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.

ANGPTL3-Targeted Therapies

Evidence Summary

Evidence suggests that drugs targeting ANGPTL3 reduce levels of LDL-C and triglycerides, potentially conferring cardiovascular disease risk reduction.

Neuroprotective Benefit: None directly expected except for secondary effects from LDL and triglyceride reductions.

Aging and related health concerns: Given the results from PCSK9 inhibitor trials and Vascepa trials, there is reasonable evidence these drugs will reduce the risk of cardiovascular disease in some patients; however, large clinical trials have not been conducted.

Safety: Currently clinical evidence suggests both drugs may be relatively safe, though no long, large-scale clinical trials have been conducted.

What is it?

Angiopoietin-like 3 (ANGPTL3) is part of an 8-member family of angiopoietin-like proteins. ANGPTL3, ANGPTL4, and ANGPTL8 are involved with plasma lipid metabolism. Both ANGPTL3 and ANGPTL4 inhibit lipoprotein lipase (an enzyme that hydrolyzes triglycerides) after feeding and fasting, respectively, while ANGPTL3 also inhibits endothelial lipase. ANGPTL3 is exclusively produced in the liver and secreted into the bloodstream while ANGPTL4 is produced and secreted from numerous tissues. Expression of ANGPTL3 is regulated by the oxysterol-activated liver X receptor (LXR). The function of ANGPTL8 is less understood, but it is thought to be involved in ANGPTL3-mediated inhibition of lipoprotein lipase (Kersten, 2017).

ANGPTL3 and ANGPTL4 have been examined as potential drug targets, though ANGPTL4 inactivation was reported to increase lipid accumulation in the mesenteric lymph nodes in animal models, reducing enthusiasm for it. Development of therapeutics targeting ANGPTL3 stem from the observation that patients with loss-of-function mutations in ANGPTL3 have lower levels of LDL-C, triglycerides, and possibly HDL-C (though results are mixed), as well as a lower risk for coronary artery disease (see below). Plasma levels of ANGPTL3 were also positively associated with plasma levels of LDL-C and HDL-C, though evidence with triglycerides was mixed (Kersten, 2017).

There are currently three drugs in clinical studies targeting ANGPTL3:

- Evinacumab (REGN1500) – monoclonal antibody developed by Regeneron, reported a successful phase 3 study in patients with familial hypercholesterolemia. If approved by the FDA, the drug will likely be available mid-2021.
- AKCEA-ANGPTL3-L_{RX} – antisense oligonucleotide (ASO) developed by AKCEA and Ionis, currently in phase 2 studies.
- ARO-ANG3 – ASO developed by Arrowhead Pharmaceuticals, currently in phase 1 studies

Neuroprotective Benefit: None directly expected except for secondary effects from LDL and triglyceride reductions.

Types of evidence:

- None specific to ANGPTL3

Aging and related health concerns: Given the results from PCSK9 inhibitor trials and Vacepa trials, there is reasonable evidence these drugs will reduce the risk of cardiovascular disease in some patients; however, large clinical trials have not been conducted.

Types of evidence:

- 2 clinical studies of evinacumab
- 1 clinical study of AKCEA-ANGPTL3-L_{RX}

Evinacumab

Evinacumab is a monoclonal antibody that binds to ANGPTL3 and is being developed by Regeneron. In 2017 it was granted Breakthrough Therapy designation for the treatment of hypercholesterolemia in patients with homozygous familial hypercholesterolemia (HoFH) (Breakthrough Therapy Designation means it will have priority review at the FDA – a review in ~6 months rather than 10 months).

In a study of 58,335 participants in DiscovEHR (a collaboration between Regeneron's Genetics Center and Geisinger Health System), Dewey et al (2017) identified 13 loss-of-function (LoF) *ANGPTL3* alleles from individuals with European ancestry. *ANGPTL3* LoF was associated with 27% lower triglyceride levels, 9% lower LDL-C levels, and 4% lower HDL-C levels. In addition, *ANGPTL3* LoF was associated with a reduced risk of coronary artery disease (OR = 0.59; 95%CI 0.41-0.85) and a non-significant lower risk of myocardial infarction (OR = 0.66; 95%CI 0.39-1.06). In addition, Dewey et al attempted to validate these results in 130,483 patients from four independent cohorts. *ANGPTL3* LoF was associated with a non-significant reduced risk of coronary artery disease (OR = 0.63; 95%CI 0.39-1.03).

Evinacumab treatment in a mouse model of atherosclerosis (APOE*3Leiden.CETP) reduced total cholesterol, triglycerides, and ApoB. It also reduced atherosclerotic lesion size (-39%) and necrotic content in severe type IV and V lesions (-45%) (Dewey et al, 2017). Triglycerides, non-HDL-C, and HDL-C were also reduced in dyslipidemic cynomolgus monkeys after evinacumab treatment (Gusarova et al, 2015).

In a phase 1 single-ascending dose safety study in 83 patients, evinacumab (given either intravenously up to 20mg/kg or subcutaneously up to 250mg) reduced levels of triglycerides by up to 76%, LDL-C by up to 23.2%, and HDL-C by up to 18.4%. The most common adverse events in treated patients was headache (11%) and transient increase in liver enzymes (3%) (Dewey et al, 2017).

In August 2019, Regeneron reported that evinacumab was successful in a phase 3 study in 67 patients with HoFH (average baseline LDL-C = 255mg/dl). Patients were already on a cholesterol-lowering therapy (statins, PCSK9 inhibitors, ezetimibe, LDL apheresis, lomitapide) and were administered evinacumab (15mg/kg) every four weeks. Evinacumab treatment resulted in a 49% further reduction in LDL-C (132mg/dl absolute change in LDL-C), and reduced ApoB, non-HDL-C, and total cholesterol. 47% of individuals achieved LDL-C levels < 100mg/dl (compared to 23% of placebo, nominal p=0.0203). Evinacumab was well-tolerated; adverse events occurring in at least 5% of patients and more commonly in the drug group included influenza-like illness (11% vs 0%) and rhinorrhea (excessive mucus in the nasal cavity, 7% vs 0%).

Regeneron announced on an investor call that they would submit to the FDA in mid-2020, suggesting that, if approved, the therapy should be available in early 2021.

AKCEA-ANGPTL3-L_{RX}

AKCEA-ANGPTL3-L_{LR} is a second-generation antisense oligonucleotide. AKCEA-ANGPTL3-L_{RX} treatment in a mouse model of dyslipidemia reduced plasma levels of total cholesterol, LDL-C, and plasma triglycerides. Weekly subcutaneous injections of AKCEA-ANGPTL3-L_{RX} over six weeks in 32 healthy adults reduced levels of ANGPTL3 (by up to 84.5%), triglycerides (by up to 63.1%), non-HDL-C (by up to 36.6%), and ApoC-III (by up to 58.5%). Levels returned to normal 13 weeks after the last treatment. There were no serious adverse events, and the treatment was generally well-tolerated (Graham et al, 2017).

Safety: Currently clinical evidence suggests both drugs may be relatively safe, though no long, large-scale clinical trials have been conducted.

Types of evidence:

- Evinacumab – one small phase 3 study
- AKCEA-ANGPTL3-L_{RX} – one phase 2 study

Although the current drugs have limited clinical experience – none has been tested long-term in a large cohort of patients – both drugs were reported to be well-tolerated. Evinacumab was associated with flu- and cold-like symptoms in up to 11% of patients. In a multiple dose study over 6 weeks in 32 healthy adults, AKCEA-ANGPTL3-L_{RX} was associated with headache (1 placebo, 2 drug) and dizziness (2 placebo, 1 drug).

ANGPTL3-targeted therapies also reduce HDL levels, so they may not be appropriate for individuals with low HDL at baseline.

Drug interactions:
The drugs are not approved and do not currently have known drug interactions. Vascepa has drug interactions with fibrates, which also lower triglycerides, so these drugs may have an interaction with other triglyceride-lowering therapies. Usually, drugs that lower LDL-C are given together to reach optimal LDL-C levels, so they may not interact with some LDL-C-lowering drugs. However, given the degree of LDL-lowering with PCSK9 inhibitors, combinations with PCSK9 inhibitors may not be advisable in some patients.

Sources and dosing:
Not currently available

Research underway:
Evinacumab is currently in a phase 2 clinical study in patients with hypercholesterolemia (NCT03175367).

AKCEA-ANGPTL3-L_{RX} is currently in a phase 2 clinical study in individuals with hypertriglyceridemia, type 2 diabetes, and nonalcoholic fatty liver disease (NAFLD) (NCT03371355).

Arrowhead Pharmaceuticals is currently testing its own ASO, ARO-ANG3, in a phase 1 study (NCT03747224).

Search terms:

- ANGPTL3 + Alzheimer
- AKCEA-ANGPTL3-L_{RX}
- Evinacumab
- ARO-ANG3

Websites:
Clinicaltrials.gov
Pubmed

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