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What’s new on therapies for elevated lipoprotein(a)

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1. Lipoprotein(a)

Lipoprotein(a) [Lp(a)] is a highly polymorphic particle comprised of a low-density lipoprotein (LDL)-like moiety covalently bound to a hydrophilic glycoprotein, termed apolipoprotein (a) [apo(a)] [1]. Lp(a) is highly heritable, with plasma levels primarily determined by the LPA gene [1]. Circulating plasma concentrations can vary considerably and hitherto no physiological function for the molecule has been conclusively established [2]. While the apo(a) component is synthesized almost exclusively in the liver, the site of Lp(a) assembly has not been confirmed [1]. Its clearance from plasma also remains unclear, with the LDL receptor thought to play only a modest role. Other possibilities include catabolism by the kidney, through scavenger or plasminogen receptors, or through proteolytic cleavage of apo(a) [1,2]. Although resistant to diet or various physiological and environmental factors [1,2] epidemiological studies have demonstrated that Lp(a) levels can be modestly dependent on dietary intake [3,4] and ethnicity [5,6].

2. Lp(a) and risk of atherosclerotic cardiovascular disease (ASCVD)

Lp(a) is thought to contribute to increased cardiovascular risk through three main mechanisms; the atherogenic nature of its LDL-like moiety, the thrombogenic and anti-fibrinolytic effects of its apo(a) moiety, and the pro-inflammatory effects of its oxidized phospholipid content [1]. Its contribution to increased ASCVD risk may be further exacerbated by the pro-atherogenic properties of both LDL-c and apo(a) [1].

Previously, Lp(a) was considered to be a weak risk factor for CVD whose significance was largely negated by good LDL-c control, which was considered to have the most effect on atherosclerosis progression or event rates [7]. Multiple epidemiological studies however, confirm a positive association between circulating Lp(a) levels and risk of ASCVD [8–15], a finding that is consolidated by Mendelian Randomisation and genome-wide association studies [16–21]. Notably, analysis of individual variants in 63,743 cases and 130,681 controls revealed that the most potent genetic association with coronary artery disease (CAD) was the LPA locus, more so than variants related to LDL, PCSK9 or 9p21 (a genetic variant on chromosome 9p21 that is strongly linked to CAD) [21].

Previous analysis revealed that the association between Lp(a) levels and risk of cardiovascular events was more significant in patients with established CAD, while its prognostic value in people with low cholesterol levels was unclear, predominantly due to marked heterogeneity across trials [22]. The JUPITER trial revealed that in white patients treated with potent statin therapy, Lp(a) was a significant determinant of residual risk, although the magnitude of risk reduction in those treated with rosuvastatin was similar amongst patients with high or low Lp(a) [23]. In the BiomarCaRE project, regional differences were seen within the European population for Lp(a) levels. However, Lp(a) was associated with an increased risk for major coronary events and CVD in patients with diabetes [24]. More recently, however, a large individual-patient meta-analysis of statin-treated patients has revealed that both elevated baseline and on statin Lp(a) levels show an independent and linear relationship with CVD risk [25].

Meta-analysis of long-term prospective studies (126,634 patients from 36 studies) reveals a continuous, independent and modest association of Lp(a) concentration and risk of CHD and stroke. This association appears to be exclusive to vascular outcomes and presents under a wide range of clinical circumstances [8]. More recent analysis has revealed that risk of coronary heart disease (CHD) is proportionally associated with the absolute change in Lp(a) mass concentration, with clear implications for the need for new therapies targeting Lp(a). The authors propose that Lp(a) must be lowered by ~100 mg/dL to achieve the same CHD risk reduction as lowering LDL-c by 38.67 mg/dL [26]. The INTERHEART study of different ethnicities revealed significant variation in Lp(a) concentration and size between ethnic groups. However, higher Lp(a) concentrations were associated with an increased risk of myocardial infarction, particularly in South Asians and Latin Americans. Isoform size did not significantly contribute to risk [27].

The National Heart, Lung and Blood Institute acknowledges that pathophysiological, epidemiological and genetic studies provide strong evidence that Lp(a) is a causal mediator of both CVD and calcific aortic valve disease [28]. Recent guidelines

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from the American Heart Association and American College of Cardiology recognize elevated Lp(a) as a risk-enhancing factor in the development of ASCVD, supporting earlier guidelines from the European Atherosclerosis and Cardiology Societies [29,30]. Indications for its measurement are a family history of premature ASCVD or a personal history of ASCVD not explained by major risk factors. Enhanced risk is associated with Lp(a) levels ≥50 mg/dL or ≥125 mmol/L, although in women it is recommended that this also be accompanied by hypercholesterolemia [30]. Measurement may also be valuable in premature onset ASCVD where elevated levels of Lp(a) are both more common and associated with more advanced atherosclerosis [31,32].

Despite the strong positive association with ASCVD, plasma levels of Lp(a) are not routinely tested, nor are there any established or clinically approved drug treatments for lowering Lp(a) levels, with the exception of apheresis [33], which is approved in Germany and the US. Statin treatment does not appear to have any effect and there are reports that they may increase circulating levels of Lp(a) by 10–20%, contributing to increased residual risk [1], although the consistency of this claim remains to be confirmed. A recent study has suggested that an Lp(a) level >50 mg/dL is associated with an increased risk of recurrent events in patients on statin therapy [25]. Other pharmacological therapies including niacin, microsomal triglyceride transfer protein (MTP) inhibitors and cholesteryl ester transfer protein (CETP) inhibitors all lower Lp(a) levels to varying degrees; however, none has been specifically tested in randomized controlled trials and their clinical use remains limited [2,34]. Early studies point to a role for hormones, including estrogen and testosterone in regulating Lp(a) levels, but these are not considered standard treatments [35,36]. To date, the most promising pharmacotherapies for lowering Lp(a) are the PCSK9 monoclonal antibodies and apo(a) targeting antisense oligonucleotides (ASOs).

3. Effect of PCSK9 inhibitors – results from FOURIER and ODYSSEY outcomes

Carriers of the PCSK9 loss-of-function mutations generally display similar Lp(a) levels to non-carriers. In contrast, gain-of-function mutation carriers appear to have elevated Lp(a) compared with normolipidemic controls. Interestingly, epidemiological studies reveal no association between circulating PCSK9 and Lp(a) levels [37]. In vitro studies suggest that although PCSK9 does not significantly modify Lp(a) catabolism, it does enhance the hepatic secretion, a process that is reversed with PCSK9 inhibition [38]. More recently, PCSK9 inhibition with a monoclonal antibody has been shown to reduce plasma Lp(a) by decreasing the production of Lp(a) particles as monotherapy. When given in combination with a statin, PCSK9 inhibition resulted in an increase in the catabolism of Lp(a) particles [39]. In patients treated with PCSK9 inhibitors, reductions in plasma levels of Lp(a) have been observed by up to 30% [40], with even modest lowering associated with some clinical benefit [41]. While the mechanisms are unknown, it has been postulated to be via several receptors, including the LDL receptor, the apoE receptor or scavenger receptor class B type 1, which may also catabolize Lp(a). Other mechanisms include targeting docking, sorting and endocytic receptors or reductions in apoB or assembly of Lp(a) on hepatocyte surface [42,43].

Recent insight from the secondary investigation of other lipid targets in the large-scale PCSK9 monoclonal antibody cardiovascular outcomes trials [44,45] suggests additional beneficial effects on Lp(a) levels, which may subsequently impact cardiovascular risk.

3.1. FOURIER

The FOURIER trial, which investigated evolocumab in 25,096 patients with established ASCVD over 2.2 years, observed a significant positive association between baseline Lp(a) levels and risk of cardiovascular events, irrespective of LDL-c levels. Evolocumab significantly reduced Lp(a) levels by 26.9% (p < 0.001) from baseline to 48 weeks, with the greatest reduction seen in those with the highest baseline levels. There was also a modest positive correlation in the percent change in Lp(a) and LDL-c in those treated with evolocumab. The highest clinical benefit of evolocumab was observed in patients who had the highest baseline levels of Lp(a). Although the relationship between Lp(a) and coronary risk remained similar throughout the range of LDL-c levels, the relative risk reduction was greatest in those who achieved reductions in both LDL-c and Lp(a) [34]. This is underscored somewhat by recent data from the ANITSCHKOW study, which reveals that patients with very high Lp(a) levels treated with evolocumab had only a 14% reduction in Lp(a) levels, which resulted in persistent Lp(a) elevation and no significant impact on arterial inflammation [46].

3.2. ODYSSEY outcomes

ODYSSEY OUTCOMES investigated alirocumab in 18,924 statin-treated patients with a recent acute coronary syndrome over 2.8 years. Although currently unpublished, a recent and much debated statistical analysis revealed that the extent of reduction in Lp(a), and not baseline values, predicted the degree of benefit seen with alirocumab. Furthermore, this appeared to be independent of the magnitude of LDL-c reduction, suggesting an additional benefit from Lp(a) reduction alone. While these outcomes have not been formally accepted for publication (VA Bittner et al. presented at the 18th International Symposium on Atherosclerosis, Toronto Canada, June 12th, 2018), the results suggest (but do not prove) an additional mechanism for the benefit of PCSK9 inhibition on ASCVD risk reduction [41].

4. Antisense oligonucleotides

Antisense oligonucleotides (ASOs) can be used to target and reduce Lp(a) by reducing the production of apo(a) via inhibition of mRNA translation. This reduction in the production and subsequent coupling of apo(a) to apoB-100 prevents formation of the Lp(a) particle [2,47]. Second generation ASOs are single-stranded, chimeric, 20 nucleotide length molecules, which contain 2′-O-(2-methoxyethyl) modifications at the 5′ and 3′ termini, DNA-like nucleotides in the central region and a phosphorothioate
backbone to enhance nuclease resistance [1]. Development of these second-generation ASOs facilitated direct targeting of the apo(a) transcript without altering transcription of plasminogen. In addition to increasing potency by up to 15-fold compared to first generation ASOs, this also improved pharmacokinetic properties and therapeutic index [47]. Subsequent inclusion of a triantennary N-acetylgalactosamine (GalNAc3) complex conjugated to the oligonucleotide led to enhanced liver specificity which allows for greater potency with 20–30 fold lower dosing [48].

4.1. Mipomersen

Mipomersen, which targets apoB-100 and is approved for use in the US for treatment of homozygous familial hypercholesterolemia (FH) patients [49] has been demonstrated to lower Lp(a) levels [50–53]. Four phase III trials, which included patients with homozygous FH, heterozygous FH with CAD, severe hypercholesterolemia and hypercholesterolemia at high risk of CAD found significant reductions in Lp(a) with mipomersen. This was most frequent in the homozygous FH and severe hypercholesterolemic patients. Modest correlations were observed between apoB-100 and Lp(a) and LDL-c and Lp(a) [54]. Prospective post-hoc analysis of three randomized controlled trials demonstrated that in addition to lowering atherogenic lipoproteins, mipomersen also reduced the number of cardiovascular events in FH patients. This reduction coincided with the mean absolute reduction in LDL-c, non-HDL cholesterol and Lp(a) [55]. In statin-intolerant patients at high risk of CVD, mipomersen significantly reduced LDL-c, apo B and Lp(a) [56].

Mipomersen has several important limitations, including its restricted use in very specified patient populations and its side effect profile. This includes injection site reactions, flu-like symptoms, and elevated liver transaminase levels. Also noted, is an increase in hepatic fat accumulation, which appears to diminish with continuous exposure beyond one year and is not accompanied by fibrosis [48,52,57]. These concerns have resulted in its use not being licensed in Europe. Unlike the newer ASOs, mipomersen is not GalNAc3-conjugated which diminishes its specificity and requires higher dosing, which when combined with its limited clinical use makes its future uncertain.

4.2. IONIS-APO(a)Rx

IONIS-APO(a)Rx binds to the exon 24–25 splice site of the mature apo(a) transcript, with additional potential to bind to 11 alternative sites within the transcript. Similar to mipomersen, IONIS-APO(a)Rx is not GalNAc3-conjugated. A phase I study in healthy adults with Lp(a) ≥25 nmol/L investigated single dose (50 mg, 100 mg, 200 mg, or 400 mg) or multi-dose (100 mg, 200 mg, or 400 mg for total dose of 600 mg, 1200 mg or 1800 mg) of IONIS-APO(a)Rx. While the single dose injections did not alter Lp(a) levels, multidose injection resulted in significant dose-dependent decreases (39.6%, 59.0%, 77.8%) in plasma Lp(a) levels over 4 weeks. Similar reductions in the amount of oxidized phospholipids associated with apoB-100 and apo(a) were also observed. Mild injection site reactions were the most common adverse event [58].

A phase II trial to assess efficacy and safety was conducted in patients with elevated Lp(a) (>125–437 nmol/L in cohort A and ≥438 nmol/L in second B). Randomization was 1:1 in cohort A and 4:1 in cohort B with escalating subcutaneous doses (100 mg, 200 mg, 300 mg) for 4 weeks followed by 300 mg a week up to 12 weeks. Significant reductions in Lp(a) were observed in both cohort A (66.8%) and cohort B (71.6%), with additional reductions in LDL-c, apoB-100 and oxidized phospholipids also observed. Two serious adverse events (myocardial infarction) were reported, one in the IONIS-APO(a)Rx and one in the placebo group, while 12% of IONIS-APO(a)Rx injections reported injection-site reactions [59].

In a phase I/IIa first-in-man trial, a newly developed ligand conjugated apo(a) ASO; IONIS-APO(a)-Lrx was investigated in healthy volunteers with baseline Lp(a) levels ≥75 nmol/L, either as a single dose (10–120 mg) in an ascending dose design or multiple doses (10 mg, 20 mg or 40 mg) in an ascending dose design. Unlike its predecessor, IONIS-APO(a)-Lrx is GalNAc3-conjugated, which increases hepatic selectivity and enables reduction in dose and dosing frequency. The study found IONIS-APO(a)-Lrx was considerably more potent than its predecessor, with significant dose-dependent reductions in Lp(a) observed for all single dose groups. The multi-dose groups had significant mean reductions in Lp(a) of 66% with 10 mg, 80% with 20 mg and 92% with 40 mg. Improved tolerability was also observed with no injection site reactions or adverse effects reported [59]. On the basis of these findings, Akcea Therapeutics Inc conducted a phase IIb trial in patients with established CVD and elevated Lp(a). In a late-breaking presentation at the 2018 American Heart Association Meeting, results presented demonstrated that 98% of the patients in the 20 mg/week cohort and 81% in the 60 mg every 4 weeks cohort achieved clinically significant reductions in Lp(a), bringing them below the recommended risk threshold of <50 mg/dL. These reductions were also associated with decreases in LDL-c, apoB, and oxidized phospholipids associated with apoB and apo(a). Injection site reactions occurred in 26% of the patients, with 1 discontinuing treatment. (http://ir.ionispharma.com/node/24326/pdf)

5. Conclusion and future directions

Elevated Lp(a) is associated with ASCVD and may contribute to residual risk in patients appropriately treated with statins and/or ezetimibe. Although there is evidence to suggest PCSK9 monoclonal antibodies may also reduce Lp(a), this appears to be attenuated in comparison to their effect on LDL-c. The most promising treatment option so far appears to be ASOs, which have greater specificity. Although initial studies have demonstrated their promising Lp(a)-reducing effects, their long-term safety and efficacy in a range of patient populations, as well as their effect on arterial inflammation and cardiovascular events remain to be confirmed. Additional value will also come from the development of siRNA therapies that target apo(a) and potent agents that switch off apo(a) secretion and synthesis. In order to maximize the benefit to the widest possible patient population, these treatments need to be low cost, safe and have a long duration of action.

Additionally, International standardization of Lp(a) assays is required, with a need for uniform expression of the number of particles in molar units, overcoming issues with earlier assays
which relied on apo(a) isoform. Patient populations should also be considered, as this is essential for accurately specifying triggers and targets for new therapies. Primary prevention trials are currently not warranted, with the possible exception of the role of aspirin in people with very high Lp(a) and a family history of premature ASCVD. There is, however, a strong need for randomized controlled trials in secondary prevention due to the residual risk in patients with elevated Lp(a) despite reduced LDL-c [60]. Furthermore, the role of Lp(a) in the development of calcific aortic stenosis [61] strongly supports the need for trials of apo(a) targeting ASOs and siRNA in these populations.

Lastly, Lp(a) and its role in the development of ASCVD needs to be incorporated into major guidelines, particularly as new treatments are developed and new trials reported [62]. Studies and guidelines also need to address the role of Lp(a) and its treatments in various high-risk ethnic groups, including non-Caucasian populations and diabetics.

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Papers of special note have been highlighted as of considerable interest (•) to readers.


