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Short Review
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LDL Apheresis and/or Human Monoclonal Antibodies as Treatment in Severe Dyslipoproteinemia

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INTRODUCTION

Patients suffering from severe dyslipoproteinemia, sometimes combined with elevated lipoprotein (a) (Lp(a)), and coronary artery disease (CAD) refractory to diet and lipid-lowering drugs have a bad prognosis. Since the introduction of lipoprotein-apheresis (LA), and the human monoclonal antibodies (HMA) all severe forms of dyslipoproteinemia can be successfully treated. Different LA systems and HMAs are available which reduce LDL-cholesterol, lipoprotein (a) (Lp (a)), triglycerides and others. There is a strong correlation between dyslipoproteinemia and atherosclerosis. Besides the elimination of other risk factors in severe dyslipoproteinemia therapeutic strategies focus on a drastic reduction of serum lipoproteins.

There are more than 10,000,000 people with familial hypercholesterolemia (FH) worldwide, mainly heterozygous; FH is one of the most common inherited disorders. Mutations along the entire gene that encode for LDL receptor protein are the most common FH cause. However, mutations in apolipoprotein B and protein convertase subtilisin/kexin type 9 genes produce this phenotype are also described [1]. High concentration of circulating LDL is usually combined with an increase in VLDL, which leads to a development of atherosclerosis, and in particular to CAD. Heterogenous FH has a frequency of 1: 500 may be closer to 1: 250 and the homozygous form a frequency of 1: 1,000,000 [2]. Genetic assessment helps to identify patients at risk for developing dyslipoprotenemia and for treatment decision based on “risk allele” profiles [3].

The largest endocrine, paracrine, and autocrine participant in the regulation of numerous homeostatic vascular functions is the vascular endothelium [2, 4]. Changes in hemodynamic forces such as pressure and shear stress as well as circulating and locally formed vasoactive substances released by blood cells are sensed by endothelial cells. These endothelial cells synthesize and release biologically active substances such as nitride oxide (NO), prostacyclin, endothelium-derived hyperpolarizing factor, endothelin, prostaglandin H2, thromboxane A2, heparin sulfate, transforming growth factor, vascular endothelial growth factor, basic fibroblast growth factor, platelet-derived growth factor, tissue plasminogen activator, plasminogen activator inhibitor-1, oxygen free radical, etc. [2]. All these factors together modulate vascular tone.

Hypertriglyceridemia is prevalent in 18.6 % of men and 4.2 % of women between the age of 16 and 65 and a positive correlation between elevated triglycerides (TG) blood levels and heart attacks has been established [2]. Increased TG are often accompanied by low HDL-cholesterol blood levels. High TG represent a useful marker for risk of CAD, particular when HDL levels are low. A cumulative insult to the vasculature resulting in more severe disease which occurs at an earlier age in large and small vessels as well as capillaries is caused in dyslipoproteinemia and hyperglycemias on endothelial function [5].

Lipoprotein (a), which is very similar to LDL is a further important atherogenic substance, and contains also Apo (a), which is very similar to plasminogen, enabling Lp(a) to bind to fibrin clots and become plague compounds in the walls of the arteries [2]. High Lp(a) concentrations are associated with an early occurrence of CAD and apoplectic insult [6]. If CAD is mainly primarily associated with Lp (a) concentrations or with the six different phenotypes (S4, S3, S2, S1 Band F) has not been determined. High Lp (a) are associated with CAD and patients with premature CAD showed the highest Lp (a) concentrations. Lp (a) is a major independent risk factor for atherosclerosis, increasing cardiovascular morbidity and mortality at a younger age [7].

The newer therapy concept is the proprotein convertase subtilisin/kexin type 9 with Evolocumab, as a fully HMA directed against PCSK9. Evolocumab regulates LDL receptor

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causing increased catabolism of LDL and the reduction of LDL and is higher than of Lp(a) blood concentrations. Evolocumab could reduce LDL of 53 % to 75% and Lp(a) to 39% in monotherapy or in combination therapies, and is associated with minor adverse effects [8,9]. The inhibition of PCSK9 with HMA is as effective as the regularly weekly or every two-week lipoprotein-apheresis. In the most severe cases both LA and HMA can be used alone or combined.

For all these patients with severe forms of hypercholesterolemia, reduction intake of dietary fats is advised. Various medications are available, such as cholestyramine, colestipol, β-pyrdylcarbinol, probucol, etc. With HMGCoA-reductase inhibitors, alone or in combination with other lipid-lowering drugs, an LDL reduction up to 50 percent of the original concentration can be reached. This appears to be sufficient in most cases. Numerous side effects like diarrhea, obstipation, other gastrointestinal diseases, myositis, rhabdomyolysis, and others were observed [2]. Before the LA is indicated in hypercholesterolemia, a maximum dietetic and medicational therapy is required. If this maximum therapy is failed or due to therapy intolerance, LDL cholesterol cannot be constantly held below 150 mg/dl, then LA is indicated. In patients with isolated Lp(a) higher than 60 mg/dL, normal LDL and a progressed cardiovascular disease the LA is indicated, too. All patients should be placed under cardiologic observation.

Lipoprotein apheresis methods

Cascade filtration (ASAHI Japan), membrane differential filtration, or lipid filtration is superior to conventional plasmapheresis but less effective than adsorption or precipitation techniques (10) (Table 1).

Immunoadsorption (IA) has sepharose columns coated with LDL antibodies or other antibodies. The LDL molecules in the plasma after primary separation are adsorbed in the columns onto the antibodies [11]. This is a reversible antigen-antibody bond accord based on the principle of affinity chromatography. Antibodies against the protein component of the LDL particles gained from sheep as heteroclonal sheep antibodies against apo protein B are covalently bound to sepharose particles. Before one column is saturated with the absorbed lipoprotein (600-800 ml plasma), the plasma flow is switched to the other column for LDL adsorption, and the off-line column is regenerated. The treated plasma is then mixed with the cellular components of the blood and returned to the patient [6]. After the treatment, the columns are rinsed and filled with sterile solution (Table 1)

Lipoprotein (a) apheresis is the most effective therapeutic method in lowering Lp(a) (Lipopak, Pocard, Russia). Two special immunoadsorption polyclonal antibody columns containing sepharose bound anti-Lp(a) are assigned to each patient for treatment. These columns are reusable [15] (Table1).

Table 1: Extracorporeal methods, human monoclonal antibodies and other drugs for elimination of LDL.

Year	Authors	Methods	Advantage	Disadvantage
1980	Agishi et al. [10]	Cascade filtration	Semi-selectivity	Expensive technology
1981	Stoffel et al [11]	Immunoadsorption	Selectivity, ef-fectiveness, regeneration, reusable	Expensive technology
1982	Seidel et al. [12]	Heparin-induced LDLprecipitation (HELP)	Selectivity, effectiveness	Expensive technology
1985	Nosé et al. [13]	Thermo-filtration	Selectivity, effectiveness	Expensive Technology, Not available
1987	Mabuci et al. [14]	Dextran sulfate LDL adsorption	Selectivity, effectiveness	Expensive Technology
1991	Pokrovsky et al. [15]	Lp(a) immune-adsorption	Selectivity, effectiveness	Expensive technology
1993	Bosch et al. [17]	LDL hemoperfusion (DALI)	Selectivity, effectiveness	Simple technology
2002	Klingel et al. [18]	Lipid filtration	Semi-selectivity	Expensive technology
2003	Otto et al. [20]	LDL hemoperfusion (Liposorber D)	Selectivity, effectiveness	Simple technology
2010	Kreuzer et al. [22]	Lipoprotein-filtration	Semi-selectivity	Expensive technology
1995	Grossmann et al. [23]	Lomitapide, Mipomersan	Low effectiveness	Unkown, not available
2014	Raal et al. [8]	Evolocumab	Selectivity, effectiveness	Unknown
2014	Gaudet et al. [24]	Alirocumab	Selctivity, effectiveness	Unknown

Heparin-induced LDL precipitation (HELP, Braun, Germany) in which after primary separation, the plasma is mixed in a ratio of 1:1 with acetate-acetic acid buffer (pH 4.8), so that the pH of this mixture is 5.1. Then 100,000 U heparin per litre are added to the buffer [12]. The plasma has been mixed then thoroughly with the acetate acetic acid buffer and heparin. LDL particles precipitate in the acid environment together with fibrinogen and heparin to form insoluble precipitates and these are the removed from the plasma by means of a polycarbonate membrane. The remaining free heparin is completely removed by a heparin absorber. The acidulous plasma is returned to a physiological pH value using bicarbonate dialysis, and the plasma, free of LDL, is returned to the patient´s blood [12] (Table1).

Dextran sulfate low-density lipoprotein (Liposorber, Kaneka, Japan), in which low-molecular dextran sulfate (MW 4,500) can selectively absorb all substances containing apolipoprotein B [14]. The dextran sulfate was selected as an affinity ligand of LDL adsorbent for its high affinity and low toxicity. The binding mechanism is the direct interaction between dextran sulfate and the positively charged surface of apolipoprotein B-containing lipoproteins (LDL, VLDL, and Lp(a). The dextran sulfate has a structure similar to that of the LDL receptor and seems to act as a type of pseudo receptor. Low of cholesterol the plasma and the blood cells are returned to the patient. The columns are reusable for use again [16] (Table 1).

The low-density lipoprotein hemoperfusion (DALI, Fresenius, Germany) uses a matrtix of polyacrylate beads. Whole blood is perfused through the adsorber, which contains 480 ml polyacrylate coated polyacrylamide, without regeneration. The column has a capacity of more than 1.5-2.0 blood volumes for effective adsorption of LDL, Lp(a), triglycerides etc. The hemoperfusion system is a simpler extracorporeal circuit, in which the blood is pumped through the LDL adsorber. The sponge-like structure of the beads offers a very large inner and outer surface for adsorption in which more than 99 % of the overall surface of over 1,000 m^2 is located within the beads [19] (Table 1).

Another whole blood LA system is the Liposorber D (Kaneka, Japan). On the basis of the technology of the dextran, it adsorbs all positively charged LDL, VLDL, and Lp(a) particles from whole blood using negatively polyanions. Liposorber D contains negatively charged dextran sulfate covalently bound to cellulose [20]. The negatively charged surfaces activate the intrinsic coagulation pathway. Coagulation factors XI and XII were reduced by dextran sulfate adsorption, but those coagulation factors returned to normal range within one or two days after the treatment [21]. Adverse events were hypocalcemia, during treatment caused by ACD-A solution; the symptoms disappeared by administration of calcium, and slight hypotension (Table 1).

The DALI- and the Liposorber system have a clear advantages over the usual LA systems that require plasma separation. These systems are simpler to handle, and the advantages are good selectivity, and effectiveness [6]. The DALI- and the Liposorber system are comparable.

Propertin convertase subtilisin/kexin type 9 is a sereine protease involved in cholesterol metabolism that is enzymatically inactive following secretion. The PCSK9is a proprotein convertase belonging to the subtilase subfamily [25]. In healthy humans, plasma PCSK9 concentration decrease with fasting and increase following meals [26]. Gain-of-function mutations in PCSK9 are associated with FH [25]. Loss-of-function mutations in PCSK9 are associated with reduced LDL concentrations and that these lifetime reductions confer substantial protection against CAD [27]. Concentrations of sterol regulatory element-binding protein-2 are increased by statin therapy, which thus also increases PCSK9 concentration. PCSK9 is a useful therapeutic strategy in hypercholesterolemia; PCSK9 is expressed predominantly in the liver, and to a lesser extent in the intestine and kidney in adults. The only known physiologically relevant function of circulating PCSK9 is to regulate receptor in the liver [28].

Human monoclonal antibody are target-specific antibodies created through recombinant DNA technology and exert their therapeutic action through a variety of mechanisms, including direct effect associated with the binding of the antibody to the target and indirect effects involving depletion of cells targeted by the HMA [2].

CONCLUSION

The LA techniques described here are all effective and well tolerated (6), With weekly or biweekly treatment, the average LDL concentration can be reduced to approximately 30-60 % and more of the original levels. LDL concentration increases again after each LA session. The increase after apheresis can be slowed down by lipid lowering drugs. The decrease of Cholesterol from 400 mg/dL to 200 mg/dL treatment could almost double a patient´s life expectancy. The LA treatment must be repeated in homozygous and severe heterozygous FH life-long or until other therapy technologies such as HMA or gene therapy are available for everyone. Not only LDL mass decreases but also it improves the patient´s life expectancy and performed with different techniques decreases the susceptibility of LDL to oxidation by LA. This decrease may be related to a temporary mass imbalance between freshly produced and older LDL particles [6].

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With LA and the HMA G2 (Evolocumab or Alirocumab) all severe hypercholesterolemia with cardiovascular disease are treatable. However, the indication of LA should be considered after a period of 12 months and refractory to diet and maximum lipid-lowering drugs only in Germany. The application of HMA could be easier in future if no antibody expression is found. The costs of PCSK9 inhibitor therapy amount approximately 9,650 Euro per year against the LA therapy costs of approximately 50,000 Euro in Germany. However, the number of patients with extremely elevated Lp(a) who need the extracorporeal therapy or the HMA- or gene therapy will increase. Larger studies must be showing which method the LA or the PCSK9 inhibition therapy would be preferred or a combination of both.

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