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Low-density lipoprotein plasmaphaeresis with and without lovastatin in the treatment of the homozygous form of familial hypercholesterolaemia*

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Abstract. A 7-year-old girl with homozygous familial hypercholesterolaemia and plasma low-density lipoprotein(LDL)-cholesterol levels of 820 mg/dl (21.2 mmol/l) and progressive xanthomata was treated with heparin extracorporeal low-density lipoprotein precipitation (HELP) to lower her plasma LDL. On weekly HELP treatment she maintained her pre-HELP treatment LDL-cholesterol levels at 409 mg/dl (10.6 mmol/l). The long-term HELP treatment was well tolerated and led to regression of her xanthomata. Subsequently, lovastatin [Mevacor; Merck Sharp & Dohme, Westpoint, Pa., USA (20 mg/day)] was added to the regimen, causing a further 20% decrease in her pre-HELP treatment plasma LDL-cholesterol levels. Lovastatin alone did not sufficiently lower her plasma LDL and could not replace the weekly HELP therapy. Our data show that lovastatin is an effective adjunctive therapy for lowering plasma LDL-cholesterol in a homozygous patient, once plasma LDL levels have already been lowered by regular HELP treatment.

Key words: Homozygous familial hypercholesterolaemia – low-density lipoprotein plasmaphaeresis – Heparin extracorporeal low-density lipoprotein precipitation – Lovastatin

Introduction

Autosomal dominant familial hypercholesterolaemia (FH) is caused by mutations in the gene encoding the low-density lipoprotein receptor. In the severe homozygous form, plasma cholesterol levels between 700 and 1000 mg/dl (18.1–25.86 mmol/l) are encountered [5, 10]. Untreated, these patients often die of myocardial infarction before the age of 20 [10]. Treatment by diet and drug therapy alone is ineffective [17, 18, 20], but encouraging results have been obtained by plasma exchange [25]. In five homozygotes treated with regular plasmaphaeresis for a mean of 8 years, survival improved compared with the untreated siblings [26]. Conventional plasmaphaeresis requiring replacement of the patient's plasma with fresh frozen plasma or with plasma protein fractions may lead to complications due to the introduction of foreign proteins or to infections. Attempts to selectively remove LDL from plasma, which was then returned to the patient, involved the adsorption of LDL to heparin-agarose beads [22] or to immobilized antibodies [13, 24]. Other methods for the removal of LDL involve cascade filtration [29] or adsorption to immobilized dextran sulphate [33]. We developed a system termed HELP (heparin extracorporeal LDL precipitation), which is based on LDL precipitation at low pH in the presence of heparin [2, 8, 23].

We now describe long-term application of the HELP procedure with and without lovastatin, a hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitor, in a 7-year-old child with the homozygous form of hypercholesterolaemia. Even though lovastatin has only marginal benefits as monotherapy in homozygous FH [15, 19, 21], it was of interst to establish whether this drug in combination with HELP would lower the plasma LDL in our patient to a level which could not be achieved by HELP treatment alone.

Patient and methods

Patient

A girl, born in 1979, was referred to us in 1984 with plasma cholesterol levels of 862 mg/dl (22.28 mmol/l). Physical examination showed xanthomas on elbows, interdigital webs of hands, buttocks, knees and achilles tendons. Arcus corneae and xanthelasmas in the

* This work is dedicated to Professor Fritz Scheler, Department of Internal Medicine, University of Göttingen, on his 65th birthday

Offprint requests to: D. Seidel

Abbreviations: ACTH = adrenocorticotropic hormone; FH = familial hypercholesterolaemia; HELP = heparin extracorporeal low-density lipoprotein precipitation; HMG-CoA = hydroxymethylglutaryl-CoA; LDL = low-density lipoprotein

Table 1. Biochemical characterization of familial hypercholesterolaemia in the patient and her family

	Age (years)	Plasma cholesterol concentration				Triglycerides	CAD	Achilles tendon xanthomas	% Normal LDL receptor activity in fibroblasts[a]	
		Total	VLDL	LDL	HDL				^{125}I LDL	^{3}H oleate incorporated
Patient	9	868	32.7	820	15	142	−	+	7%–11%	7%–9%
Mother	40	258	19.0	195	44	79	−	−	55.9%	59%
Father (deceased 14.7.83)	39	350	ND	ND	ND	−	+	−	ND	ND
Paternal uncle	50	241	29.3	165	46	150	−	−	55.5%	56%
Paternal uncle	40	360	21.3	308	30	118	+	−	43.4%	50%

[a] LDL-recptor activity: (a) degradation of ^{125}I LDL at a concentration of 10 µg ^{125}I LDL-protein/ml in five normal fibroblast cell lines (degradation values of 4079 ± 825 ng/mg cell protein during 6 h incubation is defined as 100%); (b) ability of 10µg LDL protein/ml to stimulate incorporation of ^{3}H oleate in cholesterylester in five different fibroblast cell lines was 0.659 ± 0.0448 nmol/mg per cell protein per 2 h and is defined as 100% activity. CAD = Coronary artery disease; ND = not determined

soft tissue of the eyelids were also present. Her father, whose plasma cholesterol levels were reported to be around 360–400 mg/dl (9.30–10.34 mmol/l), had died at the age of 39 from cardiac failure. Measurement of total and LDL-cholesterol levels of the patient's mother and two paternal uncles were consistent with the diagnosis of homozygous FH. They showed no xanthelasmas, xanthomata or arcus lipoides. Skin fibroblasts were cultured from the patient, her mother and her two paternal uncles. The low LDL-receptor activity established the diagnosis of FH in the family and that the patient was receptor-defective (Table 1). Diet and drug therapy proved unsatisfactory in lowering the patient's plasma total and LDL-cholesterol concentrations.

HELP therapy

The apparatus necessary for the continuous elimination of LDL from plasma was provided by B. Braun (Melsungen, FRG). Details of the therapy have been published elsewhere [4, 8]. In brief, a 0.55-µm plasma filter is used to separate plasma from whole blood. The plasma is continuously mixed with an equal volume of 0.2 *M* sodium acetate adjusted to pH 4.85 containing 100 units/ml heparin. Precipitation of LDL and fibrinogen occurs rapidly at a final pH of 5.12 and the suspension is continuously recirculated through a 0.4-µm polycarbonate filter to retain the precipitate. The clear filtrate is then passed through an anion exchange filter to remove excess heparin. After the passage through this absorbant, the plasma buffer mixture is subjected to a bicarbonate dialysis/ultrafiltration to restore the physiological pH and to remove excess fluid. Finally, the LDL and fibrinogen-free plasma is mixed with the blood cells from the plasma filter and returned to the patient. The various tubing, filters, etc. required for the procedure are disposable and are discarded after use. Plasma flow rates in the case of adults are usually between 20 and 30 ml/min and treatment lasts between 2 and 3 h (for 3000 ml plasma). The total extracorporeal volume of the system excluding filter 1 and the tubing amounts to approximately 1100 ml, of which half will be plasma and half buffer during the treatment.

For the treatment of our now 9-year-old homozygous patient, plasma to buffer ratio was first adjusted to 1:3 (v/v) in order to reduce the volume of plasma in the extracorporeal system and the flow rates were of the order of 10 ml/min. A total of 1000 ml plasma was treated at any one session. The interval between sessions was 7 days in general and treatment was performed on an outpatient basis, requiring approximately 2 h per session. No adverse effects or complications were observed during more than 90 treatments spread over 2 years.

Lovastatin was administered at a dosage of 20 mg/day for 5 weeks in combination with weekly HELP treatment and for 4 weeks without HELP. Informed consent was obtained from the patient's mother for the HELP therapy with and without lovastatin, use of which was sanctioned by the Ethics Committee of the University of Göttingen Medical Centre.

Laboratory determinations

Chemical, haematological and blood coagulation indices were measured using standard laboratory techniques. The concentrations of the different lipoproteins were determined by quantitative lipoprotein electrophoresis [31] and precipitation techniques for LDL-cholesterol (Cholesterol Quantolip-LDL, Immuno, Heidelberg, FRG) and HDL-cholesterol (Boehringer, Mannheim, FRG). Lipoproteins were also separated from 0.5 ml plasma by sequential centrifugation techniques [14] using a Beckmann Rotor TY 25 (Beckman Instruments, Irvine, Calif., USA). Tests for adrenocortical responsiveness to adrenocorticotropic hormone (ACTH) both off and on lovastatin were performed. Synacthen (Ciba Geigy, Wehr, FRG) 0.25 mg (25 IU ACTH) was given intravenously and plasma cortisol levels measured at 0 and 60 min. [1].

LDL-receptor studies in cultured fibroblasts

Fibroblast cell lines were grown in monolayers and LDL-receptor activity measured between 5 and 10 passages [3, 30]. The LDL-receptor activity was measured by using ^{125}I-LDL as well as ^{3}H-oleate esterification procedures [11]. The assay for cholesteryl ester formation was used to provide an assessment of the total LDL-receptor activity pathway. LDL was used at a concentration of 10, 50 and 100 µg protein/ml incubation medium for receptor activity assay. Since the percentage of receptor activity was almost the same at these concentrations, only values for 10 µg protein/ml are given in Table 1.

Results

HELP treatment was started in early 1986. Serum LDL-cholesterol levels during the first 90 treatments are presented in Fig. 1. The first HELP procedure lowered her plasma LDL-cholesterol from 820 mg/dl (21.2 mmol/l) to around 240 mg/dl (6.20 mmol/l). After the first ten treatments, her pre-HELP plasma LDL-cholesterol, i.e. values immediately before HELP treatment, were maintained at approximately 410 mg/dl (10.6 mmol/l). Over a period of 2 years (90 HELP treatments) pre-HELP plas-

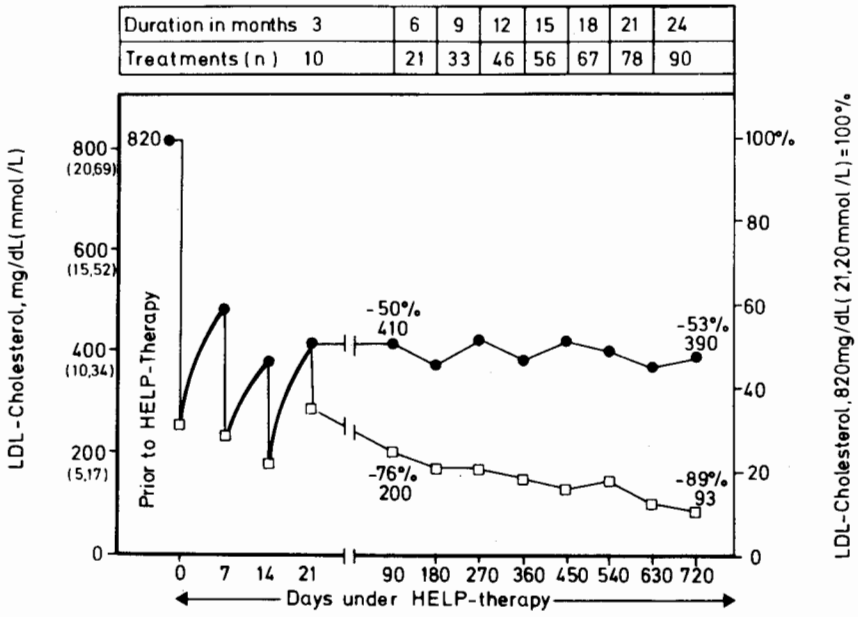

Fig. 1. Plasma LDL-cholesterol levels in a familial hypercholesterolaemic homozygous child during weekly HELP treatment for 2 years. All 3-month values in the curve represent average of all the measurements within this period. *n* denotes the number of treatments. The *closed circles* represent the LDL-cholesterol concentrations prior to HELP therapy (pre-HELP) and the *open squares* the levels immediately after HELP therapy (post-HELP)

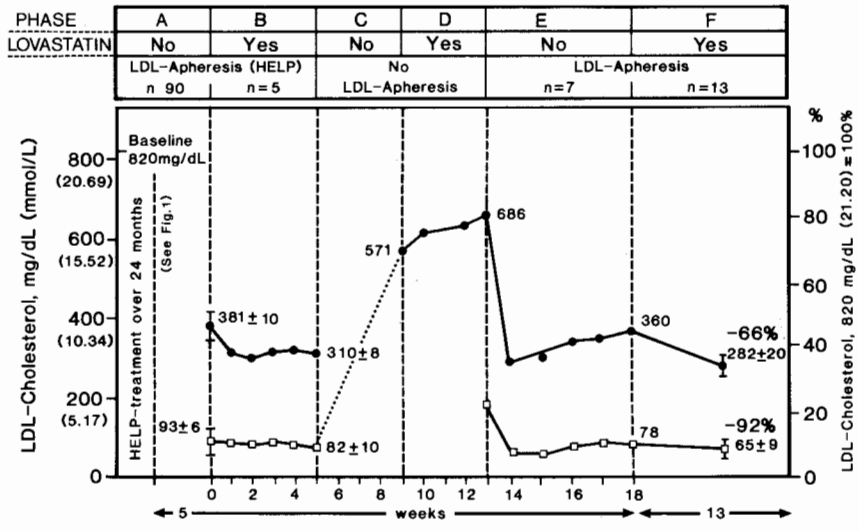

Fig. 2. Effect of lovastatin on serum LDL-cholesterol levels in combination with HELP treatment. *Phase A:* HELP treatment alone. *Phase B:* lovastatin together with weekly HELP therapy. *Phase C:* 4 weeks without HELP and lovastatin. *Phase D:* 4 weeks lovastatin (20 mg/day) without HELP. *Phase E:* HELP treatment alone. *Phase F:* combined lovastatin and HELP therapy (13 weeks). Symbols as for Fig. 1

ma LDL-cholesterol levels, i.e. values immediately before HELP treatment of 409 mg/dl (10.6 mmol/l) and post-HELP plasma LDL-cholesterol levels, i.e. values immediately after HELP treatment of 148 mg/dl (3.82 mmol/l), were maintained. The mean plasma LDL-cholesterol levels (post-HELP value + last pre-HELP value divided by 2) was approximately 279 mg/dl (7.21 mmol/l). This value represents a 66% decrease in initial plasma LDL-cholesterol levels. At this time our patient weighed 30.5 kg and, assuming a plasma volume of 45 ml/kg, had a calculated plasma volume of 1372 ml [7]. Accordingly her plasma LDL-cholesterol pool before HELP therapy (pre-HELP) was 5.6 g and 2 g after the HELP therapy. Thus on an average 3.6 g LDL-cholesterol was removed from the circulation during one HELP treatment. Because of a rather steady state of pre- and post-treatment values in the 7-day interval, her mean gain of plasma LDL-cholesterol between the intervals of HELP treatment equals the removal of LDL-cholesterol by the HELP treatment. Assuming that post-treatment gain is linear over 1 week, we calculated a daily increase of approximately 0.5 g LDL-cholesterol in the plasma pool. Plasma fibrinogen followed the same pattern as LDL.

Even though the HELP treatment maintained her mean LDL-cholesterol value at approximately 280 mg/dl (7.24 mmol/l), it was considered desirable to lower this value further and to test whether a combination of the HELP treatment with lovastatin would be helpful in this respect. During a control period of the last 5 weeks before starting the drug therapy, her pre-HELP plasma LDL levels averaged at 381 mg/dl (9.85 mmol/l) and post-HELP values at 93 mg/dl (2.40 mmol/l), representing a total plasma LDL-cholesterol pool of 5.2 g and 1.3 g, respectively. Thus 3.9 g plasma LDL-cholesterol was removed during this period by each HELP treatment. After the 5-week control period she was next administered 20 mg/day lovastatin for 5 weeks. The data are presented in Fig. 2.

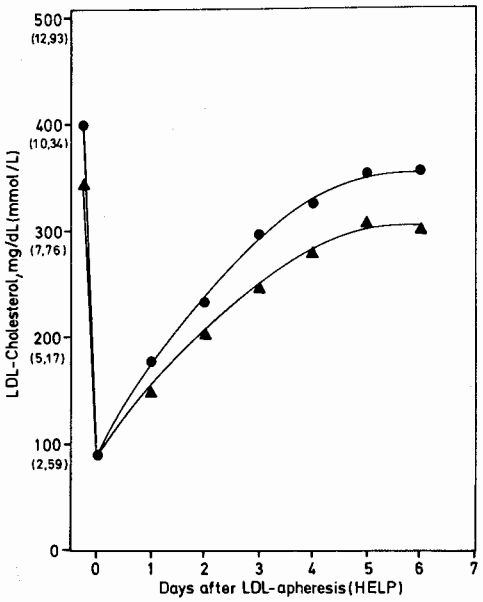

Fig. 3. Recovery of plasma LDL-cholesterol between two HELP treatments in the presence and absence of lovastatin. ●, No drug; ▲, lovastatin (20 mg/day)

During the drug medication with lovastatin (phase B) her average pre-treatment and post-treatment values stabilized at 310 and 82 mg/dl (8.01 and 2.12 mol/l) respectively, indicating about 19% reduction when compared to phase A. This accounts for a decrease in reaccumulation of plasma LDL pool of about 1 g/week or 140 mg/day with combined lovastatin/HELP therapy as compared to HELP treatment alone. For the following 4 weeks (phase C), the patient received neither HELP nor lovastatin treatment. Her plasma LDL-cholesterol concentration increased from a previous post-HELP value of 82 mg/dl (2.12 mmol/l) to 571 mg/dl (14.76 mmol/l). For 4 weeks in phase D, she was put on lovastatin without HELP. Her plasma LDL-cholesterol concentration increased further to 666 mg/dl (17.22 mmol/l). At the end of phase D lovastatin administration was stopped and the patient was put back on HELP treatment alone (phase E). The first HELP treatments performed at intervals of 3, 4 and 7 days led to a post-treatment value for plasma LDL-cholesterol of around 50 mg/dl (1.29 mmol/l). From this period onwards she was treated regularly every 7 days for 5 weeks without lovastatin. Combined lovastatin and HELP treatment was started again as in phase B. A similar degree of reduction in her pre-HELP levels of LDL-cholesterol in plasma was observed (phase F). In order to follow the kinetics of reaccumulation of the LDL in the plasma pool during the HELP treatment in the presence or absence of lovastatin, blood samples were collected daily between two HELP treatments (end of phase A) and during the last week of lovastatin administration (end of phase B). The data are presented in Fig. 3. There was an absolute diminution of plasma LDL-cholesterol reaccumulation by 25%, which accounts for approximately 1 g LDL-cholesterol/week. This is in agreement with the data calculated over the whole 5-week time-course (phase B; see above).

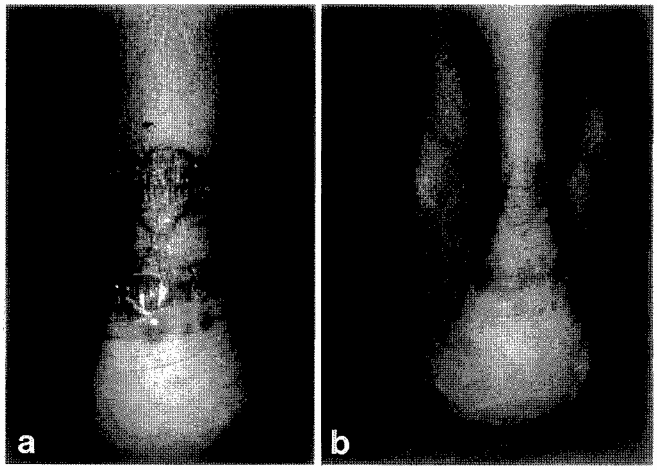

Fig. 4. Regression of achilles tendon xanthomas after 2 years (**a** 1986; **b** 1988) of weekly HELP treatment

Because HMG-CoA-reductase inhibitors may suppress endogenous cholesterol synthesis in various tissues, we also determined whether clinical signs or symptoms of adrenal insufficiency developed during lovastatin therapy in our patient. ACTH stimulation test in the presence and absence of lovastatin administration remained essentialy unchanged. Before lovastatin administration her baseline cortisol levels were 5.4 μg/dl (149.04 nmol/l) and 60 min after ACTH stimulation 18.5 μg/dl (510.6 nmol/l). After lovastatin administration her baseline was 9.5 μg/dl (262.2 nmol/l) and 60 min after stimulation 20.2 μg/dl (557.5 nmol/l), an increase of 13.1 and 10.7 μg (351.6 and 295.3 nmol/l) respectively. This increase is within the normal range [9, 16, 27]. Long-term HELP therapy alone or in combination with lovastatin did not affect liver and muscle enzymes or other routine clinical chemical parameters [4]. HELP treatment reduced fibrinogen and haemoglobin by about 21% (from 300 to 237 mg/dl) and 9% (from 12.4 to 11.4 g/dl) respectively, but plasma HDL-cholesterol increased from 15 mg/dl to 25 mg/dl. Paediatric examinations were performed at 1-year intervals to assess the patient's physical development. There were no abnormal clinical and neurological findings under HELP and lovastatin therapy. Two-dimensional echocardiography revealed no valvular obstruction, normal cardiac sounds, and no heart murmurs. The ECG showed a sinus rhythm and a normal electric activity. Pulse (96/min) and blood pressure (110/65 mm Hg) were in a physiological range. The body weight increased from 24 kg at 6 years to 29.6 kg at 8 years, the height from 127 cm to 140 cm. At the age of 8 years the head circumference was 50.8 cm. The skin was free of infections. A regression of cutaneous xanthomas on HELP therapy was noted (Fig. 4).

Discussion

Our clinical experience with HELP treatment for the removal of plasma LDL-cholesterol in patients suffering from severe familial and non-familial hypercholes-

terolaemia encouraged us to treat a homozygous child with the HELP procedure. As with other patients, HELP treatment drastically reduced the plasma LDL-cholesterol and fibrinogen levels [2, 4, 8, 23]. Furthermore, regression of her cutaneous xanthomata under this therapy was observed. During 90 treatments spread over a period of 2 years no adverse effects were noted. She maintained a pre-HELP plasma LDL-cholesterol level of about 380 mg/dl (9.82 mmol/l), a post-LDL-cholesterol of about 80 mg/dl (2.07 mmol/l) and a mean LDL-cholesterol of about 280 mg/dl (7.24 mmol/l). Calculated on the basis of her plasma volume a single HELP treatment removed approximately 3.9 g LDL-cholesterol from the circulation.

Our next aim was to determine whether a combination of HELP and lovastatin would further lower the plasma post-LDL-cholesterol concentration in our patient. The administration of this drug over a 1-year-period to a 7-year-old homozygous FH girl who had received a combined heart-liver transplant caused no adverse effects [7]. During a 5-week combination of lovastatin and HELP treatment we observed a further 20% reduction in her pre-HELP plasma LDL-cholesterol levels. Thus, administration of lovastatin in a period of disrupted cholesterol homeostasis brought about by the HELP treatment reduced the reaccumulation of LDL in plasma and the LDL-pool size. When her plasma LDL-cholesterol was 571 mg/dl (14.77 mmol/l), lovastatin without HELP treatment did not prevent the further rise in plasma LDL levels.

Compactin, a congener of lovastatin, was reported to lower plasma cholesterol levels in FH homozygotes by only about 7% at a high dosage of 200 mg/day [32]. Lovastatin also showed only marginal benefits in FH homozygotes [19]. Lovastatin was also administered in combination with plasmaphaeresis at intervals of 2 weeks in two homozygous FH patients [27]. Lovastatin decreased pre-plasma exchange serum cholesterol by 7% at 40 mg/day or 11.5% at 80 mg/day in these patients. The efficacy of this HMG-CoA reductase inhibitor in combination with HELP in our patient may be due to maintaining her pre-HELP LDL-cholesterol levels around 380 mg/dl (9.83 mmol/l) by weekly HELP treatments before the administration of lovastatin. This is in contrast to previous studies where pre-plasma exchange cholesterol levels were about 500 mg/dl [27].

HMG-CoA reductase inhibitors, which lower plasma LDL-cholesterol by increasing the number of LDL receptors in liver [20], should be relatively ineffective in patients with homozygous FH [7, 19]. Whether lovastatin caused a small increase in the number of LDL receptors in our patient or changed the quality of the already available small number of LDL receptors, which became effective in removing LDL, remains to be clarified. Lovastatin may, however, decrease the hepatic very low-density lipoprotein (VLDL) synthesis and thereby reduce LDL formation via VLDL-IDL-LDL cascade, since it has been reported to lower plasma LDL-cholesterol levels without altering the fractional catabolic rate of LDL apoprotein B [6, 12, 28].

The precise identification of the mechanisms responsible for the reduction of the pre-HELP plasma LDL concentrations and decrease in the recovery rates of plasma LDL-cholesterol pool after each HELP treatment in the presence of lovastatin needs to be resolved. Nevertheless, combined HELP and lovastatin therapy lowered the plasma LDL-cholesterol concentrations and pool to levels not previously achieved in the homozygous form of FH. Whether combined LDL-plasmaphaeresis and lovastatin will prove to be the treatment of choice in homozygous FH must await the results of further long-term studies.

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