The role of Lp(a) in cardiovascular diseases and treatment options

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ABSTRACT

Based on Centers for Disease Control and Prevention and World Health Organization statistics, cardiovascular disease (CVD) is the leading cause of death globally, especially in developed countries. Atherosclerosis, associated with inflammation and endothelial dysfunction, is one of the major causes of cardiovascular disease, and several studies have tried to identify risk factors for atherosclerosis. Lipoprotein (a) [Lp(a)] has become increasingly appreciated in the past decades as a strong independent risk factor. Although there are several clinical trials on lipid-lowering drugs to reduce the risk of CVD, most drugs not only fail to drop Lp(a) levels significantly but also do not specifically target Lp(a). While PCSK9 inhibitors are currently regarded as the best therapeutic drug for elevated Lp(a), recently, the development of novel drugs targeting the RNA of the Lp(a) gene (LPA), small interfering RNAs and antisense oligonucleotides, has progressed rapidly, and they have been assessed for their clinical efficacy. The objective of this case study/focused review is to review what Lp(a) is, why it has clinical significance in developing CVD, and more importantly how its level is controlled.

Keywords: Lipoprotein (a), cardiovascular diseases, atherosclerosis, PCSK9 inhibitors, antisense oligonucleotides, small interfering RNA.

CASE

A 71-year-old woman with significantly elevated Lp(a), 271 mg/dL (normal range: 5–29 mg/dL; 13–73 nmoles/L), presented with a proximal RCA lesion after developing intrascapular pain with exertion and a previous history of a drug-eluting stent in this region in early 2021. Her lipid-lowering regimen included alirocumab 150 mg every 2 weeks and rosuvastatin 40 mg daily, and her lipid levels in May 2022, were total cholesterol 87 mg/dL, triglyceride 83 mg/dL, HDL 60 mg/dL, and LDL 10 mg/dL, and non-HDL 27 mg/dL. She complained of upper back pain in a certain position when standing. Her elevated Lp(a) had not caused aortic stenosis, and no other significant cardiovascular-related symptoms, including murmurs, pedal edema, or neurological symptoms were present.

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THE UNIQUE STRUCTURE OF LP(A)

Lipoprotein (a) [Lp(a)] was discovered in 1963 by geneticist Kåre Berg.[1] Encoded by the LPA gene, also known as APOA gene, Lp(a) consists of low-density lipoprotein (LDL) with its apolipoprotein B-100 (apoB) linked to apolipoprotein A [apo(a)] in a 1:1 molar ratio by disulfide bonds. The human LPA gene that has evolved from the human plasminogen (PLG) gene via gene duplication, deletion of exons for kringle domain I to III, and possible gene conversion[2] expresses kringle domain IV and V in apo(a). The number of repeats of kringle domain IV-2 sequence in apo(a) is not only inversely associated with Lp(a) plasma concentration but also responsible for varying molecular weights of Lp(a).[3] This size polymorphism of apo(a) causes different apo(a) immunoreactivities to antibodies,[4] resulting in unreliable measurement of Lp(a) in immunoassays and in challenges to sound clinical decision making. Therefore, standardized methods of measuring Lp(a) are necessary by using nmol/L to eliminate the discrepancy between the level in traditionally used units

(mg/dL) and the level of Lp(a) measured by immunoassays.[5] However, there are concerns that the conversion from mg/dL to nmol/L does not always represent the real levels of Lp(a), depending on its composition of apo(a) isoforms; this method could overestimate Lp(a) levels when it has large isoforms and underestimate when small isoforms.[6]

Lp(a) metabolism

Lp(a) is exclusively synthesized in the liver, as LDL is. Since Lp(a) contains apoB, one might speculate that Lp(a) is synthesized from other lipoproteins containing apoB, such as LDL. However, LDL is not a precursor of Lp(a).[7] Also, due to their structural similarities, it was hypothesized that LDL receptors may have a role in controlling the levels of both LDL and Lp(a). Since some studies showed that familial hypercholesterolemia (FH) patients with LDL receptor (LDLR) mutation present with higher levels of Lp(a), it was believed that LDLR has a critical role in the clearance of Lp(a).[8] However, although statins, which increase the LDL clearance by upregulation of LDL receptors and inhibit HMG-CoA reductase, decrease the level of LDL cholesterol, most studies have concluded that statins do not affect or may even increase Lp(a).

Lp(a) ends up in the liver where it is produced. Similar to the hypothesis on LDL receptor-assisted clearance of Lp(a), the asialoglycoprotein receptor (ASGPR) in the liver may explain the reuptake of Lp(a) by the liver.[9] Also, one of the identified pathways that can lower the apo(a) transcription level involves Farnesoid-X receptor (FXR); activation of FXR in hepatocytes by its cognate ligand, bile acids, can interfere with the binding of transcription factor Hepatic Nuclear Factor (HNF) 4α to apo(a) promoter region in the LPA gene.[6] In addition, several studies have suggested that the kidney also has an important role in Lp(a) metabolism, considering that patients with defects in renal function (e.g., creatinine clearance lower than 70 ml/minute) have elevated Lp(a) levels.[10,11]

Clinical significance

Although multiple factors, including lifestyle, influence the risk of developing CVD, numerous studies have reported that a high Lp(a) level is one of the most important risk factors for CVD, including aortic valve stenosis and even myocardial infarction.[12] Since genetics among other factors have a crucial role in the level of Lp(a), based on Hyperlipidemia Education and Atherosclerosis Research Trust UK (HEART UK), patients with a family history of or high risk for CVD are strongly recommended to measure Lp(a) at least once in a lifetime to gauge Lp(a)-related risk. Also, low kringle domain IV-2 repeat in LPA gene, which results in high Lp(a) levels, is one of the strong genetic risk predictors of coronary heart disease.[3] Similarly, even though the consensus on Lp(a) level cutoff is >30–50 mg/dL, different criteria for Lp(a) level cutoff are needed in various ethnic groups[13]; a recent observational study showed that white, South Asian, black, and Chinese have different median Lp(a) concentrations: 19, 31, 75, and 16 nmol/L, respectively.[14]

Besides Lp(a)'s pro-thrombotic and pro-inflammatory activities,[15] high atherogenicity is probably the most recognized characteristic of Lp(a). It is also well-documented that the deposition of intact Lp(a) or apo(a) expedites the formation of atherosclerotic plaques in the coronary arteries and aorta. The several mechanisms of Lp(a) in the development of atherosclerosis include its ability to allow more macrophages to permeate the endothelial cell layers, increase the formation of foam cells, induce the proliferation of smooth muscle cells, and upregulate adhesion molecules, such as ICAM-1.[8,16] Another proposed mechanism is Lp(a)'s higher reactivity to macrophages and binding capacity to glycosaminoglycans (GAG), which both promote atherosclerosis.[17] In addition, Lp(a) is a preferred carrier of oxidized phospholipids (OxPL) that can cause inflammation in the arterial wall and potentiate atherosclerosis.[18]

Lp(a)'s affinity for fibrin and homologous structure to plasminogen without protease activity, given that human LPA gene sequence is highly homologous to the human PLG gene sequence,[2] may contribute to its inhibiting fibrinolysis and increasing thrombotic complications. However, a recent study demonstrated that *ex vivo* clot lysis time and biomarkers of fibrinolysis and coagulation did not change upon treatment of IONIS-APO(a)$_{RX,}$[19] antisense oligonucleotides that downregulate the production of Lp(a), but contrasting

data were also reported in different study methods as well as *ex vivo*; one retrospective study found a higher risk of deep vein thrombosis and pulmonary embolism in female patients younger than 50 years with elevated Lp(a).[20] Therefore, more investigation is necessary to identify the role of Lp(a) *in vivo* in the pathophysiology of cardiovascular thrombosis.

Pharmacological intervention for high Lp(a) levels

Aspirin, a nonsteroidal anti-inflammatory drug (NSAIDs), has a broad range of activities, including antiplatelet effects at a low dose. Due to its significant clinical benefits in the prevention of cardiovascular events, it is one of the most commonly used cardiovascular drugs. Even though low-dose aspirin appeared to be effective at decreasing Lp(a) levels by 20% in a small group of Japanese patients with high Lp(a), a clinical trial in a larger patient population was necessary to provide clarification on the intriguing role of aspirin.[8] The latest available large-scale clinical trial confirmed its efficacy in reducing the risk of cardiovascular events among carriers of allele variant (rs3798220) of apo(a).[21]

Niacin, vitamin B3, affects Lp(a) level either by downregulating the production of its components, apo(a) and apoB-100, in DM patients [22] or by inhibiting hepatic APOA mRNA by interfering with the promoter region.[23] Unfortunately, based on some clinical trials providing conflicting data, niacin is not considered the first-line drug for high Lp(a), and niacin in high doses has some undesirable side effects, such as hyperuricemia, hyperglycemia, and flushing.

Proprotein convertase subtilisin/Kexin type 9 (PCSK9) inhibitors are non-statin lipid-lowering drugs that decrease LDL levels by preventing LDL receptor degradation so that the liver can maximize the uptake of LDL from the blood. While the mechanism of its action on Lp(a) is still unclear, various studies have confirmed the importance of PCSK9 in Lp(a) levels from the findings that PCSK9 loss of function variants have comparably low Lp(a) level as therapeutic effects of PCSK9 inhibitors do.[24] Two FDA-approved PCSK9 inhibitors, indicated for patients with a high risk of cardiovascular events and high LDL levels, include alirocumab and evolocumab. Compared to the currently available drugs, PCSK9 inhibitors have shown greater efficacy in lowering Lp(a) in addition to LDL levels. Some clinical trials found that PCSK9 inhibitors can reduce Lp(a) levels by up to 25%.[25] In a recent clinical trial, subcutaneous injection of evolocumab 420 mg once a month for 12 weeks and measurement of Lp(a) at week 16 showed that this PCSK9 inhibitor can decrease the level of Lp(a) by approximately 13% in patients with hyperlipidemia [ClinicalTrials.gov Identifier: NCT02729025]. A clinical trial on alirocumab also showed a 29.1% decrease in Lp(a) levels in 24 weeks from 150 mg administration of alirocumab with statin.[26] Also, 61.7% of patients whose Lp(a) is ranged from 50–75 mg/dL achieved Lp(a) <50 mg/dL in the same regimen.[26]

Cholesteryl ester transfer protein (CETP) inhibitors act by inhibiting the transfer of cholesteryl ester facilitated by CETP from HDL to LDL and VLDL (so that theoretically atherosclerosis is less likely to occur. Moreover, several studies found that CETP inhibitors are associated with a significant increase in HDL and a decrease in LDL.[27] The recent phase 3 clinical study on the efficacy and tolerability of Anacetrapib, a CETP inhibitor, in the combination with statin therapy showed a 31.8% decrease in Lp(a) levels in heterozygous familial hypercholesterolemia patients upon oral administration of 100 mg once daily for 52 weeks [ClinicalTrials.gov Identifier: NCT01524289].

Lipoprotein apheresis (LA) has demonstrated its potential in lowering various lipoproteins, including Lp(a) by removing them in circulation. In a recent clinical trial, after 3 months of weekly lipoprotein apheresis, patients with refractory angina with high Lp(a) had a decrease in thrombogenesis and carotid atherosclerosis as well as an increase in exercise capacity, myocardial perfusion, SF-36 quality of life score, and improvement in Seattle Angina Questionnaire Score [ClinicalTrials.gov Identifier: NCT01796912]. Although apheresis has some limitations, such as high cost, long duration procedure, and low blood pressure as a common side effect, results from several clinical trials have demonstrated that the benefits of Lp(a) removal outweigh the limitations due to

decreases in inflammation, prothrombic events, and atherosclerotic plaques progression.[28]

Antisense oligonucleotides (ASO) have emerged as novel therapeutic agents to specifically target the production of Lp(a). Sharing the similar targets of small interfering RNAs (siRNAs), ASOs are complementary to the target mRNA sequence, then promote degradation of the mRNA, and decrease mRNA translation. Several clinical studies on ASOs reported a significant reduction in Lp(a). For example, ISIS681257 (AKCEA-APO(a)-LRx), a second-generation antisense oligonucleotide, is now in a phase 2 clinical trial and demonstrated a 78% decrease in Lp(a) upon subcutaneous injection of 20 mg once weekly [ClinicalTrials.gov Identifier: NCT03070782]. Moreover, the third-generation ASOs with greater resistance to nuclease as well as better binding affinity are undergoing development in the hope of achieving more significant clinical benefits.

siRNAs, among all clinical interventions to lower the Lp(a) level, seem to have the highest potential to accomplish this goal. In contrast to single-strand ASOs, siRNAs enter the cytoplasm as a double strand, and the guide strand associates with an RNA-induced silencing complex (RISC), which contributes to the prolonged effects of siRNAs, to downregulate the translation of the mRNA.[29] Several challenges including stability of RNA in circulation, immune response, and effective delivery to the system, were overcome by chemical modifications; for instance, conjugation with GalNAc that binds to ASGPR predominantly expressed on hepatocytes improves the delivery of drugs to the liver. To date, Inclisiran (ALN-PCSsc), the FDA-approved siRNA targeting PCSK9, in a phase 2 clinical trial showed up to a 25% decrease in Lp(a) on day 180 after 300 mg subcutaneous administration on days 1 and 90 [ClinicalTrials.gov Identifier: NCT02597127]. Olpasiran (AMG890), an siRNA against Lp(a) mRNA, also has been evaluated in a phase 2 clinical trial that would be completed on November 2, 2022 [ClinicalTrials.gov Identifier: NCT04270760]. Finally, another promising novel siRNA targeting Lp(a) mRNA, SLN360, was recently proven to decrease Lp(a) levels by 98% after subcutaneous administration of a single dose of 600 mg, with two adverse episodes irrelevant to SLN360.[30] Given that the siRNA is expected to be introduced into the market in 3 years, the drugs targeting RNA may become the treatment of choice for high Lp(a) and CVD risks.

Summary

Cardiovascular diseases have been the number one cause of mortality in the United States, and studies have demonstrated that elevated Lp(a) levels are a significant factor in the development of CVD. Even if a patient's lipid levels are in the normal range and well-controlled, a significantly high Lp(a) should be closely monitored. One of Lp(a)'s structural characteristics, a size polymorphism, challenges the accurate measurement of Lp(a) and sound clinical decisions. In addition to the challenge posed by its significant size variability, implementation of unit standardization of Lp(a) concentration (nmol/L) seems to be necessary to eliminate the discrepancy between levels expressed in mg/dL and those measured by immunoassays. To substantially lower the levels of Lp(a), a fundamental understanding of the Lp(a) metabolic pathways is needed. Even though the Lp(a) metabolism is not fully understood, several hypotheses about the factors that affect the level of Lp(a) include clearance by LDL receptors, asialoglycoprotein receptors, the kidney, and a decrease in transcription levels by Farnesoid-X receptors. Due to Lp(a)'s strong association with the risk of CVD, there have been trials to lower the level of Lp(a) to reduce the development of atherosclerosis. However, unlike novel drugs directly targeting the translation of Lp(a) mRNA, none of other commonly used cardiac medications have had the dramatic effects. At present, PCSK9 is currently the best therapy for elevated Lp(a) levels.

Conclusion

Lp(a) is a strong independent risk factor for cardiovascular diseases, and its clinical significance indicates the need for more study on its activities and metabolism, which could offer alternative approaches for the development of Lp(a) lowering drugs. Also, with the promising clinical trial results, the novel siRNA targeting Lp(a) mRNA could have the potential to become the drug of choice in the hope of decreasing the morbidity and mortality of CVDs.

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