Case Report

Lipoprotein Apheresis in the Treatment of Hyperlipoproteinaemia(A) with Progressive Cardiovascular Disease: Case Report and Review

Lia Ferreira1*, Maria Helena Ramos1, José Alexandre Queirós2, Anselmo Madureira2, João Silveira3, José Carlos Oliveira4, and Isabel Mangas Palma1

1Department of Endocrinology, Hospital Santo António - Centro Hospitalar do Porto, Portugal
2Department of Nephrology, Hospital Santo António - Centro Hospitalar do Porto, Portugal
3Department of Cardiology, Hospital Santo António - Centro Hospitalar do Porto, Portugal
4Department Clinical Pathology, Hospital Santo António - Centro Hospitalar do Porto, Portugal

Abstract

Elevated lipoprotein (a) (Lp (a)) concentrations are an independent and causal risk factor for premature atherosclerosis. Most scientific societies recommend Lp (a) measurement in patients with premature cardiovascular disease (CVD) and recently the European Guidelines on vascular disease prevention included Lp (a) determination in the extended screening of patients at moderate risk for CVD. We report a case of a 53-year-old woman with extreme high Lp (a) plasma concentrations and premature coronary disease, resistant to medical therapy and with favorable evolution after initiation of lipoprotein apheresis. Lipoprotein apheresis is a highly effective approach to lower Lp (a). Although it is an invasive, expensive, time-consuming approach and only available in specialized centers, it is a safe technique and currently is the only therapeutic option available for these high-risk patients.

ABBREVIATIONS

ACS: Acute Coronary Syndrome; Apo(a): Apolipoprotein (a); Apo (B): Apolipo protein B100; BMI: Body Mass Index; CVD: Cardiovascular Disease; CT: Total Cholesterol; DM: Diabetes Mellitus; EAS: European Atherosclerosis Society; HDL-c: High-density Lipoprotein Cholesterol; LDL: Low-density Lipoprotein; LDL-c: Low-density Lipoprotein Cholesterol; Lp (a): Lipoprotein (a); NYHA: New York Heart Association; PCSK9: Pro protein Convertase Subtilisin/Kexin Type 9; TG: Triglycerides

INTRODUCTION

Lipoprotein(a) (Lp (a)) is a unique lipoprotein particle comprising a composite structure of a low-density lipoprotein (LDL)-like particle and apolipoprotein B-100 covalently bound to an additional glycoprotein, the apolipoprotein (a) (apo (a)) [1]. The apo(a) chain contains five kringles and the fourth kringle (K-IV) is homologous to the fibrin-binding domain of plasminogen [2]. There are ten different types of K-IV sequences. K-IV type 2 is present in a widely differing number of tandem repeats in

LPA gene locus and this size polymorphism of apo(a) isoforms give rise to the extreme size heterogeneity in Lp(a) seen in the population [3-5]. Apo(a) is able to interfere with plasminogen activation, which inhibits thrombolysis [6]. By the LDL part Lp(a) it is potentially atherogenic, by the apo(a) part it is potentially thrombogenic. The apo(a) also confers several unique proatherosclerotic effects on endothelial cells, smooth muscle cells, monocyte and macrophages that are not related to homology to either plasminogen or LDL [7-12].

Plasma Lp(a) concentrations in the population vary in more than 1000-fold range (from < 0.1 to > 100 mg/dL). Up to 90 % of this variation is attributable to genetic factors largely confined to LPA, the gene encoding apo(a) [13].

Lp(a) was first described in 1963 by Berg, who found high serum levels of Lp (a) to be inherited and associated with an increased risk for premature atherosclerosis [14]. However, only recently, a series of large prospective epidemiological and genetic studies has firmly established elevated plasma Lp(a) concentrations as an important, independent, causal risk factor for cardiovascular disease (CVD) [15,16]. The Copenhagen City Heart Study demonstrated an increase in risk of myocardial infarction with increasing levels of Lp(a) and showed that patients with Lp(a) levels > 50 mg/dl have an two-to-tree-fold increased risk to suffer from myocardial infarction [17,18]. Kamstrup et al., found a causal association between Lp(a) K-V type 2 size polymorphism genotype, the resulting Lp(a) plasma levels and the incidence of myocardial infarction [19]. In a similar approach Kamstrup and collaborators found an association between elevated levels of Lp(a), the corresponding genotype and an increased risk for aortic valve stenosis, with Lp(a) levels of > 90mg/dl, predicting a threefold increase of the risk for aortic valve stenosis [20]. Lp(a) concentration has also been associated with the risk of peripheral arterial occlusive disease, cerebrovascular ischemia and calcific aortic valve disease [21-23].

While most scientific societies recommend Lp(a) measurement in all patients with premature coronary disease or premature stroke, they are prudent in the measurement of Lp(a) routinely for assessing CVD risk [24,25]. Despite all data establishing Lp(a) as an independent causal factor for the development of premature atherosclerosis, there are concerns about Lp(a) measurement for determination of cardiovascular risk. These concerns are related with the challenges in Lp(a) determination, the highly variable Lp(a) concentrations among different ethnic groups, the lack of intervention studies demonstrating that lowering Lp(a) reduces cardiovascular events and the lack of effective medications lowering Lp(a). For the first time, in 2016, the European Guidelines on vascular disease prevention in clinical practice included Lp(a) determination in the extended screening of patients at moderate risk for CVD [26]. Also the European Atherosclerosis Society (EAS) Consensus Panel recommended that Lp(a) should be measured in patients with premature CVD, familial hypercholesterolemia, a family history of premature CVD and/or elevated Lp(a), recurrent CVD despite statin treatment and patients with intermediate or high risk of CVD [15].

The consensus statement of the EAS considers Lp(a) concentrations below the 80th percentile (<50 mg/dl) as desirable [15]. Plasma Lp(a) concentrations have been found to be relatively resistant to dietary or other lifestyle interventions, as well as to classical lipid-lowering therapies such as statins and fibrates [27]. Niacin (nicotinic acid) reduces Lp(a) but is often poorly tolerated. Some of the lipid modifying drugs in development lower Lp(a) to some extent in addition to low-density lipoprotein cholesterol (LDL-c) reduction, but the only specific approach to reduce Lp(a) levels in investigation is the apo(a) antisense oligonucleotide [28,29]. Since lipoprotein apheresis lowers not only LDL-c but also Lp(a) significantly, its use is recommended in very high-risk patients with early or progressive CVD [30]. We report a case of a woman with extreme high Lp(a) plasma concentrations and premature cardiovascular disease, resistant to medical therapy and with favorable evolution after initiation of lipapheresis.

CASE PRESENTATION

A 53-year-old woman had been diagnosed with ischemic heart disease with moderate depression of ventricular function at the age of 46, after an acute coronary syndrome (ACS) in January 2011. Coronary angiography documented two-vessel coronary artery disease, proximal circumflex sub-occlusive stenosis and critical stenosis of the right coronary artery (small vessel and diffusely infiltrated) and angioplasty was performed with stent placement in the proximal circumflex.

She was a smoker (120 pack-years), with grade 1 obesity (BMI 34Kg/m²), hypertension, type 2 diabetes mellitus (DM) and dyslipidemia since the age of 25. She had no family history of premature ischemic heart disease or dyslipidemia. She presented poor control of cardiovascular risk factors despite medical therapy, including uncontrolled DM (HbA1c: 10%) and established microvascular complications namely diabetic retinopathy and peripheral neuropathy. Her dyslipidemia was not medicated and her baseline lipid profile was total cholesterol (CT) 174 mg/dl, LDL-c 102 mg/dl, triglycerides (TG) 66 mg/dl, high-density lipoprotein cholesterol (HDL-c) 59 mg/dl and apolipoprotein B100 (apo(B)) 94 mg/dl.

After the coronary event the patient medication was optimized and smoking cessation was encouraged. She was medicated with intensive insulin therapy, rosuvastatin 10mg, aspirin, clopidogrel, carvedilol, ramipril and ivabradine. Six months later she presented good glycemic (HbA1c 7.8%) and blood pressure control and the following lipid profile: CT 174 mg/dl, LDL-c 89 mg/dl, TG 117 mg/dl, HDL-c 56 mg/dl, apo(B) 180 mg/dl and Lp(a) 430 mg/dl. Therapy with nictinic acid 1g and laropiprant 20mg was instituted with initial Lp(a) reduction up to 409 mg/dl, but later increase to 529 mg/dl after one year of treatment. During this period her clinical condition deteriorated with progression to NYHA functional class III and several episodes of acute pulmonary edema. In February 2012 the patient suffered a second ACS due to circumflex stent restenosis and angioplasty was performed with good final angiographic result. Six months later the echocardiogram showed severe depression of ventricular systolic function and moderate-to-severe mitral
regurgitation. She was proposed to aortocoronary bypass and mitral valve replacement surgery, which were performed in February 2013. Genetic study for familial hypercholesterolemia with investigation of LDLR, APOB and proprotein convertase subtilisin/kexin type 9 (PCSK9) genes was negative, but apo(a) gene investigation is not yet completed.

Since her lipid profile proved to be refractory to medical therapy, nicotinic acid and laropiprant were suspended, rosuvastatin 20mg and ezetimibe 10mg were initiated and the patient was proposed for lipoprotein apheresis. She started lipoprotein apheresis biweekly in August 2012. The patient underwent a total of 120 treatments between August 2012 and April 2017, using the direct adsorption of lipoproteins (DALI) 750 technique with Fresenius Medical Care equipment. We achieved mean acute reductions of Lp(a) of 60.5% (min-máx 47.3 – 69.2%) and LDL-C of 76.4% (min-máx 52.8 – 83.3%) per session (Figures 1 & 2). The patient experienced three adverse events during lipoprotein apheresis treatments, namely an episode of hypotension, an episode of angina and one acute pulmonary edema, all promptly resolved. Since the beginning of lipopheresis the patient is in NYHA functional class II, without record of new cardiovascular events.

**DISCUSSION**

The treatment of elevated Lp(a) is troublesome because there are no effective medications lowering Lp(a). Plasma Lp(a) concentrations have long been considered resistant to therapeutic interventions, with exceptions being niacin and lipoprotein apheresis. Nicotinic acid (2–4 g/day) reduces Lp(a) levels in a

---

**Figure 1** Lp (a) plasma concentrations before and after LA. LA –Lipoprotein Apheresis.

**Figure 2** LDL-c plasma concentrations before and after LA. LA –Lipoprotein Apheresis.
dose-dependent manner, with reductions of approximately 20 to 40% and sustain effects throughout 2 years of treatment along with beneficial effects on LDL-c and HDL-c [31,32]. The major side effect of niacin is flushing but is attenuated with concomitant administration of laropiprant, an anti-flushing agent. However, since 2013 niacin is not available in Europe.

Lipoprotein apheresis is the only highly effective approach to lower Lp(a) by more than 50%. This extracorporeal technique utilizes binding matrices or filters to remove apo B100 containing lipoproteins from blood or plasma, namely LDL-c and Lp(a). A single treatment reduces both by about 60–70%, but the following increase is rapid, which requires weekly or biweekly treatments [33,34]. Guidelines of several countries recommend lipoprotein apheresis in very high risk patients to lower LDL-c in addition to maximal tolerated lipid lowering medication. Some countries also consider high levels of Lp(a) as an indication for lipoprotein apheresis in very high risk patients [30,35,36].

We reported a case of a young woman with high Lp(a) plasma concentrations and recurrent cardiovascular disease despite lifestyle interventions and oral lipid-lowering therapeutics, namely nicotinic acid. Our patient underwent a total of 120 lipopheresis treatments and achieved acutely reductions of Lp(a) in a range of 50 to 70% after lipoprotein apheresis treatments, which are similar to reports in the literature [30]. The overall incidence of adverse events was 2.5%, lower than reported by other authors [37,38]. The adverse events observed in our patient were a case of hypotension, probably caused by the initial transfer of blood to the extracorporeal circuit and resolved with intravenous fluid therapy; an episode of angina reversed by reducing flow rate and administering fluids, oxygen and nitrates and an episode of pulmonary edema reversed by reducing flow rate and administering diuretics.

In this patient, there were no cardiovascular events reported since the beginning of lipid apheresis treatment. Several retrospective studies have demonstrated a significant reduction on cardiovascular events with lipoprotein apheresis regular treatments as well as its safety in patients [39–41]. Safarova and co-workers carry out a randomized prospective trial and documented by angiography a significant regression of coronary atherosclerosis after 18 months of treatment with atorvastatin plus aselective Lp(a) lowering apheresis system [42]. The ProLiFe study, a prospective observational multicenter trial to study the effect of chronic lipoprotein apheresis on cardiovascular events in 170 patients undergoing LDL apheresis to lower Lp(a), demonstrated a reduction on incidence rates of cardiovascular events after two and five years of regular treatment [43,44].

There are new classes of therapeutic agents with some Lp(a)-lowering effect in investigation, such as apoB antisense oligonucleotides, apo(a) antisense oligonucleotides, microsomal triglyceride transfer protein inhibitors (lomitapide) and cholesterol ester transfer protein inhibitors [45]. The trials with PCSK9 inhibitors, involved in LDL-receptor degradation, have demonstrated that in addition to dramatically lowering LDL-C (up to 70 %), they also are able to lower plasma Lp(a) (up to 30%) [46–48]. This effect on Lp(a) is probably due to PCSK9 inhibitors capacity for modulating Lp(a) internalization via the LDL-R [49]. However, these therapeutic agents are still not available in our center.

This case shows the efficacy of lipid apheresis in reducing cardiovascular events along with its safety. Although it is an invasive, expensive, time-consuming approach, which requires weekly or biweekly treatments and is only available in specialized centers, currently there are no alternative therapeutic options for these high-risk patients. Therefore, Lipoprotein apheresis should be considered an essential and safe therapy for familial hypercholesterolemia or patients with very high Lp(a) levels.

REFERENCES

4. van der Hoek YY, Wittekoek ME, Beisiegel U, Kastelein JJ, Koschinsky ML. The apolipoprotein (a) ringle IV repeats which differ from the major repeat kringle are present in variably-sized isoforms. Human molecular genetics. 1993; 2: 361-366.
Apolipoprotein (a) gene accounts for greater than 90% of the variation in plasma lipoprotein (a) concentrations. J Clin Invest. 1992; 90: 52.


41. Von Dryander M, Fischer S, Passauer J, Müllerg, Bornstein SR, Julius U. Differences in the atherogenic risk of patients treated by lipoprotein apheresis according to their lipid pattern. Atheroscler Suppl. 2013; 14: 39-44.


