Protocol

Lipid Apheresis

(80204)

Medical Benefit		**Effective Date**: 04/01/18	**Next Review Date**: 11/19
Preauthorization	No	**Review Dates**: 05/09, 05/10, 05/11, 05/12, 05/13, 05/14, 05/15, 11/15, 11/16, 11/17, 11/18	

Preauthorization is not required.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

Populations	Interventions	Comparators	Outcomes
Individuals: • With homozygous familial hypercholesterolemia unable to achieve target LDL-C with maximally tolerated pharmacotherapy	Interventions of interest are: • Low-density lipoprotein apheresis	Comparators of interest are: • Medical management with lipid-lowering medications • Plasmapheresis	Relevant outcomes include: • Overall survival • Disease-specific survival • Change in disease status • Morbid events • Treatment-related morbidity
Individuals: • With heterozygous familial hypercholesterolemia unable to achieve target LDL-C with maximally tolerated pharmacotherapy	Interventions of interest are: • Low-density lipoprotein apheresis	Comparators of interest are: • Medical management with lipid-lowering medications	Relevant outcomes include: • Overall survival • Disease-specific survival • Change in disease status • Morbid events • Treatment-related morbidity
Individuals: • With nonfamilial hypercholesterolemia	Interventions of interest are: • Low-density lipoprotein apheresis	Comparators of interest are: • Medical management with lipid-lowering medications	Relevant outcomes include: • Overall survival • Disease-specific survival • Change in disease status • Morbid events • Treatment-related morbidity
Individuals: • With treatment-resistant nephrotic syndrome	Interventions of interest are: • Low-density lipoprotein apheresis	Comparators of interest are: • Standard of care	Relevant outcomes include: • Symptoms • Change in disease status • Treatment-related morbidity
Individuals: • With sudden sensorineural hearing loss	Interventions of interest are: • Low-density lipoprotein and fibrinogen apheresis	Comparators of interest are: • Standard of care	Relevant outcomes include: • Symptoms • Change in disease status • Treatment-related morbidity

Populations	Interventions	Comparators	Outcomes
Individuals: • With severe diabetic foot ulcerations	Interventions of interest are: • Low-density lipoprotein apheresis	Comparators of interest are: • Standard of care	Relevant outcomes include: • Symptoms • Change in disease status • Morbid events • Treatment-related morbidity
Individuals: • With peripheral artery disease	Interventions of interest are: • Low-density lipoprotein apheresis	Comparators of interest are: • Standard of care	Relevant outcomes include: • Change in disease status • Treatment-related morbidity
Individuals: • With preeclampsia	Interventions of interest are: • Low-density lipoprotein apheresis	Comparators of interest are: • Standard of care	Relevant outcomes include: • Overall survival • Disease-specific survival • Change in disease status • Morbid events • Treatment-related morbidity
Individuals: • With non-arteritic acute anterior ischemic optic neuropathy	Interventions of interest are: • Low-density lipoprotein apheresis	Comparators of interest are: • Standard of care	Relevant outcomes include: • Symptoms • Change in disease status • Treatment-related morbidity
Individuals: • With acute coronary syndrome	Interventions of interest are: • Selective high-density lipoprotein delipidation and plasma reinfusion	Comparators of interest are: • Medical management with lipid-lowering medications	Relevant outcomes include: • Overall survival • Disease-specific survival • Change in disease status • Morbid events • Treatment-related morbidity

DESCRIPTION

This use of low-density lipoprotein (LDL) apheresis has been proposed to treat various types of familial hypercholesterolemia (FH) and other significant hyperlipidemia and to reduce atherosclerosis in cardiovascular disease. Lipid apheresis discriminately removes LDL particles from plasma while leaving other factors intact, allowing the filtrated plasma to be returned to the patient.

SUMMARY OF EVIDENCE

FAMILIAL HYPERCHOLESTEROLEMIA

For individuals with homozygous FH and unable to achieve target LDL-cholesterol (LDL-C) with maximally tolerated pharmacotherapy who receive LDL apheresis, the evidence includes multiple nonrandomized prospective and retrospective small cohort studies and a systematic review. Relevant outcomes are overall survival, disease-specific survival, change in disease status, morbid events, and treatment-related morbidity. Studies have reported reductions in LDL-C levels after apheresis, with means ranging from 57% to 75%. Currently, the direct evidence does not demonstrate that reductions in LDL-C levels seen with LDL apheresis will reduce adverse cardiovascular events. Randomized controlled trials (RCTs) comparing drug therapy alone, apheresis alone, no intervention, usual care, or apheresis plus drug therapy are not feasible, and unlikely to resolve any clinical uncertainty because lipid apheresis is generally used as a treatment of last resort when maximally tolerated pharmaco-

therapy has failed to achieve target LDL-C levels. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals with heterozygous FH and unable to achieve target LDL-C with maximally tolerated pharmacotherapy who receive LDL apheresis, the evidence includes multiple nonrandomized prospective and retrospective small cohort studies as well as a systematic review. Relevant outcomes are overall survival, disease-specific survival, change in disease status, morbid events, and treatment-related morbidity. Studies have reported reductions in LDL-C levels after apheresis with means ranging from 58% to 63%. Currently, there is no direct evidence that reductions in LDL-C levels seen with LDL apheresis will reduce adverse cardiovascular events. RCTs comparing drug therapy alone, apheresis alone, no intervention, usual care, or apheresis plus drug therapy are not feasible, and unlikely to resolve any clinical uncertainty because lipid apheresis is generally used as a treatment of last resort when maximally tolerated pharmacotherapy has failed to achieve target LDL-C levels. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

NONFAMILIAL HYPERCHOLESTEROLEMIA

For individuals with non-FH who receive LDL apheresis, the evidence includes multiple retrospective and prospective nonrandomized cohort studies. Relevant outcomes are overall survival, disease-specific survival, change in disease status, morbid events, and treatment-related morbidity. These studies have reported improvements in lipid levels pre- and posttreatment. Randomized trials in patient populations that are well-characterized regarding previous treatments, lipid levels, and comorbidities are necessary to demonstrate improvements in health outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

NEPHROTIC SYNDROME

For individuals with treatment-resistant nephrotic syndrome who receive LDL apheresis, the evidence includes multiple nonrandomized prospective and retrospective cohort studies. Relevant outcomes are symptoms, change in disease status, and treatment-related morbidity. Using variable schedules of LDL apheresis with short-term follow-up, these studies have reported that LDL apheresis may improve proteinuria and lipid abnormalities in patients with steroid-resistant nephrotic syndrome. Additional studies with concurrent controls and longer term follow-up are necessary to determine whether outcomes are improved with the use of LDL apheresis in nephrotic syndrome. The evidence is insufficient to determine the effects of the technology on health outcomes.

OTHER INDICATIONS

For individuals with sudden sensorineural hearing loss who receive LDL and fibrinogen apheresis, the evidence includes two RCTs. Relevant outcomes are symptoms, change in disease status, and treatment related morbidity. One RCT compared LDL apheresis with the standard treatment of prednisolone, hydroxyethyl starch, and pentoxifylline; it reported no statistically significant differences in hearing recovery between groups. The second RCT compared the combination of a single lipid apheresis procedure plus standard treatment with standard treatment alone; it reported statistically significant differences in hearing recovery with the addition of apheresis to standard treatment. An a priori primary end point, power calculations, and the statistical plan to control for type I error for multiple comparisons were not reported in the second trial. Further evaluation and replication of these findings are required given the inconsistent reporting. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with severe diabetic foot ulcerations who receive LDL apheresis, the evidence includes a single prospective case series. Relevant outcomes are symptoms, change in disease status, morbid events, and treatment-related morbidity. In the case series, patients underwent from one to seven treatment procedures and were followed for two to 73 months. Authors reported improved wound healing and reductions in the risk of lower leg amputations but results were insufficient to ascertain the effects on outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with peripheral artery disease who receive LDL apheresis, the evidence includes a single prospective case series. Relevant outcomes are change in disease status and treatment-related morbidity. Improvements in symptomatic parameters such as coldness, numbness, and resting pain were reported, but were insufficient to ascertain the effects on outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with preeclampsia who receive LDL apheresis, the evidence includes a prospective case series. Relevant outcomes are overall survival, disease-specific survival, change in disease status, morbid events, and treatment-related morbidity. Improvements in gestation were reported, but were insufficient to ascertain the effects on outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with non–arteritic acute anterior ischemic optic neuropathy who receive LDL apheresis, the evidence includes a prospective case series. Relevant outcomes are symptoms, change in disease status, and treatment-related morbidity. Improvement in visual outcomes was reported, but was insufficient to ascertain the effects on outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

ACUTE CORONARY SYNDROME

For individuals with acute coronary syndrome who receive selective high-density lipoprotein (HDL) delipidation and plasma reinfusion, the evidence includes an RCT. Relevant outcomes are overall mortality, disease-specific survival, change in disease status, morbid events, and treatment related morbidity. Results have shown improvements in certain biochemical measures (e.g., pre-β-like HDL and α-HDL levels). There were no significant changes in atheroma volume. Larger randomized trials, with longer follow-up and clinically relevant outcomes, are needed to determine the impact of delipidated HDL plasma on acute coronary syndrome. The evidence is insufficient to determine the effects of the technology on health outcomes.

POLICY

Low-density lipoprotein (LDL) apheresis may be considered **medically necessary** in patients with homozygous familial hypercholesterolemia as an alternative to plasmapheresis.

LDL apheresis may be considered **medically necessary** in patients with heterozygous familial hypercholesterolemia who have failed diet therapy and maximum tolerated combination drug* therapy AND who meet the following U.S. Food and Drug Administration–approved indications: (All LDL levels represent the best achievable LDL level after a program of diet and drug therapy):

1. Functional hypercholesterolemic heterozygotes with LDL ≥300 mg/dL
2. Functional hypercholesterolemic heterozygotes with LDL ≥200 mg/dL* AND documented coronary artery disease.*

LDL apheresis is considered **investigational** for other uses, including nonfamilial hypercholesterolemia, nephrotic syndrome, sudden sensorineural hearing loss, severe diabetic foot ulcerations, peripheral artery disease, preeclampsia and non-arteritic acute anterior ischemic optic neuropathy.

Therapeutic apheresis with selective high-density lipoprotein delipidation and plasma reinfusion is considered **investigational** for all indications, including but not limited to acute coronary syndrome.

* For definitions of maximum tolerated drug therapy and documented coronary artery disease, see the Policy Guidelines.

POLICY GUIDELINES

A scientific statement from American Heart Association (Gidding et al [2015]) for the treatment of heterozygous FH has indicated that adults should be treated with available pharmacotherapy with an initial goal of reducing LDL-C by at least 50%, usually with a statin. This treatment can be followed by achieving an LDL-C of less than 100 mg/dL (absent coronary artery disease [CAD] or other major risk factors) or 70 mg/dL (presence of CAD or other major risk factors).

*The following approach for pharmacotherapy is suggested:

- High-intensity statin therapy to target >50% LDL-C reduction, such as rosuvastatin or atorvastatin.
- If the patient is adherent and LDL-C is above the target goal after three months, consider adding ezetimibe.
- If the patient is adherent and LDL-C is above the target goal after three months, consider adding a PCSK9 inhibitor or colesevelam (or other bile acid sequestrant or niacin).
- If the patient is adherent and LDL-C is above the target goal after three months, proceed to complex therapy combination such as a four-drug combination plus LDL apheresis.

Documented CAD includes a history of myocardial infarction, coronary artery bypass surgery, percutaneous transluminal coronary angioplasty or alternative revascularization procedure, or progressive angina documented by exercise or nonexercise stress test.

The frequency of LDL apheresis varies, but typically averages once every two weeks to obtain an interapheresis level of LDL-C at less than 120 mg/dL. Patients with homozygous FH may be treated more frequently. Patients are simultaneously treated with diet and drug therapy.

BACKGROUND

HYPERLIPIDEMIA

A dominantly inherited disorder, familial hypercholesterolemia results from a variant in the gene that encodes for the specific cell surface receptor responsible for LDL uptake by the cells. The heterozygous form affects about one in 500 people. The number of LDL receptors is halved in this condition, resulting in serum low-density lipoprotein cholesterol levels that are approximately two to three times levels considered acceptable (i.e., >300 mg/dL). Affected male patients typically develop coronary heart disease in their thirties and forties, while women develop the disease in their fifties. Depending on the patient, heterozygous familial hypercholesterolemia may or may not respond adequately to lipid-lowering drugs.

Homozygous hypercholesterolemia is rare, occurring in only in one in one million subjects. Due to the total lack of functioning LDL receptors, serum levels of low-density lipoprotein cholesterol may be elevated six fold (>500 mg/dL). Homozygotes may develop severe aortic stenosis and coronary heart disease by 20 years of age. These patients typically do not adequately respond to drug or diet modification therapies. In the past, patients with homozygous familial hypercholesterolemia may have been treated with plasma exchange, but the advent of LDL apheresis provides a more targeted approach by permitting selective removal of LDL from plasma.

Treatment

Low-Density Lipoprotein

LDL apheresis (also referred to as lipid apheresis) involves the extracorporeal removal of apolipoprotein B (apo B)–containing lipoproteins, including LDL, lipoprotein (a), and very low-density lipoprotein. The apheresis procedure is designed to isolate plasma. The LDLs are then selectively removed from the plasma by immunoadsorption, heparin-induced extracorporeal LDL precipitation, dextran sulfate adsorption, or double-filtration plasma

pheresis of lipoprotein. In immunoadsorption, polyclonal antihuman apo B antibodies from sheep selectively bind and remove LDL, because apo B is the protein moiety of LDL. In heparin-induced extracorporeal LDL precipitation, LDL and other particles containing apo B are precipitated by heparin at an acidic pH. Dextran sulfate adsorption removes LDL by binding the positively charged apo B to dextran sulfate particles bound to cellulose.

High-Density Lipoprotein

Therapeutic apheresis with selective HDL delipidation and plasma reinfusion removes plasma from the body, processed through a delipidation device, and then returned to the patient. The delipidation procedure selectively removes cholesterol from HDL, converting the major α-HDL to pre-β-like HDL, a form of HDL that enhances cholesterol transport to the liver and is thought to reduce atherosclerosis development and burden. The plasma with pre-β-like HDL is then reinfused into the patient.

REGULATORY STATUS

Two LDL apheresis systems have been approved by the U.S. Food and Drug Administration (FDA) for marketing. In 1996, the Liposorber LA-15® System (Kaneka Pharma), dextran sulfate device, was approved by the FDA through the premarket approval process for use to "acutely remove LDL-C from the plasma of high-risk patient populations for whom diet has been ineffective or not tolerated."

In 1997, the HELP® System (B. Braun), a heparin-induced extracorporeal LDL precipitation, was approved by the FDA through the premarket approval process for the same indication. FDA product code: MMY.

In 2013, the Liposorber LA-15® System was approved for additional indications through the humanitarian device exemption[1] process for the treatment of pediatric patients with primary focal segmental glomerulosclerosis when the following conditions apply:

- "Standard treatment options, including corticosteroid and/or calcineurin inhibitor treatments, are unsuccessful or not well-tolerated, and the patient has a GFR [glomerular filtration rate] ≥60 mL/min/1.73 m^2 or
- The patient is post renal transplantation."

No devices have been approved by the FDA specifically for HDL delipidation. The Lipid Sciences Plasma Delipidation System-2 (Lipid Sciences) was tested in clinical studies, but the company ceased business operations in 2012.

RELATED PROTOCOL

Plasma Exchange

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

REFERENCES

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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