

OHTAC Recommendation

Low-Density Lipoprotein Apheresis

November 2007

This recommendation summary has been prepared by the Medical Advisory Secretariat of the Ministry of Health and Long Term Care on behalf of the Ontario Health Technology Advisory Committee.

OHTAC Ontario
Health Technology
Advisory Committee

Issue Background

The Ontario Health Technology Advisory Committee (OHTAC) met on September 28, 2007 to review the effectiveness, safety and cost-effectiveness of low-density lipoprotein (LDL) apheresis for the treatment of familial hypercholesterolemia (FH). Low-density lipoprotein apheresis is an extracorporeal process that selectively removes LDL cholesterol (LDL-C) and other atherogenic lipoproteins from the blood.

Familial hypercholesterolemia is a genetic autosomal dominant disorder that is caused by several mutations in the LDL receptor gene. The reduced number or absence of functional LDL receptors results in impaired hepatic clearance of circulating LDL-C particles, which results in extremely high levels of LDL-C in the bloodstream. Familial hypercholesterolemia is characterized by excess LDL-C deposits in tendons and arterial walls, early onset of atherosclerotic disease and premature cardiac death.

Familial hypercholesterolemia occurs in both heterozygous (HTZ) and homozygous (HMZ) forms.

Heterozygous FH is one of the most common monogenic metabolic disorders in the general population, occurring in approximately 1 in 500 individuals. Nevertheless, HTZ FH is largely undiagnosed and only 15% of patients are accurately diagnosed. It is estimated that there are approximately 3,800 diagnosed and 21,680 undiagnosed cases of HTZ FH in Ontario. In HTZ FH patients, half of the LDL receptors do not work properly or are absent, resulting in plasma LDL-C levels 2- to 3-fold higher than normal. Without lipid-lowering treatment, 50% of males die before the age of 50 and 25% of females before the age of 60 from myocardial infarction or sudden death.

In contrast to the HTZ form, HMZ FH is rare, occurring in 1 case per million persons, and is more severe with a 6- to 8-fold elevation in plasma LDL-C levels. Homozygous FH patients are typically diagnosed in infancy and their average life expectancy is 23 to 25 years. In Ontario, it is estimated that there are 13 to 15 cases of HMZ FH. An Ontario clinical expert confirmed that 9 HMZ FH patients have been identified to date.

The primary aim of treatment in both HTZ and HMZ FH is to reduce plasma LDL-C levels in order to reduce the risk of developing atherosclerosis and coronary artery disease. Standard treatment consists of diet and drug therapy, however mostly all HMZ FH patients are refractory to diet and drug therapy and roughly 3% of HTZ FH patients are refractory. It is estimated that there are approximately 765 refractory HTZ FH patients in Ontario, of which 115 are diagnosed and 650 are undiagnosed.

An option currently available in Ontario for FH patients who do not respond to standard diet and drug therapy is plasma exchange (PE). Patients are treated with this life-long therapy on a weekly or biweekly basis with concomitant drug therapy. Blood is removed from the patient, plasma is isolated, discarded and replaced with a substitution fluid. The substitution fluid and the remaining cellular components of the blood are then returned to the patient.

The major limitation of PE is its nonspecificity. In addition to acutely lowering LDL-C by about 50%, PE eliminates virtually all plasma proteins, including high-density lipoprotein cholesterol (HDL-C) which prevents successful vascular remodeling of the areas stenosed by atherosclerosis. In addition, there is an increased susceptibility to infections and costs are incurred by the need for replacement fluid.

LDL Apheresis

An alternative to PE is LDL apheresis. Unlike PE, LDL apheresis is a selective treatment that removes LDL-C and other atherogenic lipoproteins from the blood while minimally impacting other plasma

components such as HDL-C, total serum protein, albumin and immunoglobulins. FH patients require life-long therapy with LDL apheresis on a weekly/biweekly basis with concomitant drug therapy.

Heparin-induced extracorporeal LDL precipitation (HELP) is one of the most widely used methods of LDL apheresis and is the only LDL apheresis device currently licensed by Health Canada. It operates on the principle that at a low pH, LDL and lipoprotein (a) (Lp(a)) bind to heparin and fibrinogen to form a precipitate which is then removed by filtration.

HELP LDL apheresis has several advantages over the current treatment of PE, including decreased exposure to blood products, decreased risk of adverse events, conservation of nonatherogenic and athero-protective components, such as HDL-C and lowering of other atherogenic components, such as fibrinogen.

OHTAC Findings

The Medical Advisory Secretariat (MAS) conducted a systematic review of the literature to assess the effectiveness and safety of LDL apheresis performed with the HELP system for the treatment of patients with refractory HMZ and HTZ FH.

Based on the MAS analysis and following discussion, OHTAC found the following:

Homozygous FH Patients:

Overall, there is very low quality evidence that LDL apheresis with the HELP system improves plasma lipid outcomes and indirect evidence that LDL apheresis with the HELP system improves survival in HMZ FH patients.

Refractory Heterozygous FH Patients:

Overall, there is low quality evidence that LDL apheresis with the HELP system improves plasma lipid outcomes and coronary artery disease status in refractory HTZ FH patients.

Limitations in the literature related to HELP LDL apheresis for the treatment of FH patients included the following:

- No controlled studies were identified and no studies directly compared the effectiveness of the HELP system with PE or with diet and drug therapy. Conducting trials with a sufficiently large control group would not have been feasible or acceptable given that HELP represents a last alternative in these patients who are resistant to conventional therapeutic strategies.
- For HMZ FH patients, it is unlikely that better quality evidence will become available as HMZ FH is rare and LDL apheresis is a last therapeutic option for these patients.
- There is limited data on the long-term effects of LDL apheresis in FH patients. No studies with HELP were identified that examined long-term outcomes such as survival and cardiovascular events. The absence of this data may be attributed to the rarity of the condition and the large number of subjects and long duration of follow-up that would be needed to conduct such trials.

A budget-impact analysis was conducted to forecast future costs for PE and HELP LDL apheresis in FH patients. Based on epidemiological data of 13 HMZ, 115 diagnosed HTZ and 765 cases of all HTZ patients (diagnosed + undiagnosed), the annual cost of weekly treatment was estimated to be \$488,025,

\$4,332,227 and \$24,758,556 respectively for PE. For HELP LDL apheresis, the annual cost of weekly treatment was estimated to be \$1,025,338, \$9,156,209 and \$60,982,579 respectively. Costs for PE and HELP LDL apheresis were halved with a biweekly treatment schedule.

The cost per coronary artery disease death avoided over a 10-year period comparing HELP LDL apheresis with PE and with no intervention in HTZ FH-diagnosed patients was estimated to be \$37.5 million and \$18.7 million for weekly and biweekly treatment respectively, when comparing HELP LDL apheresis with PE and with no intervention. Although HELP LDL apheresis costs twice as much as PE, it helped to avoid 12 deaths compared with PE and 22 deaths compared with no intervention over a period of 10 years.

In addition to the substantial costs, it is unknown whether the current health care system could cope with the additional demand.

OHTAC Recommendation

Based on the above, OHTAC recommends the following with regard to LDL apheresis:

- LDL apheresis with the HELP System, being the only licensed LDL apheresis technology in Canada, be made available as a replacement to plasma exchange for all indications currently licensed by Health Canada and insured by the Ministry of Health and Long-term Care. This includes 3 high risk patient populations with FH for whom a 6 month trial of diet and maximum drug therapy has either been ineffective or not tolerated:
 - homozygous FH LDL-C levels > 500 mg/dL (>13mmol/L)
 - heterozygous FH with LDL-C levels > 300 mg/dL (>7.8mmol/L)
 - heterozygous FH with LDL-C levels > 200 mg/dL (>5.2mmol/L) and documented coronary artery disease
- LDL apheresis is not cost-effective when compared to plasma exchange according to our usual interpretation of reasonable uses of our limited health resources. However, it is affordable for HMZ FH patients for whom OHTAC recommends unconditional uptake.
- The diffusion of LDL apheresis for refractory HTZ FH patients should take into account affordability as well as potential capital and human resource constraints which may argue against making this technology available to this sub-population.