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Review

LDL apheresis in Japan

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ABSTRACT

LDL apheresis has been developed as the treatment for refractory familial hypercholesterolemia (FH). Currently, plasma exchange, double membrane filtration, and selective LDL adsorption are available in Japan, and selective LDL adsorption is most common method. LDL apheresis can prevent atherosclerosis progression even in homozygous (HoFH). However, in our observational study, HoFH who started LDL apheresis from adulthood had poor prognosis compared with patients who started from childhood. Therefore, as far as possible, HoFH patients need to start LDL apheresis from childhood. Although indication of LDL apheresis in heterozygous FH (HeFH) has been decreasing with the advent of strong statin, our observational study showed that HeFH patients who were discontinued LDL apheresis therapy had poor prognosis compared with patients who were continued apheresis therapy. These results suggest that high risk HeFH need to be treated by LDL apheresis even if their LDLC is controlled by lipid-lowering agents. However, by launching new class of lipid lowering agents, that is, PCSK-9 antibody and MTP inhibitor, indication of LDL-apheresis in FH may be changed near the future. LDL-apheresis can provide symptom relief of peripheral artery disease (PAD). Therefore, PAD patients who have insufficient effect by other therapeutic approach including revascularization are also treated by LDL apheresis. Thus, LDL apheresis is still one of good therapeutic options for severe atherosclerotic diseases in Japan.

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Contents

1. Introduction

Low density lipoprotein (LDL) apheresis, which depletes circulating LDL cholesterol (LDL-C) mechanically, has been developed as the treatment for refractory familial hypercholesterolemia (FH) patients.

FH is autosomal dominant disorder caused by a mutation in the gene encoding the LDL receptor. Patients homozygous for FH have severe hypercholesterolemia (600–1000 mg/dL), cutaneous and tendon xanthomas, and premature atherosclerosis [1].

The development of HMG-CoA reductase inhibitors (statin) has enabled effective treatment for most of heterozygous (HeFH) [2]. Indeed, the average age at coronary artery disease (CAD) onset was significantly higher after widespread use of statins compared to before October 1989 when statins were approved in Japan [3].

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However, patients homozygous (HoFH) are resistant to these drugs because statins reduce LDLC levels mostly via an increase in the number of LDL receptors in the liver. Therefore, LDL apheresis is the only practical method to control LDL levels in patients homozygous for FH and in some other types of severe hypercholesterolemia such as autosomal recessive hypercholesterolemia.

LDL apheresis is also effective for other disease such as peripheral artery disease (PAD) and focal segmental glomerular sclerosis (FSGS), a glomerular disease which causes refractory nephrotic syndrome. Therefore, LDL apheresis for these diseases is also covered by health insurance in Japan. Currently, plasma exchange, double filtration plasmapheresis, and LDL selective adsorption, are available as LDL apheresis therapy in Japan. Among them, LDL selective absorption is most popular method.

2. Method of LDL apheresis

The first trial of LDL apheresis in HoFH patients was performed as plasma exchange by DeGenne et al. in 1967 [4]. This therapeutic approach provided improvement of coronary artery stenosis, withdrawal of xanthoma accompanied with LDLC reduction. However, plasma exchange has disadvantage that various important substances such as immunoglobulin are removed along with LDLC. Therefore, today, plasma exchange is only used for FH patients aged ≪10 years who cannot be treated with LDL absorption because of small capacity of extracorporeal circulation.

The double membrane filtration (DFPP) and LDL selective adsorption are now widely used in Japan. The advantage of DFPP is the selective removal of macromolecules based on molecular weight and filter pore size. Initially, treatable plasma volume was limited in this procedure because of the increase in the membrane pressure. An improvement of the sieving properties, however, has enabled us to treat a larger plasma volume.

In 1980s, dextran sulfate-coated cellulose beads was proved a potent specific sorbent of apolipoprotein B-containing lipoproteins [5]. The early system of LDL absorption (LA-40 system) had large column (400 ml) using this sorbent. However, this system could not remove LDLC adequately, since the column was saturated if treated plasma volume was large. Currently, LDL-adsorption system (LA-15 system, Kaneka, Osaka, Japan) has two small columns whose volume is 150 ml. Each column is alternately reused during apheresis therapy by eluting adsorbed LDL on saturated column by 5% NaCl. This current system can treat large volume of plasma and reduce cardiovascular burden during apheresis therapy. Therefore, this system can be available for patients with cardiac dysfunction or small body mass, and today, LA-15 system is widely used all over the world. LDL absorption system promotes the production of bradykinin by activation of coagulation system since adsorption column has negative charge [6]. Therefore, it is important to note that patients who were received angiotensin converting enzyme inhibitor must not be treated with this system.

3. LDL apheresis for atherosclerosis

3.1. Mechanism of preventive effect on atherosclerosis

LDL adsorption therapy can remove not only LDL-C but also cell adhesion molecule such as intracellular adhesion molecule-1 and vascular cell adhesion molecule [7,8], fibrinolytic factor such as fibrinogen and plasminogen activator inhibitor-1 [9]. LDL adsorption also can remove inflammatory cytokine such as tumor necrosis factor-α and interleukin-1 [10], and reduce reactive oxygen species production via suppression of NAPDH oxidase [11]. These factors play a key role in the progression of atherosclerosis. Thus LDL adsorption can prevent atherosclerosis dependent and independent of LDLC removal. LDL adsorption therapy was also reported to improve vascular endothelial function via induction of bradykinin and nitric oxide production [12].

LDL apheresis also improves atherogenic lipid metabolism in addition to direct removal of LDLC. In patients of peripheral artery disease, oxidized LDL was removed by LDL adsorption and removal rate of oxidized LDL was associated with the improvement of walk distance [13]. We also found that small dense LDL-C which has strong atherogenic action was efficiently removed by LDL apheresis in FH patients. Furthermore, we reported that LDL apheresis could remove ApoC3 [14] which is an endogenous lipoprotein lipase inhibitor and promote atherosclerosis progression [15]. LDL adsorption could remove proprotein convertase subtilisin/kexin type 9 (PCSK9) [16,17]. PCSK9 play a pivotal role in lipid metabolism by enhancing endosomal and lysosomal degradation of LDL receptor in the liver [18]. In addition, PCSK9 is involved in inflammatory process by upregulating proinflammatory gene expression [19]. Thus, LDL adsorption has various anti-atherosclerotic effect as well as LDL-C removal.

3.2. LDL apheresis in FH

HoFH patients usually are started with LDL apheresis therapy at about 10 years old. Before LDL adsorption therapy, they are treated with plasma exchange therapy if possible. We investigated the long term effect of LDL apheresis in 8 patients with HoFH (observation period was 3–20 years.) (Table 1) [20]. Five patients started to be treated with LDL apheresis from childhood. Among these five patients, one was free from atherosclerotic disease, one revealed remission of atherosclerosis. Other three patients had supravalvular aortic stenosis or coronary artery stenosis, but atherosclerotic diseases in these three patients were relatively mild. On the other hand, three patients who started to be treated LDL apheresis from adult had severe atherosclerosis. Two of these three patients died from myocardial infarction, and one was carried out coronary artery bypass before initiation of LDL apheresis. Græsdal et al. also reported that patients who received LDL apheresis therapy from ≪10 years old revealed mild atherosclerotic change whereas two patients who started LDL apheresis at adult already had coronary artery disease before LDL apheresis initiation [21]. Thus, LDL apheresis should be initiated as early as possible in HoFH to prevent atherosclerotic disease progression. Although there is no international guideline of target LDLC level of LDL apheresis therapy, generally, LDL-apheresis is performed every 1–2 weeks, and LDL-C level after LDL apheresis is below 50 mg/dL in Japan.

Previously, some FH patients withdrew LDL apheresis for the financial burden even though they needed this therapy. After 2009, medical expense of Ho-FH is covered by publicly funded health care in Japan. Moreover, there are many medical setting which can perform LDL apheresis in Japan. Therefore, currently, Japanese Ho-FH patients can appropriately receive LDL apheresis. There are increased stresses on the cardiovascular system throughout pregnancy and delivery. Both blood volume and cardiac output increase by 25–80% [22]. The main point of concern has been the aggravation of coronary insufficiency of the mother, mainly due to these hemodynamic changes in pregnancy [23]. Therefore, during pregnancy, HoFH and HeFH with severe coronary artery disease should be treated by LDL apheresis to prevent further progression of coronary atherosclerosis and to tolerate the increased stress of delivery. In fact, our recent report of 7 FH patients with pregnancy showed that a patient who refused LDL apheresis during pregnancy and another patient whose adherence of LDL apheresis was poor died from acute myocardial infarction [24]. High lipid levels may also affect placental vasculature and cause retardation of fatal growth [25]. Therefore, in Japan, HoFH and HeFH with severe coronary artery disease are treated by LDL apheresis during the course of

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