Lipoprotein Apheresis

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Combined with high Lp(a) levels, familial hypercholesterolemia (FH) leads to a greater CVD risk. In suspected FH patients, the proportion of cases explained by a rise of Lp(a) levels ranges between 5% and 20%. In the absence of a specific pharmacological approach able to lower Lp(a) to the extent required to achieve CV benefits, the most effective strategy today is lipoprotein apheresis (LA).

Keywords: lipoprotein(a), lipoprotein apheresis

1. Introduction

In the absence of a specific pharmacological approach able to lower Lp(a) to the extent required to achieve CV benefits, the most effective strategy today is lipoprotein apheresis (LA).

2. Lipoprotein Apheresis (LA) to Reduce Lipoprotein(a)

Although LA, within the therapeutic regimen of lipid disorders, is often considered as a therapy of last resort, guidelines differ in defining which patients to treat, and under which circumstances[1]. Some of these guidelines recommend apheresis as a first-line treatment in patients with HoFH, and after drug therapy failure in patients with heterozygous (He)FH, with differences also in LA treatment frequency (weekly or biweekly)[2][3]. LA is highly effective in reducing Lp(a) levels, i.e., approximately 57 mg/dL or 39% when comparing Lp(a) levels measured before the start of apheresis and the interval mean values during the apheretic procedure[4]. Currently, LA is mainly used in two different clinical settings, i.e., significantly elevated LDL-C or Lp(a). In patients with hyperlipoproteinemia(a), and on maximally tolerated lipid-lowering medications, LA seems to lower the progression of atherosclerosis, leading to a reduced number of CV events[5][6][7]. In the case of CV events, when comparing the time intervals from the start of LA to a similar time on no LA, LA may lead to a more than 80% risk-reduction[8][9][10]. Evidence from case studies showed that apheresis is more effective in patients with elevated Lp(a) levels when compared with those with normal concentrations[11]. Data from the Low-Density Lipoprotein Apheresis Coronary Atherosclerosis Prospective Study (L-CAPS) trial showed that intensive cholesterol lowering by apheresis prevented coronary atherosclerosis progression. The restenosis rate was 12.5% in the FH patients whose Lp(a) levels dropped more than 50%, compared to 53% in those with lesser Lp(a) reductions[12].

The European Atherosclerosis Society Consensus Panel recommended that Lp(a) levels should be reduced below 50 mg/dL in extreme cases by LA[13]. The HEART UK Guidelines recommended LA for patients on maximally tolerated lipid-lowering therapies and with progressive coronary heart disease and persistent elevations of Lp(a) > 60 mg/dL and LDL-C > 125 mg/dL (3.23 mmol/L)[14]. In Germany, Lp(a) levels exceeding 60 mg/dL, along with progressive CVD, were approved as an indication for regular LA in 2008 by the Joint Federal Committee. The American Society for Apheresis recommends the use of LA for the treatment of elevated Lp(a) (> 50 mg/dL) in CVD patients[15]. In the US, the Food and Drug Administration approved LA for HoFH patients with LDL-C > 500 mg/dL (12.92 mmol/L) (beginning in childhood), for HeFH with LDL-C >300 mg/dL (7.75 mmol/L) and no sign of CVD, or with known CVD and LDL-C > 200 mg/dL (5.17 mmol/L)[16]. In Japan, LA is approved for patients with CVD and total cholesterolemia > 250 mg/dL (6.46 mmol/L)[17]. As elsewhere reviewed in detail[18], available LA techniques are categorized as selective (immune adsorption, dextran sulfate adsorption, heparin precipitation, cascade filtration and polyacrylamide adsorption) or non-selective (plasma exchange; Table 1).

Table 1. Impact of different lipoprotein apheretic approaches on LDL-C and Lp(a) levels.

Lipoprotein Apheresis	Description	Reduction

Adsorption	DALI (*direct adsorption of lipoproteins*). Electrostatic interaction of negatively charged polyacrylate anions with positively charged apoB	LDL-C [1]: 53–76% Lp(a) [2]: 28–74%
	DSA (*Dextran sulfate-cellulose-based-adsorption*). Electrostatic interaction of negatively dextransulfate with positively charged apoB	LDL-C: 49–75% Lp(a): 19–70%
	IMA (*immunoadsorption*). Plasma is passed through columns containing polyclonal anti-apoB100 antibodies	LDL-C: 62–69% Lp(a): 51–71%
	Lipopac (*Lp(a) specific*). Plasma is passed through columns containing polyclonal anti-apo(a) antibodies	LDL-C: 7% Lp(a): 59–88%
Filtration	MONET (*Membrane Filtration Optimized Novel Extracorporeal Treatment*). Series of filters eliminate LDL and Lp(a) from plasma based on size properties	LDL-C: 52–62% Lp(a): 53–59%
	Lipid filtration. Series of filters eliminate LDL and Lp(a) from plasma based on size properties	LDL-C: 61% Lp(a): 61%
Precipitation	HELP (*Heparin-induced extracorporeal LDL precipitation*). Precipitation of a complex consisting of heparin, LDL, Lp(a), and fibrinogen at pH = 5.2	LDL-C: 55–61% Lp(a): 55–68%
Plasma Exchange	Although plasma exchange is still used in some centers, it is increasingly being replaced by selective LA, except when treating patients with severe hypertriglyceridemia[19]	

Variability among procedures relates partially to differences in the volume of plasma and blood treated. [1] LDL-C, low-density lipoprotein-cholesterol; [2] Lp(a), lipoprotein(a).

Briefly, the most commonly used LA systems share the specific adsorption of apoB, constitutive of VLDL, LDL and Lp(a). ApoB-containing lipoproteins are removed either by precipitation in the excess of heparin (HELP Braun) at acidic pH (5.2), or by the binding of positively charged apoB to the negatively charged surface dextran sulfate coupled to cellulose beads (DSA), or by apoB-immunoabsorption[20]. While removal efficiency differs among the systems[21], in FH patients all techniques rapidly remove LDL-C (55–70%) as well as Lp(a) mass (50–60%)[22]. Later publications by the same group indicated a higher removal rate[4]. However, the percentage changes reported in Table 3 reflect not only the intrinsic efficiency of each method in removing plasma lipoproteins, but also differences in the volume of blood or plasma treated and the extent of haemodilution caused by the anticoagulant used[23]. Typically, from 4- to 6-L exchanges of plasma are carried out for 2–4 h weekly or biweekly[24].

An inherent drawback of LA is the cyclical rebound of LDL-C within 1 to 2 weeks between apheretic procedures. Lp(a) rebounds at a slower rate than LDL-C, but with a similar monoexponential function[1]. Thus, despite an acute decrement of 70–75%, regular apheresis can translate into a significant interval mean Lp(a) reduction between 25% and 40%[25]. Specifically, depending on the Lp(a) baseline and the selected interval, a biweekly apheresis generally results in a much lower interval mean reduction (20%), compared to a weekly procedure (36%)[5][26]. This bulk of reduction also persisted in

patients undergoing long-term LA, wherein mean pre-apheresis levels of Lp(a) were reduced by 22% after 1 year, and by 19% after three years[27][28]. To reduce the lipoprotein rebound, one strategy is the use of lipid-lowering therapies in between the procedures. The effect of PCSK9 inhibition on the frequency of standard LA treatments was the focus of the ODYSSEY ESCAPE study[29]. Although LA was discontinued in 63.4% of patients on alirocumab and the rate was reduced at least 50% in 92.7% of patients, any additive effect of alirocumab on top of LA on Lp(a) levels was not found[30]. Santos et al.[31], in HoFH and severe HeFH patients, showed that long-term administration of evolocumab (over a median of 4.1 years) allowed 3 out of 34 HoFH, and 13 out of 27 severe HeFH, patients to discontinue LA. The DE LAVAL study showed that among patients on weekly or every-two-week LA and with a moderate- to high-intensity statin background, evolocumab led > 50% of patients to reach LDL-C < 68 mg/dL (1.76 mmol/L), demonstrating that evolocumab may, in these cases, replace LA[32]. Finally, the EVOLAFER01 trial enrolling HeFH patients on long-term LA therapy reported evolocumab to be superior to LA in reducing LDL-C and Lp(a), and that the combination of evolocumab plus LA could represent a therapeutic alternative to lowering LDL-C and Lp(a) levels in patients with very high CV risk[33]. However, these studies did not specifically address the lowering of Lp(a). Relative to real-life studies on long-term apheresis patients, the use of PCSK9 inhibitors seems unable to replace LA in 75% of patients, and in 45% of people with isolated hypercholesterolemia, thus pointing out the role of LA as a last resort lipid-lowering option[34].

From a clinical point of view, LA can also modify a number of pathological processes associated with CVD: it improves markers of vascular inflammation, and decreases fibrinogen, E-selectin, vascular cellular adhesion molecule-1, intercellular adhesion molecule-1, monocyte chemoattractant protein-1, lipopolysaccharide binding protein, matrix metalloproteinase and tissue inhibitor of metalloproteinase[35][36][37][38]. Among these effects, the most important one is the restoration of an effective myocardial blood flow induced by LA, well established many years ago[39] and recently confirmed[40], in clinical cases of refractory angina associated with raised Lp(a). Improvement of myocardial blood flow can be assessed, among other means, by Positron Emission Tomography (PET) and by echo-doppler sonography[41]. These hemodynamic effects are not far from those exerted by percutaneous transluminal coronary angioplasty (PTCA). This additional value attributable to Lp(a) apheresis in this condition makes this technique more impactful in cardiological practice. Furthermore, cardiac magnetic resonance imaging allows one to detect treatment-related changes in regional myocardial perfusion in patients with elevated Lp(a) (≥ 117 mg/dL) and coronary artery disease undergoing LA[42]. The possible application of selective Lp(a) apheresis also appears to offer a promising approach to the prevention of Lp(a) associated to CV risk. The specific immunosorbent column named ‘Lp(a) Lipopak’ (POCARD, Moscow, Russia) represents, so far, the most efficient LA able to selectively reduce Lp(a) levels by 88%, compared to pretreatment[43] (Table 1). In patients with ischemic heart disease, an 18-month application of Lp(a) apheresis reduced the diameter of stenosis (−5.05%) and total atheroma volume (−4.60 mm^3), and raised minimal coronary lumen diameter (+14%)[44]. Another crucial aspect worth mentioning is the ability of Lp(a) to bind and transport oxidized phospholipids (OxPLs) that represent a key component of the atherothrombotic risk associated with Lp(a)[45]. OxPLs are sequestered on Lp(a) and subjected to degradation by the Lp(a)-associated lipoprotein-associated phospholipase A2 (Lp-PLA2), suggesting that Lp(a) might be a scavenger of OxPL[46]. Upon LA, there is an acute reduction of Lp-PLA(2) (roughly −20%), an effect independent of LDL-C when LA becomes a chronic treatment. This could explain the potential mechanism by which LA reduces coronary heart disease risk[37].

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