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Lipoprotein apheresis: State of the art and novelties

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Abstract

Lipoprotein apheresis (LA) is an extracorporeal technique which permits the unselective or specific removal of lipoproteins, namely Low Density Lipoproteins (LDL), as well as other apolipoprotein B100-containing lipoproteins from plasma. LA represents a selective upgrade (with both clinical and metabolic advantages) from conventional forms of extracorporeal therapy such as plasma-exchange (PEX) which was used in the seventies to treat severe hypercholesterolemia. The primary reason for using is the treatment of homo-, double- (or compound) and heterozygous familial hypercholesterolemia (Hoz-, DHtz,- Htz,-FH). This technique has also been shown to be efficacious in the treatment of other severe forms of hyperlipoproteinemia such as: hyperLp(a)lipoproteinemia, the familial combined hyperlipoproteinemia and other varieties associated with an elevated cardiovascular risk (CVR) when used in patients who are poor- or non-responders to pharmacological treatment following specific guidelines for the reduction of cholesterol in plasma. Patients with these severe forms of dyslipidemia and, particularly, those affected by FH are subject to coronary ischemic events and thus require an intensive, efficacious, continuous, and personalized form of therapy. A therapy based solely on current available drugs does not achieve the desired results in the Hoz- and DHtz forms of FH or in approximately 10–20% of the Htz form. For the aforementioned clinical conditions, LA treatment offers a necessary therapeutic approach. LA can also be applied in the prevention of secondary recurrence of coronary ischemic events and of arterial stenosis which appears, rather frequently after vascular surgery (coronary by-pass, percutaneous transluminal angioplasty). Clinical trials have shown that statins provide a major reduction in cardiovascular morbidity and mortality, but often fail to attain desirable LDL-cholesterol target level in Hoz- and DHtz- (Compound) FH high cardiovascular risk patients. Intolerance to statins is also relatively frequent in Htz-FH and non-FH patients. LA has effectively replaced pharmacological cholesterol-lowering therapy for decades. Young high CVR risk patients survived to adulthood thanks only to LA. More recently, promising novel compounds aimed at other molecular targets are being studied for the treatment of severe dyslipidemia: Lomitapide, Mipomersen, PCSK9 inhibitors and HDL-enhancers. It is expected that these potent new agents will be combined with LA in the treatment of the most severe forms of hyperlipidemia.

Keywords: Lipoprotein apheresis; Severe hypercholesterolemia; Pediatric treatment; Lomitapide; PCSK9 inhibitors; Mipomersen; HDL-enhancers; Lipoprotein apheresis in pregnancy

1. Background

Lipoprotein apheresis (LA) is the obvious choice of treatment for Hoz-FH [1–3]. This procedure is safe when administered by trained personnel in appropriate environments and is used to significantly reduce plasma levels of total- and LDL-cholesterol (T-Chol, LDL-C). Comparing the various methods of treatment in patients affected by FH and those not affected, one can conclude the mean efficacy of reducing LDL-C utilizing the different methodologies is more or less similar (61.9% for immunoadsorptive LA (IMA-LA), 63.7% for dextrane sulphate cellulose LA (DSC-LA) and 60% or over for heparin lipoprotein precipitation LA (HELP-LA) [4–10]. Only the

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direct adsorption of lipids (DALI-LA) method showed a slightly reduced efficacy in reducing plasma levels of LDL when compared to IMA-LA and DSC-LA (77% *vs*. 82% and 84%, respectively) [11,12]. However, these comparisons must take into account the amount of whole blood or plasma being treated and the degree of dilution post-treatment. Large quantities of plasma or whole blood must be treated in the case of Hoz-FH with respect to patients afflicted by other forms of severe hypercholesterolemia but who have slightly lower LDL-C levels. Also of note is the volume of extracorporeal circulation in the single apheretic technique. Smaller volumes permit a greater flexibility in the use of the system and can be used in pediatric patients [13–15]. In patients affected by FH not undergoing pharmacological treatment, weekly LA treatment for 6 months did not substantially alter overall cholesterol; in fact, cholesteryl-esters stored in the tissues were not significantly depleted and/or mobilized in the short-term. On the contrary, a long-term continuous and adequate treatment (in relation to the interval between sessions and the processing volume) is necessary to mobilize a significant amount of cholesteryl-esters from tissutal, intracellular storages. A process called delipidation, which accounts for skin xanthomas, induced regression by LA after 1.5–2 years of appropriate treatment without interruption. After each treatment a transitory increase of mevalonic acid in plasma levels was noted in relation to "lanosterol/cholesterol" levels in patients who were treated with statins but not in those not undergoing statin therapy [16]. This contradiction is explained hypothesizing an increment of cholesterol synthesis in the presence of LDL-C of plasma under 1.56 mmol/L (60 mg/dL) which appears most frequently when apheretic treatment is performed simultaneously with statins, at least in Htz-FH subjects. LA does not stimulate the synthesis of apolipoprotein B (apoB) [17,18]. On the contrary, this synthesis is stimulated in patients undergoing "combined" treatments of LA plus atorvastatin (80 mg/day). Visible effects of LA treatment in Hoz-FH and DHtz-FH patients are evident in the appearance and extension of xanthomas (tendinous or cutaneous) and on xanthelasmas, which can be partially reduced after only 1.5–2 years of treatment and eliminated after 5 years of continuous treatment. In terms of LA effects on ischemic cardiopathy and cardiovascular atherosclerosis, Thompson et al. reported a study based on 5 sets of "monocorial" twins affected by Hoz-FH. In each case, only one twin was treated by apheretic means, while the other received no therapeutic treatment. Of the five sets of twins, only those who received LA survived while the others faced precocious cases of coronary atherosclerosis [19]. Another controlled study is the "Hokuriko Study" [20] in which 43 FH patients were treated with a combination of LA and lipid-lowering drugs compared to 87 FH patients treated only pharmacologically. Mortality rates were unchanged in each group; however fatal and non-fatal coronary ischemic events in those patients undergoing LA treatments were 72% lower than in the other group. The study in itself posed incongruencies at the moment of protocol application. T-Chol levels in the group undergoing apheresis were higher than in the other group; the group undergoing only pharmacological treatment had a higher instance of smokers; and, in addition, in this group the reduction of LDL-C was of 28% *vs*. 58% of that of the apheresis group due to the low doses of therapy administered. One certainty derived from this study is that a dramatic reduction of LDL-C led to a decrease of fatal and non-fatal coronary events. A meta-analysis of 8 coronary angiographic studies in patients who underwent at least 2 years of apheresis treatment compared the coronary atherosclerosis observed in these 8 studies (consisting of a total of 114 patients) with the results found in angiograms of 150 patients treated with statins and another 89 patients who remained untreated. Respectively, 18%, 33%, and 46% of patients in these three groups demonstrated an increase in atherosclerotic lesions while, at the same time, 82%, 67%, and 54% of patients in the three groups showed a stabilization or even regression of atherosclerotic lesions. In addition, small, recently developed instable coronary plaques showed a marked improvement in patients under apheresis compared to those undergoing statin and pharmacological treatment. In fact, intravascular ultrasounds showed a reduction in overall area of these plaques in patients undergoing LA and a worsening of the plaques in patients undergoing pharmacological therapy. Similarly, when myocardial perfusion and the IMT of the internal carotids are considered, the patients receiving LA treatment showed improvement over those patients treated solely pharmacologically [2]. Other favorable effects have been correlated to LA such as: the reduced susceptibility to the oxidation of LDL, the improvement of endothelial and hemorrhagic functions, the plasma reductions of Lp(a) and the procoagulatory pattern, the reduction of the molecules and inflammatory peptides involved in the adhesion and inflammation, and reduction of CRP. The changes in these "lipid-unrelated" parameters are observed solely due to the methodology used [21–33]. Improvement of hemorheological parameters has also been reported [32,33]. Most authors however, have suggested these characteristics associated with the use of LA should be considered pleiotropic or pleiotropic-equivalent effects. These effects surely have a favorable influence on the halt in progression or even the reduction of atherosclerosis; they appear at the instance of treatment and are independent in the reduction of plaque volume for which at least two years of continuous and intensive treatment is required [34–37]. Not entirely proven is the reduction of restenosis following PTCA (percutaneous transluminal coronary angioplasty) in patients treated with apheresis [38,39]. On the contrary, the reduction of vascular tone, and indirect levels of nitric acid (NO) in coronary and cerebral levels after a single apheretic treatment is well demonstrated. This same reduction was noted 4 months after initiating treatment; in fact, a 30%