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

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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 ODYSEEY 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: $LDL\text{-}C_{corrected}=LDL\text{-}C_{uncorrected}-(0.3xLp(a))$. 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.

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

Table 1: Baseline Characteristics of New LA Center Patients.

N=6	Pre-LA therapy	Post-LA therapy
Uncorrected LDL-C (mg/dL) (range)	61 (18-107)	18 (-70%) (14-21)
Corrected/Treatable LDL-C (mg/dL (range)	25 (2-86)	6 (-75%) (2-16)
Lp(a) (mg/dL) (range)	121 (54-219)	33 (-73%) (14-64)

Table 2: Acute LA Therapy Reductions in New LA Center Patients.

	Retrospective Period	Prospective Period 2019	Prospective Period 2020
	Before initiating LA therapy	Ongoing LA treatment	Ongoing LA treatment
Patients	14	14	14
Mean Duration, months (range, months)	72 (12-96)	48 (8-105)	58 (15-115)
MACE (total)	36	2 (-94%)	3 (-92%)
Myocardial Infarction	10	0	0
CABG	12	0	1
Stent	10	2	2
Stroke	4	0	0

Table 3: LA Center Patients with Elevated Lp(a) and CVD.

Ongoing LA Research

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

1. Tsimikas S, Hall JL. Lipoprotein (a) as a potential causal genetic risk factor of cardiovascular disease: a rationale for increased efforts to understand its pathophysiology and develop targeted therapies. Journal of the American College of Cardiology. 2012 Aug 21;60(8):716-21.

2. Marcovina SM, Koschinsky ML. Lipoprotein (a) as a risk factor for coronary artery disease. The American Journal of Cardiology. 1998 Dec 17;82(12):57U-66U.

3. Tsimikas S. A test in context: lipoprotein (a): diagnosis, prognosis, controversies, and emerging therapies. Journal of the American College of Cardiology. 2017 Feb 6;69(6):692-711.

4. Tsimikas S. Lipoprotein (a): novel target and emergence of novel therapies to lower cardiovascular disease risk. Current Opinion in Endocrinology, Diabetes, and Obesity. 2016 Apr;23(2):157-64.

5. Goldberg A, Alagona Jr P, Capuzzi DM, Guyton J, Morgan JM, Rodgers J, et al. Multiple-dose efficacy and safety of an extended-release form of niacin in the management of hyperlipidemia. The American Journal of Cardiology. 2000 May 1;85(9):1100-5.

6. Bittner VA, Szarek M, Aylward PE, Bhatt DL, Diaz R, Edelberg JM, et al. Effect of Alirocumab on Lipoprotein (a) and Cardiovascular Risk After Acute Coronary Syndrome. Journal of the American College of Cardiology. 2020 Jan 13;75(2):133-44.

7. Beliard S, Gallo A, Duchêne E, Carrié A, Bittar R, Chapman MJ, et al. Lipoprotein-apheresis in familial hypercholesterolemia: long-term patient compliance in a French cohort. Atherosclerosis. 2018 Oct 1;277:66-71.

8. Waldmann E, Parhofer KG. Lipoprotein apheresis to treat elevated lipoprotein (a). Journal of Lipid Research. 2016 Oct 1;57(10):1751-7.

9. Arai K, Orsoni A, Mallat Z, Tedgui A, Witztum JL, Bruckert E, et al. Acute impact of apheresis on oxidized phospholipids in patients with familial hypercholesterolemia. Journal of Lipid Research. 2012 Aug 1;53(8):1670-8.

10. Stefanutti C, Mazza F, Pasqualetti D, Di Giacomo S, Watts GF, Massari MS, et al. Lipoprotein apheresis downregulates IL-1α, IL-6 and TNF-α mRNA expression in severe dyslipidaemia. Atherosclerosis Supplements. 2017 Nov 1;30:200-8.

11. Moriarty PM, Gibson CA, Kensey KR, Hogenauer W. Effect of low-density lipoprotein cholesterol apheresis on blood viscosity. The American Journal of Cardiology. 2004 Apr 15;93(8):1044-6.

12. van Wijk DF, Sjouke B, Figueroa A, Emami H, van der Valk FM, MacNabb MH, et al. Nonpharmacological lipoprotein apheresis reduces arterial inflammation in familial hypercholesterolemia. Journal of the American College of Cardiology. 2014 Oct 7;64(14):1418-26.

13. Eliaz I, Weil E, Dutton JA, McCalley AE, Nolte B, Moriarty PM. Lipoprotein apheresis reduces circulating galectin-3 in humans. Journal of Clinical Apheresis. 2016 Aug;31(4):388-92.

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

Messa MG, et al. HELP LDL apheresis reduces plasma pentraxin 3 in familial hypercholesterolemia. PloS one. 2014;9(7).

15. Horváth L, Császár A, Falus A, Dieplinger H, Horváth A, Puskás É, Halm G, Bányai A, Pálóczi K, László E, Kalabay L. IL-6 and lipoprotein (a)[LP (a)] concentrations are related only in patients with high APO (a) isoforms in monoclonal gammopathy. Cytokine. 2002 Jun 1;18(6):340-3.

16. Moriarty PM, Hemphill L. Lipoprotein apheresis. Cardiology Clinics. 2015 May 1;33(2):197-208.

17. Goldberg AC, Hopkins PN, Toth PP, Ballantyne CM, Rader DJ, Robinson JG, et al. Familial hypercholesterolemia: screening, diagnosis and management of pediatric and adult patients: clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. Journal of Clinical Lipidology. 2011 May 1;5(3):133-40.

18. Khan TZ, Pottle A, Pennell DJ, Barbir MS. The expanding role of lipoprotein apheresis in the treatment of raised lipoprotein (a) in ischaemic heart disease and refractory angina. Global Cardiology Science and Practice. 2014 Jun 1;2014(1):3.

19. German Federal Ministry of Health. Publication of a decision of Federal Joint Committee on apheresis for isolated Lp(a)-elevation with progressive cardiovascular disease. Transactions Ger Fed Ministries (BAnz). 2008;138:3321.

20. Klingel R, Heibges A, Fassbender C. Lipoprotein apheresis results in plaque stabilization and prevention of cardiovascular events: comments on the prospective Pro (a) LiFe study. Clinical Research in Cardiology Supplements. 2015 Apr 1;10(1):46-50.

21. Moriarty PM, Gray JV, Gorby LK. Lipoprotein apheresis for lipoprotein (a) and cardiovascular disease. Journal of Clinical Lipidology. 2019 Nov 1;13(6):894-900.

22. Schettler VJ, Neumann CL, Peter C, Zimmermann T, Julius U, Roeseler E, et al. The german lipoprotein apheresis registry (GLAR)–almost 5 years on. Clinical research in cardiology supplements. 2017 Mar 1;12(1):44-9.

23. Jaeger BR, Richter Y, Nagel D, Heigl F, Vogt A, Roeseler E, Parhofer K, Ramlow W, Koch M, Utermann G, Labarrere CA. Longitudinal cohort study on the effectiveness of lipid apheresis treatment to reduce high lipoprotein (a) levels and prevent major adverse coronary events. Nature Reviews Cardiology. 2009 Mar;6(3):229-39.

24. Viney NJ, Yeang C, Yang X, Xia S, Witztum JL, Tsimikas S. Relationship between "LDL-C", estimated true LDL-C, apolipoprotein B-100, and PCSK9 levels following lipoprotein (a) lowering with an antisense oligonucleotide. Journal of Clinical Lipidology. 2018 May 1;12(3):702-10.

25. Hohenstein B, Julius U, Lansberg P, Jaeger B, Mellwig KP, Weiss N, et al. Rationale and design of MultiSELECt: A European Multicenter Study on the Effect of Lipoprotein (a) Elimination by lipoprotein apheresis on Cardiovascular outcomes. Atherosclerosis Supplements. 2017 Nov 1;30:180-6.

26. Ray KK, Wright RS, Kallend D, Koenig W, Leiter LA, Raal FJ, et al. Two phase 3 trials of Inclisiran in patients with elevated LDL cholesterol. New England Journal of Medicine. 2020 Apr 16;382(16):1507-19.

27. Melquist, S., et al., Melquist S, Wakefield D, Hamilton H, Chapman C, Grondolsky J, Schienebeck C, Almeida L, Klas C, Hagen C, Almeida A, Hegge J. Targeting apolipoprotein (a) with a novel RNAi delivery platform as a prophylactic treatment to reduce risk of cardiovascular events in individuals with elevated lipoprotein (a). Circulation. 2016 Nov 11;134(suppl_1): A17167.

28. Tsimikas S, Karwatowska-Prokopczuk E, Gouni-Berthold I, Tardif JC, Baum SJ, Steinhagen-Thiessen E, Shapiro MD, Stroes ES, Moriarty PM, Nordestgaard BG, Xia S. Lipoprotein (a) Reduction in Persons with Cardiovascular Disease. New England Journal of Medicine. 2020 Jan 1;382(3):244-255.

29. Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H, et al. 2016 ESC/EAS guidelines for the management of dyslipidaemias. European Heart Journal. 2016 Oct 14;37(39):2999-3058.

30. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, De Ferranti S, Faiella-Tommasino J, Forman DE, Goldberg R. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Journal of the American College of Cardiology. 2019 Jun 17;73(24):3168-209.