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Effect of specific lipoprotein(a) apheresis on coronary atherosclerosis regression assessed by quantitative coronary angiography

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Abstract

Aim: To evaluate the effect of specific lipoprotein(a) [Lp(a)] apheresis on coronary atherosclerosis progression in coronary heart disease (CHD) patients with elevated Lp(a) levels.
Methods: A total of 30 subjects (mean age 53.5 ± 8.3 years, 70% male) with CHD verified by angiography, Lp(a) > 50 mg/dL, and low density lipoprotein cholesterol (LDL-C) ≤ 2.5 mmol/L on chronic statin treatment were prospectively evaluated for 18 months. Patients were allocated to receive specific Lp(a) apheresis, which was carried out weekly with Lp(a) Lipopak® columns (POCARD Ltd., Russia) ($n = 15$), or atorvastatin only ($n = 15$). Blinded quantitative coronary angiography analyses of percent diameter stenosis and minimal lumen diameter (MLD) were performed at baseline and after the 18-month treatment period.
Results: By the single specific Lp(a) apheresis procedure, Lp(a) level decreased by an average of 73 ± 12% to a mean of 29 ± 16 mg/dL, and mean Lp(a)-corrected LDL-C decreased by 7% to a mean of 1.4 mmol/L. Median percent diameter stenosis was reduced by −2.0 (95% confidence interval [CI], −5.0–0.0) with apheresis ($p < 0.01$ in comparison with baseline), and increased by 3.5 (0.0–6.9) with atorvastatin ($p < 0.001$ between the groups). The effect on MLD was more favorable with apheresis than with atorvastatin: 0.20 ± 0.39 mm, as compared with 0.01 ± 0.34 mm, $p = 0.04$. Lp(a) apheresis had greater efficacy regarding the amount of regressed/stabilized coronary segments than atorvastatin alone in the majority of patients (chi-square test 13.61, $p < 0.005$).
Conclusion: Specific Lp(a) apheresis for 18 months produced coronary atherosclerosis regression in stable CHD patients with high Lp(a) levels and reached LDL-C goals.

Keywords: Lipoprotein(a); Lp(a) apheresis; Coronary atherosclerosis; Regression; Angiography; Plaque

1. Introduction

Although it has been known for 50 years, lipoprotein(a) [Lp(a)] has finally been acknowledged as an independent cardiovascular risk factor [1]. It was clearly demonstrated in the series of experimental, epidemiological, and genetic studies that this apolipoprotein B100-S–S-apo(a)-containing particle with atherothrombogenic properties is directly associated with coronary disease. But available therapeutic approaches are quite limited in this field, especially in patients with extremely high Lp(a) levels. No intervention trials have shown the causality of this relation, and no recommendations for Lp(a) reduction could be found in current guidelines. Studies of the effect of statins on Lp(a)

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levels show contradictory results at best, including reports of both decreases and increases of Lp(a) levels upon statin therapy. Nonetheless, it has been reported that statin therapy does prevent Lp(a) atherogenicity, with no documentation of this phenomena *in vivo*. Since 1981 several original systems for extracorporeal low density lipoprotein (LDL) elimination, called lipoprotein apheresis, have been designed. Comparisons of these systems were made in several reviews [2–4]. It should be mentioned that due to the close structural resemblance between LDL and Lp(a) particles, lipoprotein apheresis removes both lipoprotein classes from the blood. However, the number of Lp(a) particles in human plasma is significantly less than it is for LDL, even in cases with extremely elevated Lp(a) levels. With regard to Lp(a), technologies designed for removal of LDL are less selective for Lp(a), and eliminate Lp(a) from the blood on the basis of LDL/Lp(a) ratio. Specific Lp(a) apheresis is the only possible method that solely targets Lp(a) [5]. The usefulness, safety and efficacy of Lp(a) apheresis have been already shown in a clinical setting, representing a more specific potential than lipoprotein apheresis regarding Lp(a). This approach allows the most efficient elimination of the particle with a decrease of at least 88% of the pre-treatment Lp(a) level [6,7]. Later our columns were used in the UK [8], and in Germany for specific Lp(a) apheresis [9–12]. However the indication for the treatment of patients with Lp(a) excess is still under debate. Based on the hypothesis that Lp(a) excess has a detrimental role in atherogenesis, we evaluated the efficacy of specific Lp(a) apheresis on coronary atherosclerosis burden in patients with CHD on the background of optimal medical treatment.

2. Methods

2.1. Study design and population

This prospective, open-label, parallel-group, partially blinded clinical trial was performed at two centers: Cardiology Research Center, a federal state institution of the Ministry of Health, and MEDSI clinic, a private care hospital, both located in Moscow, Russia. The protocol was approved by the Institutional Ethics Committee, and written informed consent was obtained from all patients. Between September, 2009, and October, 2010, we enrolled men and women $\geq$18 years of age with stable CHD requiring a clinically indicated coronary angiography. Inclusion required at least one documented stenosis of $\geq$50% angiographic luminal diameter narrowing by visual estimation in any coronary vessel. All participants had an Lp(a) level of more than 50 mg/dL, and an LDL-C of less than 2.5 mmol/L on a statin therapy for more than one month before the enrollment. Patients were excluded if they had experienced: acute coronary syndromes within the prior three months; familial hypercholesterolemia; triglycerides (TG) $>$ 4.5 mmol/L; uncontrolled diabetes; hypertension; or heart failure; had renal or thyroid dysfunction; liver disease; or current treatment with other than statins lipid-lowering drugs. Individuals who needed urgent myocardial revascularization were not included. After a run-in period with open-label atorvastatin, a total of 30 eligible subjects were divided with an allocation ratio of 1:1 into two main groups for the treatment during 18 months which was followed by a second angiography. In the active group patients received apheresis procedures weekly with specific for Lp(a) immunosorbent columns. Patients from both groups received standard medical therapy in accordance with the recommendations for secondary prevention of CHD [13]. Basic lipid-lowering medication consisted of atorvastatin. There were no protocol-directed changes in medication; dose of atorvastatin could be titrated with the variation in LDL-C concentration $<$1.0 mmol/L for the whole study period from the initial visit.

2.2. Lp(a) apheresis

Lp(a) apheresis procedures were carried out weekly with Lp(a) Lipopak® columns (POCARD Ltd., Russia) according to the standard protocol [7,14]. Patients were connected via cubital venous catheter with a centrifuged type plasmaseparator (COBE® Spectra system, USA); plasma was then passed through immunoadsorption columns with sheep polyclonal monospecific antibodies against human apolipoprotein(a). For each patient, we used a pair of 200 mL columns, designed for personal multiple use. The total duration of a procedure was approximately 3 h in which 3–5 chromatography cycles were run in order to treat 5.5 $\pm$ 1.0 L of plasma. Anticoagulation was performed with unfractionated heparin.

2.3. Quantitative coronary angiography

All patients underwent selective coronary angiography according to a defined protocol as part of the entry criteria for patients to be enrolled in the study, and follow-up angiography was performed at the end of the study. After administration of intracoronary nitroglycerin (250 μg), standard angiographic images were obtained with the Philips Allura Xper FD10 cardiovascular X-ray system and recorded on a DICOM-formatted CD. During the baseline angiogram, the sequence of projections, the degree of axial rotation, the degree of cranial/caudal angulation, the type and size of catheter used were documented. A single operator performed all angiographic examinations. All films were read in one angiographic laboratory by two observers who were unaware of the treatment assignments. Measurements were performed at the end of the study, after both baseline and follow-up examinations were available. For the evaluation, the researchers used an American Heart Association 15-segment model [15] to score a coronary artery tree. Angiographic analysis neglected coronary segments with diameters smaller than 2 mm. Segments that