Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Lp(a) Therapies

Evidence Summary

There is evidence that Lp(a) antisense oligonucleotides (ASOs) can reduce Lp(a) levels, though phase 3 clinical trials are needed to determine whether these reductions are associated with a reduced risk of cardiovascular disease.

Neuroprotective Benefit: There is some evidence that lower Lp(a) levels are associated with an increased risk of dementia, though the cardiovascular benefits of lower Lp(a) levels would suggest raising Lp(a) is not a good therapeutic strategy.

Aging and related health concerns: AKCEA-APO(a)-L_{Rx} reduces Lp(a) levels, though cardiovascular outcomes studies are needed.

Safety: Phase 2 studies do not suggest serious adverse events, though the drug has not been tested in large, long-term studies.

Availability: AKCEA-APO(a)-L_{Rx} not yet available, currently in clinical trials	**Dose**: Not established for AKCEA-APO(a)-L_{Rx}	**Molecular Formula:** N/A **Molecular weight:** N/A
Half life: Approximately 1 month	**BBB**: Unknown	
Clinical trials: two phase 2 studies completed for AKCEA-APO(a)-L_{Rx}, one phase 3 study underway	**Observational studies**: Several for Lp(a) levels and risk of CHD and Alzheimer's	

What is it?

Lipoprotein(a) (Lp(a) – pronounced "Lp little a") is a lipoprotein similar to LDL with regards to its lipid composition and the presence of an ApoB100 molecule. However, it also contains a unique glycoprotein, apolipoprotein(a) (apo(a) – not to be confused with apoA1). Apo(a) proteins have various numbers of kringle-domain type 2 repeats depending on the *LPA* allele causing a high heterogeneity between individuals in a population. Lp(a) levels are largely determined genetically and remain stable throughout life. Levels also vary by ethnic populations with higher levels in those of African descent than those of European or Asian descent. The population distribution of Lp(a) levels is characterized by a long tail, with the average levels low but higher levels much higher than average (Nordestgaard and Langsted, 2016).

LPA is expressed in the liver, though where Lp(a) lipoproteins are assembled is still not fully resolved. Plasma Lp(a) levels are determined by the amount of Lp(a) production (and not necessarily clearance). Lp(a) is cleared by the liver through unelucidated mechanisms. One of the difficulties in determining how Lp(a) is produced and cleared is the lack of animal research since the *LPA* gene is only present in Old World monkeys and humans (Boffa and Koschinsky, 2019).

High levels of Lp(a) are associated with an increased risk for cardiovascular diseases, such as myocardial infarction, atherosclerosis, and aortic valve stenosis. Many epidemiology studies suggested that high Lp(a) levels were *associated* with cardiovascular disease (CVD), but recent Mendelian randomization

studies suggest a causal role for high Lp(a). CVD risk increases at Lp(a) levels above 30mg/dl, though current guidelines suggest preferred Lp(a) levels should be below 50mg/dl (~20% of the population is over 50mg/dl) (Nordestgaard and Langsted, 2016).

Interestingly, Lp(a)'s useful role may also be associated with its pathogenic mechanisms. Lp(a) is speculated to be involved with wound healing by binding of fibrin to its kringle domains, transporting it to the site of injury and inhibiting fibrinolysis. Though this may prevent bleeding, in old age it could increase the risk of thrombosis (Nordestgaard and Langsted, 2016). Alternatively, Lp(a) is an efficient scavenger of oxidized phospholipids. However, at high levels it may be more likely to deliver oxidized phospholipids to vascular lesions (Boffa and Koschinsky, 2019).

There are no approved therapies indicated for lowering Lp(a). Several different therapies have been reported to lower Lp(a) to some extent, such as PCSK9 inhibitors or niacin (Gencer and Mach, 2020).

There are currently two therapies under development targeting Lp(a):

- AKCEA-APO(a)-L_{Rx} – an antisense oligonucleotide (ASO) under development by Akcea and Ionis. A phase 2 study was recently completed, and a phase 3 study will start soon in patients with elevated levels of Lp(a).
- AMG 890 – an ASO originally developed by Arrowhead Pharmaceuticals, now being developed by Amgen. It is currently in a phase 1 safety study.

Neuroprotective Benefit: There is some evidence that lower Lp(a) levels are associated with an increased risk of dementia, though the cardiovascular benefits of lower Lp(a) levels would suggest raising Lp(a) is not a good therapeutic strategy.

Types of evidence:

- One Mendelian randomization study
- Two prospective cohort studies
- Three case control studies

Clinical research to suggest benefits to patients with dementia or cognitive aging

In a Mendelian randomization study of 446,696 European individuals (stroke) and 54,162 European individuals (Alzheimer's), genetically predicted 1-standard deviation log-transformed increase in Lp(a) concentration was associated with an increased risk of large artery stroke (OR=1.20; 95%CI 1.11-1.30), a

reduced risk of small vessel stroke (OR=0.92; 95%CI 0.88-0.97), and a ***reduced*** risk of Alzheimer's disease (OR=0.94; 95%CI 0.91-0.97) (Pan et al, 2019).

In a prospective cohort study of 2,532 men in eastern Finland (avg. age at baseline = 53; avg. follow-up = 24.9 years), comparing the top quartile of Lp(a) levels to the bottom quartile was associated with a reduced risk of dementia (HR=0.68; 95%CI 0.47-0.99). These results were attenuated when controlling for all-cause mortality and CVD mortality (HR=0.91, p=0.781 and HR=0.71; p=0.124, respectively) suggesting the results were no longer significant when taking into account the known vascular mortality risk of high Lp(a) levels (Kunutsor et al, 2016).

In another prospective cohort study of 9,350 paticipants in the Atherosclerosis Risk in Communities (ARIC) cohort (avg. age 63.4; avg. follow-up 15 years), each 10mg/dL increase in Lp(a) was associated with an improved global cognitive z score (0.007; p=0.04) and those in the highest Lp(a) quintiles had improved cognitive scores than those in the lowest quintile. These effects were more pronounced in those taking statins (Pokharel et al, 2019).

Previous case-control studies have mixed results on the association of Lp(a) and dementia with some showing increased Lp(a) increasing risk, some showing decreased Lp(a) increasing risk, and some show no significant effect. However, these studies are limited by the potential confounds with case-control studies (Pan et al, 2019).

ApoE4 interactions

Only a few case-control studies have examined the association of Lp(a) levels, ApoE4 genotype and Alzheimer's risk. One study reported that higher Lp(a) increased the risk of Alzheimer's disease in ApoE4 carriers, but not in ApoE4 negative carriers. However, this was only significant in patients >75 years of age (Mooser et al, 2000).

Another case-control study suggested that Lp(a) levels (70.0-355.0mg/l) were associated with an increased risk of Alzheimer's disease, though the increased risk was independent of ApoE status, and, interestingly, the risk dropped (not significant) in those with the highest Lp(a) levels(Solfrizzi et al, 2002).

Finally, a third case-control study suggested that those with an Lp(a) null genotype had a later age-of-onset for Alzheimer's disease than those with at least some Lp(a) (76.8 vs 66.9 years). This association was also independent of ApoE4 status (Emanuele et al, 2004).

Summary

Prospective studies and Mendelian randomization studies suggest that high levels of Lp(a) may be associated with a reduced risk of Alzheimer's disease. The results with case-control studies are mixed. Prospective cohort and Mendelian randomization studies are not as subjected to the same confounding as case-control studies, where individuals with Alzheimer's may be frailer or have increased Lp(a) levels because of the disease. Interestingly, one cohort study found that the reduced risk of Alzheimer's was no longer significant when controlling for CVD or all-cause mortality. Possibly, individuals who survive without cardiovascular disease are more protected from Alzheimer's.

The potential protective mechanisms of Lp(a) are speculative. Lp(a) was associated with a reduced severity of small vessel disease which could increase the risk of Alzheimer's. Lp(a) levels in the CSF were correlated with plasma levels of Lp(a) which could mean it crosses the blood/CSF barrier. In the brain, Apo-A1 regulates cholesterol levels, amyloid levels, and neurogenesis, and possibly Lp(a) may also influence lipoprotein dynamics or ApoE metabolism in the brain (Pan et al, 2019).

Aging and related health concerns: AKCEA-APO(a)-L_{Rx} reduces Lp(a) levels, though cardiovascular outcomes studies are needed.

Types of evidence:

- 1 Mendelian randomization study
- 2 phase 3 studies of PCSK9 inhibitors
- 2 phase 2 studies of AKCEA-APO(a)-L_{Rx}

Burgess et al (2018) conducted a Mendelian randomization study to assess the effect of Lp(a) reduction on coronary heart disease (CHD) outcomes. A genetically predicted 10mg/dl reduction in Lp(a) was associated with a 5.8% reduced risk of CHD (OR=0.942; 95%CI 0.933-0.951) while a 10mg/dl reduction in LDL-C was associated with a 14.5% reduced risk of CHD (OR=0.855; 95%CI 0.818-0.893). Thus, a 101.5mg/dl decrease in Lp(a) was required for the same risk reduction as a 38.67mg/dl (1 mmol/L) decrease in LDL-C.

To estimate the potential effects of short-term Lp(a) reduction in a clinical trial, they made an assumption that it would have the same effect of LDL-C reduction in previous clinical trials. The estimated effects of short-term (5 years) reduction in Lp(a) on CHD risk reduction would be about 27.7% (120mg/dl), 19.4 (80mg/dl), 7.8% (30mg/dl).

In an effort to anticipate whether Lp(a) reduction would have an additive benefit to LDL-C reduction, the authors examined the effect of a genetically estimated 10mg/dl reduction in Lp(a) in three groups of individuals based on LDL-C lowering alleles. All three groups showed a reduced risk of CHD per 10mg/dl estimated Lp(a) reduction (~5%). Similar findings were obtained with genetic variants for *PCSK9* and *NPC1L1* (genetic targets for PCSK9 inhibitors and ezetimibe, respectively). Thus, Lp(a) reduction may have an additive benefit to LDL-C reduction.

One implication of this study is that only individuals with very high Lp(a) may be likely to benefit in an RCT of an Lp(a)-lowering drug, despite the genetic association of Lp(a) with CHD. Furthermore, these findings might explain why drugs that lower Lp(a) to a lower extent (e.g. PCSK9 inhibitors and niacin which lower Lp(a) by ~20%-35%) may not reduce the risk of CHD in individuals with moderately high Lp(a) in clinical trials.

(Non-ASO drugs that reduce Lp(a))

Evolocumab (Repatha)

In the Repatha phase 3 FOURIER trial in patients with Lp(a) measurements (n=25,096), patients with the highest Lp(a) levels had the greatest absolute Lp(a) reductions but lower percentage change in Lp(a) . There was a greater reduction in major coronary events in treated patients with Lp(a) levels above the median level (HR = 0.77; 95%CI 0.67-0.88) versus those below the median level (HR = 0.93; 95%CI 0.80-1.08). At the clinical threshold for high Lp(a) (50mg/dl), there was a greater absolute risk reduction with evolocumab treatment (2.41%) than for those below the clinical threshold (1.41%). After adjusting for LDL-C, each decile decrease in Lp(a) was associated with a 15% relative risk reduction. These results suggest that reductions in Lp(a) by evolocumab may provide some additional risk reduction in patients with high levels of Lp(a), though this reduced risk may be due to the fact that patients with high levels of Lp(a) have an already increased risk for cardiovascular disease and that they may derive the most benefit from PCSK9 inhibition (O'Donoghue et al, 2019).

Alirocumab (Praluent)

Similar results were seen with alirocumab. In patients who had acute coronary syndrome within the last 12 months, alirocumab treatment reduced levels of Lp(a) by ~23%. Patients in the highest two quartiles of Lp(a) levels had a greater risk reduction for a major cardiovascular event (HR = 0.83; 95%CI 0.70-0.98) than those in the lowest quartile (HR=0.95; 95%CI 0.79-1.15) (Bittner et al, 2020).

(ASO drugs that reduce Lp(a) in clinical trials)

AKCEA-APO(a)-L_{Rx}

AKCEA-APO(a)-L_{Rx} is an antisense oligonucleotide (ASO) that targets hepatic *LPA* messenger RNA. It is a second-generation ASO conjugated with a triantennary N-acetylgalactosamine ($GalNAc_3$) moiety. $GalNAc_3$ targets the ASO to the asialoglycoprotein receptor on the surface of hepatocytes leading to 15x-30x increase in potency.

A phase 2a study reported that weekly dosing of AKCEA-APO(a)-L_{Rx} reduced Lp(a) levels by 66%-92% with a half-life of approximately 1 month. Therefore, a phase 2b study was conducted with a more infrequent dosing schedule over 6 months in patients with established cardiovascular disease and elevated levels of Lp(a) (>60mg/dl). Most of the patients were also taking lipid-lowering therapies and platelet aggregation inhibitors (chart below, adapted from Tsimikas et al, 2020).

Results:

Percent change	20mg every 4 weeks (n=48)	40mg every 4 weeks (n=48)	20mg every 2 weeks (n=48)	60mg every 4 weeks (n=47)	20mg every week (n=48)	Placebo (n=47)
Lp(a)	-35%	-56%	-58%	-72%	-80%	-6%
OxPL-apoB	-37%	-57%	-64%	-79%	-88%	+14%
OxPL-apo(a)	-28%	-49%	-45%	-63%	-70%	-20%

US guidelines recommend a target of <50mg/dl (125nmol/l) for circulating Lp(a) levels. The percentage of patients reaching the recommended Lp(a) levels were:

Lp(a)	23%	62%	65%	81%	98%	6%

Levels of LDL and ApoB were also slightly reduced after treatment (up to ~20%) with no change in HDL, triglycerides, or hsCRP.

Serious adverse events occurred in 10% of treated patients and 2% of placebo patients. The most common adverse event was injection-site reactions (27%). Other adverse events that occurred in at least 10% of treated patients and were more common than placebo included urinary tract infections (13% vs. 6%), myalgia (12% vs. 11%), and headache (11% vs. 8%) (Tsimikas et al, 2020).

Safety: Phase 2 studies do not suggest serious adverse events, though the drug has not been tested in large, long-term studies.

Types of evidence:

- Two phase 2 studies of AKCEA-APO(a)-L_{Rx}

The most common adverse event after AKCEA-APO(a)-L_{Rx} was injection site reactions. Other side effects included urinary tract infections, myalgia, and headache. However, there are no long-term studies using AKCEA-APO(a)-L_{Rx}.

Drug interactions:
Drug interactions are currently unknown, but unlikely – unless there are interactions specific for ASOs.

Sources and dosing:
Not available – currently in clinical trials.

Research underway:
AKCEA-APO(a)-L_{Rx} will soon be in a phase 3 study in patients with high levels of Lp(a).

AMG 890 is currently in a phase 1 safety study (NCT03626662).

Search terms:

- AKCEA-APO(a)-L_{Rx}
- AMG 890
- Lp(a) antisense
- Lp(a) + apoe + Alzheimer, dementia

Websites visited:
Clinicaltrials.gov
Pubmed

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