Therapeutic Efficiency of Lipoprotein(a) Reduction by Low-Density Lipoprotein Immunoapheresis

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This study was performed to investigate the effect of low-density lipoprotein (LDL) immunoapheresis on lipoprotein(a) [Lp(a)] reduction in patients with heterozygous and homozygous familial hyperlipidemia (N = 16) and insufficient response to lipid-lowering agents. By desorption of approximately 5,700 ± 500 mL of plasma, a mean reduction in total cholesterol of 62% ($P < .001$) and in LDL-cholesterol of 70% ($P < .001$) was achieved. Lp(a), which was elevated at study entry in seven of these patients (82.1 ± 34.3 mg/dL; range, 48 to 148 mg/dL), was reduced during the initial LDL-apheresis procedure by 74.8% ± 14.1% ($P < .001$). Long-term apheresis treatment performed at weekly intervals resulted in an mean reduction in Lp(a) pretreatment values to 39.1 ± 28.5 mg/dL (−54%; $P < .001$). Desorbed Lp(a) was measured at the waste of the columns for 31 apheresis treatments. Lp(a) concentration of the column waste was higher in patients with elevated serum Lp(a) pretreatment values as compared with those with Lp(a) serum values within the normal range (elevated Lp(a), 1,420 ± 380 mg; without elevated Lp(a), 235 ± 190 mg; $P < .001$). The rate of return of Lp(a) following apheresis treatment scheduled at weekly intervals was comparable to that of LDL-cholesterol.

LIPOPROTEIN(a) [Lp(a)] is made up of a low-density lipoprotein (LDL)-cholesterol–like structure in terms of lipid and protein composition, but it also contains the glycoprotein apolipoprotein(a) [apo(a)], which is linked through a disulfide bridge to apolipoprotein-B (apo-B).[1-8]

Many clinical investigations provided evidence that increased Lp(a) level is associated with the occurrence and severity of coronary artery disease (CAD), as well as with the appearance of further cardiovascular events after percutaneous transluminal angioplasty (PTCA) and bypass grafting.[1,3,5,9-18] However, in two recent published studies, no association was found between the occurrence of CAD and Lp(a) levels of the patients.[19,20] Farrer et al[21] demonstrated larger isoform size to be associated with an increased incidence of CAD in patients with elevated Lp(a) levels. In contrast, several reports indicated smaller isoforms to be associated with an increased risk of atherosclerotic vascular disease.[9,22-24] To date, 34 different isoforms have been identified that differ only in the number of kringle 4 repeats, which correlates inversely with the plasma Lp(a) levels.[25,26] Apo(a) exhibits a high degree of structural homology with kringle 4 and one kringle 5–like domain of human plasminogen followed by a protease region structurally similar to that of plasminogen.[6,18,27] Thus, Lp(a) has been suggested to interfere with plasminogen-mediated thrombolysis.[6,27,28]

Furthermore, laboratory and pathological investigations supported the potential effects of Lp(a) on the development of atherosclerotic vascular disease by promoting intracellular cholesterol accumulation,[9,29] by binding apo-B–containing lipoproteins,[30] by stimulating smooth muscle cell proliferation,[6,31] and by accumulation in atherosclerotic plaques.[6,32]

Although high plasma Lp(a) levels are implicated as an important contributor to atherosclerosis and CAD, the issue as to whether elevated Lp(a) should be treated, particularly for primary prevention, is still a matter of dispute.[9,19,20,33] Furthermore, no satisfactory dietary and/or pharmacological interventions for increased Lp(a) levels currently exist. Seed et al[34] reported a 36% decrease in elevated Lp(a) levels in hypercholesterolemic patients treated with nicotinic acid. However, only 54% of the patients completed the 2-month study period, because of side effects due to high dosage of nicotinic acid.[34] Recently published data on long-term administration of niceritrol, a derivative of nicotinic acid, demonstrated a 26% decrease in Lp(a) values,[35] which, however, might not be satisfactory for treatment of patients with moderate or severe elevated Lp(a) levels. Further attempts to treat Lp(a) with lipid-lowering drugs, including 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, have been generally disappointing.[33,36,37]

At present, LDL apheresis is performed primarily to decrease LDL-cholesterol in patients with familial hypercholesterolemia (FH) who are resistant to conventional lipid-lowering therapy. Due to the close structural relationship of LDL-cholesterol and Lp(a), both of these lipoproteins are removed by extracorporeal lipid-lowering interventions.[38-49] Additionally, specific Lp(a) apheresis with no reduction in plasma LDL-cholesterol levels has been reported.[45]

The present study was designed to determine the potential therapeutic efficiency of Lp(a) reduction by immunospecific LDL apheresis in patients with FH. Additionally, one patient with selectively elevated Lp(a) and serious CAD was treated by this procedure. Suspected therapeutic efficacy of Lp(a) reduction was estimated by duration of Lp(a) reduction in between two apheresis treatments.

MATERIALS AND METHODS

Sixteen patients (14 males and two females) who were maintained on long-term LDL immunoapheresis at weekly intervals (48 to 50 treatments/year) for treatment of hyperlipoproteinemia [four with homozygous FH, 11 with heterozygous FH, and one without FH but elevated

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Lp(a)] were studied for therapeutic efficacy of Lp(a) reduction during a total of 203 apheresis treatments. Initial lipoprotein values were obtained in patients with elevated Lp(a) either at onset of apheresis treatment (n = 2) or after a period without apheresis treatment of 3 weeks due to holidays (n = 5). Efficacy of long-term LDL apheresis scheduled at weekly intervals on Lp(a) reduction was estimated thereafter for 15 subsequent apheresis treatments in each of these patients. All of these investigations were performed within a period of 8 months.

The one male patient (age, 65 years) with elevated Lp(a) (148 mg/dL; without FH and maintained on chronic hemodialysis treatment) had serious symptomatic cardiovascular disease without any risk factor of CAD other than elevated Lp(a). This patient had a history of myocardial infarction and quadruple bypass grafting 6 months before the start of apheresis treatment. As the patient had developed angina symptoms already 4 months after bypass grafting, coronary angiography was performed and showed occlusion of two of the grafts, as well as stenosis (>75%) of the two other grafts. For these reasons, the patient was maintained on LDL apheresis at weekly intervals. Each apheresis procedure was combined with hemodialysis for this patient.

All patients with FH were maintained on LDL immunoapheresis at weekly intervals because dietary restrictions as recommended by the American Heart Association[50] and pharmacological interventions had failed to sufficiently improve hypercholesterolemia. None of the patients received fibric acid analogs during LDL-apheresis treatment.

Patients' characteristics are listed in Table 1. All subjects underwent coronary cineangiography before LDL apheresis. In symptomatic patients and after PTCA (n = 5), coronary angiography was repeated within a 6- to 12-month interval. For asymptomatic heterozygous FH patients and one homozygous patient (age, 23 years; on LDL-apheresis treatment for 7 years) without atherosclerotic vascular disease, coronary angiography was performed after 2 years.

The results of the coronary angiography and previous cardiac events obtained at the beginning of LDL apheresis are listed in Table 2.

Table 1. Clinical Characteristics of Patients With FH Maintained on Long-Term Apheresis Treatment Subdivided According to Lp(a) Values

Characteristic	Patients With FH and Elevated Lp(a) Levels	Patients With FH and Lp(a) Levels Within the Normal Range	*P*
No. of patients	7	9	NS
Age (years)			
Mean ± SD	42 ± 17	47 ± 21	NS
Range	18-65	30-61	NS
Sex			
Male	6	8	NS
Female	1	1	
Primary disease			
Homozygous FH	2	2	NS
Heterozygous FH	4	7	
Selective Lp(a) elevation	1		
No. of apheresis treatments	228 ± 86	203 ± 46	NS
Months of apheresis treatments	51 ± 22	41 ± 22	NS
Mean desorbed plasma volume (mL)	5,670 ± 480	5,730 ± 520	NS
Lp(a) values at study entry (mg/dL)	82.1 ± 34.3	13.2 ± 11.0	<.001

Abbreviation: NS, not significantly different.

Table 2. Cardiac Events and CAD in Patients With FH on Long-Term LDL Apheresis With/Without Elevated Lp(a) Levels

	No. of Patients	MI	Bypass Graft	PTCA
Patients with FH and elevated Lp(a) levels (n = 7)				
No CAD	1	0	0	0
1 VD	0	0	0	0
2 VD	1	1	0	1
3 VD	5	3	3	2
Total	7	4	3	3
Patients with FH and Lp(a) levels within the normal range (n = 9)				
Coronary spasms	1	0	0	0
1 VD	2	2	1	1
2 VD	2	1	1	0
3 VD	4	1	1	1
Total	9	4	3	2

Abbreviations: MI, myocardial infarction; PTCA, percutaneous transluminal coronary angiography; VD, coronary vessel disease.

LDL Immunoadsorption

For LDL immunoadsorption, blood was drawn from an antecubital vein via a 17-gauge needle at a flow rate of 50 to 80 mL/min. The Autopheresis-C therapeutic plasma system (TPS; Baxter, Deerfield, IL) was used for primary plasma separation.[51] The functional separation unit of the device is the Plasmacell-C, a rotating cylindrical membrane housed in a plastic casing. The Plasmacell-C is capable of fast and highly efficient plasma separation using a small membrane-surface area (70 cm^2) with a blood-processing volume of only 7 mL.

Sodium-heparin (input rate, 1,000 U/h; not >5,000 U) and citrate (ACD-A, anticoagulant citrate dextrose, formula A; Baxter, Munich, Germany) were added for anticoagulation. The ratio of citrate to whole-blood flow was kept at 1:20 (5%). LDL immunoapheresis was performed in an automated double-needle, continuous-flow operation in which the TPS is connected with an adsorption-desorption automate (Medicap, Düsseldorf, Germany). Two columns each containing 150 mL Sepharose 4B gel, coupled with polyclonal sheep apolipoprotein B-100 antibodies (LDL-Therasorb; Therasorb, Munich-Unterschleissheim, Germany), were used for lipoprotein removal.[38,39,44,52,53] In each adsorption cycle, approximately 1,000 mL of plasma was loaded on one column (plasma flow rate, 25 to 35 mL/min), while the other column was regenerated. A total of five to seven cycles was performed at each immunoadsorption session (lasting for 3.5 ± 0.4 hours).

Columns were regenerated by elution of apo-B–containing lipoproteins with glycine buffer at pH 2.8, and a subsequent rinse with phosphate-buffered saline (PBS) and 9 g/L isotonic sodium chloride solution. To determine the total amount of Lp(a) desorbed, the waste was obtained during the glycin phase of each cycle and Lp(a) was quantified from entire volume. Two columns were assigned to each patient, which were reused for up to 107 treatment sessions and stored under sterile conditions.

Laboratory Methods

Total cholesterol and triglycerides were measured enzymatically using a commercial kit (Boehringer-Mannheim, Mannheim, Germany). Lipoprotein lipids were measured according to the Lipid Research Clinic's methods with slight modifications as recently described.[44,52,53] Very–low-density lipoproteins (VLDLs) were removed by ultracentrifugation ($d < 1.006$ g/mL), LDLs were separated from the infranatant ($d < 1.063$ g/ml) by heparin and polyanion precipitation using manganese chloride, and high-density lipoprotein (HDL)-cholesterol was

determined from the supernatant. Lp(a) was determined quantitatively using an enzyme immunoassay [Innotest Lp(a); Innogenetics, Belgium]. Apolipoproteins were quantified by radial immunodiffusion.

Statistical Analysis

Values are presented as means ±1 SD. Differences between pretreatment and posttreatment values were evaluated for statistical significance using Student's *t* test. Reincrease in lipoproteins in between of two treatments was tested for statistical significance by ANOVA with Bonferroni correction for multiple comparison. Data representing progression and regression of CAD were compared by χ^2 test. Generally, *P* values less than .05 were considered significant.

RESULTS

The metabolic changes obtained during LDL-apheresis treatment in 16 patients are summarized in Table 3. For the entire study population (203 LDL-apheresis treatments in 16 patients), mean Lp(a) levels were reduced from 23.0 ± 26.9 mg/dL to 9.9 ± 7.6 mg/dL ($P < .001$) during a single LDL apheresis, representing an average decrease in Lp(a) of 56.6% ± 27.6% ($P < .001$).

Lp(a) pretreatment values were elevated (>30 mg/dL) in seven patients at study entry (82.1 ± 34.3 mg/dL; range, 48 to 148 mg/dL). By the initial LDL-apheresis treatments (n = 7), Lp(a) was reduced to 20.7 ± 7.3 mg/dL (−74.8% ± 14.1%; $P < .001$; Fig 1). LDL apheresis scheduled at weekly intervals resulted in a reduction in Lp(a) pretreatment values from 82.1 ± 34.3 mg/dL to 39.1 ± 28.5 mg/dL (range, 11 to 41 mg/dL; −54%; $P < .001$).

Based on these reduced Lp(a) pretreatment levels (39.1 ± 28.5 mg/dL), a similar efficiency in Lp(a) removal by each single LDL apheresis during subsequent treatments was obtained (from 39.1 ± 28.5 mg/dL to 11.0 ± 7.8 mg/dL; −71.9% ± 9.7%; $P < .001$) when compared with the 74.8% achieved by the initial treatment. Three patients with elevated Lp(a) levels at study entry (n = 7) exhibited a reduction in Lp(a) pretreatment values to the estimated normal range (<30 mg/dL) when treated long-term at weekly intervals.

One patient without FH but seriously elevated Lp(a) (148 mg/dL) showed a decline of Lp(a) pretreatment values to levels of approximately 60 mg/dL (Fig 2) after only three LDL-apheresis treatments. Although the Lp(a) levels were reduced to

Table 3. Reduction in Lipoproteins During LDL-Apheresis Treatment in Patients With FH

Variable	Before	After	Decrease %	*P* Value
Total-c (mg/dL)	292 ± 104	114 ± 84	62.4 ± 9.9	<.001
LDL-c (mg/dL)	259 ± 91	78 ± 43	69.9 ± 11	<.001
HDL-c (mg/dL)	34 ± 7	31 ± 5	8.8 ± 1.1	<.05
Tg (mg/dL)	380 ± 125	237 ± 99	37.6 ± 25	<.01
Lp(a)* (mg/dL)	23.0 ± 26.9	9.9 ± 7.6	56.6 ± 27.6	<.001
Lp(a)† (mg/dL)	82.1 ± 34.3	20.7 ± 7.3	74.8 ± 14.1	<.001
Lp(a)‡ (mg/dL)	39.1 ± 28.5	11.0 ± 7.8	71.9 ± 9.7	<.001

Abbreviations: c, cholesterol; Tg, triglycerides.

*Patients on LDL apheresis (n = 16). Lp(a) reduction achieved by LDL-apheresis treatment (N = 203).

†Patients with elevated Lp(a); values determined at study entry.

‡Patients with elevated Lp(a); values obtained during long-term apheresis treatment scheduled at weekly intervals.

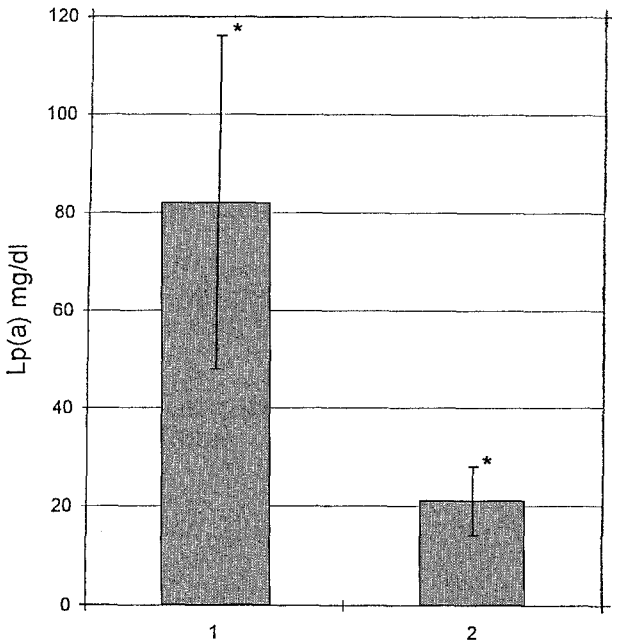

Fig 1. Lp(a) values before (1, 82.1 ± 34.3 mg/dL) and after (2, 20.7 ± 7.3 mg/dL) the initial LDL-apheresis treatment in patients (n = 7) with elevated Lp(a) serum levels. Values are means ±1 SD; *$P < .001$.

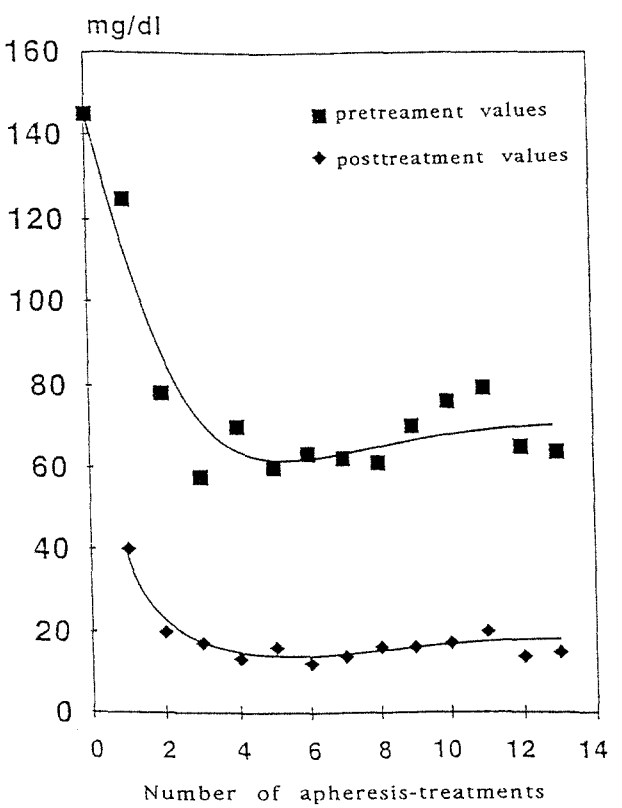

Fig 2. Reduction in Lp(a) pretreatment values in 1 hemodialysis patient without FH but seriously elevated Lp(a) serum levels maintained on LDL apheresis at weekly intervals.

14.9 ± 10.4 mg/dL by the following apheresis procedures (n = 14), treatments at weekly intervals did not result in a further reduction of Lp(a) pretreatment values (Fig 2). The rate of return of Lp(a) and LDL-cholesterol in the seven patients with elevated serum Lp(a) was measured following the initial apheresis treatment.

The recovery of Lp(a) and LDL-cholesterol was comparable for each patient with elevated Lp(a) serum levels (n = 7; Fig 3A and B). Mean Lp(a) reduction during the initial LDL apheresis (from 82.1 ± 34.3 mg/dL to 20.7 ± 7.3 mg/dL) was followed by a continuous increase in Lp(a) for the subsequent days (day 1, 29.3 ± 12.6 mg/dL, ie, 35.9% ± 5.4% of the pretreatment

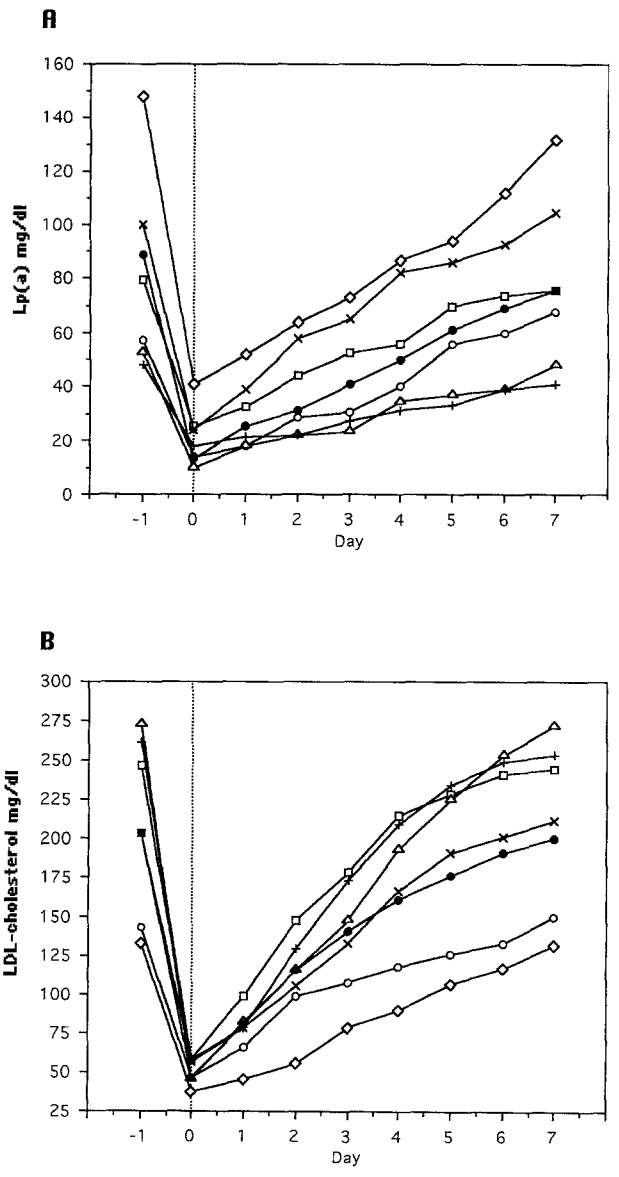

Fig 3. Rate of return for (A) Lp(a) and (B) LDL-cholesterol during 2 apheresis treatments for each individual patient with FH and elevated Lp(a) values (n = 6) and 1 patient without FH but seriously elevated Lp(a) and LDL-cholesterol before LDL apheresis. 0, Lp(a) and LDL-cholesterol values obtained at the end of LDL apheresis; 1-7, Lp(a) and LDL-cholesterol values determined on the days following apheresis treatment.

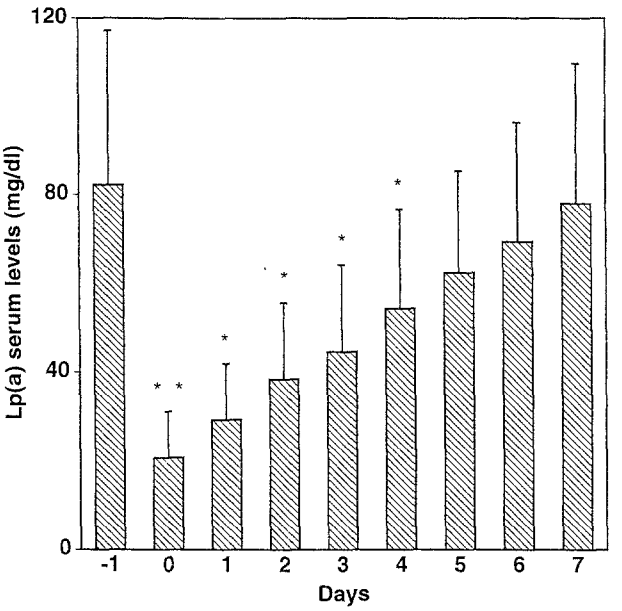

Fig 4. Mean Lp(a) values obtained between 2 LDL-apheresis treatment sessions in patients with elevated Lp(a) pretreatment values (n = 7). −1, Lp(a) value before LDL apheresis; 0, Lp(a) values obtained at the end of LDL apheresis; 1-7, Lp(a) values determined on the days following apheresis treatment. Values are means ±1 SD; **$P < .001$; *$P < .01$.

value, $P < .01$; day 2, 38.4 ± 17.2 mg/dL, ie, 46.8% ± 7.9% of the pretreatment value, $P < .01$; day 3, 44.6 ± 19.6 mg/dL, ie, 54.1% ± 8.9% of the pretreatment value, $P < .01$; Fig 4).

Lp(a) remained significantly below pretreatment values until day 4 after initial LDL apheresis (day 4, 54.3 ± 22.4 mg/dL, ie, 66.5% ± 8.6% of the pretreatment value, $P < .01$; Fig 4). At day 5 and 6 after initial treatments, Lp(a) concentrations were not significantly different from that obtained before apheresis treatment (day 5, 62.4 ± 22.9 mg/dL, ie, 77.5% ± 13.0% of the pretreatment value; day 6, 69.4 ± 26.9 mg/dL, ie, 85.5% ± 11.7% of the pretreatment value). The mean daily recovery rate in Lp(a) after the initial LDL apheresis was 10.1% ± 5.6% (range, 7.3% to 12.4%; Fig 4).

The total amount of Lp(a) was measured in the waste obtained during desorption (glycin phase) of the columns in 31 treatments. Patients with elevated serum Lp(a) values (n = 7) demonstrated a higher Lp(a) concentrations of the column waste (1,420 mg ± 380 mg; plasma desorbed during treatment [n = 14], 5,670 ± 480 mL; preapheresis serum Lp(a) levels obtained for these procedures, 63 ± 22 mg/dL) as compared with patients with normal Lp(a) serum values (235 ± 190 mg, $P < .001$; plasma volume desorbed during treatment [n = 17], 5,730 ± 520 mL; preapheresis serum Lp(a) levels obtained for these procedures, 6.9 ± 7.6 mg/dL, $P < .001$).

Coronary angiography was performed in all patients before and during long-term LDL-apheresis treatment. For patients (n = 7) with high Lp(a) values, regression of coronary atherosclerosis was observed in one patient and cardiovascular disease remained stable in three patients, whereas progression of disease occurred in two.

One patient with homozygous FH had no angiographic signs of CAD before LDL apheresis and remained without CAD

during the 8 years on treatment. For the other nine patients with FH [Lp(a) values within the normal range [ie, <30 mg/dL] maintained on long-term LDL apheresis, repeated coronary angiography exhibited regression of coronary atherosclerosis in four patients. Cardiovascular disease remained stable in a further four patients, whereas progression of disease occurred in one of these patients. The patient with selective elevation in Lp(a) died 6 months after the initial LDL apheresis due to a further myocardial infarction.

With the exception of local complications due to the venovenous approach in 5% of the treatments, no side effects were observed during long-term LDL-apheresis treatment.

DISCUSSION

The influence of Lp(a) on atherosclerotic vascular disease is still a matter of dispute. However, Lp(a) has been suspected to be the main discriminating factor for future cardiovascular disease in patients with familial hyperlipidemia.[3,13,54-56] This view is supported by the observation that among patients with high Lp(a) levels, clinical events have been shown to occur predominantly in association with persistently elevated LDL-cholesterol levels (40%), whereas only 10% ($P < .05$) of these patients had cardiovascular events when LDL-cholesterol levels were within the normal range.[9,57] Thus, elevated Lp(a) levels might contribute to the clinical outcome in patients with homozygous or serious heterozygous familial hyperlipidemia maintained on long-term LDL apheresis. The high efficacy of different systems of LDL apheresis in patients with FH recently has been demonstrated by the LDL-Apheresis Atherosclerosis Regression Study (LAARS) investigators[54,55] and by the Lipsorber Study Group.[42]

The present study was mainly concerned with the therapeutic efficiency of Lp(a) removal by LDL apheresis evaluated during initial (n = 7) and long-term treatments scheduled at weekly intervals in patients with elevated Lp(a) levels. Initial lipoprotein values were obtained in these patients either at onset of apheresis treatment (n = 2) or after a period without apheresis treatment of 3 weeks (n = 5). Comparison of the highest Lp(a) levels found in these patients before apheresis treatment were comparable to that determined at study entry [highest Lp(a) levels, 90.7 ± 35.6 mg/dL; range, 53 to 148 mg/dL; Lp(a) at study entry, 82.1 ± 25.9 mg/dL; difference not significant).

Reduction of elevated Lp(a) levels (−72%) by a single LDL immunoadsorption was comparable to the removal rate for LDL-cholesterol (−70%). This reduction in lipoproteins exceeds that reported for the heparin-induced extracorporeal LDL-precipitation (HELP) system.[40] This difference is due to the limited plasma volume of 3,000 mL that can be treated by the HELP system, whereas the immunospecific device allows an unlimited volume of plasma to be processed.[38-44,52,53] Similar reduction rates during a single apheresis session for LDL-cholesterol and Lp(a) were achieved for our patients maintained on immunoadsorption as compared with that reported for the LAARS population treated by dextran sulfate cellulose columns.[54,55] However, long-term LDL apheresis with treatments scheduled at weekly intervals, as prescribed in the study population presented (48 to 50 treatments/year), resulted in a more pronounced reduction in Lp(a) pretreatment values of 54% as compared with the 19% reported by the LAARS investigators.[54,55] These different results are due to different study populations and to the biweekly treatment intervals, which additionally resulted in a much less reduction of time-averaged Lp(a) values in comparison to LDL-cholesterol.[54] Bambauer et al[47] described a similar reduction rate in Lp(a) serum values in two patients with heterozygous FH during LDL apheresis using the Liposorber system (−44.4%) and the immunoadsorption procedure (Lipopak; −55.9%). This difference in Lp(a) reduction as compared with that achieved for our patients is due to the smaller plasma volume desorbed by each single procedure (4,100 ± 1,000 mL *v* 5,700 ± 500 mL). An additional two patients with homozygous FH maintained on the Liposorber system have been described by Fadul et al.[48] In this study, the investigators described a similar recovery rate of serum Lp(a) as compared with the seven patients presented in our study. Recently, Angelin discussed the few studies on Lp(a) reduction during LDL apheresis.[49] He concluded from the few data available that Lp(a) reduction achieved by extracorporeal procedures[42,54,58] does not show a specific advantage, but is beneficial when lowering LDL-cholesterol levels substantially in patients with elevated Lp(a) and LDL.

Besides removal of Lp(a) during LDL apheresis, the potential therapeutic efficacy is mainly dependent on the reappearance of Lp(a). Our results demonstrate an increase in Lp(a) following apheresis treatment that is comparable to that determined for LDL-cholesterol (Fig 3 and 4). Similar LDL-cholesterol kinetics following apheresis treatment have been recently published.[38,44,48,53]

Besides the reported increase in Lp(a) serum concentrations during HMG-CoA reductase inhibitor treatment,[56,57] an increased rebound of Lp(a) after apheresis has been suspected.[54,58-60] Although all of our patients studied received lipid-lowering drugs to delay LDL-cholesterol increase after LDL apheresis,[38] we did not obtain any significant difference in the Lp(a) and LDL-cholesterol kinetics between two treatments scheduled at weekly intervals. Thus, the observed differences in Lp(a) kinetics as compared with the regression studies might be mainly due to the different treatment intervals instituted,[54,55,58-60] resulting in a more pronounced effect of HMG-CoA reductase inhibitor treatment on LDL-cholesterol metabolism and enhanced synthesis of Lp(a) within the 2 weeks without LDL-apheresis treatment.[56-58] As LDL apheresis did not reduce Lp(a) preapheresis values to the normal range in patients with seriously altered Lp(a) metabolism, the recovery rate exceeded extracorporeal removal by the plasma volume desorbed.

In particular, for the patient without FH but seriously elevated Lp(a) (Fig 2 and 3A), reduction of Lp(a) pretreatment levels to the normal range could not be achieved by LDL apheresis at weekly intervals, although Lp(a) was reduced to 14.9 ± 10.4 mg/dL by each single subsequent treatment. As the values of Lp(a) obtained after LDL apheresis were comparable in patients with mild to moderate and seriously elevated Lp(a) values, the different metabolism of this lipoprotein and/or redistribution from tissue stores might be responsible for the different Lp(a) pretreatment levels.

Patients with elevated Lp(a) pretreatment levels demonstrated a higher mean reduction in Lp(a) during each LDL-

apheresis session (−72%) as compared with patients with Lp(a) values within the estimated normal range. The lower efficacy of Lp(a) reduction in patients with normal Lp(a) concentrations is largely due to methodical limitations to precisely determine values less than 1 mg/dL as obtained in the serum after LDL apheresis in patients with low Lp(a) pretreatment values.[9] However, an efficient therapeutic reduction of Lp(a) levels by LDL-apheresis treatment is only expected in patients with elevated Lp(a) levels.

As most of the patients reported were concerned by seriously complicated CAD, coronary angiographic data were evaluated for patients with and without elevated Lp(a) values. Due to the limited institution of LDL apheresis, the total number of patients was low within both groups. However, the clinical course of CAD was remarkably different. Patients with elevated Lp(a) values had a lower rate of regression and a higher frequency of progression of CAD than patients with Lp(a) levels within the estimated normal range. This observation is in line with several reports suggesting enhanced Lp(a) values further increase the risk of CAD in patients with FH.[1,3,4,9,11,13] Hence, high serum Lp(a) appears to be a potent predictor of restenosis in subjects after PTCA[61] and after femoropopliteal PTA[62]; this fact has to be considered in particular in apheresis patients, with their high incidence of vascular complications necessitating different interventions besides lipid-lowering treatment.

In conclusion, our study shows that LDL immunoapheresis is capable of therapeutically reducing elevated serum Lp(a) values, which results in markedly attenuated pretreatment levels when the procedure is performed at weekly intervals. In view of the suggested association of Lp(a) and an advanced risk of vascular complications, in particular in patients with FH following intervention with PTCA or PTA, extracorporeal lipid-lowering interventions might become a therapeutic option for elimination of this lipoprotein.

In patients maintained on long-term LDL apheresis, reduction in Lp(a) seems to be at least in part responsible for the beneficial outcome reported for these patients.[38,54,55,57-59]

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