LDL Apheresis TOOLKIT

HEART UK
THE CHOLESTEROL CHARITY

Section 1
Introduction

- **Introduction to the Toolkit**
- **Explanation of lipoprotein apheresis, who it is intended for and its benefits**
- **Summary of current apheresis sites**

This toolkit is designed to inform clinicians, patients and commissioners about lipoprotein apheresis treatment in the UK. The toolkit provides information about the nature of the treatment, patients being treated, referral and funding mechanisms for apheresis, and current sites in the UK.

The toolkit has been developed because lipoprotein apheresis is a crucial form of treatment for people with severe, statin-resistant hypercholesterolaemia (high cholesterol). Apheresis is often the only effective treatment to help prolong the health and life of these patients who are at very high cardiovascular risk. Apheresis is used less in the UK, when compared to similar countries such as the United States and Germany. However, for the patients described in this toolkit, apheresis remains an essential treatment that can often be the difference between life and death. The toolkit fills an important gap in resources, since the treatment is not widely known or understood, even among many in the medical fraternity.

The toolkit is divided into four sections:

1. Introduction
2. Setting up and protocols for a lipoprotein apheresis service
3. Patient information and referral
4. Commissioning and the case for apheresis

Each section includes appendices containing documents that can be utilised or adapted for local use.

Explanation of lipoprotein apheresis, who it is intended for and its benefits

Apheresis (Greek for take away) is the term used to describe a technique for the extracorporeal removal of macromolecules and cells from the circulation. Lipoprotein (Lp) apheresis involves the removal of atherogenic low density lipoprotein (LDL) and lipoprotein (a) (Lp(a)) particles from whole blood or plasma at weekly or bi-weekly intervals by adsorption, precipitation or differential filtration. Both types of lipoprotein share a common protein moiety, apolipoprotein B (apoB), and are roughly the same size. Hence they are removed to a similar extent by most apheresis systems. Those in current use have been described in detail previously and usually involve the initial separation of plasma from blood cells and its subsequent passage through columns containing dextran sulphate bound to cellulose or through selective membrane filters. Alternatively, LDL and Lp(a) can be precipitated from plasma by the addition of heparin at low pH or adsorbed from whole blood using non-haemolytic adsorbent columns. Commonly one to two plasma volumes are treated over a period of 3 hours during each session, using peripheral veins to access and return blood although in some patients, especially young children, an arterio-venous fistula is required. The efficiency of removal depends both on the volume of blood or plasma treated and on the system and size of columns used and should aim to achieve acute reductions in LDL or Lp(a) of >65%. Owing to the rapidity and curvilinear nature of the post-apheresis rebound in lipoproteins the best criterion of long-term efficacy is the interval mean concentration between consecutive procedures, calculated as previously described. Lp apheresis is a remarkably

safe procedure and has been used repetitively in individual patients for up to 31 years. Its frequency of use varies, reflecting remuneration criteria utilised by health providers and insurance companies, and estimates range from 1.2 per 100,000 persons in Germany to 0.13 per 100 000 in North America and 0.06 per 100 000 in the UK.

Clinical indications

Lp apheresis is a treatment of last resort and is used only when conventional therapy has failed. Because of this it has proved impossible to obtain randomised, controlled evidence of its efficacy in reducing cardiovascular morbidity and mortality. Currently, there are three main indications for undertaking long-term Lp apheresis:

(1) Patients with homozygous familial hypercholesterolaemia (FH) whose serum cholesterol remains >9 mmol/L or decreases by < 50% despite treatment with high dose statin, plus ezetimibe and/or bile acid sequestrants. Homozygous FH is a very rare disorder with a prevalence of approximately 1: 1,000,000 in the UK. Untreated, most homozygotes die from accelerated atherosclerosis of the aortic root and coronary arteries before the age of 30. Long-term treatment with Lp apheresis and concomitant high dose statin/ezetimibe can reduce mean LDL cholesterol by over 70% and has been shown to increase the longevity of affected individuals. Surprisingly, a recent study showed that the average age of death of South African homozygotes increased from 18 years during the pre-statin era to 33 years after the introduction of statins, even though LDL cholesterol only decreased from 16 to 12 mmol/L during the statin period, a reduction of just 26%. Current HEART UK guidelines stipulate that the mean LDL cholesterol of homozygotes should be reduced to < 6.5 mmol/L or by >65% from baseline, which nearly always necessitates apheresis and combined drug therapy, as defined above. However, a European Atherosclerosis Consensus Panel recently recommended the following LDL cholesterol targets for both heterozygous and homozygous FH, regardless of age, but admitted that in patients with homozygous FH, these values are extremely difficult to achieve with current treatments, including lipoprotein apheresis:

(i) children, 3.5 mmol/L (135 mg/dL)
(ii) adults, 2.5 mmol/L (100 mg/dL)
(iii) adults with CHD or diabetes, 1.8 mmol/L (70 mg/dL).

(2) Patients with heterozygous FH or other forms of severe hypercholesterolaemia and with progressive coronary heart disease (CHD) whose LDL cholesterol remains > 5 mmol/L or decreases by < 40% on maximally tolerable doses of combined drug therapy. Heterozygous FH has a prevalence of 1:500 but, unlike homozygotes, the great majority of heterozygotes respond remarkably well to combined drug therapy, as defined above. However, a very small proportion of patients in this category are refractory to or intolerant of statins and their CHD progresses. The beneficial effects on coronary events of combining Lp apheresis with drug therapy compared with drug therapy alone were convincingly demonstrated in a 10 year study of FH heterozygotes in Japan. The mechanisms by which apheresis has beneficial effects may extend beyond the anti-atherogenic effect of lowering LDL. Aengevaeren et al demonstrated improvements in regional myocardial perfusion and exercise tolerance in heterozygotes with extensive CHD when treated with Lp apheresis and speculated this may have been mediated by improved endothelial function.

(3) Patients with a raised level of Lp(a) (> 600 mg/L, measured with a Kringle IV- independent assay) (HyperLp(a)) and with progressive CHD despite treatment with maximally tolerable combined drug therapy. Evidence confirming the strength and independence of Lp(a) as a cardiovascular risk factor was summarised recently by a Consensus Panel of the European Atherosclerosis Society. Lp(a) has both atherogenic and thrombogenic properties but, unlike LDL, it does not respond to statins. Nevertheless, the latter should be prescribed so as to mitigate the effects of concomitantly raised levels of LDL in promoting the atherogenicity of Lp(a). Nicotinic acid lowers Lp(a), but the drug is no longer marketed in Europe. However, two observational studies from Germany have shown impressive reductions in coronary events when patients with hyperLp(a) were treated with Lp apheresis, this outcome being independent of the LDL-lowering effects of the procedure. A recent report provides anecdotal evidence of the benefits of Lp apheresis in a British patient with hyperLp(a) and progressive CHD.

Service requirements

Lp apheresis in the UK is carried out by designated lipid or renal units and NHS Blood & Transplant Centres. This treatment could equally well be delivered safely and practically in a designated day case unit. Apheresis is a safe and well tolerated procedure, side effects being infrequent and mild. However, provision of resuscitation equipment is required in the event of acute haemodynamic compromise. Most patients undergo their apheresis sessions on treatment couches or beds, which should have a tilt mechanism so as to enable appropriate treatment of hypotensive episodes. Adequate consideration should be made to maintain patient dignity and privacy, although most units do not have provision for a single-sex environment. For more information on service requirements, see Section 2 of this toolkit.

When to treat?

Recommendations of the HEART UK LDL Apheresis Working Group

The HEART UK Working Group for Apheresis recommends that:

"LDL apheresis should be the treatment of choice for: (1) all FH homozygotes from the age of seven onwards unless their serum cholesterol can be reduced by >50% and/or decreased to ≤9 mmol/L by drug therapy; (2) individual patients with either heterozygous FH or a bad family history of premature cardiac death whose coronary disease progresses and where LDL cholesterol remains >5.0 mmol/L or is decreased by <40% with maximal drug therapy. Apheresis may also occasionally be indicated on a case-by-case basis for patients with lower levels of LDL. (3) LDL apheresis should also be considered for patients with aggressive progressing coronary disease and Lp(a) > 600 mg/L whose LDL cholesterol remains >3.2 mmol/L despite maximal drug therapy."

See full recommendations at:

http://www.atherosclerosis-journal.com/article/S0021-9150(08)00102-0/abstract

US apheresis guidelines

The American Society of Apheresis has also published guidelines on apheresis at:

Schwartz, J. et al Guidelines on the Use of Therapeutic Apheresis in Clinical Practice—Evidence-Based Approach from the Writing Committee of the American Society for Apheresis: The Sixth Special Issue. Journal of Clinical Apheresis 2013; 28: 145–284.

See full guidelines at:
http://onlinelibrary.wiley.com/doi/10.1002/jca.21276/abstract;jsessionid=363E875D0DABAB491EF371E47529B4EC.f04t02

Current sites

As at May 2014, lipoprotein apheresis is offered at eight sites in England and Wales. Apheresis is not currently available in Northern Ireland or Scotland.

The HEART UK website features a list of those clinics where apheresis is offered. Appendix 1.1 opens directly onto the lipid clinic map, where apheresis units can be found.

Further reading (Appendix 1.2)

Dev Datta and Gil Thompson paper for HEART UK, 'Lipoprotein apheresis for refractory hyperlipidaemia: clinical indications and service requirements.'

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