Effects of Alirocumab on Carotid Plaque Lipid Content and Inflammation

A Time Course Study Using Serial Vessel Wall Imaging

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Purpose

Evidence on plaque-stabilizing effects of non-statin therapies remains scarce. Using serial vessel wall MR imaging, we studied the effects and time course of PCSK9 inhibition with alirocumab on carotid plaque lipid content and inflammation.

Background

- Monoclonal antibodies against PCSK9 have been shown to reduce cardiovascular events in recent clinical trials (Sabatine et al, NEJM, 2017; Schwartz et al, NEJM, 2018), but the underlying mechanisms are not fully understood.
- Notably, circulatory inflammation markers were not reduced with PCSK9 inhibitors, thus their effects on plaque inflammation remain elusive.
- Vessel wall imaging with magnetic resonance has enabled serial monitoring of changes in carotid plaque lipid content and inflammation noninvasively that correlates with coronary and carotid vascular events (Sun et al, JACC Imaging, 2017).

Methods

- **Study population:** 1) LDL-C≥70 mg/dl but unable to take high-intensity statin therapy due to drug interactions or statin intolerance; and 2) non-calcified plaque on carotid ultrasound with confirmed lipid core by screening MRI. All patients received alirocumab 150 mg every 2 weeks during the study.
- **Carotid MRI:** Carotid MRI was performed at screening (also serves as baseline) and then serially at 3, 6, 12 months after treatment using: 1) 3T GE scanner and a bilateral 6-channel carotid coil (GE Healthcare); 2) multi-contrast MRI for plaque lipid content measured as % lipid core (Fig 1); 3) dynamic contrast-enhanced (DCE) MRI for plaque inflammation measured as K^{trans} (Fig 2).

Methods

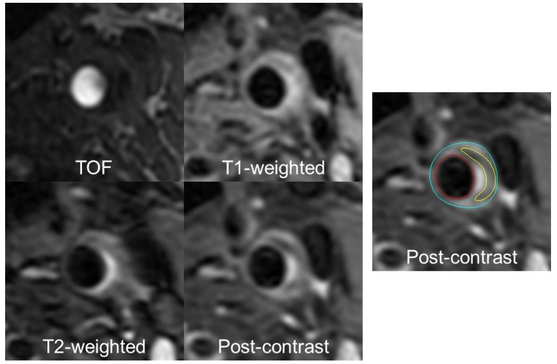

Fig 1: Measuring % lipid core on multi-contrast MRI. Red and azure contours mark the lumen and outer wall boundaries. Yellow contour marks the lipid core, which has little enhancement compared to the surrounding fibrous tissue.

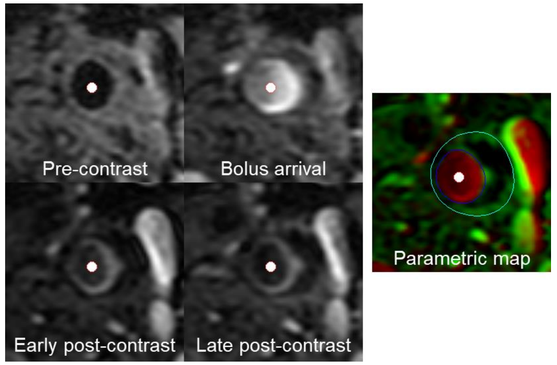

Fig 2: Measuring K^{trans} on DCE-MRI. The DCE time series was processed with pharmacokinetic modeling to generate a parametric map showing transfer constant (K^{trans}) in green channel and fractional plasma volume (v_p) in red channel. Lumen and outer wall boundaries are then delineated to measure K^{trans}.

Results

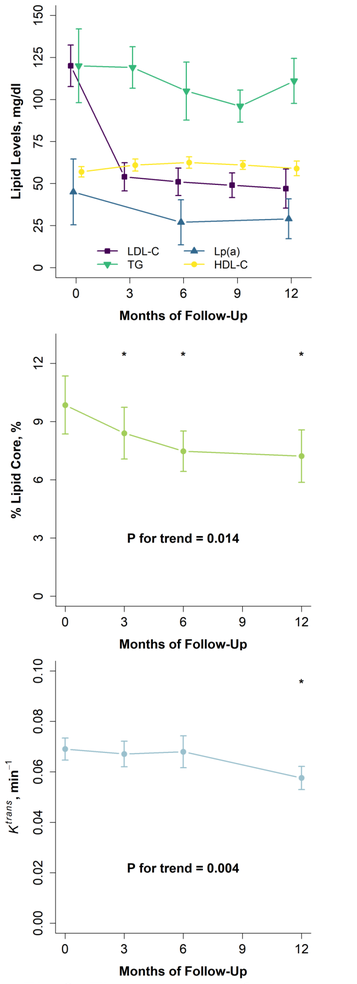

Fig 3: Time course of changes in serum & imaging biomarkers

- Of 55 screened, 31 met inclusion criteria and 27 completed the study: mean age: 69±9; male: 67%; on statin/ezetimibe: 41%; baseline LDL-C (median [interquartile range]): 120 (99, 158) mg/dl.
- At 12 months, there were a 62% reduction in LDL-C (p<0.001) and a 31% reduction in Lp(a) (p<0.001) whereas HDL-C (p=0.61) and triglycerides (p=0.077) did not change significantly (Fig 3).
- From 9.8% at baseline, % lipid core was progressively reduced to 8.4% at 3 months (p=0.032), 7.5% at 6 months (p=0.016), and 7.2% at 12 months (p=0.019) (Fig 3). K^{trans} was not reduced at 3 or 6 months but was significantly reduced at 12 months (p=0.029) (Fig 3).
- Changes in % lipid core or K^{trans} were not significantly correlated with changes in LDL-C or Lp(a) at the individual level (Fig 4).

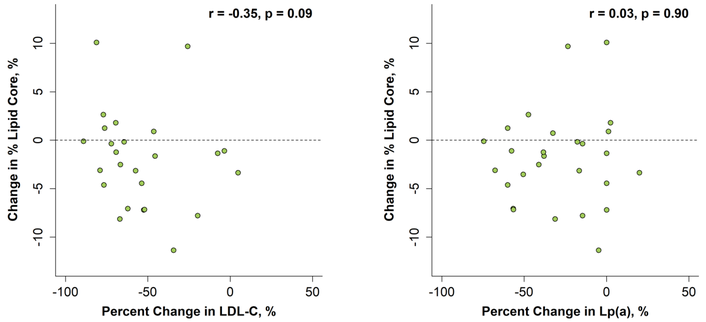

Fig 4: Serum lipid reduction vs. plaque delipidation

Conclusions

- Serial vessel wall MRI documented plaque-stabilizing effects of PCSK9 inhibition, including plaque delipidation and attenuation of plaque inflammation, which did not correlate with changes in serum lipids.
- Reduction in plaque lipid content was apparent as early as 3 months. Reduction in K^{trans} was not seen until 12 months of treatment and may indicate a later effect on microvascular structure and/or function.

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Declaration of interest: I have nothing to declare