Low-Density Lipoprotein Apheresis in Patients with Severe Familial Hypercholesterolemia Refractory to, or Intolerant of, Lipid-Lowering Drug Therapy: Preventing the Onset or Progression of Cardiovascular Disease

Katie D. Evans

Pacific University School of Physician Assistant Studies, Hillsboro, OR, USA

Introduction

Familial hypercholesterolemia (FH) is a genetic disorder of lipoprotein metabolism characterized by extremely high plasma concentrations of low-density lipoprotein cholesterol (LDLc), tendon xanthomas, and increased risk of premature cardiovascular disease (CVD). Worldwide, over 10 million people are currently afflicted with FH. If appropriate preventive efforts are not employed before the age of 65, approximately 85% of males and 50% of females will suffer a coronary event. LDL apheresis is an efficacious method of decreasing LDLc concentrations in patients with FH who are either refractory to, or intolerant of, pharmacologic therapy. LDL apheresis refers to the extracorporeal removal of circulating LDLc by plasma exchange or by more selective methods. Additionally, lipoproteins (LPs), triglycerides (TGs), high-density lipoprotein cholesterol (HDLc), and fibrinogen are eliminated to varying degrees. A typical apheresis treatment session is as follows: the patient is seated, both arms extended to gain bilateral antecubital area (PA), mean segment diameter (MSD), minimal obstruction diameter (MOD), mean percent diameter stenosis of atherosclerotic lesion (MSD, % DS), and secondary to CVD. Thus, the primary treatment outcomes of LDL apheresis are evidenced to be regression and/or retardation of coronary atherosclerosis. Usually safe and well-tolerated, LDL apheresis is not without its shortcomings. The mere delivery of apheresis treatment is limited by its expense, ranging from $2,000-$2,500 per treatment session. Moreover, there are estimated to be less than 50 treatment centers within the entire United States. Treatment time for the procedure may require up to four hours. Known side effects of apheresis are few, including fatigue and hypotension following a treatment cycle. Antithrombotic medications must be avoided on the day of the apheresis treatment, specifically angiotensin-converting enzyme (ACE) inhibitors, as increased bradycardia levels during the procedure may instigate severe hypotension. The frequency of, and need for, LDL apheresis depends on the response to treatment and the degree of hypercholesterolemia at baseline. The post-apheresis rebound in LDLc is determined by both the rate at which LDL particles are catalyzed and the rate at which they are produced. The rate of rebound LDLc reaches a plateau in FH heterozygotes in around 14 days and a similar plateau is reached in FH homozygotes in three to four weeks. A single treatment session with LDL apheresis reduces LDLc concentration 70-80% from baseline in both heterozygotes and homozygotes. LDLc promptly begins to rise following the procedure, necessitating repeat sessions at approximately seven to ten day intervals in patients with homozygous FH and two-week intervals in patients with severe heterozygous FH. With regular apheresis treatments, long-term decreases are produced in the LDLc levels both pre-treatment and post-treatment. In patients who derive even minimal benefit from lipid-lowering medications, diet and pharmacotherapy should be maintained to help reduce LDLc levels. Figure 1 depicts a stylized rendition of the effect of LDLc apheresis on LDLc levels over time. GRADE provides healthcare practitioners sufficient information for making well-informed decisions, and subsequent clinical actions, regarding LDL apheresis. This review assesses quality of evidence and strength of recommendations for the utilization of LDLc apheresis. This review assesses quality of evidence and strength of recommendations for the utilization of LDLc apheresis.

Purpose

This systematic review focuses on the efficacy of LDL apheresis to prevent the onset or progression of CVD in patients with severe FH who are refractory to, or intolerant of, lipid-lowering drug therapy. The following studies indicating the advantages of LDL apheresis on cardiovascular morbidity and mortality will be discussed: The Familial Hypercholesterolemia Regression Study (FHRS), the Japan Low-Density Lipoprotein Apheresis Coronary Atherosclerosis Morbidity Study (L-CAPS), the Low-Density Lipoprotein Apheresis Coronary Morphology and Reserve Trial (LACMART), and the LDL Apheresis Atherosclerosis Regression Study (LAARS). The Gradating of Recommendations Assessment, Development and Evaluation (GRADE) criteria will be applied to the four studies included in the review in order to assess the quality of evidence and strength of recommendations for the utilization of LDL apheresis.

Method

An extensive literature search was performed in October through November of 2010 using the databases of PubMed, Endotext, Science Direct, and the Journal of the American Heart Association. The key words searched included “low-density lipoprotein apheresis” and “familial hypercholesterolemia” individually and in various combinations. Exclusion criteria consisted of full text articles in the English language pertinent to LDL apheresis and its effect on cardiovascular disease risk factors and events. Exclusion criteria consisted of articles discussing the use of LDL apheresis in non-cardiovascular disease processes, articles older than 15 years, and study designs other than randomized, controlled trials, cohort and case control studies. In total, four articles pertinent to LDL apheresis and its effect on cardiovascular disease risk factors or events were selected for the current systematic review.

Results

From this review, practitioners can ascertain that LDL apheresis drastically improves markers of CVD, namely LDLc, total cholesterol (TC), Lp(a), minimal lumen diameter (LDM), mean lumen diameter (LMD), plaque area (PA), mean segment diameter (MSD), minimal obstruction diameter (MOD), mean percent diameter stenosis of atherosclerotic lesions (% DS), and substantially reduce risk factors for cardiovascular events in this high risk population. Another tendency may be to neglect lipid-lowering surgical procedures, namely partial ileal bypass surgery, portacaval shunt, and liver transplantation.

Conclusion

The risk of a coronary event in patients with familial hypercholesterolemia is extremely high. Therefore, the ability to delay the onset or slow the progression of cardiovascular disease would provide a significant benefit. LDL apheresis is an efficacious therapy to lipid-lowering drugs, demanding a vital role in the prevention of cardiac events through revascularization and stabilization of coronary plaque. In addition to patients suffering from severe FH refractory to, or intolerant of, lipid-lowering drugs, LDL apheresis may be beneficial for patients with CVD at high risk of acute coronary syndrome. The quality of evidence and strength of recommendation of LDL apheresis to arrest further progression of CVD and induce regression of atherosclerotic plaque in patients with FH is moderate. This recommendation holds true after the application of exhaustive criteria set forth by the Gradating of Recommendations Assessment, Development and Evaluation Working Group. Per the GRADE Working Group, with moderate quality of evidence further research is likely to have an important impact on the confidence in the estimate of effect and may change the estimate. For this reason, studies of longer intervention periods are warranted to confirm these findings and observe the expected angiographic regression of CVD.