Lipoprotein Apheresis

Patrick M. Moriarty, MD[a,*], Linda Hemphill, MD[b]

KEYWORDS

• Lipoprotein apheresis • Familial hypercholesterolemia • LDL-C • CVD • Atherosclerosis • Lp(a)

KEY POINTS

- Patients with familial hypercholesterolemia (FH) have early development of atherosclerosis and cardiovascular disease (CVD).
- Lipid level–lowering medications are not always successful in reducing increased low-density lipoprotein C (LDL-C) levels.
- Lipoprotein apheresis (LA) reduces LDL-C levels by more than 60% in patients with FH and reduces CVD events.
- LA also reduces lipoprotein (a) (Lp(a)) levels and CVD events.
- LA reduces inflammatory markers and blood viscosity.

INTRODUCTION

Apheresis, derived from the Greek word aphairein, meaning to take away, is applied to patients with familial hypercholesterolemia (FH) who are resistant to standard lipid level–lowering medications. Apheresis devices used for the reduction of plasma cholesterol levels can be separated into 3 general groups:

1. Nonselective plasma exchange, which simply removes all of the plasma volume through centrifugation, and was first introduced in 1967 by de Gennes and colleagues.[1]
2. Semiselective ultrafiltration, developed by Agishi and colleagues[2] in 1980, which uses a double-membrane filtration and involves elimination of atherogenic lipoproteins based on particle size and geometric properties.
3. Selective lipoprotein apheresis (LA), which was developed in 1981 by Stoffel and colleagues[3] using a device containing 2 columns of sapharose gel coupled with polyclonal sheep apolipoprotein B (apoB)-100 antibodies. Newer selective LA devices have been developed involving not only antibodies to lipoproteins but negative charged environments to capture the positive charged apoB. The devices approved for use in the United States and Canada are based on the removal of charged lipoprotein particles.

CRITERIA FOR LIPOPROTEIN APHERESIS

The US Food and Drug Administration (FDA) set the criteria for LA in 1997, when the Kaneka Liposorber and B Braun HELP (heparin-induced extracorporeal low-density lipoprotein precipitation) systems were approved in the United States based on the following criteria.

Patients must show that, after 6 months of the maximum tolerated lipid level–lowering therapy and compliance with a low-saturated-fat, low-cholesterol diet, one of the following is still met:

1. Functional homozygous FH with low-density lipoprotein cholesterol (LDL-C) level greater than or equal to 500 mg/dL

Disclosures: Dr P.M. Moriarty, Research for Amgen, Kowa, Lilly, Novartis, Sanofi, Regeneron, Genzyme, Pfizer, Catabasis, Espirion, B. Braun, and Kaneka; Consultant for Regeneron, Duke Clinical research Institute, Lilly, Catabasis, B Braun, Kaneka, and Genzyme; Honoraria from Esperion.
Dr L. Hemphill, Research: Regeneron, Sanofi and ISIS.

[a] Division of Clinical Pharmacology and Atherosclerosis/Lipoprotein-Apheresis Center, University of Kansas Medical Center, 3901 Rainbow Boulevard, Mail Stop 3008, Kansas City, KS 66160, USA; [b] Massachusetts General Hospital, Harvard Medical School, Boston, MA 02115, USA
* Corresponding author. Atherosclerosis/Lipoprotein-Apheresis Center, University of Kansas Medical Center, 3901 Rainbow Boulevard, Mail Stop 3008, Kansas City, KS 66160.
E-mail address: pmoriart@kumc.edu

Cardiol Clin 33 (2015) 197–208
http://dx.doi.org/10.1016/j.ccl.2015.02.002

2. Functional heterozygous FH with LDL-C level greater than or equal to 200 mg/dL in the presence of documented coronary artery disease (CAD)
3. Functional heterozygous FH with LDL-C level greater than or equal to 300 mg/dL in the absence of documented CAD

These requirements for therapy are much sterner than those of other countries that perform LA. In Germany, treatments are allowed for patients with CAD and LDL-C levels greater than 130 mg/dL, whereas Japan approves LA therapy for patients with CAD with a total cholesterol level greater than 250 mg/dL. To deal with this gap in treatment, some LA sites have negotiated with health care providers in allowing some high-risk patients with LDL-C levels greater than 160 mg/dL to receive LA.

Panels from the National Lipid Association (NLA) and the American Society for Apheresis (ASFA) recently recommended modifying the criterion for initiating LA therapy to include patients with any atherosclerotic cardiovascular disease (CVD), not just CAD, and lowering the LDL-C threshold in these patients to greater than or equal to 160 mg/dL.[4]

POTENTIAL PATIENT POPULATION WHO QUALIFY FOR LIPOPROTEIN APHERESIS

An estimate of the LA eligible population in the United States by the strict FDA criteria, assuming a prevalence of heterozygous FH of 1 in 500, is approximately 15,000 patients eligible for LA.[5] From the population of individuals intolerant of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) (prevalence 10%–25%), another 10,000 patients could be added to the number who would qualify for LA.[6,7] Despite these estimates the current census in the United States of patients receiving LA is only 550. Potential explanations for the low number of patients receiving LA therapy include a lack of awareness; insufficient numbers of LA centers (fewer than 50 in the United States), resulting in patients traveling long distances for treatments; complexity of initiating an LA center; and the likelihood that patients with poor venous access will require a shunt/fistula or the belief by physicians that future lipid level–lowering drugs such as proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors will provide adequate treatment of these extremely high-risk patients. In contrast, to achieve a successful LA program requires a team effort by the patients, medical staff, and health care providers.

BILLING AND CODING INFORMATION

LA therapy is covered by most private health insurers and government payers (eg, Medicare, Department of Veterans' Affairs). Coverage policies are typically based on the FDA indications but exceptions have been allowed (ongoing CVD and increased Lp(a) or LDL-C level more than 160 mg/dL). These exceptions are made on a case-by-case basis and may also depend on the health care provider and the state residency of the patient. Reimbursement for LA in the hospital or outpatient setting can be highly variable ($2000–$4000 per session) according to the insurer and the location in the United States.

In 2005, relative value units (RVUs) were specified for current procedural terminology (CPT) 36516. This specification applies exclusively to LA. In 2005 and 2006, about 85 RVUs were designated for this procedure and associated services under the direct supervision of physicians. Under the applicable ambulatory payment classification (APC 0112), Medicare payments are usually less than reimbursement under contracts negotiated between hospital providers and private insurers. It is recommended that all cases separately bill the insurer for professional services and again under CPT 36516.

APPROVED LIPOPROTEIN APHERESIS MACHINES IN THE UNITED STATES

Futura, B Braun, Melsungen, Germany

Heparin-induced extracorporeal low-density lipoprotein precipitation

In 1983, Wieland and Seidel[8] introduced the HELP system (Fig. 1). Following separation, the plasma is mixed 1:1 with a 0.3-M acetate buffer (pH 4.8) solution containing heparin at a concentration of 100 U/mL. Precipitation of heparin and low-density lipoprotein (LDL) occurs when the plasma buffer solution reaches an approximate pH of 5.2. The mechanism for the selective removal of lipoproteins is attributed to the negatively charged heparin precipitating with the positively charged apoB of LDL-C, very-low-density lipoproteins (VLDLs), and Lp(a). High-density lipoprotein cholesterol (HDL-C), which has a negatively charged membrane,[9] is normally spared from the precipitation process. A diethylaminoethyl cellulose filter adsorbs the residual heparin in the LDL-free plasma. Physiologic pH of the plasma and removal of excess fluid are achieved by dialysis and ultrafiltration.[10]

MAO3 Liposorber, Kaneka, Osaka, Japan

Dextran sulfate low-density lipoprotein adsorption

In 1987, Mabuchi and colleagues[11] reported on the dextran sulfate LDL adsorption (DSA) system (LA-15, Kaneka, Osaka, Japan) (Fig. 2). Plasma is exposed to a column of cellulose beads coated