The discovery and development of HMG-CoA reductase inhibitors

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INTRODUCTION

Extensive epidemiologic studies performed in many countries have shown that increased blood cholesterol levels, or, more specifically, increased levels of LDL-cholesterol, are causally related to an increased risk of coronary heart disease. Coronary risks rises progressively with an increase in the cholesterol level, particularly when cholesterol levels rise above 200 mg/dl (1, 2). There is also substantial evidence that lowering total and LDL-cholesterol levels will reduce the incidence of coronary heart disease (2).

In 1971 we started a project to search for microbial metabolites that would inhibit HMG-CoA reductase, the rate-limiting enzyme in the synthesis of cholesterol. We hoped that the suppression of de novo cholesterol synthesis in the body by inhibiting HMG-CoA reductase would reduce plasma cholesterol levels in humans. These studies led to the discovery of a potent reductase inhibitor, named mevastatin (formerly called ML-236B or compactin) (3). Subsequently, we elucidated the biochemical mechanisms of action of mevastatin (4, 5) and by 1980, had shown that mevastatin markedly lowers the levels of LDL-cholesterol in both experimental animals and humans (6-8). These findings stimulated the world-wide development of mevastatin analogues in the 1980s and, by 1990, three drugs—lovastatin (formerly called mevinolin), simvastatin, and pravastatin—had been approved and marketed in many countries (9, 10). These drugs have been well established as effective and safe cholesterol-lowering drugs and are used by many patients. Beneficial effects from their administration in patients with coronary heart disease are being observed (11).

Supplementary key words  HMG-CoA reductase • cholesterol • LDL-cholesterol • atherosclerosis

HISTORICAL BACKGROUND

During the 1950s and 1960s, many cholesterol-lowering agents were reported and introduced into clinical use, including nicotinic acid (12), cholestyramine (13), clofibrate (CPIB) (14), neomycin (15), plant sterols (16), triparanol (MER-29) (17), D-thyroxine (18), and estrogenic hormones (19). Of these drugs, nicotinic acid reduces both cholesterol and triglyceride (especially the latter) in humans. These effects are due to a decrease in lipoprotein synthesis, resulting in a fall in LDL-cholesterol. The most prominent side effect of nicotinic acid is cutaneous vasodilation. Other adverse effects include rash, gastrointestinal upset, hyperuricemia, hyperglycemia, and hepatic dysfunction (20).

Cholestyramine, an anion-exchange resin, acts by binding bile acids within the intestinal lumen, thus interfering with their reabsorption and enhancing their fecal excretion. As a result, bile acid synthesis is markedly stimulated. This leads to an increased requirement for cholesterol in the liver, which causes an elevation of hepatic HMG-CoA reductase activity. Cholestyramine is highly effective in the treatment of many patients with high cholesterol levels, but unfortunately, it is not tolerated by all patients. Therefore, in spite of its proven usefulness, the bile acid sequestrant is not an ideal cholesterol-lowering agent.

Clofibrate and its derivatives are the hypolipidemic agents most commonly used worldwide. Its major effect in hyperlipoproteinemia is to reduce VLDL-cholesterol; in most patients the cholesterol-lowering effect is minimal to moderate. Clofibrate has several pharmacological actions, including stimulation of lipolysis by increasing adipose tissue-derived lipoprotein lipase. However, details of its actions at the biochemical level are not well understood.

Neomycin is an effective cholesterol-lowering agent in patients with FH. It acts by precipitating cholesterol within the intestinal tract and thus inhibiting its absorption. Side effects, including nausea and diarrhea, limit long-term administration.

Abbreviations: HMG, 3-hydroxy-3-methylglutaryl; VLDL, very low density lipoprotein; LDL, low density lipoprotein; IDL, intermediate density lipoprotein; HDL, high density lipoprotein; FH, familial hypercholesterolemia.
Plant sterols, which interfere with the absorption of cholesterol in the intestinal tract, have no effect on VLDL-cholesterol, and their effect on LDL-cholesterol is variable. The long-term effects of plant sterols are unknown.

Triparanol is effective in reducing serum cholesterol. This drug inhibits cholesterol synthesis in the final stage(s) in the synthetic pathway, resulting in the accumulation of other sterols. Because of side effects including cataracts, it was withdrawn from the market early in the 1960s (21).

D-Thyroxine, the optical isomer of L-thyroxine, effectively lowers LDL-cholesterol in both euthyroid and hypothyroid patients. The use of D-thyroxine in a long-term trial (Coronary Drug Project) in men with established ischemic heart disease was discontinued because of increased mortality in patients with arrhythmias, angina pectoris, or multiple infarctions (20).

Estrogens have been used to treat hyperlipidemia. However, estrogens are unsuitable as hypolipidemic agents in men because of their feminizing effects and because they elevate VLDL and triglycerides (20).

In the 1960s, cholesterol metabolism in experimental animals and human subjects was extensively studied by many groups. Cholesterol can be derived either from the intestinal absorption of dietary cholesterol or from synthesis de novo within the body (22, 23). Experiments in several animal species showed that when cholesterol is removed from the diet, the liver increases its capacity to synthesize cholesterol and that this organ, together with the intestine, is able to synthesize sufficient cholesterol to meet the needs of all the other cells in the body. Although virtually all other tissues also possess the capacity to synthesize cholesterol, their synthetic rates, in contrast to those of liver and intestine, remain low (24, 25).

In 1971, with Dr. Masao Kuroda, to search for HMG-CoA reductase inhibitors of microbial origin. We hoped that certain microorganisms would produce such compounds as a weapon in the fight against other microbes that required sterols or other isoprenoids for growth. Inhibition of HMG-CoA reductase would thus be lethal to these microbes.

Over a 2-year period, approximately 6,000 microbial strains were tested for their ability to block lipid synthesis. As a result, the antibiotic citrinin was first isolated as an active compound from the mold Pythium ultimum (29). Citrinin was shown to irreversibly inhibit HMG-CoA reductase (30). Subsequently, a strain of Penicillium citrinum was found to produce active compound(s). To isolate the active component(s), 600 l of culture filtrate was extracted with organic solvents and applied to silica gel chromatography, followed by crystallization, giving crystals (23 mg) of mevastatin (formerly called ML-236B). By the end of 1973, the structure of mevastatin was determined by a combination of spectroscopic, chemical, and X-ray crystallographic methods (Fig. 1) (3).
sterols. The results demonstrated mevastatin to be a potent inhibitor of HMG-CoA reductase. The same compound (designated compactin) was also isolated as an antibiotic from *Penicillium brevicompactum* by Brown et al. in 1976 (31). Along with mevastatin, two less active compounds closely related to mevastatin were also isolated from *Pen. citrinum* (3, 32). Subsequently, the search for additional HMG-CoA reductase inhibitors was continued for another 10 years, leading to the isolation of several compounds of the mevastatin family (32).

**INHIBITION OF HMG-CoA REDUCTASE BY MEVASTATIN**

The water-soluble, open-ring acid of mevastatin (Fig. 2) gave more potent and reliable inhibition than the lactone form in the assay of both sterol synthesis from radiolabeled substrates and HMG-CoA reductase (4). The inhibition of HMG-CoA reductase by mevastatin was reversible and competitive with respect to HMG-CoA. The $K_i$ value for the acid form was $\sim 1 \times 10^{-9}$ M (Fig. 3), while under the same conditions, the $K_a$ for HMG-CoA was $\sim 10^{-5}$ M (4). Thus, the affinity of HMG-CoA reductase for compactin is 10,000-fold higher than its affinity for the natural substrate HMG-CoA, showing mevastatin to be a highly potent inhibitor. The mechanism by which mevastatin inhibits reductase appeared to be ideal for its development as a drug.

At that time, adenosine-2'-monophospho-5'-diphosphoribose, a synthetic NADP analogue, was found to be competitive with NADPH in the reaction of HMG-CoA reductase (33). Kinetic analysis suggested that HMG-CoA first binds to the enzyme, followed by the binding of NADPH. Reduction then occurs, with release of NADP, CoA, and mevalonate from the enzyme. These results suggested that the lactone portion of the mevastatin molecule is the active center and binds to the HMG binding site of the reductase molecule. The structural similarity between the lactone and HMG portions supports this conclusion. Later, it was shown that the tight binding of mevastatin is the result of its simultaneous interaction with the HMG binding domain of the enzyme and the adjacent hydrophobic pocket. This region is itself not utilized in substrate binding (34).

The structural similarity between mevastatin and HMG-CoA and the observed competition by these two molecules helped to clarify preliminary structure–activity relationships in the inhibition of HMG-CoA reductase. The mevastatin molecule is composed of four moieties (Fig. 2): a) the β-hydroxy-δ-lactone (or the 3,5-dihydroxyheptanoic acid portion), b) the moiety bridging the lactone and the lipophilic groups, c) the hexahydronaphthalene nucleus, and d) the side chain ester. Our preliminary study of the structure–activity relationships suggested a crucial role for the 3- and 5-hydroxy groups in HMG-CoA reductase inhibition, as activity is abolished by the conversion of either of these hydroxyl groups into the methyl ester. Replacement of the carboxyl group of the acid form with carboxamide also ablates activity (32). Furthermore, the distance between the lactone and decalin ring influences the inhibitory activity which suggests that certain spatial relationships need to be maintained between the reactive site (lactone) and the putative binding site (decalin ring) (32, 35). Another functionally essential region of mevastatin is its hexahydronaphthalene ring. This is shown by evidence that HMG, which lacks a hexahydronaphthalene ring, is more than 106-fold less competitive with NADPH.
active than mevastatin. On the other hand, the C3-methyl-substituted analogue lovastatin is slightly more active than mevastatin (3, 36, 37), while hydroxylation at C8 shows reduced activity (38). In addition, the α-methylbutyrate ester plays a significant role, since analogues that lack this moiety (ML-236A and ML-236C) have one-tenth or less activity, as compared with mevastatin (3).

In 1973, Brown, Dana, and Goldstein (39) reported that HMG-CoA reductase activity of cultured mammalian cells is suppressed by LDL, but not by HDL. Subsequently these investigators discovered a cell surface receptor for LDL and elucidated the mechanism by which this receptor mediates feedback control of cholesterol synthesis and HMG-CoA reductase (40-42). Familial hypercholesterolemia (FH), a genetic disorder in humans, was shown to be caused by inherited defects in the LDL receptor; these defects disrupt the normal control of cholesterol metabolism. These landmark studies of cholesterol metabolism strongly supported our studies in both experimental techniques and in the general idea of developing HMG-CoA reductase inhibitors.

By using the techniques developed by Goldstein and Brown, we demonstrated that mevastatin strongly inhibited sterol synthesis from [14C]acetate in a variety of cultured mammalian cells, including L cells and cells from patients with homozygous FH, at concentrations as low as 10^{-9} M (Fig. 4) (5, 32, 43). Inhibition of [14C]acetate incorporation was 50% at 1 nM (0.4 ng/ml) in normal human cells and cells from patients with FH; in contrast, LM cells, which grow in a lipid-free, synthetic medium, were far more sensitive, with inhibition of sterol synthesis at mevastatin concentrations of 0.1 nM (44). Sterol synthesis from [3H]mevalonate and fatty acid synthesis from [14C]acetate in cultured cells were not inhibited (5).

At higher concentrations where sterol synthesis was strongly reduced, mevastatin inhibited cell growth as well.
When grown in the presence of whole serum, growth of L cells was completely inhibited by 1.3 μM (5 μg/ml) mevastatin. This inhibition was, however, overcome with resultant normal growth by the addition of a small amount of mevalonate, the product of HMG-CoA reductase reaction (Fig. 5) (5).

Subsequently, studies by other investigators showed that in cultured fibroblasts high concentrations of mevastatin block passage through the cell cycle (45-47) and alter cell morphology (48). Both effects could be prevented by the addition of mevalonate but not by the addition of cholesterol, which suggested that either mevalonate or one (or more) of its nonsterol products was involved. In 1984, Schmidt, Schneider, and Glomset (49) incubated Swiss 3T3 cells in the presence of both mevastatin and just enough exogenous radioactive mevalonate to prevent the effects of mevastatin on cell growth and discovered that specific cell proteins were modified by one or more prenyl groups. The prenyl proteins include growth-regulating p21c proteins, a family of GTP-binding and hydrolyzing proteins that regulate cell growth (50, 51), and lamin B (52, 53), a structural component of the nuclear lamina that is associated with the inner nuclear membrane. Overproduction of p21c proteins or mutations that abolish their GTPase activity lead to uncontrolled cell division (54). (The discovery of prenyl proteins and studies of their structure and enzymology have been reviewed previously (55-57).)

The mevastatin-mediated inhibition of HMG-CoA reductase activity in cultured mammalian cells led to the production of large amounts of enzyme that could be completely suppressed by the addition of mevalonate together with LDL (43). Chin et al. (58) developed a mevastatin-resistant line of Chinese hamster ovary cells, designated UT-1 cells. UT-1 cells produced enormous amounts of reductase (1% of total cell protein), owing to a combination of an amplification of the reductase gene, an increased rate of transcription, and a decreased rate of protein degradation (59). The high levels of reductase mRNA in UT-1 cells led to the initial cloning of the complementary DNA through differential hybridization even before the intact enzyme had been purified (60, 61) and opened a new area into the molecular biology of this crucial and important enzyme (62, 63).

CHOLESTEROL-LOWERING ACTIVITY OF MEVASTATIN IN ANIMALS

Both efficacy and safety are essential for drugs, and both these factors were thoroughly investigated in animal models during the development of specific agents. In the development of most cholesterol-lowering agents, effectiveness has been evaluated predominantly in rats. In some cases, other animal species, such as rabbits, dogs, or monkeys were used. During initial investigations in early 1974, we administered mevastatin orally to rats and measured plasma lipid levels 3 to 8 h later. When given at 20 mg/kg, mevastatin reduced plasma cholesterol by about 30% (3). The results were, however, difficult to reproduce, and at the time, it was unclear whether or not this was due to technical problems. Unexpectedly, the feeding of rats with a diet supplemented with 0.1% mevastatin for 7 days caused no changes in plasma cholesterol levels (64). Plasma cholesterol was not lowered even when the agent was given to the animals at a dose as high as 500 mg/kg for 5 weeks. Furthermore, mevastatin was ineffective in mice, producing no detectable effects on plasma lipids at 500 mg/kg for 5 weeks. By 1977, these discouraging observations had been modified by a variety of biochemical and pharmacological experiments, some of which are described below.

To improve cholesterol-lowering activity, many analogues were either derived from mevastatin or synthesized de novo and evaluated. These new agents were, however, unsuccessful as none were more efficacious than mevastatin (35).

When given to rats, mevastatin inhibited sterol synthesis in vivo in the liver for 3-8 h, indicating that mevastatin is acutely active in rats (65). However, when rats received multiple doses of the drug, hepatic HMG-CoA reductase rose by 3-10 times compared with the control animals (64).
We felt that mevastatin should be evaluated more pertinently in animal models comparable to FH in humans, since in patients with FH, regulation of HMG-CoA reductase is partially or completely lost, resulting in high reductase activity (42). At that time, however, such an animal model was not available.

The nonionic detergent Triton WR-1339 was shown to produce hypercholesterolemia in rats (66). Using this model, several groups suggested that the elevated levels of hepatic HMG-CoA reductase were responsible for the increase in plasma cholesterol (67-69). Mevastatin was found to be slightly effective in these animals, giving up to 21% reduction of plasma cholesterol at 100 mg/kg (70). These results aroused a glimmer of hope, but were still not sufficient.

Commercial eggs contain ~300 mg of cholesterol, and according to our preliminary analyses, two-thirds of this amount of cholesterol is derived from diet and the remainder is supplied by de novo synthesis. We expected that the level of cholesterol synthesis in hens that were actively producing eggs would be higher than that in roosters. We fed hens a commercial diet supplemented with 0.1% mevastatin for 30 days. As expected, plasma cholesterol was reduced by as much as 50%, while body weight, diet consumption, and egg production were not significantly changed throughout the experiments (71).

The success in the experiments in hens opened up an opportunity to conduct experiments in dogs and monkeys. In dogs, mevastatin reduced plasma cholesterol by 30% at a dose of 20 mg/kg and as much as 44% at 50 mg/kg (Fig. 6) (6). β-Lipoprotein (LDL) was markedly reduced by mevastatin while α-lipoprotein (HDL) was not lowered but, rather, increased slightly. In early 1977, we gave mevastatin to monkeys for 11 days. The reduction of plasma cholesterol was 21% at a dose of 20 mg/kg and 36% at 50 mg/kg (Fig. 7) (7). Plasma triglyceride levels were not changed significantly in either dogs or monkeys. Fecal excretion of bile acids was slightly elevated in dogs but not significantly changed in monkeys (6, 7).
In summary, mevastatin is highly effective in lowering plasma cholesterol in poultry, canine, and primate models but has no effect in rodents. From these findings, we theorized that the species differences in mevastatin efficacy was secondary to the ability of certain species to metabolize plasma lipoprotein via hepatic pathways. Administration of mevastatin should cause a transient decrease of hepatic cholesterol. To meet this deprivation, an increased consumption of plasma cholesterol would occur in hens, dogs, and monkeys, while hepatic HMG-CoA reductase would be elevated in rats and mice due to their inability to catabolize plasma lipoproteins in the liver. This elevation of hepatic reductase, which overcomes mevastatin inhibition, appears to account for the lack of effectiveness of mevastatin in rats and mice. In addition, decreased excretion of bile acids in rats treated with mevastatin would partly contribute to the ineffectiveness in these animals.

CLINICAL TRIALS OF MEVASTATIN

Since early 1976, Dr. Akira Yamamoto had been following two patients with homozygous FH at the Osaka University Hospital. One of these patients (S.S.), a 17-year-old girl, had a total cholesterol level of 1000 mg/dl and was shown to be "receptor-negative" (72). In late 1977, she sustained repeated episodes of angina pectoris, and was shown to have elevated, and muscular weakness at the proximal part of the extremities similar to muscular dystrophy was observed (8). These adverse reactions were reversible on discontinuation of the drug. After 5 months at 200 mg per day, total cholesterol was not reduced detectably while, surprisingly, vascular bruits and tiberoous and Achilles tendon xanthomas reduced markedly. No adverse effects occurred during treatment at 200 mg/day. Mevastatin reduced total cholesterol by ~14% in a 3-year-old “receptor-defective” homozygous FH (female patient) at 150 mg/day (8). Early in 1978, Dr. Yamamoto gave mevastatin to four patients with combined hyperlipidemia and to five patients with type IIa hyperlipoproteinemia (apparent FH heterozygotes) for 4-8 weeks. These patients had a 22-28% reduction in total cholesterol levels at 50-150 mg/day (8). In one of the patients (S.I.), who is an FH heterozygote, total cholesterol was reduced by 25% after 2 months at 50 mg/day (Fig. 8). As in dogs, plasma LDL (plus VLDL) was markedly lowered in all patients by mevastatin treatment while plasma HDL was not affected or was even slightly elevated. These clinical trials demonstrated that mevastatin was highly effective in lowering total and LDL-cholesterol levels in patients with primary hyperlipidemia, with the exception of those who were homozygous for the defects.

In healthy volunteers, mevastatin strikingly reduced total cholesterol at 60 mg/day without side effects (73). Subsequently, Hata et al. (74) gave mevastatin for 6-20 weeks to 26 patients with hyperlipidemia, including type IIa (17 cases), type IIb (4 cases), type III (1 case), and type IV (2 cases) hyperlipoproteinemia and diabetic dyslipidemia (2 cases). Of these patients, 23 were studied in detail. Seven patients with type IIa, one with type III, and one with diabetic dyslipidemia had a substantial reduction in total cholesterol levels at a dose of 1-5 mg/day; the other four patients with type IIa, two with type IIb, and another patient with diabetic dyslipidemia at 7-10 mg/day; and the remaining four patients with type IIa, the other two with type IIb, and one with type IV at 15-25 mg/day. The results demonstrated that mevastatin was effective in all the types of hyperlipidemia studied at a dose up to 25 mg/day.

Since early 1979, clinical trials of mevastatin were carried out in patients with severe hypercholesterolemia by over 10 groups in Japan. In mid 1980, however, most of these clinical trials were suspended, because mevastatin had been found to produce toxic effects in some dogs at higher doses in a long-term toxicity study. In this experiment, mevastatin was given to the animals at doses of 25, 100, and 200 mg/kg per day for 104 weeks. Although details of the experiment have not been reported, the purported toxicity was apparently due to the accumulated toxicity of the drug. It should be noted that mevastatin is effective in humans at as low as 0.2 mg/kg or less (74); thus a dose of 200 mg/kg given to dogs is 1000 times higher than the effective dose in man.
In 1981, Mabuchi et al. (75) reported data on the LDL-cholesterol-lowering effects of mevastatin in seven patients with FH. These patients received the agent for 24 weeks without serious side effects. LDL-cholesterol was reduced by 29% at a dose of 30 or 60 mg/day (mostly at 30 mg/day) and its effect was sustained during the period of treatment. HDL increased slightly (Fig. 9) (75). Subsequently, these investigators used the combination of mevastatin and cholestyramine, a bile acid sequestrant in patients with heterozygous FH. LDL-cholesterol was reduced as much as 50-60% by the combination without serious side effects (Fig. 10) (76). A similar striking reduction of plasma cholesterol by the combination of mevastatin and cholestyramine was also reported by Yamamoto et al. (77). These studies appeared to greatly accelerate the development of HMG-CoA reductase inhibitors in the 1980s.

Fig. 9. Effects of mevastatin on IDL-, HDL-, and LDL-cholesterol level in patients with heterozygous FH. Of seven patients studied, mevastatin was given three times daily for 24 weeks at doses of 60 mg/day in two patients and 30 mg/day in the other five patients. Data are means ± SEM. P values obtained with Student's paired t-test: before treatment versus after treatment, *P < 0.05, **P < 0.01, and ***P < 0.001; after treatment versus after cessation of treatment, †P < 0.05, ‡P < 0.01 (75). (Reprinted with permission from N. Engl. J. Med. 1981. 305: 478-482.)

LOVASTATIN

Since 1976, we provided Merck & Company with samples of and unpublished data concerning mevastatin, as Merck's investigators took an interest in the agent. They repeated our biochemical and pharmacological experiments, including those with cultured mammalian cells and in vivo in rats and dogs, and by late 1978, achieved the same results. Shortly afterwards, they isolated another mevastatin analogue, named lovastatin (formerly called mevinolin or monacolin K), from Aspergillus terreus. This new agent proved to be slightly more active in inhibiting HMG-CoA reductase than the parent compound (Fig. 1) (36, 37). Because of structural similarity between mevastatin and lovastatin, it can readily be imagined that both agents have the same biochemical and pharmacolog-
ical activities. Since the early 1980s, the mechanism of action and efficacy of lovastatin had been studied extensively by investigators in the United States.

As described previously (64), there should, theoretically, be two mechanisms for lowering plasma cholesterol by an HMG-CoA reductase inhibitor—an inhibition of the hepatic formation of plasma lipoproteins and enhanced lipoprotein catabolism in the liver. Kovanen et al. (78) demonstrated in dogs that this lowering of LDL-cholesterol occurs via these two pathways. Later, Bilheimer et al. (79) showed that the hypocholesterolemic action of lovastatin is primarily a result of enhanced LDL receptor-mediated catabolism in patients with heterozygous FH. Patients with receptor-negative, homozygous FH have no capacity to synthesize LDL receptors. Uaay et al. (80) showed that during treatment with lovastatin at very high doses (2 mg/kg per day), there was no decrease in LDL-cholesterol levels, nor was the turnover rate of LDL affected by the drug. These findings strongly supported the view that the principal action of HMG-CoA reductase inhibitors is to increase the number of LDL receptors, but not to inhibit the synthesis of lipoproteins. Rates of synthesis of LDL receptors are inversely correlated with the amount of cholesterol in cells (81). Studies of lipoprotein kinetics in patients with primary moderate hypercholesterolemia who do not have the clinical characteristics of heterozygous FH, lovastatin lowered the rates of production of LDL but had little effect on its fractional clearance rates (83). Cholesterol balance studies demonstrated that reductase inhibitors increase messenger RNA for LDL receptors in the liver (82) and enhance the number of LDL receptors expressed on the surface of liver cells (78).

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AsLovastatin was shown to be safe and effective in normal subjects in 1982 (86), the efficacy of the drug was studied primarily in patients with type II hyperlipoproteinemia. Lovastatin markedly lowered plasma levels of total cholesterol and LDL-cholesterol in heterozygous FH (87-89) in a dose-dependent manner (87, 89). At dosages of 20 mg twice daily, lovastatin reduced LDL-cholesterol levels by 25-30%; at 40 mg twice daily it reduced levels by 35-40%. As was demonstrated in earlier studies with mevastatin (76), a multicenter trial (89) showed that lovastatin alone generally did not reduce LDL concentration to desirable levels in patients with FH. Nevertheless, relatively high doses produced a substantial reduction of LDL cholesterol in many patients (87).

The combination of lovastatin and colestipol, a bile acid sequestrant, reduced LDL-cholesterol levels in patients with familial FH by 50-60% (90, 91). This combination enhanced the decrease in LDL and permitted the use of smaller doses of both drugs. For example, reductions in LDL-cholesterol of 50-60% were obtained with use of colestipol and only 20 mg of lovastatin given twice daily (91).

By 1987, lovastatin had been shown to strikingly reduce LDL-cholesterol levels in most patients with primary moderate and severe hypercholesterolemia (83, 92, 93). In addition, lovastatin effectively lowered the levels of β-VLDL in patients with familial dysbetalipoproteinemia (94, 95) and the level of VLDL- and LDL-cholesterol in patients with diabetic dyslipidemia (96) and nephrotic dyslipidemia (97). Combination therapy with lovastatin and gemfibrozil lowered the levels of both VLDL- and LDL-cholesterol (98). The findings of these trials and other studies in humans, together with the proven safety of lovastatin in experimental animals, provided the basis for the approval of the drug by the U.S. Food and Drug Administration in 1987 (9).

OTHER MEVASTATIN DERIVATIVES

The development of mevastatin and lovastatin have inspired efforts to identify and/or synthesize even more effective cholesterol-lowering agents. Because of their unique structures and biological activities, these compounds have represented significant models from which other agents have been designed. Many synthetic studies have focused on replacing the highly functionalized decalin ring of the fungal products with a variety of aromatic and heteroaromatic nuclei. Several of the compounds synthesized, like fluvastatin, BAY W 6228, and HR 780, have been approved or are under development (Fig. 11) (99-101). Likewise, some chemical modifications to the natural products themselves have been made, particularly to the acyl group at C1. Simvastatin, which has been developed in many countries, is a product of these modifications (Fig. 12) (102-109). There also exists a number of related products, some of which have been obtained by microbial modification of others. Pravastatin is such a product derived from mevastatin (Fig. 12) (110-115). This drug was introduced to the market in 1989.

CONCLUSION

Lovastatin, pravastatin, and simvastatin are now being prescribed in many different countries, and the number of patients using one of these three drugs is well over one million (116). The potency of lovastatin and pravastatin appears to be similar, and simvastatin is approximately twice as potent in comparison (102, 112, 117). Mevastatin is apparently somewhat less active than are lovastatin and
pravastatin (36, 37, 112). Nonetheless, the effects of these drugs on blood cholesterol and lipoprotein levels are quantitatively similar when administered at equivalent doses.

HMG-CoA reductase inhibitors are administered primarily to reduce total and LDL-cholesterol levels. With the usual clinical doses the reduction in total cholesterol ranges from 15 to 30%, LDL-cholesterol from 20 to 40%. The dose response in terms of percentage reduction in total and LDL-cholesterol is similar for the different forms of primary and secondary hypercholesterolemia (9, 10). These drugs in combination with a bile acid sequestrant reduce total and LDL-cholesterol levels by 50–60%. HMG-CoA reductase inhibitors produce modest increases in HDL-cholesterol levels, generally in the range of 5–10% (83, 89, 92, 103, 104). This response could be an added benefit in the reduction of coronary risks. No major serious side effects associated with HMG-CoA reductase inhibitors have been reported, despite their extensive use. Undoubtedly, HMG-CoA reductase inhibitors have been established as effective and safe cholesterol-lowering agents.

Studies that demonstrate the beneficial effects of HMG-CoA reductase inhibitors on coronary heart disease are beginning to appear. Thus, lovastatin in combination with colesitipol reduces the frequency of progression and increases the frequency of regression of coronary heart disease (10, 11). Several large-scale studies on a possible role in the primary prevention of coronary atherogenesis have been initiated. The results are not yet available but will appear soon.

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