained on a low cholesterol diet, they received subsequently increasing doses of 5, 10, 20 and 40 mg of Lovastain twice daily for one month on each dose. The mean reductions of plasma cholesterol concentrations on Lovastatin doses of 5mg, 10mg, 20mg and 40mg twice daily were 19.8%, 28.4%, 35% and 37.7% respectively. All of these values were statistically significant. Concentration of high-density-lipoprotein cholesterol remained the same on all doses. While concentrations of plasma triglycerides fell significantly [15] .

In a double-blind, placebo-controlled, radomized, crossover trial Hoeg et al compared the efficacy and safety of Lovastatin in 24 patients with type II hyperlipoproteinemia. Six of these patients had type II hyperlipoproteinemia with familial hypercholesterolemia while the remaining 18 patients had type II hyperlipoproteinemia without familial hypercholesterolemia. Both apolipoprotein B and LDL cholesterol concentrations were reduced significantly in both familial hypercholesterolemia and non familial hypercholesterolemia patients by 28 – 34 percent. Moreover, high density-lipoprotein cholesterol concentrations increased significantly [6] .

Efficacy in Homozygous Familial Hypercholesterolemia

Uauy et al evaluated the efficacy of Lovastatin in 3 children with homozygous familial hypercholesterolemia. On 2 mg/kg/day of Lovastatin, changes in concentrations of plasma lipoproteins from base line were negligible. This suggests that there was no change in the number of LDL receptors [12] . East et al evaluated the efficacy of Lovastatin in a child with homozygous familial hypercholesterolemia who underwent liver transplantation and subsequently had 81 percent reduction in low-density-lipoprotein cholesterol level. Lovastatin 10 mg twice daily resulted in a further 41 percent reduction in the low-density-lipoprotein cholesterol level. In addition there was a 41 percent reduction in the level of very-low-density lipoprotein and a 28 percent reduction in the level of triglycerides [9] . On the other hand Thompson et al reported "only a slight effect of Lovastatin in 2 patients with homozygous familial hypercholesterolemia " [7] .

Efficacy in Non familial (polygenic) Hypercholesterolemia

The efficacy of Lovastatin in non-familial hypercholesterolemia was evaluated in a double blind, placebo-controlled multicenter trial. In this trial, Lovastatin produced a dose related reduction in total and low-density-lipoprotein cholesterol concentrations with daily doses of 10-80 mg [8,12] . The mean reductions of low-density-lipoprotein concentrations from base line were 25 percent and 24 percent in the 5 and 10 mg groups and 34 percent and 39 percent in the 20 and 40 mg twice daily groups. Total plasma cholesterol concentration was also reduced significantly, for patients on 40 mg twice a day, the mean reduction was 32 percent. High-density-lipoprotein cholesterol increased over the dosage range 5-40 mg twice a day. However, the increase in high-desity lipoprotein level did not achieve statistical significance. Plasma triglyceride concentrations fell significantly on 40 mg twice a day. Plasma concentrations of apolipoprotein B decreased substantially with increasing doses of

Lovastatin. Since each low-density-lipoprotein particle contains one molecule of apolipoprotein B and since other lipoproteins contain little apolipoprotein B, this indicates that Lovastatin decreases the level of apolipoprotein B by decreasing the level of low density-lipoprotein particles [8,12] . The results of this study also indicate that Lovastatin is not only useful in treating primary hypercholesterolemia but it may also be of value in treating combined hypercholesterolemia and hypertriglyceridemia [8] .

Efficacy in Non-Insulin-Dependent Diabetus Mellitus

Non-insulin-dependent diabetus mellitus is one of the najor risk factors in coronary heart disease, which is the main cause of death in white patients with diabetus [16] . The efficacy of Lovastatin was evaluated in 16 white patients with non-insulin-dependent diabetus mellitus in a double blind, placebo-controlled trial. Lovastatin 20 mg twice daily for four weeks produced substantial reductions in the concentrations of serum lipoproteins. As compared with placebo, Lovastatin reduced the concentration of total cholestrol by 26 percent, two-density-lipoprotein remained constant with Lovastatin therapy. The ratio of total cholesterol to high-density-lipoprotein cholesterol fell by 29 percent [16] . Although the number of patients in this trial is small, Lovastatin may turn out to be beneficial in treating non-insulin-dependent diabetus mellitus.

Efficacy in Nephrotic Dyslipidemia

Hypercholesterolemia and hypertriglyceridemia are disorders that are frequently present in patients with the nephrotic syndrome. These disorders, apart from being difficult to treat predispose patients to coronary heart disease early in life. Recently Vega and Grundy observed that Lovastatin reduced plasma concentrations of VLDL and LDL cholesterol significantly in patients with hyperlipidemia and the nephrotic syndrome. [17]

Lovastatin alone and in combination with other lipid lowering agents

The decision to use Lovastatin alone or combined with other hypolipidemic drugs depends on whether an added efficacy is needed. Lovastatin when used alone appears to be comparable in efficacy to resin therapy (i.e. it lowers total and LDL cholesterol levels and raises HDL cholesterol levels), although the extent of these changes is less [12] . The combination of Lovastatin and a resin produces an additional 15-25% reduction in total and LDL cholesterol concentrations [12] . The combination of colestipol (a resin) and Lovastatin produces a 54 percent reduction in low-density-lipoprotein concentration and is one of the most effective combination regimens [18] . When probucol is administered with Lovastatin, low-density-lipoprotein concentration was reduced by an additional 8 percent, high-density lipoprotein was reduced by an additional 33 percent, while triglyceride levels were minimally increased [12] .

Adverse Drug Reactions

The efficacy and safety of Lovastatin was compared with different hypolipidemic drugs in a five year trial. In this trial, Lovastatin was found to be the safest hypolipidemic agent [18] . Headache and gastrointestinal complaints were the most prevalent side effects reported by patients on Lovastatin [4,12] . The most frequent gastrointestinal side effects were flatulence and diarrhea; they were mild to moderate in intensity and transient [8] . Nausea, dyspepsia, constipation and abdominal cramps were also reported [12] .

The most common biochemical abnormalities during therapy with Lovastatin were elevations in the levels of the liver enzymes SGoT and SGPT [5,12,14] . In some patients Lovastatin have had to be discontinued because aminotransferase levels increased over three times the upper limit of the normal range and persisted [12,14] . However, these patients remained asymptomatic, bilirubin and alkaline phosphatase levels remained normal in most patients. This indicates a hepatocellular mechanism of injury rather than a cholestatic one [12] . Aminotransferase levels returned to normal a few weeks after cessation of therapy [14] . Alkaline phosphatase [15] and CPK [12,14] were also increased in some trials. Because of the potential risk of hepatoxicity that may occur with Lovastatin therapy, the manufacturer recommends that the liver function tests be monitored every 4 – 6 weeks during the first 15 months and periodically thereafter [12,14] . Very high doses of Lovastatin can cause cataracts in dogs [16] . In humans slit-lamp opthalmologic examinations in an eighteen month trial involving 431

patients revealed that 34 percent had an opacity before starting therapy and 32 percent had one after therapy [12,14] . Thirty four patients developed new opacities, while in forty five patients lens opacities disappeared at the end of the study [12] . No change in visual acuity was observed in patients who developed opacities [4,14] . However, a recent study by Tobert revealed that Lovastatin does not increase the rate of cataract formation over a period of one to two years. However, since diabetics are at a greater risk of developing cataracts, these patients should have their eyes checked yearly while on Lovastatin [16] .

Myositis characterized by myalgias and elevated levels of CPK can occur with Lovastatin therapy [12,14] . The incidence of this disorder is higher in patients who are concurrently receiving gemfibrozil (Lopoid) or cyclosporine [12,14] . Patients who are receiving steroids for immunosuppression [12] and patients with impaired liver function are also more prone to develop this disorder [14] .

Plasma cortisol, testesterone, and leuteinizing hormone were not affected by Lovastatin therapy [7,12] .

Dosing schedules

Studies have demonstrated that there is a correlation between the rate of cholesterol synthesis and plasma mevalonic acid concentrations [19] . Plasma mevalonic acid concentrations follow a diurnal rhythm pattern, with peak concentrations occuring between midnight and 4 a.m. This indicates that cholesterol synthesis is greatest during the early morning hours and an optimum effect will be obtained from a drug that inhibits cholesterol synthesis if it is administered prior to this time interval [12] .

Several clinical trials revealed that twice daily dosing regimen of Lovastatin is superior in efficacy to once daily evening regimen [3,7, 8,12,20] . However, to ensure patients' compliance it is preferable to start the patients on once daily evening dosing and switch to twice daily dosing if additional efficacy is desired [12] .

Dosing

Clinical trials have shown that there is a clear cut relationship between doses of 10 to 80 mg and the degree of reduction of total and low-density-lipoprotein levels [5,6, 7,15] . The lowest dose (5 mg twice daily) produces a 20 percent reduction in low-density-lipoprotein concentrations; while the highest dose (40 mg twice daily) reduces low-density lipoprotein concentration by 38 percent [15] .

Since Lovastatin is available as 20 mg unscored tablets, it will be impossible to administer it 5 mg twice daily or 10 mg twice daily. Therefore, therapy should be initiated with 20 mg every evening and gradually increased by 20 mg increments added to the evening dose or given in the morning [12] . If the cholestrol concentration exceeds 300 mg/dl, the starting dose should be 40 mg per day; the maximum dose is 80 mg per day [20] .

CONCLUSION

Lovastatin significantly lowers the levels of low-density-lipoprotein, very-low-density lipoprotein, apolipoprotein B and triglycerides. The convenience of its administration leads to a better patient's compliance. If long term trials prove its safety, Lovastatin will offer a major advance in the treatment of hypercholesterolemia.

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