Lp-PLA₂ ¿Why does it matter?

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Despite continued progress in the field of coronary artery disease (CAD), cardiovascular events remain high, and heart disease is still the leading cause of death among Americans¹. The PROVE IT-TIMI 22 trial found that despite high dose statin therapy, patients had a 22.4% residual risk for death or major adverse cardiovascular events in the two years after an acute coronary syndrome². In the Treating to New Targets trial, patients with stable coronary artery disease treated with intense statin therapy still had an 8.7% residual risk of a major adverse cardiovascular event within 4 years³,⁴. Consequently, new therapies are needed to augment the current standard of care if progress is to be made.

Lp-PLA₂

Lipoprotein-associated Phospholipase A₂ (Lp-PLA₂) is an enzyme produced and secreted by many cells of the immune system (monocytes, macrophages, T-lymphocytes and mast cells)⁵. In humans, 80% of Lp-PLA₂ in plasma circulates bound to the c-terminus of ApoB in low density lipoprotein (LDL) fragments. The remaining fraction circulates bound to high density lipoprotein (HDL) or is produced locally at the site of inflammation⁶. After LDL is oxidized at a site of inflammation such as a neointimal plaque, Lp-PLA₂ cleaves it into two inflammatory mediators, lysophosphatidylcholine (Lyso-PC) and oxidized nonesterified fatty acids (oxNEFAs)⁵. It has a particular affinity for small, dense LDL fragments that are believed to be more highly pathogenic⁷.

Lp-PLA₂ AND VULNERABLE PLAQUES

Lp-PLA₂ has been shown to be highly upregulated in vulnerable and ruptured plaques, with significantly lower levels of expression in stable plaques⁸,⁹. Lp-PLA₂ may contribute to as well as be a marker for plaque instability¹⁰. Both of its products, Lyso-PC and oxNEFAs, are chemoattractants for macrophages, and Lyso-PC has been shown to induce the apoptosis of macrophages in a plaque³. The Lp-PLA₂ on LDL particles that enter a developing plaque produce Lyso-PC, which recruits macrophages to the site. These migrating macrophages then produce and secrete additional Lp-PLA₂ before being induced to apoptosis by Lyso-PC. The resultant positive feedback loop may drive the progression and expansion of the necrotic core and thinning of the fibrous cap (Figure 1)¹¹.

Lp-PLA₂ and Lyso-PC also contribute to atherosclerosis through the induction of endothelial dysfunction. Lyso-PC causes an increase in oxidative stress, downregulation of endothelial nitric oxide synthase, and decreased endothelial cell migration to sites of damage¹².

DARAPLADIB

Darapladib is a selective, reversible, potent, competitive inhibitor of Lp-PLA₂ that has been shown to reduce Lp-PLA₂ activity up to 95% in a dose-dependent manner¹⁸. Darapladib also remains effective as an adjunct to current lipid lowering therapies. Even
in the presence of intensive statin therapy, darapladib reduced Lp-PLA₂ activity by 66% at the 160 mg/day dose (Figure 3)²⁰.

Inhibition of Lp-PLA₂ has been shown to limit plaque development and improve patient outcomes. In diabetic, high cholesterol swine, darapladib reduced the progress of atherosclerosis¹⁰. The Integrated Biomarkers and Imaging Study (IBIS-2) showed that darapladib use resulted in a 50% reduction in Lp-PLA₂ activity and halted the expansion of the necrotic core. In the placebo group, the necrotic core continued to expand despite adherence to standard of care (Figure 4)²².

Two ongoing trials have been designed to further investigate darapladib and its therapeutic potential. The Stabilization of Atherosclerotic Plaque by Inhibition of Darapladib Therapy Trial (STABILITY) is a phase III, multicenter, randomized, double-blind, placebo controlled study of darapladib vs. placebo in patients with chronic CAD. It is intended to test whether darapladib reduces the risk of death by cardiovascular event, nonfatal MI, or nonfatal stroke. STABILITY has a target enrollment of 15,500 patients and an expected follow-up of 3 years²¹.

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POSSIBLE ATEROPROTECTIVE EFFECTS OF Lp-PLA2

When first discovered, Lp-PLA2 was described as an atheroprotective factor. Subsequent studies suggest that the pro-atherothrombotic effects outweigh any possibly atheroprotective abilities, but some controversy remains. Lp-PLA2 was initially discovered and described as Platelet Activating Factor Acetylhydrolase (PAF-AH) because of its ability to degrade PAF in vitro. This effect, however, has not been shown to persist in vivo. Initial studies of groups with missense mutations in the Lp-PLA2 gene result in reduced expression have yielded mixed results. The first two studies found a higher prevalence of cardiovascular disease in carriers of the mutation, but a larger, more recent study with greater power found no evidence of increased risk. STABILITY and SOLID should provide more insight into the role of Lp-PLA2 and the potential therapeutic benefit of its inhibition by darapladib.

BIBLIOGRAPHY

2. Murphy SA, Cannon CP, Wiviott SD, McCabe CH, Braunwald E: Reduction in recurrent cardiovascular events with intensive lipid-lowering statin therapy compared with moderate lipid-lowering statin therapy after acute coronary syndromes from the PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22) trial. JACC 2009; 54: 2358-2362.


