Full Title: Effect of PCSK9 Inhibition on Oxidized Phospholipids

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Background

Lipoprotein(a) [Lp(a)] is involved in the pathogenesis of atherosclerosis, and is notable for its preferential binding of oxidized phospholipids (OxPL), which lead to endovascular inflammation and atherosclerosis. As Lp(a) and OxPL are not lowered by statins, elevated levels may partially explain the residual inflammatory risk for atherosclerotic cardiovascular disease (ASCVD) despite statin use. Proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9) significantly reduce LDL with at most modest reduction of Lp(a) without reducing inflammatory biomarkers. To better understand the impact of PCSK9 inhibition on inflammation related to risk of atherosclerosis, we performed a secondary analysis of participants from clinical trials of PCSK9 inhibitors, including the RG7652 Phase I and Phase II EQUATOR studies as well as the ANITSCHKOW study to evaluate the effect of PCSK9 inhibition on levels of OxPL.

Methods

Serial blood samples from the Phase I and Phase II studies of RG7652 as well as the ANITSCHKOW study were obtained for measurement of OxPL on apolipoprotein(a) [OxPL-apo(a)] and apolipoprotein(B) [OxPL-apoB]. Levels of OxPL, Lp(a), LDL and apolipoprotein(B) [apo(B)] were compared within and across groups at baseline and final follow-up visit. Across groups, median percent change of lipid biomarkers over follow-up was compared using Mann-Whitney U tests. Within groups, median percent change of lipid biomarkers at follow-up versus baseline was compared using Wilcoxon signed-rank tests.

Results

For the EQUATOR Phase 2 study, there were 48 participants in the treatment group and 30 in the placebo group. OxPL-apo(a) was significantly reduced at follow-up compared with baseline in the treatment group (median percent change -12.47 [-27.69, 6.26], p=0.033), but there was no significant change in OxPL-apoB. Lp(a) was not significantly changed in follow-up compared with baseline in either treatment group or the placebo group. Apo(B) and LDL were both significantly reduced in the treatment group and unchanged in placebo. For the ANITSCHKOW study, there were 18 participants in the treatment group and 14 in the placebo group. As seen in EQUATOR, there were significant reductions in LDL and apo(B) in the treatment group. In contrast to the EQUATOR study, Lp(a) was significantly reduced in the treatment group. OxPL-apoB and OxPL-apo(a) were unchanged in the treatment group.

Conclusions

In this secondary analysis of participants from multiple clinical trials, we found no significant change in OxPL levels after treatment with a PCSK9 inhibitor, while noting expected decreases in LDL and apo(B), and reduction in Lp(a) levels in the ANITSCHKOW study. These findings suggest that while PCSK9 inhibitors reduce apo(B) and LDL, they may only modestly reduce Lp(a) and thus not affect the associated inflammatory risk conferred by OxPL.