Is LDL apheresis a thing of the past?

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Patients with severe hypercholesterolaemia have a high lifetime risk for developing cardiovascular disease. These patients are traditionally treated with high-intensity statins and ezetimibe. Some patients are refractory to treatment and cannot achieve a desirable reduction in low-density lipoprotein cholesterol (LDL-C). LDL apheresis or lipoprotein apheresis (LA) is a radical treatment which involves the intermittent extracorporeal removal of atherogenic apolipoprotein B-100-containing lipoproteins from the systemic circulation. The procedure requires the use of highly specialised equipment and is carried out under medical supervision for patients with severe hypercholesterolaemia, refractory to treatment with high-intensity statins and ezetimibe. The advent of targeted therapies, including monoclonal antibodies and gene silencing therapies, offer treatment options that could replace LA for these patients. Large scale clinical trials for the PCSK inhibitors evolocumab and alirocumab show favourable outcomes in terms of lipid lowering, with a 50% to 60% improvement in baseline LDL-C levels. This suggests that these therapies could reduce the need for LA in patients with hypercholesterolaemia. This review describes the main clinical trials for the PCSK inhibitors and discusses the place of these therapies in the management of severe hypercholesterolaemia. While these new therapies show promise as an effective option for lowering LDL-C levels in patients refractory to conventional treatment and have added benefits of ease of administration and compliance to treatment, long-term safety data is still needed. Favourable safety data could relegate the use of LA for a select few patients who may not tolerate the new therapies.

Keywords: LDL apheresis, statin therapy, PCSK 9 inhibitors, evolocumab, alirocumab

Introduction

Cardiovascular diseases (CVDs) are the uppermost cause of death globally (31% of deaths worldwide), with 85% of those deaths being due to heart attack and stroke.1 Hyperlipidaemia is a risk factor that pointedly contributes towards CVD.1 Severe hypercholesterolaemia is a clinical presentation where a patient has an elevated low-density lipoprotein cholesterol (LDL-C) level of ≥ 4.9 mmol/l.2 These patients have a high lifetime risk of developing CVD, which negates the use of a cardiovascular scoring system.2 Patients with severe hypercholesterolaemia derive benefit from CVD risk reduction through interventions that increase the expression of LDL receptors in the liver.2 Data from current trials suggest that statin therapy produces the highest CVD risk reduction when compared to a placebo or ezetimibe, and that high-intensity statin therapy is preferred to moderate-intensity statin therapy in patients with severe hypercholesterolaemia.2 Current guidelines recommend that these patients be placed on a maximally-tolerated statin dose with the aim of reducing LDL-C levels by at least 50% from baseline.2,4 However, not all patients taking high-intensity statins will achieve the goal of 50% reduction in LDL-C. The use of LDL apheresis is recommended as part of the management of these patients.5 This review will explore whether LDL apheresis will continue to be part of the management of severe hypercholesterolaemia in the future, especially with the advent of proprotein convertase subtilisin/kexin type 9 (PCSK 9) inhibitors and other novel treatments in the pipeline.

LDL apheresis

LDL apheresis or lipoprotein apheresis (LA) is a radical treatment which involves the intermittent extracorporeal removal of atherogenic apolipoprotein B-100-containing lipoproteins from the systemic circulation.6,7 LA reduces LDL-C levels by 50–70% from baseline, after a single treatment.6,7 Current guidelines suggest that LA improves coronary outcomes as well as the progression of atherosclerotic cardiovascular disease (ASCVD).6,8 Evidence also demonstrates reduction in endothelial dysfunction, inflammation and coagulation by LA.6,8 LA is preferred in patients who have homozygous familial hypercholesterolaemia (HoFH) or patients with compound heterozygous familial hypercholesterolaemia (HeFH), as well as in patients with classical HeFH who have progressive ASCVD and are refractory to maximally-tolerated pharmacotherapy.3,9 The criteria for selection of patients to undergo LA includes having an LDL-C ≥ 5 mmol/l, being treated with diet and maximally-tolerated pharmacotherapy.5,9 Furthermore, patients with very high plasma levels of lipoprotein(a) [Lp(a)] may benefit from LA.3,7,9,10

LA is carried out in highly specialised centres on patients in a clinically stable condition, that are psychologically prepared for the treatment.7 There must be excellent vascular access and the
patient must undergo anticoagulation therapy with heparin and citrate. The treatment involves the exchange of 4–6 L of plasma, carried out over 2–4 hours, either on a weekly or bi-weekly basis. The efficacy, tolerability and safety of the treatment should be monitored continually while the patient is undergoing LA. Patients need to remain on statin therapy to reduce the rebound of LDL-C following the exchange period.

Side-effects of LA include hypotension, vasovagal episodes, hypocalcaemia, and anaemia. Psychological status changes and the patient’s quality of life may be impaired as a result of treatment. There may also be problems with venous access. Besides the complexities and the adverse effects of LA, there is also a high cost associated with the treatment. The average annual cost of a twice-weekly regimen of LA can range between $33 187 (USD) and $114 478 (USD) per patient.

### PCSK 9 and its effect of statins and LDL-C

PCSK 9 limits the number of patent LDL receptors in the liver. Limiting the number of LDL receptors keeps circulating levels of LDL-C at normal homeostatic levels. It is worth noting that statins by their nature increase the number of LDL receptors in the liver with a consequent reduction in plasma LDL-C levels. In order to curb the reduction in circulating LDL-C the production of PCSK 9 is increased. Many statins increase PCSK 9 levels; the effect of this increase is dependent on the type of statin (Table I). Essentially, PCSK 9 reduces the effectiveness of statin therapy. This could possibly be a reason for the use of high-intensity statin therapy failing to effectively reduce LDL-C.

| Statin                  | PCSK change |
|------------------------|-------------|
| Atorvastatin 80 mg     | + 47%       |
| Atorvastatin 40 mg     | + 37%       |
| Rosuvastatin 20 mg     | + 28% (men) + 33% (women) |

| Controls               |
|------------------------|
| Statin therapy         | + 45%       |
| Statin ezetimibe therapy | + 77%      |
| Titration of atorvastatin 5 to 80 mg/day | + 30% |
| Titration of atorvastatin 5 to 40 mg/day | + 37% |

### PCSK 9 inhibitors

Studies have suggested that individuals with low circulating levels of PCSK 9 have a lower risk of CVD, thus inhibiting PCSK 9 may reduce cardiovascular risk. Furthermore, people with low circulating levels of PCSK 9 also have reduced LDL-C levels. Two monoclonal antibodies that inhibit PCSK 9, evolocumab and alirocumab, have been developed and approved by the FDA. Both drugs have demonstrated reduction in LDL-C of between 50–60% from baseline. The drugs have also demonstrated benefit in reducing LDL-C levels in patients with HeFH and HoFH. PCSK 9 inhibitors also modulate the effects of statins, which leads to an increased reduction in LDL-C levels as demonstrated in the ODYSSEY LONG TERM trial.

### PCSK 9 inhibitors and cardiovascular risk reduction

Both the FOURIER trial and the ODYSSEY OUTCOME trial have demonstrated cardiovascular risk reduction benefits with PCSK 9 inhibitors in patients with established CVD (Table II). In both studies, the PCSK 9 inhibitors decreased the incidence of the primary composite outcomes of cardiovascular events between 15–20% when compared to the placebo. Both trials, patients had been taking maximum-tolerated doses of statins and were unable to achieve their LDL-C targets. Furthermore, the benefits in terms of cardiovascular risk reduction seemed to be more pronounced in patients with higher baseline LDL-C levels.

The ODYSSEY OUTCOME trial also demonstrated that alirocumab was able to produce a consistent reduction in Lp(a) levels of 30% from baseline, irrespective of LDL-C reduction. It is worth noting that in both clinical trials, there was no significant difference in terms of adverse events between either alirocumab or evolocumab and their respective placebo groups.

Furthermore, the most commonly experienced adverse events when participants took either evolocumab or alirocumab were injection-site reactions.

### PCSK 9 inhibitors vs lipoprotein apheresis

The available data has suggested that PCSK 9 inhibitors may be a suitable replacement for LA in some patients who are currently on statin therapy and are failing to meet their LDL-C targets. Among the advantages noted for the use of PCSK 9 inhibitors are their efficacy, tolerability and safety. The available data has also suggested that PCSK 9 inhibitors may reduce the frequency or the need for LA altogether. Despite deficient data, it is clear that PCSK 9 inhibitors may reduce the frequency or the need for LA altogether.

### Alirocumab and evolocumab

Both alirocumab and evolocumab have demonstrated significant reductions in LDL-C and Lp(a) levels and recent large scale clinical trials (FOURIER and ODYSSEY OUTCOMES) have demonstrated that these drugs also reduce cardiovascular risk as part of secondary prevention with minimal adverse effects. Comparatively, there is a paucity of clinical trial data demonstrating that LA reduces cardiovascular risk, however, there is certainly evidence demonstrating large scale reductions in both LDL-C levels and Lp(a) levels. Combining this information with the results of the relatively small ODYSSEY ESCAPE trial, the use of PCSK 9 inhibitors may change the need for LA, or reduce the number of LA treatments a patient requires. It is important to remember, however, that the ODYSSEY ESCAPE trial was conducted on a relatively small number of patients with HeFH and not patients with severe hypercholesterolaemia,
Table II: Important clinical trials in this assignment 12,20,21

| Study name | Participant information and goal of study | Trial design | Results | Conclusion | Comments |
|------------|-------------------------------------------|--------------|---------|------------|----------|
| FOURIER trial 2 | 27 564 participants with atherosclerotic cardiovascular disease. 13 784 participants were randomised to the evolocumab group and 13 780 participants were randomised to the placebo group. Duration of follow-up: 26 months. Mean age of participants: 63 years. 69% of participants were on high-intensity statin therapy while 30% were on moderate-intensity statin therapy. The mean LDL-C levels in both groups was 2.37 mmol/L. | Double blind, randomised, parallel, placebo-controlled trial. Participants were randomised to receive evolocumab (140 mg subcutaneously every 2 weeks or 420 mg subcutaneously on a monthly basis) or the placebo every 2 weeks. Primary outcome: Incidence of a composite of cardiovascular death, MI, stroke, hospitalisation for unstable angina or coronary revascularisation. | Primary outcome occurred in 9.8% of participants taking evolocumab (with a statin therapy) compared to 11.3% in the placebo group with a number needed to treat (NNT) of 67. Evolocumab produced 15% reduction in the hazard (HR) of primary composite outcome (HR 0.85, 95% CI 0.79–0.92). Evolocumab (with statin therapy) reduced the risk of nonfatal MI (relative risk (RR) 0.73, 95% CI 0.65–0.82) compared to the placebo (with statin therapy). Evolocumab (with statin therapy) produced an 11% relative risk reduction in the number of nonfatal strokes (RR 0.79, 95% CI 0.66–0.95) compared to the placebo (with statin therapy). Evolocumab (with statin therapy) did not reduce the risk of cardiovascular mortality compared to the placebo (with statin therapy). There were no significant differences between the evolocumab group and the placebo group in terms of the number of adverse effects. The most common and statistically significant adverse effect was injection-site reactions in participants taking evolocumab. The mean LDL-C reduction in participants taking evolocumab when compared to the placebo was between 39–62% from baseline. Therapy with evolocumab reduced both LDL-C levels from baseline as well as cardiovascular risk without a significant increase in the number of adverse events. | Evolocumab is superior to the placebo in reducing the number of cardiovascular events in patients with established ASCVD. Despite lower LDL-C levels in the group taking evolocumab, there was no increase in the number of reported adverse events. This trial is limited by the relatively short duration of the follow-up. Longer-term trials are required to see if the cardiovascular risk reduction of evolocumab is preserved. Patients with higher levels of LDL-C from baseline benefits more from the introduction of evolocumab. |
| ODYSSEY OUTCOMES trial 21 | 18 924 participants with previous acute coronary syndrome (ACS). 9 462 participants were randomised to receive alirocumab. 9 462 participants were randomised to receive the placebo. Duration of follow-up: median of 2.8 years. Mean age of participants: 53 years. Patients included in this trial had inadequate control of their lipids i.e. LDL-C > 1.8 mmol/l, non-HDL-C > 2.6 mmol/l or Apo B ≥ 80 mg/dl. | Double blind, randomised, placebo-controlled trial. Participants were randomised to receive alirocumab (75 mg subcutaneously) or a matching placebo every two weeks. Dose of alirocumab was adjusted under blinded conditions to achieve an LDL-C target of between 0.6–1.3 mmol/l. Primary outcome: Incidence of a composite of cardiovascular death, MI, stroke, hospitalisation for unstable angina or coronary revascularisation. | Primary outcome occurred in 9.5% of participants taking alirocumab (combined with a statin), compared to 11.1% of participants on the placebo (combined with a statin) with a NNT of 63. Alirocumab (combined with a statin) produced a 15% hazard reduction (HR) in the primary outcome (HR 0.85, 95% CI 0.78–0.93) compared to the placebo (combined with a statin). Alirocumab (combined with a statin) reduced all-cause mortality by 15% (HR 0.85, 95% CI 0.73–0.98) compared to the placebo (combined with a statin). The most commonly occurring adverse event in the alirocumab group was injection site reactions. Adverse events in general between both groups were similar. Among patients with ACS, the combination of a statin with alirocumab reduced the risk of recurrent ischaemic cardiovascular events when compared to the placebo. | ODYSSEY OUTCOMES differ from FOURIER as the patients in this trial were post ACS patients while patients in FOURIER were stable CVD patients. This trial also showed a significant reduction in mortality when compared to FOURIER and could be attributed to the higher risk population (Post ACS) used in this trial. Trial reinforces the idea that lower LDL-C is better. |
Is LDL apheresis a thing of the past?

It is therefore conceivable that PCSK 9 inhibitors could potentially replace LA in the future, particularly if larger clinical trials produce similar results to the ODYSSEY ESCAPE trial and long-term safety data (beyond 3-years) demonstrates a reduced adverse effect profile for PCSK 9 inhibitors. There is a legitimate argument that PCSK 9 inhibitors would be more cost-effective than LA if favourable quality-adjusted life year (QALY) and disability-adjusted life year (DALY) data becomes available. The current annual price for alirocumab is between $4 500–$14 600 (USD), and evolocumab $5 850 (USD). Furthermore, PCSK 9 inhibitors have a more durable effect on reducing LDL-C, when compared to LA. The effects of LA wear off within two weeks and patients require weekly or even second week apheresis. However, PCSK 9 inhibitors may only be a replacement for LA in patients who demonstrate a reduction in LDL-C with PCSK 9 inhibitors or are able to tolerate PCSK 9 inhibitors. In patients who are unable to tolerate PCSK 9 inhibitors, evidence suggests that LA is currently the best option.

Microsomal transfer protein (MTP) inhibitors

Lomitapide, a MTP inhibitor, is also used to reduce LDL-C. Evidence suggests that MTP inhibitors reduce LDL-C by between 50–75% from baseline, allowing patients to achieve target LDL-C goals and reducing the need for concomitant apheresis. Lomitapide has demonstrated long-term safety and efficacy (5.7 years), but initial treatment requires dose titration to improve the drug’s tolerability. It is known to cause gastrointestinal (GIT) upset as well as hepatic steatosis and elevation of liver transaminases. Lomitapide is registered for use in patients with severe hypercholesterolaemia due to HoFH. Clinical trial evidence would be required to determine whether these benefits could be extended to patients with severe hypercholesterolaemia who do not have HoFH.

Other novel therapies in the pipeline

Other gene silencing therapies also hold promise in allying LA in patients refractory to treatment with high-intensity statins and ezetimibe. These agents include antisense oligonucleotides (ASOs) like mipomersan, and other small interfering RNA (siRNA) molecules including inclisiran. It is expected that these therapies will revolutionise the management of CVD.

Current guidance

Current guidelines suggest that LA be considered last-line treatment particularly with the advent of PCSK 9 inhibitors. Furthermore, it has been suggested that LA only be considered in patients with severe hypercholesterolaemia; if the patient is unable to reach their LDL-C goal despite the use of statin therapy, ezetimibe and PCSK 9 inhibitors for a period of one-year. There is suggesting that the results may not be generalisable to the severe hypercholesterolaemia population at large. That said, it is noteworthy that PCSK 9 inhibitors have the advantage of self-administration, thus not requiring patients to take time off work. PCSK 9 inhibitors also have a more favourable adverse effect profile, with the most common adverse effect being injection site reactions.
still a place for LA in severe hypercholesterolaemia when a trial of PCSK 9 inhibition is inadequate. LA is frequently combined with PCSK 9 inhibitors and statin therapy.\(^5,^7\)

**Conclusions**

LA does reduce LDL-C levels in patients with severe hypercholesterolaemia, particularly if they are resistant to treatment. However, the procedure finds itself lower down on the treatment algorithm with the advent of monoclonal antibodies directed against PCSK 9 and other antisense oligonucleotides and gene silencing therapies in the pipeline. These hold notable benefits in terms of ease of administration and compliance. If long-term safety data on these new agents prove favourable, LA could become a dwindling option for patients with HoFH and severe treatment resistant hypercholesterolaemia.

**Conflict of interest**

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