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Efficacy, safety, and tolerability of long-term lipoprotein apheresis in patients with LDL- or Lp(a) hyperlipoproteinemia: Findings gathered from more than 36,000 treatments at one center in Germany

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Abstract

LDL cholesterol (LDL-C) and lipoprotein(a) (Lp(a)) are main risk factors for cardiovascular disease (CVD).

Efficacy, safety, and tolerability of lipoprotein apheresis (LA) were investigated in 36,745 LA treatments of 118 patients with CVD in a retrospective, monocentric study. Indications were severe hypercholesterolemia (n = 83) or isolated Lp(a) hyperlipoproteinemia (n = 35). Average age of patients at start of LA treatment was 58.1 years for males and 62.5 years for females. Medium interval between the first cardiovascular event and LA treatment was 6.4 ± 5.6 years and the average LA treatment period was 6.8 ± 4.9 years. On average treatments were performed once a week, via peripheral venous access in 79.3% of non-hemodialysis patients.

In patients with hypercholesterolemia initial pre-LA LDL-C was lowered from 176.4 ± 67.0 mg/dL by 66.7 ± 10.8% per session, achieving a long-term interval mean value of 119.8 ± 34.7 mg/dL, i.e. reduction by 32.1 ± 19.6% ($p < 0.0001$). In patients with isolated elevated Lp(a) initial pre-LA Lp(a) was lowered from 127.2 ± 67.3 mg/dL by 66.8 ± 5.8% per session, achieving a long-term interval mean value of 60.0 ± 19.5 mg/dL, i.e. reduction by 52.8 ± 23.0% ($p < 0.0001$). After start of LA the average annual rate of major adverse coronary events (MACE) of all patients declined by 79.7% ($p < 0.0001$). Subgroup analysis showed decline by 73.7% ($p < 0.0001$) in patients with severe hypercholesterolemia, and by 90.4% ($p < 0.0001$) in patients with isolated elevated Lp(a). Adverse events (AE) occurred in 1.1% of treatments.

LA treatment of patients with high risk for CVD due to LDL and/or Lp(a) hyperlipoproteinemia was effective, safe, and well tolerated. The number of cardiovascular events, at least during a six-year period, declined by 80%.

Keywords: LDL cholesterol; Lipoprotein(a); Cardiovascular events; Lipoprotein apheresis

1. Introduction

LDL-C has been recognized as most important risk factor for coronary artery disease (CAD) for over thirty years [1]. Beginning with the 4S-study, it has been possible in numerous clinical trials with statins and related meta-analyses, to establish a clear link between lowering of LDL-C and reduction of cardiovascular event rates [2,3]. In recent years the equally atherogenic, thrombogenic, and inflammatory potential of Lp(a), which was first identified by K. Berg in 1963, has been established in epidemiological studies [4–8]. According to Ariyo, an increase in the

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Lp(a) level to 82 mg/dL is associated with an increase of CAD by the factor 3 [9]. After withdrawal of nicotinic acid in Europe in January 2013, there is no medication to significantly lower an excessively high Lp(a) level. Unlike with hypercholesterolemia, it was unclear for a long time whether Lp(a) level reduction would positively influence cardiovascular prognosis.

With LA treatment effective lowering of both LDL-C as well as Lp(a) by 60%–80% is possible during a single session. Systematic research in that field started with the publication of Thompson et al. in 1975 on the successful application of plasma exchange for the treatment of homozygous familial hypercholesterolemia (FH) [10]. Further observation showed that the long-term application of plasma exchange had a positive influence on the risk of atherosclerosis of coronary vessels and other vascular regions [11].

In the eighties and early nineties of the twentieth century in order to replace unselective plasma exchange, several selective LA methods were developed using physico-chemical principals of precipitation, filtration, and adsorption to remove only those substances from plasma or blood that cause atherosclerosis - in particular LDL-C and Lp(a) [12–16]. For all LA methods it has been shown for hypercholesterolemic patients that there was a long-term effect of improved lipid metabolism. In conjunction with hypothesized additional pleiotropic effects of LA rate of major adverse coronary events (MACE) of chronic LA patients is reduced by an average of 80% [17–19].

After encouraging observations of individual patients with isolated Lp(a) hyperlipoproteinemia, the results of LA treatment were published for this new indication in a multicenter, longitudinal cohort study with 120 patients [20]. Through an average reduction of the Lp(a) level by 36.3% from 117.9 mg/dL to 75.1 mg/dL with LA treatment, the per year and per patient MACE count could be significantly reduced from 1.06 to 0.14, i.e. a reduction of 86%. Due to methodological weaknesses in this study and considering cost of LA reimbursement a prospective study was stipulated. A randomized design of the study, which was initially suggested, was rejected by ethics committees in view of the favorable results of the retrospective study.

The multicenter study "Pro(a)LiFe" was published in September 2013. Here 170 patients were included matching the criteria for isolated elevated Lp(a) according to the German reimbursement authority Federal Joint Committee [21]. Over the course of two years of patient observation before and after commencing LA treatment, a medium reduction of the Lp(a) level was achieved from 104.9 ± 45.7 mg/dL to 70.9 ± 26.8 mg/dL, i.e. by 32.4%. The annual per patient MACE rate declined from 0.41 ± 0.45 to 0.09 ± 0.22 meaning a significant reduction of 78%. Overall, this prospective study was able to firmly underpin the results of the earlier retrospective study.

In Germany, LA is covered by regular reimbursement of statutory health insurance since 1991. Recognized indications include: "patients with homozygous familial hypercholesterolemia or patients with severe hypercholesterolemia, whose LDL-C could not be sufficiently reduced over a documented twelve month course of medication and prescribed diet." The comprehensive risk profile has to be considered for the indication of LA [22]. Since 2008, LA additionally has been recognized as a treatment for "patients with an isolated elevated Lp(a) level above 60 mg/dL and LDL-C within the norm, and concomitant progressive CVD (coronary, peripheral arterial, or cerebrovascular) as assessed and documented clinically and by imaging techniques."

Currently, more than 2000 patients are being treated in Germany within LA programs of about 300 medical centers. Indications are homozygous FH app. 6% of patients, severe hypercholesterolemia app. 64%, and isolated elevated Lp(a) app. 30% [23]. LA treatments should preferably be carried out in medical centers that practice apheresis treatments on a large scale (>500 per year) while maintaining an appropriate level of quality and entering treatment data into a national, or ideally even an international registry [24–28].

2. Patients and methodology

2.1. Study design, treatment location, and patient recruitment

A monocentric, retrospective, longitudinal cohort study was carried out at our medical competence center for apheresis, performing nearly 6000 LA treatments per year. All investigated patients were approved for chronic LA treatment according to the Guidelines of the Joint Federal Committee, following an initial and annually renewable application, due to the following diagnoses: severe hypercholesterolemia or isolated elevated Lp(a) with progressive CVD.

The observation period covered October 1996 to December 2013. Retrospective analysis of side effects was based on the complete archives of treatment records of all lipoprotein apheresis sessions of the center.

Following the examination of the study protocol by the Bavarian State Medical Association, a letter was received on January 21, 2014, which declared that the study could proceed and be published without the approval of an ethics committee, given that it was intended as a quality assurance measure for the clinical treatment of patients in our center.

2.2. Lipoprotein apheresis

Selective LA methods used within this study period were described in the literature and were performed according to the instructions for use supplied by manufacturers [26]. Methods were: heparin-induced LDL precipitation apheresis (H.E.L.P., Plasmat Futura: B. Braun, Melsungen, Germany), polyacrylate adsorption from whole