Lipoprotein Apheresis: First FDA Indicated Treatment for Elevated Lipoprotein(a)

Anne K. Nugent, Jessica V. Gray, Lauryn K. Gorby, Patrick M. Moriarty

Division of Clinical Pharmacology, Department of Internal Medicine, University of Kansas Medical Center, Kansas City, KS, USA

*Correspondence should be addressed to Patrick Moriarty; pmoriart@kumc.edu

Received date: 23 April, 2020, Accepted date: 22 May, 2020

Copyright: © 2020 Nugent AK, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

Background: Elevated lipoprotein(a) [Lp(a)] is an independent risk factor for cardiovascular disease (CVD) for which no commercially available pharmacotherapy exists. Currently, lipoprotein apheresis (LA) is the only available therapeutic option for patients with elevated Lp(a) and established CVD and in 2020, the FDA revised approval criteria for LA acknowledging elevated Lp(a) in its guidelines.

Hypothesis: LA has been shown to lower Lp(a) 60-75% in a single session and to reduce major adverse cardiovascular events 61-81%. Similar results were expected in patients at our large LA center in the United States.

Methods: In 2019, we evaluated the clinical significance of Lp(a) reduction with LA therapy. Since that time, six patients have initiated treatment with similar clinical profile. Results from the original paper have been updated as well as clinical profile of the additional patients.

Results: Fourteen of our 60 LA patients who were treated bi-weekly for an elevated Lp(a) with near normal LDL-C were evaluated. Following a mean period of 4 years, CV events were reduced by 94% compared to previous CV history. A greater than 70% acute reduction in mean pre- and post-LA corrected LDL-C and Lp(a) levels.

Conclusion: LA dramatically lowers Lp(a) and has demonstrated reductions in CVD events in retrospective trials. Prospective trials are under way to confirm clinical benefit of LA. Promising new pharmacological agents that reduce Lp(a) are in development; however, LA will continue to be the only FDA-approved therapy for Lp(a) reduction until these agents become commercially available.

Keywords: Lipoprotein(a), Myocardial infarction, Aortic valve stenosis, Ischemic stroke; Peripheral vascular disease

Background

Lipoprotein(a) [Lp(a)] is a genetically determined low-density lipoprotein (LDL) particle that is comprised of apolipoprotein(a) [apo(a)] and apolipoprotein B-100 (apoB) moieties. It is well-established that elevated Lp(a) is an independent risk factor for cardiovascular disease (CVD). It is associated with an increased risk of myocardial infarction, aortic valve stenosis, ischemic stroke and peripheral vascular disease [1,2].

The structure of Lp(a) is similar to plasminogen and competes for the same binding site, which reduces fibrinolysis resulting in secretion of plasminogen activator inhibitor-1 and thrombogenesis. Reduction in LDL-C is widely recognized as a means of reducing cardiovascular events. As a form of LDL-C, Lp(a) similarly binds atherogenic proinflammatory oxidized phospholipids, which attract a cascade of inflammatory cells to the vessel wall [3]. It is not entirely clear which of these specific mechanisms contributes to increased CVD risk.

An estimated 20% of the world’s population has elevated...
Lp(a) [4] and there is increasing evidence indicating the significant need for safe and effective therapeutic options. Currently, no commercially available pharmacotherapy exists that specifically targets the reduction of Lp(a) as well as clinically reduce CVD events. High dose nicotinic acid lowers Lp(a) but has not shown any clinical improvement in CVD when added to statin therapy [5]. Proprotein convertase subtilisin kexin type 9 inhibitors (PCSK9i) have been shown to lower Lp(a). In a recent post hoc analysis of ODYSSEY OUTCOMES data, a reduction in Lp(a), independent of concurrent reduction in LDL, was shown to reduce cardiovascular risk. However, Lp(a) reductions were modest and inconsistent [6].

**Lipoprotein Apheresis**

Given the lack of currently available pharmacotherapy for elevated Lp(a), lipoprotein apheresis (LA) is the only available therapeutic option for patients with elevated Lp(a) and established CVD. LA treatment can be administered via several different devices, takes 2-3 hours on average, and is performed weekly or biweekly. While there are multiple devices available worldwide, currently only the Kaneka dextran sulfate cellulose adsorption device is available for treatment in the U.S. It is well tolerated and associated with very few adverse events. While the drawbacks of LA include a substantial time commitment for patients and clinicians, a relatively expensive therapeutic regimen, and more invasive than pharmacotherapy, patients been shown to be remarkably compliant with the therapy. In one study in France, long term patient compliance was found to be 90% [7].

LA is an efficient and effective process for acutely lowering Lp(a). A single apheresis session decreases Lp(a) by approximately 60-75%, and chronic use of LA results in an approximately 25-40% lower mean interval concentration of Lp(a) compared to baseline [8-10].

LA treatments reduce more than apoB-containing lipoproteins. Inflammatory markers such as hs-CRP, fibrinogen, oxidized phospholipids, IL-6, IL-8, TNF-alpha, MCP-1, SAA, VCAM, ICAM, E-selectin Pentraxin 3, Galactin-3 and Lp-PLA2 are acutely and occasionally chronically reduced with LA. The reduction of plasma inflammatory markers by LA results in a rapid reduction of plaque inflammation. The acute removal of plasma proteins with LA occurs with minimal change to plasma volume and improves overall blood rheology via the reduction of red blood cell (RBC) aggregation and increase in RBC deformability. These changes in rheology following LA improves microvascular function [10-16].

Recommendations and guidelines for administration of LA vary between countries. As a result, various expert panels have offered their own recommendations. The National Lipid Association, Heart-UK, the American Society for Apheresis and the European Atherosclerosis Society consider elevated Lp(a) an additional risk factor that should be taken into account when deciding if LA should be used [17,18]. The German Federal Joint Committee (GBA) approved LA for patients with isolated elevated Lp(a) (>60mg/dL), well controlled LDL-C, and progressive CVD despite effective treatment of all other cardiovascular risk factors in 2008. The German reimbursement guidelines require evaluation of a patient’s cardiovascular risk profile as well as comprehensive clinical course before a committee decision is made on the use of LA [19,20].

The US Food and Drug Administration (FDA) has resisted including isolated elevated Lp(a) in its approval criteria for LA. Subsequently, it is extremely difficult for patients with elevated Lp(a), in the absence of other abnormal lipid levels, to access LA in the United States. However, in 2020, the FDA revised approval criteria for LA acknowledging elevated Lp(a) in its guidelines. The FDA’s revision to their guidelines indicating LA in the US includes a reduction from 160 mg/dL to 100 mg/dL for Group C as well as the addition of Group D, which includes patients with elevated Lp(a). The FDA will allow LA for the following types of patients.

- **Group A**: Functional Hypercholesterolemic Homozygotes with LDL-C >500 mg/dL;
- **Group B**: Functional Hypercholesterolemic Heterozygotes with LDL-C ≥ 300 mg/dL; and
- **Group C**: Functional Hypercholesterolemic Heterozygotes with LDL-C ≥ 100 mg/dL and either documented coronary artery disease or documented peripheral artery disease
- **Group D**: Lp(a) >60mg/dL and LDL-C >100 mg/dL and with either documented coronary artery disease or documented peripheral artery disease.

**Reduction of CVD Events**

LA has consistently demonstrated a reduction in CVD events associated with an acute reduction of Lp(a) levels and similar results were observed in our large LA center in the US [21].

In order to satisfy the GBA as well as evaluate the clinical significance of LA, the German Lipoprotein Apheresis Registry (GLAR) was founded in 2011 and recently released data demonstrating the clinical significance of LA over the course of almost five years in patients with elevated Lp(a) and CVD. A total of 1435 patients were evaluated,
and more than 19,800 LA treatments were performed at 71 German apheresis centers from 2012-2016. Data regarding occurrence of major adverse cardiovascular events (MACE) was analyzed retrospectively two years prior to initiating LA, as well as prospectively two years after initiating LA. Relative to the two years prior to initiating LA, incidence of MACE decreased by 78% during two years of LA treatment [22,23].

Additionally, three retrospective/prospective trials, Jaegar, Rosada, and Pro(a)LiFe, performed in Germany evaluated the clinical impact of LA in patients with elevated Lp(a) and CVD. The results from GLAR as well as the three trials align to support the clinical relevance and therapeutic value of LA to reduce the occurrence of MACE by 61-81% through the ongoing acute reduction of Lp(a).

In 2019, we observed the clinical significance of Lp(a) reduction with LA therapy in our large center in the United States. Fourteen of our 60 LA patients who were treated bi-weekly for an elevated Lp(a) with near normal LDL-C were evaluated. Following a mean period of 4 years, CV events were reduced by 94% compared to previous CV history. Since publication in 2019, an additional six patients with elevated Lp(a) and well controlled LDL-C levels, initiated bi-weekly therapy at our center. Baseline patient characteristics are displayed in Table 1.

Table 2 shows a greater than 70% reduction in mean pre- and post-LA corrected LDL-C and Lp(a) levels. Standard laboratory measurements of LDL-C include LDL-C from Lp(a) and it is estimated that the LDL-C content of Lp(a) is between 30% and 45% [24]. A corrected LDL-C value can be calculated with the formula: LDL-Ccorrected=LDL-Cuncorrected−(0.3xLp(a)). Corrected LDL-C represents the amount of LDL-C which can be treated with lipid modifying therapy because of its disassociation with Lp(a).

Table 3 is a comparison of the 14 patients previously included in the publication. In the prior publication, we used retrospective data to compare to patients once LA had been initiated. However, since publication patients have received an additional 10 months of treatment, which further validates the previously published conclusion that LA results in a clinically significant reduction of events. Further follow-up is needed, but results remain promising. Future analysis will include a combination of all 20 patients noted here, once all patients have been followed for at least 1 year.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Starting Age (years)</th>
<th>Sex</th>
<th>Treatment Duration (months)</th>
<th>Stent Myocardial Infarction</th>
<th>CABG</th>
<th>Stroke</th>
<th>Lipid-Modifying Therapy</th>
<th>CVD Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>24</td>
<td>M</td>
<td>13</td>
<td>6</td>
<td>1</td>
<td>0</td>
<td>Statin, Ezetimibe</td>
<td>Family History</td>
</tr>
<tr>
<td>2</td>
<td>55</td>
<td>F</td>
<td>12</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>Statin, Omega 3 Fatty Acid</td>
<td>Diabetes, Hypertension</td>
</tr>
<tr>
<td>3</td>
<td>59</td>
<td>F</td>
<td>3</td>
<td>5</td>
<td>1</td>
<td>0</td>
<td>PCSK9i, Statin, Omega-3 Fatty Acid, Ezetimibe</td>
<td>Diabetes, Hypertension, Family History</td>
</tr>
<tr>
<td>4</td>
<td>54</td>
<td>F</td>
<td>5</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>Statin</td>
<td>Hypertension, Family History</td>
</tr>
<tr>
<td>5</td>
<td>71</td>
<td>F</td>
<td>4</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>Omega-3 Fatty Acid</td>
<td>Family History</td>
</tr>
<tr>
<td>6</td>
<td>53</td>
<td>M</td>
<td>14</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>PCSK9i</td>
<td>Diabetes, Hypertension</td>
</tr>
</tbody>
</table>

Table 1: Baseline Characteristics of New LA Center Patients.
While these results are impressive, caution must be exercised when interpreting LA's clinical benefit. A lack of randomized controlled trials makes it difficult to confirm the true effect of LA. As such, Hohenstein and colleagues have designed the first prospective trial (MULTISELECT) to evaluate the clinical benefit of LA on MACE in subjects with elevated Lp(a). The study will use matched pairs of subjects, matching those who are approved for weekly LA by the German Federal Joint Committee to those who do not have access to LA in countries where it is not available as a reimbursed treatment. The study will follow subjects for at least 2 years and until 60 primary end point events have occurred [25].

An American Lipoprotein Apheresis Registry (ALAR) is currently being developed for LA sites in the United States in order to evaluate the clinical significance and utility of LA for U.S. patients. This registry will allow researchers to promote awareness of LA’s effectiveness for treating FH and elevated Lp(a) levels. The information collected in the registry will help improve treatment for patients using LA and will be used to learn more about the clinical outcomes, including frequency of major cardiac events before and after LA initiation, in the U.S.

ALAR plans to prospectively follow patients for 5 years with bi-annual follow-up collection periods. The aim is to collect a comprehensive patient profile to further the understanding the extensive benefits LA offers to patients in the U.S. including those with elevated Lp(a).

**Pharmacotherapy for Lp(a) Reduction under Investigation**

Promising new pharmacological agents that reduce Lp(a) are in development. Recently inclisiran, a small
interfering RNA (siRNA) that decreases synthesis of PCSK9 in the liver, demonstrated a 20% reduction in Lp(a), similar to reductions seen in two large trials with the PCSK9i’s, alirocumab and evolocumab [26]. Studies to determine if inclisiran reduces cardiovascular events are still ongoing and if Lp(a) reductions are consistent irrespective of baseline Lp(a) levels, unlike PCSK9i.

AMG 890, a siRNA that inhibits Lp(a), is very early in development and a phase 1 trial is underway. Animal studies demonstrated an 85-90% reduction in serum Lp(a) in mice [27].

APO(a)-LRX, now called TQJ230, is an antisense oligonucleotide (ASO) that inhibits the production of apo(a) in the liver. In a recent phase 2 trial of patients with established CVD, TQJ230 treatment resulted in a mean 80% reduction at the highest dose (20 mg weekly) [28]. At the highest dose regimen, 98% of patients attained an Lp(a) level of 50 mg/dL (125 nmol/L) or lower, a target threshold associated with risk reduction and supported by guidelines in the US and Europe. The most frequent adverse events were injection-site reactions and there were no safety concerns related to platelet counts, liver function, renal function, or influenza-like symptoms [29,30]. While these results are promising, it is still unknown if TQJ230 will demonstrate clinical improvement in CVD. A phase 3 trial commenced in December 2019 to determine if TQJ230 impacts CVD outcomes.

While potent Lp(a)-lowering therapies are on the horizon, commercial availability of these drugs is still several years away.

**Conclusion**

Elevated Lp(a) is a well-established independent risk factor for CVD for which no pharmacotherapy exists. While there are some shortcomings, LA dramatically lowers Lp(a) and has demonstrated reductions in CVD events in retrospective trials. LA is the first therapy to receive FDA indication for Lp(a) reduction and will continue to be only therapy for elevated Lp(a) until emerging pharmacological agents can be thoroughly studied and approved.

**References**


14. Zanetti M, Zenti M, Barazzoni R, Zardi F, Semolic A,


