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The incidence of cardiovascular events is largely reduced in patients with maximally tolerated drug therapy and lipoprotein apheresis. A single-center experience

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Abstract

Aim: Lipoprotein apheresis (LA) is the elective therapy for homozygous and other forms of familial hypercholesterolemia (FH) and familial combined hypercholesterolemia (FCH), resistant/intolerant to lipid lowering drugs, and hyperlipoproteinemia(a) for which drugs are not available.

To assess the effect of LA on the incidence of adverse cardiac or vascular events (ACVE) at the time period of pre-initiation of apheresis and during the LA treatment.

Methods: We collected data of 30 patients (mean age 62 ± 8 years, males 73%), with FH, or FCH and cardiovascular disease on maximally tolerated lipid lowering therapy and LA treatment (median 5 years, interquartile range 3–8 years). Associated hyperlipoproteinemia(a) was present in 16/30 subjects. The LA treatment was performed biweekly as clinically indicated by dextran-sulfate or heparin-induced LDL precipitation apheresis.

The ACVE incidence, before and after treatment, was evaluated by statistical analyses.

Results: The ACVE incidence occurred before and after the LA treatment inception, were 86 and 15 events respectively. Notably, 6/15 of ACVE were secondary to stent restenosis and 7/15 follow-up events occurred during the first 5 years. The AVCE rates/year were 0.58 and 0.13 respectively ($p < 0.001$).

Conclusions: Our data confirm long-term efficacy and positive impact of LA on morbidity in patients with FH and FCH and atherosclerotic disease at maximally tolerated lipid lowering therapy.

Keywords: Lipoprotein apheresis; Familial hypercholesterolemia; Lp(a)-hyperlipoproteinemia; Cardiovascular events

1. Introduction

Lipoprotein apheresis (LA) is the elective therapy for homozygous (Ho) or other forms of familial hypercholesterolemia (FH) and familial combined hypercholesterolemia (FCH), resistant/intolerant to lipid lowering drugs, and hyperlipoproteinemia(a) for which drugs are not available [1–3]. Since the pioneering attempt made by De Gennes and Thompson, the ability of LA as rescue therapy for the Ho-FH is definitely established [1,2,4] and documented by numerous reports, so as its efficacy is well described in refractory forms of FH/FCH and hyperlipoproteinemia(a). However, reports on the LA effects on the incidence of cardio-cerebrovascular events are spare and heterogeneous [2,5–7].

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In the present work we aimed at analyzing the incidence of adverse cardiac or vascular events (ACVE) in a cohort of patients treated by LA and suffering from severe forms of inherited hypercholesterolemia. Despite the existence of guidelines [8] on this issue, specifically on the classic FH forms, the imperative to best treat the familial forms of hypercholesterolemia to halt/prevent ACVE must be taken into account whatsoever the specific gene defect is [9,10]. FCH besides FH, with or without hyper-Lp(a), was included as well into the analyses.

2. Methods

2.1. Patients

Thirty patients (mean age at the first LA was 62 ± 8 years, males 73%) with FH or FCH, with or without hyper-Lp(a), affected by cardiovascular disease and on maximally tolerated lipid lowering therapy, have undergone LA. Associated Lp(a)-hyperlipoproteinemia (defined as >60 mg/dl) was present in 16/30 (53%) subjects. The clinical characteristics of the patients are summarized in Table 1.

No relevant comorbidity – diabetes mellitus, arterial hypertension, current smoking exposure, renal failure – was present in any patient, except for cardiovascular complications; the specific patients' therapy is summarized in Table 2.

2.2. Lipoprotein apheresis

Selective LA procedures were performed according to guidelines [2,3] and manufacturer's instructions with bi-weekly inter-apheretic interval. According to the patients characteristics (biocompatibility for LA systems, concomitant ACE inhibitors/ARBs therapy, etc.) [11] two different LA systems were used: dextran-sulfate absorption from plasma (Liposorber®-LA systems; Kaneka, Osaka, Japan) in 18/30 (60%) patients and heparin-induced LDL precipitation apheresis (HELP®, Plasmat Futura®; B. Braun, Melsungen, Germany) in 12/30 (40%) [12].

Table 1
Clinical characteristics of patients.

	Patients (*n* 30)
Mean Age	62 ± 8
Males	22/30 (73%)
BMI (kg/m^2)	26 ± 3
Former smoker	11/30 (37%)
Heterozygous familial hypercholesterolemia	17/30 (57%)
Familial combined hypercholesterolemia	13/30 (43%)
Concomitant Lp(a)-hyperlipoproteinemia	16/30 (53%)
Age at first cardiovascular events (years)	44 ± 8
Time between first cardiovascular event and beginning of apheresis (years)	11 ± 8
Age at beginning of apheresis (years)	54 ± 9
Duration of apheresis treatment (years)	5 [3–8]

Table 2
Patients' medications.

	Patients (*n* 30)
Lipid lowering therapy	30/30 (100%)
Statins	22/30 (73%)
Fibrates	9/30 (30%)
Ezetimibe	10/30 (33%)
Antiplatelet agents	30/30 (100%)
β-Blockers	23/30 (77%)
Calcium channel blockers	12/30 (40%)
Nitrates	8/30 (27%)
Angiotensin II receptor blockers	7/30 (23%)
Angiotensin-converting enzyme inhibitors	6/30 (20%)
Diuretics	4/30 (13%)
Vitamin K antagonists	4/30 (13%)

By LA therapy, lipids were heavily reduced after each single treatment without reaching the basal level after one week, as illustrated in Table 3.

Cardiovascular death, non-fatal myocardial infarction, coronary bypass surgery (CABG), percutaneous coronary intervention (PTCA), cerebrovascular accidents, and peripheral vascular events were included into the definition of ACVE. The incidence of ACVE was retrospectively evaluated before and during the course of LA treatment, as reported in Table 4.

2.3. Statistical analysis

Data were expressed as mean ± standard deviation, median and interquartile range or proportions, as appropriate. Comparisons were performed with paired sample t test, Wilcoxon test or Chi-square test with continuity correction. All computations were done with R statistical software (R, version 2.11.1, 2010; R Development Core Team 2006, R Foundation for Statistical Computing, Vienna, Austria). A value of $p < 0.05$ was considered significant.

3. Results

The median of LA treatment was 5 years (interquartile range 3–8 years). Coronary artery disease was diagnosed at the age of 44 ± 8 years and 11 ± 8 years before starting chronic LA. At the first LA, 27/30 (90%) patients had a previous coronary revascularization (11 CABG, 10 PTCA/stenting, 6 both), 16/30 (53%) a previous myocardial infarction, 7/30 (23%) abdominal aortic aneurysm, 4/30 (13%) peripheral arterial disease, 3/30 (10%) heart failure, 3/30 (10%) rest angina, and 3/30 (10%) had a previous cerebrovascular accident.

Eighty-six ACVE were observed before and 15 during the course of LA treatment. We noted that 7/15 (47%) follow-up events occurred during the first 5 years, 2/15 (13%) between 6 and 10 years, and 6/15 (40%) after 10 years (Fig. 1). Furthermore, 6/15 (40%) follow-up ACVE

Table 3
Lipids values before, immediately after and at 1 week after a typical LA treatment.

	Pre-LA	Post-LA (% reduction)	1 Week after LA (% reduction)
Total cholesterol (mg/dl)[a]	256 ± 58	69 ± 15 (−73%)**	224 ± 62 (−13%)**
Triglycerides (mg/dl)[a]	157 ± 66	55 ± 48 (−65%)**	145 ± 73 (−8%)#
HDL cholesterol (mg/dl)[a]	48 ± 11	34 ± 10 (−29%)**	48 ± 15 (−0%)
Apo A-1 lipoprotein (mg/dl)[a]	143 ± 25	124 ± 19 (−13%)**	142 ± 25 (−1%)
LDL cholesterol (mg/dl)[a]	175 ± 57	24 ± 13 (−86%)**	152 ± 57 (−14%)**
Apolipoprotein B (mg/dl)[a]	135 ± 36	27 ± 6 (−80%)**	122 ± 34 (−10%)#
Lp(a) (mg/dl)[b]	113 [90–131]	14 [12–23] (−88%)**	81 [60–132] (−28%)**

**$p < 0.001$ respect to pre-LA values; #$p < 0.01$ respect to pre-LA values.
[a] Data are expressed as mean ± SD in 30/30 patients.
[b] Median [interquartile range] in 16/30 patients with Lp(a)-hyperlipoproteinemia

Table 4
Adverse cardiovascular events (ACVE) in the 5 years before LA start and during LA treatment.

	ACVE prior to LA (*n* 86)	ACVE during LA (*n* 15)
Cardiovascular death	0/86 (0%)	2/15 (13%)
Non-fatal myocardial infarction	33/86 (38%)	5/15 (33%)
Coronary bypass surgery	7/86 (8%)	0/15 (0%)
Percutaneous coronary intervention	29/86 (34%)	6/15 (41%)
Cerebrovascular accident	8/86 (9%)	2/15 (13%)
Peripheral vascular events	9/86 (11%)	0/15 (0%)

were secondary to stent restenosis and not imputable to the progression of atherosclerotic disease, 5/15 (34%) were non-fatal myocardial infarctions, 2/15 (13%) were cardiovascular deaths occurring in the first year of LA in patients with rest angina before starting LA, and 2/15 (13%) were transient ischemic cerebrovascular accidents occurring in patients with a prior cerebrovascular accident prior to first LA.

LA significantly reduced the AVCE rate/year from 0.58 before LA to 0.13 after LA start ($p < 0.001$) (Fig. 2).

4. Discussion

LA is considered the standard of care for patients with homozygous familial hypercholesterolemia or in subjects with severe dyslipidemia [3]. Drawbacks of LA include limited availability, procedure duration and permanent vascular access [11,13]. Despite those limitations, a marked improvement in the patients' health is evidenced by the significant ACVE reduction and consequent lower health care expenses to treat new events [6]. The literature on this issue is necessarily anecdotal due to the small sample in each report. This is one main reason to share each center's experience.

Our data confirm the long-term efficacy and the positive impact of LA on morbidity in patients with familial hypercholesterolemia [6,14,15] (even when combined with Lp(a)-hyperlipoproteinemia), affected by atherosclerotic disease and at maximally tolerated lipid lowering therapy.

Associated Lp(a)-hyperlipoproteinemia was present in 53% of patients. This condition is considered to play an independent active causal role in vascular inflammation/atherothrombosis [16], and usually is underestimated in patients with cardiovascular manifestation [17,18]. The extracorporeal elimination of Lp(a) by LA is associated with an effective ACVE reduction and with stabilization of the progression of this disease [5]. This could be an additional reason, besides LDL reduction, explaining why our results appear so impressive. These, as in other similar reports, strengthen the vision very clearly argued by D. Steinberg for a earlier and a more aggressive treatment of

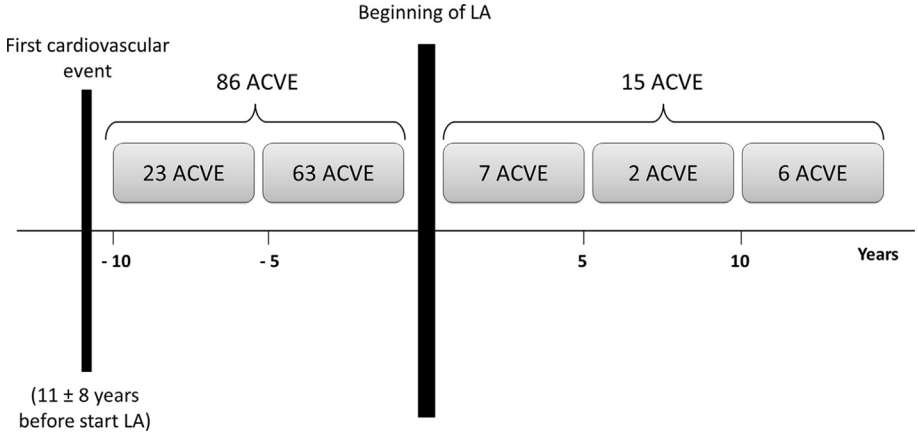

Fig. 1. Time course of adverse cardiovascular events (ACVE).

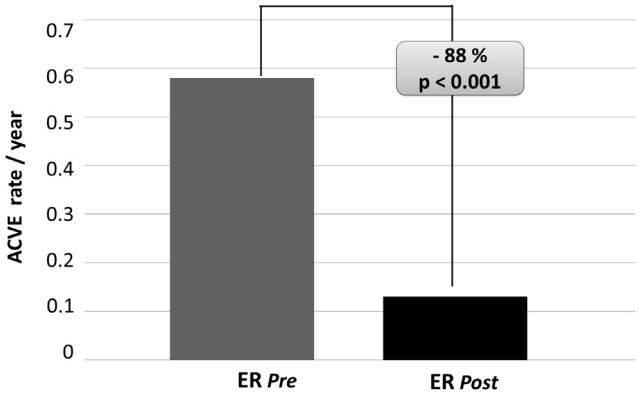

Fig. 2. Adverse cardiovascular events (ACVE) rate/year pre-LA *versus* post-LA, ER events rate.

hypercholesterolemia, since the magnitude of lipoprotein reduction mirrors the protective effect on cardiovascular mortality and morbidity; while with statins they have been reduced by ∼30%, with LA the reduction can be higher indeed.

Unfortunately, not only is LA an underused therapy even for those patients for which it is indicated but, still today, familial hypercholesterolemia may not be recognized in patients treated with coronary revascularization [19]. In this particular subgroup, the focus of treatment should be, instead, on the lipid disorder and not on its vascular manifestations [9,20]; a similar approach could avoid new ACVE, as well as their potential complications. LA can be regarded as a reasonable and effective therapeutic option in this clinical setting.

5. Conclusions

In patients who were treated at our apheresis center LA was an attractive therapeutic option in severe dyslipidemia with coronary heart disease. LA reduces atherosclerotic morbidity and the incidence of major cardiovascular events in FH and FCH, even when they are associated with elevated Lp(a) levels. In general, by applying LA in high-risk patients, costs for treating cardiovascular diseases can be saved.

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Conflict of interest

No conflict of interest for any authors.

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