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Lipoprotein-apheresis in familial hypercholesterolemia: Long-term patient compliance in a French cohort

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HIGHLIGHTS

- An as high as 87.5% compliance with Lipoprotein Apheresis (LA) is found in severe FH.
- Main causes of missed procedure are holidays and/or concomitant illness.
- The frequency of treatment is the only determinant of low-compliance.
- Patients having more than 2 LA/month have a 3-fold increased risk of low-compliance.
- Cardiovascular history and genotype are not associated with low-compliance.

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ABSTRACT

Background and aims: Lipoprotein apheresis (LA) is a complex therapeutic option and poor compliance can adversely affect treatment outcome. The aim of this study was to describe long-term compliance to treatment in patients undergoing regular LA therapy and to investigate factors related to low compliance.

Methods: We analysed 11,391 prescribed procedures of LA performed between 1990 and 2007 in 51 patients with familial hypercholesterolemia. Regular LA treatment was initiated in patients presenting with either homozygous familial hypercholesterolemia (n = 21), or severe heterozygous familial hypercholesterolemia (n = 30) with elevated LDL-cholesterol levels and who did not respond adequately to diet and drug therapy; the majority of these patients (n = 30) had cardiovascular disease at initiation of therapy.

Results: The overall observed compliance rate based on the number of achieved/programmed procedures was 87.5%. Neither cardiovascular history nor subtypes of hypercholesterolemia was associated with compliance. In addition, there was no impact of patient demography on compliance. Treatment frequency alone significantly impacted non-compliance (i.e. patient with weekly procedures were less compliant). Interestingly, a non-significant decrease in compliance was observed among patients aged < 20 years.

Conclusions: Despite the complexity of the LA procedure and its impact on the organisation of patients' daily lives, overall compliance was very high. The choice of an appropriate and adequate frequency of treatment significantly impacted patient compliance.

1. Introduction

Familial hypercholesterolemia (FH) is an autosomal dominant

genetic disorder, resulting from mutations in genes encoding the low-density lipoprotein (LDL)-receptor, the apolipoprotein B (Apo-B), and the pro-protein convertase subtilisin/kexin 9 (PCSK9) [1]. The reduced

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number or the absence of functional LDL-receptors on hepatocytes, results in a decreased uptake of LDL-cholesterol (LDL-C) particles from the plasma leading to elevated plasma LDL-C concentrations. In FH, the lifelong arterial exposure to elevated LDL-C results in cholesterol accumulation in arterial wall leading to premature atherosclerosis and cardiovascular events [2]. The heterozygous form of familial hypercholesterolemia (heFH) is one of the most frequent genetically-determined metabolic disorders in the general population with an estimated prevalence between 1/200 and 1/250 [3]. Without lipid-lowering therapy, patients with heFH, have a 13-fold increase in cardiovascular risk [4]. However, even in the statin era, cardiovascular (CV) mortality rates remain more than double in heFH patients as compared to those in patients without FH [5]. Homozygous hypercholesterolemia (hoFH) is rare (1/160,000 to 1/300,000) but severe [6,7]. Indeed, children with hoFH develop premature CV in the first or second decade of life and often die suddenly before 30 years in the absence of treatment.

Familial hypercholesterolemia is characterised by high baseline LDL-C concentrations and a significant proportion of patients with severe FH does not reach treatment goals, remaining at increased risk for cardiovascular disease (CVD) [5,8]. The available drugs are often insufficient to achieve the recommended LDL-C goal, which makes the medical management of severe cases of FH challenging. Lipoprotein apheresis (LA) was developed as a rescue therapy for the treatment of severe refractory FH [9,10]. Current guidelines recommend LA treatment, where available, for the large majority of homozygous FH patients, which should be started by the age of 5 and no later than 8 years [11–13]. In France, LA is recommended in heFH patients when LDL-C levels remain very high despite maximum tolerated lipid lowering therapy, ie. > 300 mg/dL in primary prevention or > 200 mg/dL in secondary prevention [14].

LA is a complex therapeutic option and poor compliance can adversely affect treatment outcome. Few data are available on long-term compliance with LA.

The aim of the present study was to evaluate the long-term compliance of regular apheresis therapy in a large cohort of patients with severe FH.

2. Materials and methods

In the present study, we analysed 11,391 LA procedures performed between January 1990 and December 2007 in fifty-one patients displaying severe FH who underwent LA in the Apheresis Centre at the Pitié-Salpêtrière University Hospital. Diagnosis of FH was made by

genetic analysis or clinical criteria (the DLCN score for heFH and the EAS criteria for hoFH).

The apheresis method was selected according to age, pre-apheresis LDL-C levels, individual medical history, duration of treatment and history of allergy. Each patient was monitored (heart rate, blood pressure and O₂ saturation monitoring) during the entire procedure. Levels of plasma total cholesterol (TC), lipoprotein (a) (Lp(a)), high-density lipoprotein-cholesterol (HDL-C) and triglycerides were measured and LDL-C was calculated according to Friedwald formula, before and immediately after each session for each patient.

During LA treatment, standard heparin (Heparin Immuno, Baxter-Immuno, Vienna, Austria) or a combination of heparin and acid citrate dextrose (Whole blood system; ACDA, Baxter, Munich, Germany) was used for systemic anticoagulation. The treatments were performed using a peripheral venous vascular access (occasionally via an arteriovenous fistula) at a blood flow rate of 50–80 ml/min. The blood volume to be treated was individually calculated for each patient.

The frequency of sessions was determined for each patient as a function of genetic profile and the evolution of plasma LDL-C levels between treatments; sessions were typically scheduled every 2–3 weeks, or every 7–10 days in patients displaying a more severe phenotype. Compliance was calculated as the percentage ratio of actually performed procedures on the theoretical number of expected procedures per patient.

The reasons for lack of compliance were collected from patients' files.

Informed consent was obtained from each patient included in the study and the study was performed in accordance with the recommendations of the Declaration of Helsinki.

2.1. Statistical analysis

Data are reported as mean $\pm$ standard deviation (SD) for continuous parametric and median (Interquartile Range-IQR) for continuous non-parametric variables, and as frequency (percentage) for categorical variables. Normality of continuous variables distribution was tested using Kolmogorov-Smirnov test. Differences between groups were evaluated by ANOVA for parametric variables, Mann-Whitney for non-parametric variables. Distribution of categorical variables between groups was evaluated using the χ^2 test. Correlations between two variables were assessed using a linear regression model and Pearson's correlation coefficient (r) was provided. For the multivariate logistic regression analysis, study population was stratified according to median compliance (88%) and classified as compliant/non-compliant

Table 1
Main characteristics of study population, stratified according to genotype.

	Whole population (n = 51)	HoFH (n = 21)	HeFH (n = 30)
Demographics			
Age, years	41.4 (24.6–58.3)	25.2 (19.3–28.5)	57.0 (45.4–62.2) ^a
Gender, males n (%)	27 (52.9)	9 (42.9)	18 (60) ^a
FH and LLT history			
Age at LA initiation, years	23.6 (11.4–49.1)	13.5 (5.6–19.4)	46.3 (35.3–53.0) ^a
LA frequency, n	1.9/month	2.4/month	1.5/month
Follow-up duration, years	9.52 $\pm$ 5.4	11.4 $\pm$ 5.9	8.0 $\pm$ 4.5
Statin intolerance, n (%)	1 (1.9)	–	1 (3.3)
Cardiovascular events			
Overall, n (%)	30 (58.8)	10 (47.6)	19 (63.3)
Coronary artery disease, n (%)	27 (52.9)	8 (38.1)	19 (63.3) ^a
Carotid artery disease, n (%)	3 (5.8)	2 (9.5)	1 (3.3)
Peripheral artery disease, n (%)	2 (3.9)	1 (4.8)	1 (3.3)
Aortic valve replacement, n (%)	6 (11.7)	4 (19)	2 (6.7)

HoFH, homozygous familial hypercholesterolemia; HeFH, heterozygous familial hypercholesterolemia; LLT, lipid lowering treatment; LA, lipoprotein-apheresis; LDL-C, low density lipoprotein-cholesterol.

^a $p < 0.05$ versus HoFH.

Table 2
Lipid profile before and after lipoprotein apheresis.

	Pre-LA	Post-LA	% Acute reduction	% Interval mean
LDL-C, mg/dL	223.3 ± 25.6	53.1 ± 8.9	(-76%)	(-21%)
Triglycerides, mg/dL	81.8 ± 10.3	29.2 ± 4.5	(-64%)	(-17.4%)
HDL-C, mg/dL	39.0 ± 3.0	33.2 ± 2.8	(-15%)	(-4%)

LA, lipoprotein apheresis; LDL-C, low-density-lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol. Interval means were calculated according to the following formula: $0.73 (\text{Lipid}_{\text{pre}} - \text{Lipid}_{\text{post}}) + \text{Lipid}_{\text{post}}$ [15].

accordingly. Compliance was further studied for its associations with CVD, frequency of LA, age at the beginning of treatment, genotype, sex (male = 1) and physical distance from the apheresis centre. Statistical analysis was performed using SAS® software and a *p* value < 0.05 was considered significant.

3. Results

3.1. Study population

The demographic characteristics of the study population are summarized in Table 1.

Apart from LA, all patients were on maximal tolerated lipid-lowering treatment (LLT), consisting of a high-intensity statin plus ezetimibe (added after commercialization in 2005). Only one heFH patient was not on statin therapy because of documented muscular intolerance.

Patients were treated with one of the following procedures: 24 patients by the DALI®-System, 24 patients by the Liposorber®-System and 3 patients by Double Filtration Plasma Pheresis (DFPP). The duration per treatment session varied from 2 to 4 h, according to the LA technique, to the volume of plasma processed and the rate of blood flow.

The mean % reductions in TC, LDL-C, triglycerides and HDL-C in all patients after a single LA procedure are reported in Table 2. The mean LDL-C after LA therapy was 53 mg/dl, corresponding to a 76% reduction, similar to that of ApoB (36.4 mg/dl post-LA, -75%); a higher than 50% acute reduction was also observed for triglycerides and Lp(a) (29.2 mg/dl and 10.5 mg/dl post-LA, respectively) and a small decrease (15%) was equally observed in HDL-C.

The mean decrease in LDL-C under lipid-lowering drug therapy in the hoFH patient group was 10–20% and 30–50% in heFH patients. A further 25–35% LDL-C reduction was obtained when regular treatment with LA was introduced. Such reductions in LDL-C were maintained over the long-term; further reduction in LDL-C (10–15%) was obtained

by addition of ezetimibe.

3.2. LDL-apheresis compliance

Overall, 11,391 LA procedures were accomplished out of an expected total of 13,021 over a period of 18 years, leading to a treatment compliance of 87.5%. In the whole population, 41 out of 51 patients (80.4%) had an adherence to the LA procedure above 80%, attaining 95% for 8 patients (16%) of the cohort (Fig. 1). Almost 20% of patients (*n* = 10) displayed poor compliance (< 80%).

Main causes of lack of compliance are shown in Fig. 2. The primary reasons for missed procedures were holidays and current illness or hospitalisation (31%), whereas 22% were unspecified. No differences in the reason for missed procedure were observed between hoFH and heFH patients.

Univariate analysis did not show any influence of previous CVD, genotype, gender and distance from the centre on the overall compliance.

Multivariate regression analysis showed that a decreased compliance with LA was associated with the frequency of LA procedures/month: patients undergoing more than 2 LA/month had a 3-fold increased risk of being low-compliant (Table 3). These associations were independent of age at first LA, CVD, genotype, gender and distance from the apheresis centre.

During the median 11.4 years follow-up, 4 patients died of major cardiovascular complications (3 hoFH, 1 heFH) and 2 patients (1 hoFH, 1 heFH) died of non-cardiovascular causes. Five patients suffered an event after the beginning of LA, 3 undergoing coronary angioplasty, 1 femoral stenting for peripheral artery disease and 1 left carotid thrombendarterectomy. Sixteen patients quitted the LA service, of which 12 continued LA treatment elsewhere and 4 were lost to follow-up.

Fig. 1. Distribution of lipoprotein apheresis compliance (%) in the study population.

Fig. 2. Main causes of low compliance (%).

Table 3

Determinants of low adherence to LA in the study population by multivariate regression analysis.

Dependent variable	Low compliance	
Independent variable	Multivariate ORs (95% CI)	p value
Intercept	0.145 (0.015–1.42)	0.0974
Age at first LA	1.051 (0.983–1.124)	0.1461
Sex (male = 1)	1.073 (0.515–2.235)	0.8503
CVD (yes = 1)	0.893 (0.412–1.936)	0.7743
Genotype (heFH = 1)	1.528 (0.546–4.277)	0.4196
Frequency (> 2 LA/month = 1)	3.594 (1.209–10.68)	0.0213
Distance (< 1 h drive = 1)	0.919 (0.472–1.792)	0.8049

Low compliance was defined as LA compliance lower than 88% (median LA compliance).

LA, lipoprotein-apheresis; CVD, cardiovascular disease.

4. Discussion

By analysing more than 10,000 LA procedures over 9.5 years in a cohort of 51 severe FH patients, we observed a high treatment adherence. Finally, the only significant factor associated with a low compliance was the frequency of LA procedures per month.

There are multiple reasons that can explain the high level of compliance. The first is patient-related: the awareness of the severity of the disease and familial involvement, notably the personal or family history of cardiac events may contribute to increase the motivation towards regular treatments. A second reason may arise from the fact that assistance-related: “door-to-needle” transport costs are fully covered by the French social insurance. This is in contrast with countries where financial reasons may explain treatment discontinuation [2]. A degree of flexibility in the LA agenda allows patients who cancel an appointment to obtain a new one in one to three days. Moreover, a trained nursing team is dedicated to these patients: films and cartoons are proposed to children to entertain them throughout the procedure. The same nurse looks after the same young patient over time to develop a personal relationship. A third reason is procedure-related: only a small number of mild side effects has been reported during LA treatments. Potential adverse reactions that have been associated with LA include, but may not be limited to, hypotension, nausea, abdominal discomfort, tingling, chest pain, vasovagal reaction and prolonged bleeding from anticoagulant. Anaemia, resulting from the procedure or from blood sampling, is also a risk which may be minimized by iron supplementation [14,16–18]. Severe, but very rare, adverse events including

an anaphylactic-like reaction have been reported in patients who were concomitantly treated with ACE-inhibitors [19]. In our cohort, the basic hemodynamic parameters are continuously monitored during the apheresis and the nursing team is trained to recognize any early signs of a bradykinin reaction, thus efficiently preventing the onset of any severe reaction.

Interestingly, despite these observations, a lower adherence was observed in patients with more than 2 LA procedures per month. The frequency of LA was the only significant factor affecting compliance. Only 78% of treatments were accomplished when sessions were performed weekly while 92% were achieved when LA was prescribed every three weeks. The treatment by LA is cumbersome and has incontestable consequences on the quality of life. Patients must organize one entire day consecrated to the procedures (including transport), and it is no surprise that the higher the frequency of procedures the lower the compliance. We analysed other predicting factors for non-compliance to LA. Surprisingly, we did not find any influence of age on the adherence to the LA treatment even in teenagers. We ranked patients by age categories and found that the 16-20-year-old patients had a 78% compliance to the treatment (vs 87% for the whole population) but that the difference was not significant, probably due to the small sample of patients. No direct influence of gender, neither the distance from the apheresis centre or the age at initiation were confirmed as determinants of low compliance. Also, the presence of cardiovascular disease in patients or siblings was not a factor influencing the compliance of the treatment. Genotype did not predict LA compliance, although the least compliant patients were those with hoFH undergoing weekly LA. Genotype was, however, confirmed as a predicting factor of TC, LDL-c, HDL-c and Lp(a) and a significant difference in lipid levels before LA was observed between hoFH and heFH patients (data not shown). This does not imply that a decrease in the frequency of LA would be beneficial for these patients: those who had more than 2 LA procedures per month were the most severe phenotypes, so an even higher frequency would be appropriate and adequate to address the severe condition. Also, the harm that may derive from a missed treatment has to be put in relation with the total number of procedures: the higher the frequency of LA the lower the impact of one missed procedure.

The number of missed procedures was surprisingly low: over 18 years of follow-up, as high as 87.5% of all prescribed procedures had been performed. This result was rather unexpected because LA patients have no apparent symptoms in comparison with dialysis patients and therefore we had thought that compliance would have been much lower. Patients treated by LA suffer from chronic disease and are likely to be non-compliant. Surprisingly, there is no data assessing compliance

or adherence with this prescribed procedure in such populations. Furthermore, assessing adherence is of major importance when discussing the number of procedures to be prescribed in a single patient. Poor adherence is considered a critical barrier to treatment success and premature discontinuation in such treatment may have dramatic consequences. This has been confirmed in several studies assessing compliance with drug treatment for CVD prevention [20,21]. As low adherence has been associated with increased cardiovascular outcomes, we would expect a low progression of CVD and CV mortality in our cohort.

Over the past 20 years, long-term follow-up of these patients revealed that, when apheresis is performed regularly, levels of LDL decreased to levels that cannot be obtained with drug therapy alone. Nonetheless, despite regular LA, a significant proportion of severe FH patients do not reach treatment goals or continue to develop significant atherosclerotic disease and consequently remain at increased risk for coronary events. We have recently shown that a residual risk of CVD is present in patients despite the ongoing intensive treatment: in a cohort of 53 patients treated with LA over maximally tolerated pharmacological treatment, a 100 mmol/L increase in cumulative total cholesterol was associated with a 2-fold increased risk of a cardiovascular event [8]. One of the main obstacles to lowering lifelong cholesterol exposure in LA treated patients has been the LDL-C rebound. Combination therapy of LA with statins and ezetimibe progressively reduced the magnitude of the post-apheresis rebound in LDL-C levels, although the type of LDL-R mutation significantly contributes to LDL-C rebound [22]. The reduction of other risk parameters such as other atherogenic lipoproteins (Lp(a), VLDL, TG), which are considered independent risk factors and act on inflammatory parameters (fibrinogen, C-reactive protein, blood viscosity ...), may have a complementary benefit and demand attention [23].

A residual risk is therefore still present in FH patients despite maximal therapy and these patients emphasize the need for intensive lipid-lowering regimen and new treatment options to further decrease LDL-C levels in order to provide superior benefits [24]. The recent commercialization of new therapies for hypercholesterolemia is very promising for a further reduction in CV mortality and optimization of cholesterol burden in FH patients [25,26]. A significant reduction in the frequency of LA treatment has been recently observed after the introduction of PCSK9-inhibitors in HeFH patients: 26 patients out of 41 treated by alirocumab could completely suspend LA, while overall 92.7% patients halved the LA frequency [27].

This study has several limitations. First, the number of patients was small as a result of the limiting criteria for LA. Consequently, results on adherence do probably reflect a selection bias: the acceptance of LA treatment itself represents an initial step towards higher adherence. Second, the reasons for non-attendance were given by the patients. We therefore cannot exclude the possibility that non-compliers provided a medical or non-medical explanation in order to justify a missed procedure. Third, we were not able to clearly identify whether non-compliers had a worse clinical outcome; such an analysis would be difficult because some patients might have stopped their treatment as a result of an event. Furthermore, the age at the beginning of treatment was not standardised. The number of patients treated with this combination is small and does not achieve the power and sample size required for a randomized controlled trial. Due to the severity of the disease, it is not ethical to perform randomized trials in FH patients.

In conclusion, this is the first study investigating the compliance of LA treatment which appears to be satisfactory in our cohort. The only parameter associated with low compliance was the frequency of the procedure. The good compliance observed in this study should be analysed in other groups in order to assess whether our results are generalizable.

LA in combination with drug therapy effectively reduces LDL-C levels. Together with all current available treatments, it might finally allow these patients to reach therapeutic LDL-C objectives, so as to

reduce the residual risk of CVD along with LDL-C levels both in primary and in secondary prevention.

Conflicts of interest

SB declares having received honoraria from Amgen, Sanofi; AG declares having received honoraria from AMGEN, Sanofi and Novartis; AC has received honoraria from Amgen SAS and Alexion Pharma France SAS, and is currently receiving a grant from Alexion Pharma France SAS; MJC declares having received honoraria from Amgen, MSD, Sanofi and Regeneron, Servier and Unilever; EB declares having received honoraria from AstraZeneca, AMGEN, Genfit, MSD, Sanofi and Regeneron, Unilever, Danone, Aegerion, Chiesi, Rottapharm-MEDA, Lilly, Ionis-pharmaceuticals; SS declares having received honoraria from Octapharma, Alexion, Terumo-bct, Agerion pharma, Sanofi; Remaining authors have nothing to disclose.

Author contributions

All authors contributed to conception, design, drafting and final revision and approval of the article. SB, AG, ED, SS provided to data collection and analysis; AC performed genetic analysis; RB provided lipid and biochemical profiling.

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