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A CLINICAL TRIAL TO EVALUATE THE EFFICACY OF FLUVASTATIN AND LOVASTATIN IN COMPARISON WITH PLACEBO IN HYPERCHOLESTEROLEMIC PATIENTS

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ABSTRACT

In this study, the effect of lovastatin and fluvastatin was compared with placebo in patients with high levels of total cholesterol and low density lipoprotein cholesterol (LDL-C) on the plasma lipid profile. In a prospective single blind clinical trial with convenient sampling, 120 hypercholesterolemic men and women with T-cholesterol≥220 mg/dL, LDL-C≥ 160 mg/dL, and triglyceride ≤350 mg/dL were selected and divided into 3 groups randomly. The first group took lovastatin, 20 mg daily, the second group fluvastatin, 40 mg daily, and the third group took a placebo, all for 12 weeks. Compared with placebo, drug therapy of hypercholesterolemia with either lovastatin or fluvastatin decreased total cholesterol and LDL-C levels significantly but had no effect on high density lipoprotein and triglyceride values. Decrease of total cholesterol and LDL-C levels by both drugs are similar after the first 6 weeks but lovastatin was more effective after the second 6 week period.

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INTRODUCTION

Hypercholesterolemia is a major independent risk factor for coronary heart disease.[6] Reduction of LDL-C levels in clinical trials for secondary prevention has been demonstrated to produce favorable effects on atherosclerotic coronary artery disease, resulting in retardation of the progression of stenotic lesions, regression of lesions, and prevention of thrombotic events associated with nonstenotic lesions.[4]

Reduction of LDL-C levels has also been associated with a reduced incidence of fatal and nonfatal myocardial infarctions, angina pectoris, angioplasty, and coronary artery bypass surgery.[12]

The discovery of inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in cholesterol synthesis, has significantly advanced the treatment of hypercholesterolemia.[6] The availability of 3-hydroxy-3-methylglutarylcoenzyme A (HMG-CoA) reductase inhibitors offers an effective means of reducing the levels of serum LDL-C in patients with hypercholesterolemia. HMG-CoA reductase inhibitors primarily reduce LDL-C by increasing the catabolism of LDL-C via increasing the number of available LDL-C receptors. LDL is heterogeneous, and at least seven subspecies have been identified with density gradient ultracentrifugation and gradient gel electrophoresis. The various subclasses of

LDL-C have different compositions, with associated differences in the characteristics of metabolism.[13]

By reducing hepatic cholesterol concentrations and upregulating LDL-C receptor synthesis, HMG-CoA reductase inhibitors promote clearance of LDL-C and very low density lipoprotein cholesterol (VLDL-C) remnants. As a result of these actions, the agents markedly reduce LDL-C levels and often provide modest decreases in serum triglycerides (TG) as well. Moreover, these agents are well tolerated and relatively free of adverse reactions.[7]

The HMG-CoA reductase inhibitors include lovastatin, simvastatin and pravastatin, as well as the newest agent of this class, fluvastatin. Fluvastatin is the first entirely synthetic HMG-CoA reductase inhibitor and is characterized by its biopharmaceutical profile. The agent has a high rate of absorption, is administered in active form, has no active circulatory metabolites (unlike the other available HMG-CoA reductase inhibitors) and has a biologic half-life of 30 minutes. These factors may result in a low incidence of systemic (i.e., extrahepatic) adverse events.[7] Unlike other inhibitors, fluvastatin is not derived from compactin, a fungal metabolite.[6]

HMG-CoA reductase inhibitors have been the most effective agents for reduction of plasma LDL-C levels. These drugs are appropriate therapy for hypercholesterolemia only when elevated LDL-C levels contribute to the hypercholesterolemia.[2]

In addition to their major effects on LDL-C levels, HMG-CoA reductase inhibitors cause relatively small reductions in fasting plasma triglyceride levels and a slight increase in HDL-C levels. They appear to have no effect on lipoprotein a.[2]

It was of interest to evaluate the efficacy, safety, and tolerability of the new lipid-lowering agent fluvastatin

Table I. Patient characteristics.

	Fluvastatin	Lovastatin	Placebo
Number of patients	40	40	40
Men/women ratio	17/23	9/31	12/28
Mean age (years)	55.9	55.8	54.5

Table II. Lipid levels at baseline and after 6 and 12 weeks of treatment with fluvastatin, lovastatin and placebo.

Agent	Parameter	Mean at baseline	Mean after 6 weeks	%Change after 6 weeks	Mean after 12 weeks	%Total change after 12 weeks	P-value
Placebo							
	T-cholesterol(mg/dL)	267.1±28.64	259.93±30.25	-2.7	261.10±30.68	-2.2	0.056
	TG (mg/dL)	203.30±75.81	204.65±69.01	0.6	213±110.80	4.8	0.677
	LDL-C (mg/dL)	183.70±23.36	177.30±33.06	-3.5	179.18±30.82	-2.5	0.327
	HDL-C (mg/dL)	49.45±12.21	48.08±11.55	-2.8	46.98±10.79	-5	0.203
	LDL-C/HDL-C ratio	3.91±1.15	3.93±1.19	0.5	3.98±1.01	1.8	0.888
Fluvastatin							
	T-cholesterol (mg/dL)	275.49±68.36	229.95±60.91	-16.5	223.86±48.57	-18.7	0.000
	TG (mg/dL)	223.28±113.23	204.90±114.70	-8.2	194.78±90.87	-12.8	0.068
	LDL-C (mg/dL)	197.97±47.85	149.74±59.73	-24	146.44±46.61	-26	0.000
	HDL-C (mg/dL)	43.72±13.10	42.49±8.16	-2.8	44.42±10.37	1.6	0.569
	LDL-C/HDL-C ratio	4.77±1.67	3.65±1.61	-23.5	3.44±1.18	-27.9	0.000
Lovastatin							
	T-cholesterol (mg/dL)	279.85±35.19	232.12±48.21	-17.1	217.88±41.35	-22.1	0.000
	TG (mg/dL)	221.45±106.02	225.93±119.35	2	214.40±97.21	-3.2	0.662
	LDL-C (mg/dL)	191.90±29.80	150.55±45.17	-21.5	137.30±43.56	-28.5	0.000
	HDL-C (mg/dL)	45.65±9.75	46.65±9.67	2.2	47.85±10.49	4.8	0.155
	LDL-C/HDL-C ratio	4.36±0.99	3.41±1.32	-21.8	2.99±1.12	-31.4	0.000

Table III. Effects of long-term fluvastatin, lovastatin and placebo treatment on ALT, AST, Hb and WBC levels

Agent	Parameter	Mean at baseline	Mean after 6 weeks	%Change after 6 weeks	Mean after 12 weeks	%Change after 12 weeks	P-value
Placebo							
	Aspartate aminotransferase (AST)IU/L	16.55±8.96	16.88±9	2	17.0±8.93	2.7	0.519
	Alanine aminotransferase (ALT) IU/L	13.4±6.54	13.62±6.48	1.6	14.2±6.63	6	0.222
	Hemoglobin (g/dL)	14.09±1.58	13.78±1.44	-2.2	13.85±1.33	-1.7	0.027
	White blood cells (WBC)$\times 10^3$	6.94±1.66	7.01±1.49	1	7.08±1.49	2	0.532
Fluvastatin							
	Aspartate aminotransferase (AST) IU/L	18.64±10.65	19.92±16.90	6.9	18.92±15.05	1.5	0.390
	Alanine aminotransferase (ALT) IU/L	16.26±11.59	20.41±23.89	25.5	17.5±13.07	7.6	0.075
	Hemoglobin (g/dL)	13.69±1.26	13.62±1.24	-0.5	13.76±1.40	0.5	0.686
	White blood cells (WBC)$\times 10^3$	6.36±1.49	6.52±1.32	2.5	7.02±1.39	10.4	0.002
Lovastatin							
	Aspartate aminotransferase (AST) IU/I	17.70±9.24	16.78±7.41	-5.2	15.62±6.71	-11.8	0.132
	Alanine aminotransferase (ALT) IU/L	16.22±10.72	14.60±7.50	-10.6	13.85±6.88	-14.6	0.101
	Hemoglobin (g/dL)	13.18±1.34	13.94±1.23	0.4	13.89±1.20	0.08	0.856
	White blood cells (WBC)$\times 10^3$	6.98±1.77	6.76±1.86	-3.2	6.87±1.75	-1.6	0.303

relative to lovastatin in Iranian hypercholesterolemic patients.

PATIENTS AND METHODS

In a prospective single blind clinical trial with convenient sampling, we selected 120 hypercholesterolemic men and women (total cholesterol ≥ 220 mg/dL, LDL-C ≥ 160 mg/dL, triglyceride ≤ 350 mg/dL) aged 28 to 37 years, and divided them in to 3 groups randomly. The first group took lovastatin, 20 mg/day, the second group took fluvastatin (40 mg/day) and the third group took a placebo; all for 12 weeks.

Before beginning treatment all subjects received dietary therapy for 2 months and were on the same diet during the treatment. In the beginning of the study and after 6 and 12 weeks, total cholesterol, triglyceride, LDL-C, HDL-C, LDL/HDL ratio, aspartate aminotransferase (AST), alanine amino transferase (ALT), hemoglobin and WBC counts were measured. Clinical adverse effects were also monitored during the study.

The study group consisted of 38 men and 82 women with a mean age of 55.4 years. Their characteristics are depicted in Table I.

Statistical analysis

A repeated measures analysis of variance was performed and for showing the changes in each factor we analyzed Eis; and defined E1,E2, and E3.

E1= Mean quantity at first-Mean quantity after 6 weeks.

E2= Mean quantity at first-Mean quantity after 12 weeks.

E3= Mean quantity after 6 weeks-Mean quantity after 12 weeks.

For comparing with E(s), the Tukey procedure with a significance level of 0.05 was utilized for this purpose.

RESULTS

120 patients entered the study, and 117 patients

completed it. One patient who had taken fluvastatin stopped therapy after 6 weeks because of severely elevated ALT and AST levels and 2 patients did not tolerate it because of adverse GI effects.

The effects of lovastatin, fluvastatin and placebo on plasma lipid concentrations in the beginning of the study and 6 and 12 weeks after treatment are summarized in Table II.

Fluvastatin and lovastatin decreased total cholesterol, LDL-C, and LDL-C/HDL-C ratios and these differences were statistically significant. The lovastatin group had a 22 percent decrease in total cholesterol, a 28.5 percent decrease in LDL-C and a 31.4 percent decrease in LDL-C/HDL-C ratio. The fluvastatin group had a 18.7 percent decrease in total cholesterol, a 26 percent decrease in LDL-C and a 27.9 percent decrease in LDL-C/HDL-C ratio. The placebo group had a 2.2 percent decrease in total cholesterol, a 2.5 percent decrease in LDL-C and a 1.8 percent increase in LDL-C/HDL-C ratio; none of these differences in the placebo group were statistically significant. In comparison with placebo, lovastatin and fluvastatin increased HDL-C levels by 4.8 percent and 1.6 percent, respectively, after 12 weeks. None of these differences were statistically significant. The fluvastatin group had a 12.8 percent decrease in triglycerides, and this difference was of borderline statistical significance (p= 0.068), but in the placebo group, an increase of 4.8 percent and in the lovastatin group a decrease of 3.2 percent was not statistically significant.

The effects of fluvastatin, lovastatin and placebo treatment on ALT, AST, Hb and WBC are shown in Table III.

Three patients on therapy with fluvastatin had clinical adverse effects that resulted in discontinuation of therapy. In the second 6 weeks of therapy, one patient had to stop treatment because of elevated ALT and AST levels. Two patients did not tolerate fluvastatin because of epigastric discomfort.

In addition, one patient in the lovastatin group had constipation.

DISCUSSION

Hyperlipidemia is a major risk factor for atherosclerosis and coronary artery disease. It had been known for well over a decade that reducing low-density lipoprotein cholesterol (LDL-C) levels decreases the likelihood of cardiovascular morbidity and mortality.[7]

The remarkable efficacy and tolerability of HMG-CoA reductase inhibitors in large multicenter studies[3,5,10,11] support their central role among agents of first choice in the management of hypercholesterolemia.

Inhibitors of HMG-CoA reductase are the most effective class in reducing LDL-C levels and have become widely used. It is likely that the magnitude of risk reduction produced by lipid-lowering therapy is proportional to the degree of cholesterol lowering achieved which is an important consideration when selecting an agent and determining the dosage to use. The results of several multicenter comparative trials have clearly established that the 4 drugs of the class are not all equipotent on a milligram basis in terms of their effect on lowering LDL cholesterol. They have shown that the hypolipidemic effect of 5 mg simvastatin approximately equals that of 15 mg pravastatin 15 mg lovastatin and that of 40 mg fluvastatin, all given once daily.[9]

The results of our study indicate that in comparison with placebo, drug therapy of hypercholesterolemia with either lovastatin or fluvastatin lowers total cholesterol, LDL-C, and the LDL-C/HDL-C ratio significantly, but has a slight effect on TG and no effect on HDL-C levels.

A decrease of total cholesterol and LDL-C by both drugs was the same after 6 weeks, but lovastatin was more effective after the second 6 week period. In addition, lovastatin was tolerated better than fluvastatin.

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