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Effects of Long-Term Treatment with Simvastatin on Plasma Lipids and Lipoproteins in Patients with Primary Hypercholesterolemia***

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Summary. We investigated long-term hypolipidemic effects and clinical safety of simvastatin, a new competitive inhibitor of 3-hydroxy-methylglutaryl coenzyme A reductase in 24 patients with familial and non-familial hypercholesterolemia. Patients received up to 40 mg simvastatin for a period of 30 months. Significant decreases were noted in plasma cholesterol (30%), plasma triglycerides (25%), very low density lipoprotein-cholesterol (26%), and low density lipoprotein-cholesterol (40%), whereas an increase in plasma high density lipoprotein-cholesterol (11%) was observed. Furthermore, the percentage decrease in plasma low density lipoprotein cholesterol was independent of individual baseline concentrations. Simvastatin did not alter the composition of low density lipoproteins or high density lipoproteins. The percentage decrease in total plasma and low density lipoprotein-cholesterol was independent of apoprotein E isoforms and low density lipoprotein-receptor activity as assayed in cultured fibroblasts. The drug therapy was well tolerated and clinical examinations revealed no adverse effects. Clinical chemistry indices and hematological, as well as endocrinological parameters remained within normal limits and ranges.

Key words: Hypercholesterolemia – Lipoproteins – Simvastatin – Hormones

Abbreviations: VLDL = very low density lipoprotein; LDL = low density lipoprotein; HDL = high density lipoprotein; CHD = coronary heart disease; LDL-C = low density lipoprotein-cholesterol; FH = familial hypercholesterolemia; HMG-CoA = 3-hydroxy-3-methylglutaryl-coenzyme A; HELP = heparin extracorporeal low density lipoprotein precipitation

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Premature coronary heart disease (CHD) and subsequent myocardial infarction are the leading causes of death in the western world. Today it is widely accepted that elevated concentrations of plasma cholesterol, or more precisely, low density lipoprotein-cholesterol (LDL-C), play the major role in development of atherosclerosis, possibly by avid removal of LDL by a non-receptor-mediated metabolic pathway [11, 40, 35]. Hypercholesterolemia may be caused by accelerated synthesis or retarded removal of lipoproteins by the liver. Primary hypercholesterolemia is caused by either a single-gene disorder (familial hypercholesterolemia, FH) or multifactorial disorders with multiple genes interacting with environmental factors [8]. Heterozygous FH patients with a primary defect in the gene for the LDL-receptor can produce only half the normal number of LDL-receptors; in patients with non-familial forms of hypercholesterolemia the LDL-receptor activity is reduced, either by increased hepatic chylomicron remnant cholesterol uptake via the chylomicron receptor pathway or by saturation of LDL receptors due to high circulating plasma LDL [20, 22]. In addition to impaired hepatic LDL removal, an overproduction of LDL has also been postulated [34].

Clinical intervention trials with lipid-lowering drugs such as bile acid sequestrants in combination with nicotinic acid [31] or Gemfibrozil [17] have been successful in diminishing the incidence of coronary heart disease. Furthermore, the CLAS study showed for the first time that secondary prevention of CHD by drastically lowering plasma LDL cholesterol levels leads to regression of preexisting coronary lesions [7, 10]. The most commonly used drugs, including bile acid sequestrants, nicotinic acid, probucol, gemfibrozil, and fibrates, lower plasma total and LDL cholesterol concentrations.

However, unpleasant adverse effects often prevent the widespread use of these drugs. A new class of drugs which selectively inhibit the 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase activity has opened a new therapeutic approach for the treatment of hypercholesterolemia. These drugs are effective in modifying plasma lipoprotein concentrations in low doses and without serious adverse effects. Compactin [15], lovastatin [1], simvastatin [43], and pravastatin [38] are highly effective in lowering plasma cholesterol in relatively low doses. Lovastatin has been extensively investigated [24], whereas simvastatin a methylated derivative of lovastatin, is currently under clinical trial [36, 29].

We now report data on the effects of simvastatin on plasma lipids, lipoprotein levels, and endocrinological parameters in a long-term study on 24 patients who were suffering from familial and non-familial hypercholesterolemia.

Methods

Patients, study design, and clinical investigations

Patients selected for the study suffered from primary hypercholesterolemia, with normal triglycerides but elevated plasma LDL-cholesterol (LDL-C >180 mg/dl). Twenty-four patients (7 women and 17 men), aged between 25–66 years (mean age 43.3 ± 11.6 yrs), participated in this study. All patients had been on a diet low in cholesterol and saturated fats before baseline clinical investigations were carried out and were seen and advised by a dietitian. The majority of the patients had been on one or more lipid-lowering drug therapies before. Eleven patients suffered from the heterozygous form of familial hypercholesterolemia (FH) as documented by family history and biochemical studies. Coronary heart disease was documented in 12 patients by coronary angiography; another 10 patients showed clinical symptoms for CHD, but no angiography had yet been carried out.

Patients with secondary hyperlipoproteinemia due to diabetes, impaired thyroid or liver function, or nephrotic syndrome were excluded from this study. Premenopausal women were also excluded. Further exclusion criteria included partial ileal bypass, a history of drug or alcohol abuse, a recent history of hepatitis, complete biliary obstruction or symptoms of gallstones, myocardial infarction or coronary bypass surgery within the previous four months prior to starting the study, unstable or Prinzmetall angina, ventricular ectopic beats at a rate greater than 5/min or showing coupling or the R-on-T phenomenon, and concomitant treatment with barbiturates, anticoagulants (antiplatelet drugs were permitted), corticosteroids, theophylline, quinidine, and cimetidine. During the 4 weeks before active treatment, patients underwent complete physical examination and laboratory tests including hematology, liver, renal and endocrinological function tests, oral galactose and xylose resorption, plasma lipid and lipoprotein analysis, urine analysis, 12-lead electrocardiogram, chest x-ray, and abdominal ultrasound. A complete ophthalmologic examination was done by the same ophthalmologist at the beginning, after one year, and at the end of study. Patients were treated with placebo for 4 weeks and thereafter with 20 mg simvastatin for 6 weeks; dosage was then increased to 40 mg/day. After two years of treatment 5 patients whose LDL-cholesterol was still above 180 mg/dl ($n=5$) were treated with combined simvastatin and cholestyramine therapy for another year, whereas all other patients were kept on simvastatin.

Both simvastatin and placebo were provided as capsules of identical appearance by Merck, Sharp & Dohme Research Laboratories, West Point, Pennsylvania, USA. The drug was taken immediately before the evening meal. Compliance was controlled by capsule-counting at each visit. During the trial the patients attended the clinic at 4- to 6-week intervals in the morning following a 12-hour fast. At each clinical visit, in addition to physical examination, blood and urine samples were collected for determination of clinical chemical parameters and hematological and hemostatic indices by methods used in the Clinical Chemistry Department of the University of Göttingen. The study was approved by the ethics committee of the University of Göttingen, Medical Center; the patients had given their informed consent according to the Helsinki declaration.

Analytical Methods

Lipids and Lipoproteins. Cholesterol and triglycerides were assayed by enzymatic procedures (Boehringer, Mannheim, FRG) and protein content, by the Lowry method [32]. The concentrations of the different lipoproteins were determined by quantitative lipoprotein electrophoresis [51] and precipitation techniques for LDL-cholesterol [5] and HDL-cholesterol [9]. Lipoproteins were also separated from 0.5 ml plasma by sequential ultracentrifugation techniques using Beckmann Rotor TY 25 (Beckmann Instruments, Inc., Irvine, USA) at a density of 1.006 g/ml to determine VLDL-cholesterol [30]. The lipid-protein composition of various

lipoprotein fractions isolated by sequential ultracentrifugation from plasma [23] was determined at baseline and 6 months after simvastatin treatment. Apolipoproteins A1 and B were quantitated by rate nephelometry [50], and quantification of Lp(a) was carried out by polyclonal Elisa that showed less than 0.02% cross-reactivity to plasminogen [4]. The apoprotein E isoforms were identified by isoelectric focusing in SDS-PAGE [49].

Endocrinological Paramters. Thyroxine (T_4) and triiodothyronine (T_3), cortisol, testosterone, luteinizing hormone, ACTH, and follicle stimulating hormone were measured by standard radioimmunoassays. Gastrin and gastric inhibitory polypeptide (GIP) were determined by standardized radioimmunochemical methods [41, 13]. For the cortisol stimulation test, ACTH (Synacthen®) was given intravenously (25 I.E. ACTH) and plasma cortisol levels measured at zero, 30, 60, and *120 min [2].*

Carbohydrate Absorption Tests. Passive carbohydrate absorption was established after ingestion of xylose (25 g, Merck, Darmstadt, FRG), active membrane transport for carbohydrates after ingestion of D-galactose (40 g, Merck, Darmstadt, FRG). Blood was taken at, 30, 60, 90, and 120 min after carbohydrate ingestion for determination of galactose and xylose by standard methods (Galactose enzymatic test kit from Boehringer, Mannheim, FRG, and xylose colorimetric test kit, Roche, Basel, Switzerland).

Fibroblast LDL-Receptor Studies. Skin biopsies were obtained from a medial part of the forearm from normal adult donors and patients. They were cultured in plastic dishes in Dulbecco's minimal essential medium which contained 25 mM $NaHCO_3$, 20 mM Hepes, pH 7.4 and 10% fetal calf serum [47]. All cell lines were grown in monolayers for assaying and LDL-receptor activity. As a measure of LDL-receptor activity binding, internalization and degradation of ^{125}I-LDL was assayed. With each assay, fibroblast cell lines from normolipidemic healthy subjects who served as normal controls were run [19].

Results

Long-Term Effects of Simvastatin on Plasma Lipids and Lipoproteins

The biochemical and clinical characterization of patients and percentage decrease in plasma LDL-cholesterol under simvastatin treatment (40 mg/day) are given in Table 1. In this collective of 24 patients total and LDL-cholesterol levels ranged between 246–510 mg/dl and 181–411 mg/dl, respectively. Eleven patients were suffering from angiographically confirmed coronary heart disease with plasma LDL-cholesterol levels ranging between 204–457 mg/dl, and five of these patients were suffering from familial heterozygous hypercholesterolemia as confirmed by the LDL-receptor activity in their cultured fibroblasts. Under simvastatin therapy their LDL-cholesterol levels decreased by about 40% (range 25–54%) irrespective of their LDL-receptor activity, age, and sex. Apo E isoforms of these patients had no influence on the extent of plasma LDL-cholesterol lowering by simvastatin.

There was a dose-dependent decrease in plasma total and LDL-cholesterol under simvastatin treatment (Table 2). At a dosage of 20 mg/day simvastatin reduced total and LDL-cholesterol by about *25% and 29%, and at a dosage of 40 mg/day,* by 30% and 40%, respectively. Parallel to the decrease in LDL-cholesterol an average decrease of about 19% in plasma apolipoprotein B concentrations was observed. Serum triglycerides also decreased from the baseline value 158 ± 89 to 114 ± 52 mg/dl, representing a decrease of 25%. This decrease in plasma triglycerides was accompanied by a similar decrease in VLDL-cholesterol.

HDL-cholesterol showed a small but consistent increase under simvastatin therapy (about 11%). Plasma apoprotein A1 concentration showed a similar increase. No changes in plasma lipoprotein(a) concentrations were observed. The maximum decrease of LDL-cholesterol brought about by simvastatin at a dosage of 40 mg/day at 3 months showed no appreciable changes over the entire trial period.

Effects of Combined Simvastatin and Cholestyramine Therapy on Plasma LDL Cholesterol Levels in Patients with Familial Hypercholesterolemia

Simvastatin therapy was not sufficient to lower plasma LDL-cholesterol levels below 180 mg/dl in 5 patients who were FH heterozygotes; their LDL-receptor activity in cultured fibroblasts ranged between 38–55%. We therefore administered simvastatin in combination with cholestyramine (4–8 g daily) in these patients. Under this regimen a further average decrease of about 13% (9 to 21%) in plasma LDL cholesterol was noted (Table 3). One female patient (No. 22) with severe xanthomatosis and high plasma LDL-cholesterol levels (389 mg/dl) and suffering from chronic atrophic gastri-

Table 1. Biochemical and clinical characterization of patients at baseline and percentage reduction in plasma-LDL-cholesterol under Simvastatin treatment (40 mg/day)

No.	Sex	Age (yrs)	Coronar-angiography (CHD ±)	Apo E-Isoforms	LDL-Receptor Activity (normal = 100%)	LDL-C mg/dl baseline	% Decrease in Plasma LDL-C
1	m	65	+	3/3	86	232	−47
2	m	35	n.d.	3/3	100	241	−30
3	f	64	n.d.	3/3	97	365	−50
4	m	44	+	4/3	91	256	−54
5	m	50	+	3/3	40	407	−39
6	m	25	n.d.	3/3	55	357	−46
7	m	54	+	4/3	100	204	−37
8*	m	38	+	3/3	63	411	−50
9*	m	39	+	3/3	21	336	−44
10	m	55	n.d.	4/3	100	225	−32
11	m	46	n.d.	3/3	38	271	−46
12	f	58	n.d.	3/3	47	339	−46
13	m	49	+	4/3	81	309	−38
14	m	45	−	4/3	91	181	−35
15	m	50	+	4/3	94	244	−54
16	m	34	+	3/3	70	179	−35
17	f	60	n.d.	3/3	89	220	−45
18	f	31	+	3/3	45	411	−39
19	m	56	+	3/2	47	398	−43
20	f	66	n.d.	4/3	68	332	−49
21	f	55	n.d.	3/3	100	189	−30
22*	f	53	n.d.	4/3	80	389	−25
23	m	30	n.d.	3/2	39	362	−31
24	f	52	n.d.	3/2	39	408	−35

CHD = coronary heart disease
+ = CHD positive
− = CHD negative
n.d. = not done
* Due to the clinical situation these patients are treated with combined Simvastatin and HELP therapy

tis showed only a 25% reduction in her plasma LDL-cholesterol concentrations (292 mg/dl) under simvastatin. Even after HCl substitution no significant decrease in her plasma LDL levels under simvastatin therapy was noted. This patient did not tolerate additional drug therapy with cholestyramine or nicotinic acid. We now treat this patient with combined simvastatin and weekly HELP-LDL/Fibrinogen apheresis. On weekly HELP treatments in combination with simvastatin she has maintained her pre-HELP plasma LDL-cholesterol at 220 mg/dl and immediate post-HELP plasma LDL of about 47 mg/dl. Her calculated mean plasma LDL cholesterol between two HELP treatments was about 133 mg/dl (post-HELP value + last pre-HELP value, divided by 2).

Lipid-Protein Composition of Various lipoprotein Fractions under Simvastatin Therapy

In order to determine whether simvastatin alters the lipid-protein composition of various lipoprotein fractions, we isolated lipoproteins by sequential ultracentrifugation at baseline and 6 months after the administration of simvastatin in our patients. Administration of simvastatin did not alter the lipid-protein composition of LDL and HDL from the baseline values (Table 4). However, simvastatin does appear to alter the lipid-protein composition of VLDL. We observed a decrease in cholesterol and an increase in triglyceride content in VLDL particles. These changes, though consistent, were not statistically significant ($p < 0.06$).

Clinical Chemical and Endocrinological Parameters under Simvastatin Therapy

All patients tolerated simvastatin without any side effects as judged by routine clinical examination and clinical chemical parameters (Table 5). In four patients (Nos. 6, 9, 18, 23) elevation of creatinine kinase activity in serum was noted under simvastatin therapy (values up to 592 U/l). However, elevated values were noted on one occasion only;

Table 2. Follow-up of Changes in Plasma Lipids and Lipoproteins During Simvastatin Therapy

Simvastatin (mg/day)	Values at Baseline ($n=24$)	Values at 3 Months ($n=24$) 20 mg	Values at 12 Months ($n=24$) 40 mg	Values at 24 Months ($n=21$)+ 40 mg
mg/dl				
Plasma cholesterol	373±77 (246–510)	281±68** (201–397)	259±56** (168–379)	255±56** (152–377)
Plasma triglycerides	158±89 (33–355)	110±36* (47–200)	122±50* (59–221)	114±52* (54–214)
VLDL-cholesterol	24.8±13.6 (10.7–58.7)	17±6.3* (8–32)	17.2±8.1* (6.6–36)	18.3±7.5* (8.9–32)
LDL-cholesterol	294±74 (181–411)	210±64** (127–318)	175±43* (102–300)	171±44** (98–288)
HDL-cholesterol	53.7±14.2 (34–102)	54.3±15.2 (32–100)	60±14.6* (32–94)	57.2±11.1* (37–87)
Lipoprotein(a)	51.2±56.8 (2–161)	55±57.4 (4–185)	54±46 (3–178)	52±51.3 (3–172)
Apoprotein A_1	139±36.9 (88–265)	141±39.9 (138–260)	158±36.6* (125–224)	148±20* (127–210)
Apoprotein B	176±22 (120–210)	149±30** (89–217)	152±30** (95–201)	143±20** (90–198)

+3 patients were treated with combined Simvastatin and HELP-LDL-apheresis
* $p<0.005$ vs. baseline
** $p<0.001$ vs. baseline

Table 3. Effects of combined Simvastatin and Cholestyramine therapy on plasma LDL levels in patients with familial heterozygous hypercholesterolemia

Patient No.	LDL-Receptor-Activity (%)	Baseline	Plasma-LDL-Cholesterol (mg/dl)		Additional % Changes with combined drug therapy
			Simvastatin	Simvastatin+ Cholestyramine	
5	40	407	248	226	−9%
6	55	357	193	173	−10%
19	47	398	227	208	−8%
23	39	362	248	196	−21%
24	39	408	268	229	−15%

Simvastatin was administered either alone at 40 mg/day or in combination with 8 g Cholestyramine/day. Percentage of changes represent additional decrease in plasma LDL under combined drug therapy

Table 4. Lipid and Protein Composition of Plasma Lipoprotein Fractions at Baseline and at 6 Months after Simvastatin Therapy (40 mg/day)

		Cholesterol %	Triglycerides %	Phospholipids %	Protein %
VLDL	Baseline	16.0±3.3	53.7±7.8	18.4±6.7	11.4±3.2
	Drug	11.9±2.3*	59.8±8.8*	15.0±1.1	12.8±3.3
LDL	Baseline	42.3±2.4	6.5±2.6	24.8±1.0	26.4±2.6
	Drug	42.5±2.6	8.7±3.0	22.5±1.2	26.4±1.5
HDL	Baseline	24.5±3.5	4.4±1.5	24.0±1.7	48.2±4.3
	Drug	22.7±4.2	3.4±1.0	22.6±2.1	51.8±4.6

* $p<0.06$ vs. baseline

Table 5. Effects of Simvastatin on clinical chemistry and hematological indices after 30 months of drug treatment

Parameters	Baseline	After 30 months of Simvastatin treatment (40 mg/day)
Substrates and electrolytes		
Sodium (mmol/l)	140 ±2.2	140.8±2.7
Potassium (mmol/l)	4.0±0.2	4.2±0.3
Calcium (mg/dl)	9.3±0.4	9.5±0.4
Phosphate (mg/dl)	3.2±0.5	3.1±0.6
Iron (μg/dl)	85.4±28.0	94.0±26.5
Creatinine (mg/dl)	1 ±0.18	0.9±0.1
Blood urea nitrogen (mg/dl)	17.0±4.1	15.4±4.1
Uric acid (mg/dl)	5.6±1.3	4.8±1.5
Glucose (mg/dl)	96.8±1.1	97.6±7.7
Total bilirubin (mg/dl)	0.5±0.15	0.6±0.2
Total protein (g/dl)	7.6±0.4	7.5±0.5
Albumin (%)	63.4±5.2	60.0±4.2
a1-Globulin (%)	3.0±0.8	3.8±0.8
a2-Globulin (%)	8.0±1.7	9.0±1.1
β-Globulin (%)	11.8±1.5	13.5±2.0
Gamma-Globulin (%)	13.8±3.5	13.8±3.6
Enzymes:		
ALAT (U/l)	10.7±2.8	11.4±4.2
ASAT (U/l)	14.8±7.1	15.7±8.4
GGT (U/l)	17.6±11.2	19.7±15.0
CK (U/l)	44.4±20.4	58.7±32.2
LDH (U/l)	144.6±23.7	155.6±25.7
Amylase (U/l)	13.2±4.1	15.7±5.3
PChE (U/l)	6283 ±1233	6469 ±1268
ALP (U/l)	113.1±27.4	126.4±26.4
Hematological indices		
Hemoglobin (g/dl)	14.7±1.4	15.5±1.2
Hematocrit (%)	44.0±4.2	46.2±3.1
Erythrocytes (10^6 μl)	4.9±0.5	5.1±0.4
Thrombocytes (10^3 μl)	224.5±47.4	232.3±41.5
Leucocytes (10^3 μl)	6.2±2.2	6.2±1.6
Lymphocytes (%)	34.6±7.8	32.1±4.8
Neutrophils (%)	54.8±6.4	55.9±5.5
Monocytes (%)	5.6±1.3	7.4±1.2
Eosinophils (%)	2.6±1.8	2.7±1.5
Basophils (%)	1.1±0.3	0.9±0.3
Hemostasis		
Prothrombine time (%)	99.7±1.4	99.8±0.6
Thrombin time (s)	14.0±0.6	13.8±0.4
Fibrinogen (mg/dl)	285.0±51.3	266.7±69.1

these increases were single, isolated observations. The follow-up of endocrinological parameters is documented in Table 6). After one year of therapy with simvastatin, the plasma cortisol response to ACTH stimulation in the patients was similar to that of normal subjects. Before ACTH administration serum cortisol levels were 12.8±3.7 μg/dl and at 30, 60, and 120 min after ACTH stimulation 25.3±4.9, 27.1±5.3 and 31.9±5.4 μg/dl, respectively. These increases are within the normal range. There was no difference in plasma cortisol levels under ACTH stimulation before and after simvastatin administration. No significant differences in the values at baseline and after two years of simvastatin treatment were noted in plasma ACTH, cortisol, testosterone, or luteinizing and follicle stimulating hormones. No differences were observed in thyroid hormones at the baseline and after simvastatin treatment. In order to examine whether simvastatin influences active or passive transport in the gut, we performed an oral galactose and xylose test in our patients at baseline and 3 months after simvastatin therapy. Maximum concentrations of galactose and xylose in plasma were attained at 30 and 90 min after oral ingestion respectively. No changes were observed in the kinetics of appearance or disappearance of these carbohydrates in plasma under simvastatin therapy.

Table 6. Effects of Simvastatin treatment on endocrinological indices

	Baseline	After 24 months of Simvastatin treatment (40 mg/day)
Cortisol (μg/dl)	19.6±7.9	12.8±3.0
ACTH (ng/l)	41.8±13.4	36.4±19.4
Testosterone* (ng/ml)	7.6±2.7	5.4±1.0
LH* (mU/ml)	7.7±0.9	2.5±2.6
FSH* (mU/ml)	4.9±3.2	5.0±3.8
T4 (μg/dl)	8.0±2.3	8.2±1.5
T3 (ng/dl)	162.2±22.9	152.5±16.7
Gastrin (pg/ml)	13.4±11.7	14.8±13.8
GIP (pmol/l)	14.1±12.3	9.5±8.7

* These hormones were assayed only in the plasma of male patients since female patients were post-menopausal

Discussion

Our study reports the effects of simvastatin on the concentrations of plasma lipids and lipoproteins and its suitability in the treatment of patients suffering from familial heterozygous hypercholesterolemia and non-familial hypercholesterolemia. The main effects of this drug were a consistent diminution of plasma LDL-cholesterol by about 40% and an increase in plasma HDL-cholesterol levels by about 11% as compared to baseline values. The magnitude of lipid lowering by simvastatin observed in this study was similar to that reported for both lovastatin and simvastatin in clinical trials [24, 36, 18, 44, 25]. The efficacy of simvastatin in lowering plasma LDL-cholesterol levels was independent of apolipoprotein E isoforms. Further-

more, no correlation existed between genetic LDL-receptor activity and the percentage reduction in plasma LDL-cholesterol levels in either FH heterozygotes or patients with non-familial hypercholesterolemia. Administration of simvastatin did not alter the lipid-protein composition of either LDL or HDL [48], but did decrease the cholesterol content and increase the triglyceride content in VLDL. Simvastatin was well tolerated by all patients. The reduction of plasma cholesterol by simvastatin influenced neither the circulating levels of steroid hormones in plasma nor the degree of plasma cortisol response to ACTH stimulation. Similar results have been reported for treatment with lovastatin [28, 16]. The elevation of activity of liver and muscle enzymes in serum were only moderate and transient. No rhabdomyolysis, which has been reported as a rare adverse effect of lovastatin therapy, was noted in the present study [39, 45, 12]. We did not observe any ocular side effects under simvastatin treatment [26, 6].

The effectiveness of HMG-CoA reductase inhibitors in drastically lowering plasma total and LDL-cholesterol levels is well established. However, the precise mechanisms responsible for their hypolipidemic action are still unclear. It has been postulated that these drugs decrease the plasma LDL levels either by increasing the number of hepatic LDL-receptors [33] or by enhancing the removal of VLDL remnants by the liver [46]. Since both lovastatin and simvastatin decrease plasma triglycerides and more specifically VLDL levels, this action could also diminish conversion of VLDL to LDL. Thus, both the enhanced removal of LDL particles and the decreased synthesis of VLDL by the liver could lower LDL formation via the VLDL-IDL-LDL cascade [37, 3]. These mechanisms could effectively lower plasma LDL-cholesterol levels without an increase in the number of already existing hepatic LDL-receptors. Studies on patients suffering from primary moderate hypercholesterolemia showed no enhanced FCR of ^{125}I-LDL under lovastatin treatment [21]. Thus lowering of plasma LDL levels by HMG-CoA reductase inhibitors cannot be explained solely on the basis of drug-increased numbers of LDL-receptors.

Bile acid sequestrants have been reported to alter the chemical composition of LDL and thereby modulate its affinity to LDL receptors [52]. No change in the chemical composition of LDL and its quality as a ligand for LDL-receptor was noted in this study. The affinity of LDL isolated from plasma of patients under simvastatin therapy to LDL-receptors in cultured fibroblasts was comparable to the affinity of LDL isolated from plasma of either normal subjects or patients at baseline [48]. Even though simvastatin did not affect the active or passive resorption of carbohydrates, the possibility of diminished cholesterol resorption under this drug therapy cannot be excluded. A recent study showed that simvastatin decreased the activity of acyl cholesterol acyl transferase (ACAT) activity in intestinal mucosa of rabbits [27]. The decreased resorption of cholesterol by intestinal mucosa could diminish the transport of cholesterol by chylomicrons. Decreased chylomicron formation, and also cholesterol-poor chylomicrons, could effectively lead to increased LDL-uptake by hepatic LDL-receptors, since the uptake of chylomicron remnants influences the uptake of LDL by hepatic LDL-receptors. Thus, reduced formation of LDL via the VLDL-IDL-LDL cascade, and possibly low rates of chylomicron formation, could effectively lower plasma LDL levels without greatly increasing the number of hepatic LDL-receptors. Further detailed studies are needed to elucidate these mechanisms.

In summary, in this long-term study simvastatin was found to be an effective and safe drug for the treatment of hypercholesterolemic patients. The drug is effective in low doses and thus facilitates patient compliance. Whether this treatment alone is sufficient in secondary prevention of CHD may depend upon baseline LDL-cholesterol levels and the severity of coronary sclerosis [42].

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