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COMBINATION OF SIMVASTATIN AND HEPARIN-INDUCED EXTRACORPOREAL LDL/FIBRINOGEN-PRECIPITATION (HELP) IN THE TREATMENT OF HYPERCHOLESTROLEMIA IN CAD-PATIENTS.

JOACHIM THIERY, VICTOR W. ARMSTRONG, THOMAS EISENHAUER, REGINA ADAM, GOTTFRIED JANNING, WERNER CREUTZFELDT, HEINRICH KREUZER, DIETRICH SEIDEL

University Clinics - Center of Internal Medicine, Department of Clinical Chemistry, Robert-Koch-Str.40, D-3400 Göttingen, F.R.G.

INTRODUCTION

Extracorporeal procedures to eliminate LDL from plasma now allow us to drastically lower the plasma LDL concentrations to virtually every desired level (1,2). Recent epidemiological prospective and case control studies indicate a threshold value of about 120 mg/dl for plasma LDL-cholesterol in the development of atherosclerosis (3,4). Clinical intervention trials such as the CLAS-study have shown an inhibition and, to a lesser extent, a regression of coronary sclerosis (5).In those CAD-patients with only mild hypercholesterolemia a maintenance of plasma LDL-cholesterol under 120 mg/dl was possible by maximal treatment with colestipol and niacin for two years. However, in the case of severe, primarily genetically determined hypercholesterolemia it is not possible to lower LDL below the atherosclerosis threshold level by dietary and drug regimens alone (6). Therapeutic measures for lowering high plasma fibrinogen concentrations which impair blood rheology and stimulate progression of atherosclerosis have also not been successful (7).

HEPARIN-INDUCED EXTRACORPOREAL PRECIPITATION OF LDL/FIBRINOGEN (HELP) IN COMBINATION WITH SIMVASTATIN-THERAPY.

In a new therapeutic approach the combination of the HMG-CoA reductase inhibitor Simvastatin with an LDL/fibrinogen-apheresis procedure based on their heparin-induced precipitation at acid pH (the HELP-system) (1) was evaluated in hypercholesterolemic CAD-patients. The HMG-CoA reductase inhibitors are fungal metabolites with a 1000-fold higher affinity than the natural substrate to the key enzyme of cholesterol synthesis (8). The competitive inhibition of HMG-CoA reductase results in a diminuition of hepatocellular cholesterol levels, which leads to increased uptake of LDL-cholesterol by the hepatic LDL-receptor. Simvastatin may also reduce the hepatic VLDL-production (9,10). Simvastatin, a methylated derivative of the

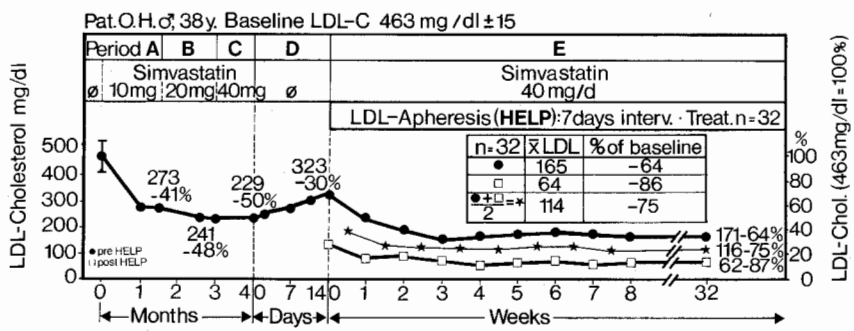
HMG-CoA reductase inhibitor Lovastatin, lowers LDL-cholesterol in hypercholesterolemic patients by about 40 % (11,12). However, the normalization of plasma LDL to a value below the atherosclerosis threshold of 120 mg/dl is dependent on the baseline plasma LDL-cholesterol concentration. Therefore we investigated the additive effect of combined HELP and Simvastatin treatment in six patients with familial as well as non familial hypercholesterolemia and coronary heart disease.

CLINICAL EVALUATION

In all HELP-Simvastatin treated patients mean LDL-cholesterol values were decreased by about 70 to 80 % and remained below the postulated atherogenetic threshold value of 120 mg/dl. The course of plasma LDL-cholesterol under Simvastatin treatment alone and in combination with the HELP-treatment in two FH-patients with CAD are demonstrated in figure 1 and 2.

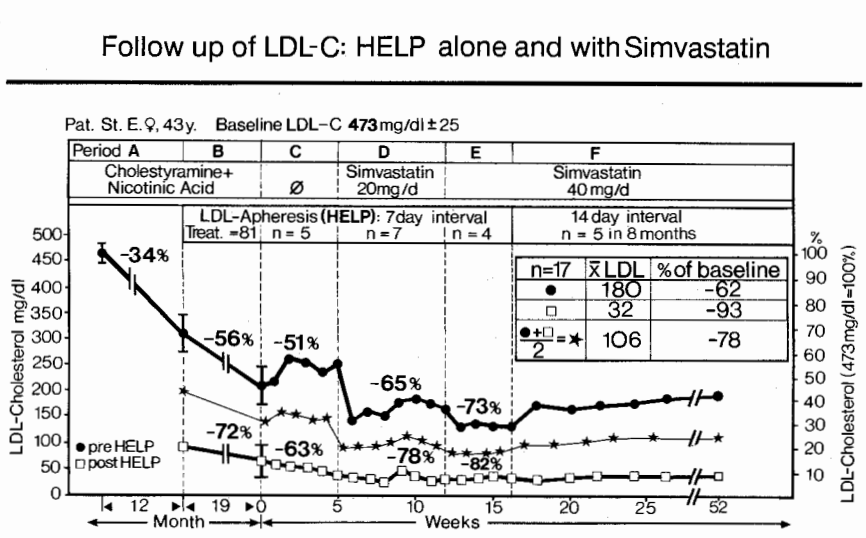
Figure 1

Follow up of LDL-C: Simvastatin alone and with HELP



● LDL concentration pre-HELP □ LDL concentration post-HELP * mean LDL concentration = (o + o):2. The mean values (*) are calculated as LDL-concentration at the end of therapy (□) plus LDL concentration before the next (●) therapy divided by two.

Figure 2



Clinical and laboratory investigations at regular intervals gave no indication for any serious adverse effect under HELP and Simvastatin-therapy. An improvement in the clinical symptoms of ischemic heart disease was observed. After one year of this therapy the performance in the exercise ECG expressed in watts increased or remained unchanged (table 1). Control coronary angiographies in two patients showed no progression of the CAD. Signs of regression were noted. A further invasive diagnostic examination in the two patients with marked heterozygous FH is planned at the end of the second year.In the two remaining patients no coronary angiography was performed before the start of HELP-treatment; after one year of the combined HELP-Simvastatin-therapy coronary angiograms revealed diseased coronary arteries but without critical stenoses. Because of the clinical improvement of CAD-symptoms in these two patients HELP-therapy has been stopped for the present, but the Simvastatin treatment continued. Should symptoms of myocardial ischemia reoccur it is intended to start the combined HELP plus Simvastatin treatment again.

Table 1

Clinical evaluation of 6 hypercholesterolemic CAD-patients treated with HELP and Simvastatin for 1year

Initials	Sex	Age	Mean LDL-C (mg/dl) / % diff. to baseline	Angina pectoris: baseline	Angina pectoris: under treatment	Exercise ECG: baseline	Exercise ECG: under treatment	Coronary arteriography: baseline	Coronary arteriography: under treatment
M.E.	m	53	60 / -70%	+++	–	150W	175 W	3-vessel CAD with crit. stenoses; after CAS	no progression
H.K.	m	57	62 / -68%	+++	+	100W	150 W	diffuse CAD with crit. stenoses; inoperable	no progression, signs of regression
O.H.	m	37	106 / -78%	++	–	100W	200 W	diffuse CAD with non crit. stenoses; inoperable	intended
F.E.	m	37	88 / -74%	+	–	180W	180 W	diffuse CAD with non crit. stenoses; after MI	intended
St.E.	f	46	114 / -75%	+++	–	75W	150 W	not done	diffuse CAD with non crit. stenoses
E.H.	m	35	120 / -75%	+	–	225W	225 W	not done	1-vessel CAD with non crit. stenoses

+++symptoms at rest ++symptoms with minor effort +symptoms with major effort
– no symtoms

Our results demonstrate that the HELP-treatment in combination with administration of a HMG-CoA reductase inhibitor can reduce the plasma LDL-cholesterol concentration by more than 70 %. The high efficacy and safety of this combined treatment in CAD-patients now offers a new therapeutic approach to normalize even markedly severe heterozygous hypercholesterolemia with plasma LDL-cholesterol concentrations of about 450 mg to ideal LDL-cholesterol levels of below 120 mg/dl. The major indication for this combined therapy lies in the secondary prevention of CAD. We believe that one to two years of treatment will be required to retard the CAD and to initiate a regression of the atherosclerotic vessels (13). Thereafter a well monitored drug therapy with HMG-CoA reductase inhibitors alone or in combination with resins will be necessary to maintain the clinical improvement.

CONCLUSION

HELP-treatment alone can lower the mean plasma LDL-cholesterol by about 50-60 %, Simvastatin-therapy in a daily dosage of 40mg reduces the plasma LDL-cholesterol by about of 40 %. The combination of both treatments results in a lowering of mean LDL-cholesterol to about 80 % of baseline values. No relevant adverse effects were noted over a period of one year. This

therapeutic strategy for maximal LDL-cholesterol lowering may be useful in the secondary prevention of CAD in FH and non FH patients if plasma LDL-cholesterol cannot be reduced by diet and drug treatment to desirable plasma levels (LDL-cholesterol lower than 120 mg/dl). Preliminary data show an improvement in the symptoms of our CAD-patients treated with this combined therapy.

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