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Recent Developments with Lipoprotein-Associated Phospholipase A₂ Inhibitors

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Abstract

Lipoprotein-associated phospholipase A₂ (Lp-PLA₂) is a calcium-independent phospholipase A₂ enzyme secreted by leukocytes and associated with circulating low-density lipoprotein and macrophages in atherosclerotic plaques. Until recently, the biological role of Lp-PLA₂ in atherosclerosis was controversial, but now the preponderance of evidence demonstrates a proatherogenic role of this enzyme. Lp-PLA₂ generates two proinflammatory mediators, lysophosphatidylcholine and oxidized nonesterified fatty acids, which play a major role in the development of atherosclerotic lesions and formation of a necrotic core, leading to more vulnerable plaques. These findings have opened the door to a potential novel therapeutic target, selective inhibition of Lp-PLA₂. Recently, both animal models and human studies have shown that selective inhibition of Lp-PLA₂ reduces plasma Lp-PLA₂ activity, plaque area, and necrotic core area. This article reviews the most recent developments with Lp-PLA₂ inhibitors.

Keywords

Phospholipase; Lipoprotein; Atherosclerosis; Myocardial infarction; Atherothrombosis

Introduction

Atherosclerosis remains the leading cause of death, myocardial infarction (MI), and stroke in the Western world, and its incidence continues to increase. It is now recognized that atherosclerosis is not only a lipid disease, but a complex, intertwined, inflammatory-immunomodulatory disease [1,2]. This likely explains why despite current aggressive treatment strategies with statins, antiplatelet agents, and angiotensin-converting enzyme inhibitors, significant residual risk of morbidity and mortality from cardiovascular disease persists [3]. Several recent important studies either directly or indirectly reveal this residual risk despite aggressive use of pharmacologic agents. The Pravastatin or Atorvastatin

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Evaluation and Infection Therapy (PROVE IT) trial demonstrated beneficial effects of early, aggressive reduction of serum low-density lipoprotein (LDL) levels in acute coronary syndrome [4]. Despite significant reductions in cholesterol levels, the risk of MI and/or acute coronary syndrome and death over the 2.5-year follow-up period was still high, at one in five [4]. In the Heart Outcomes Prevention Evaluation (HOPE) study, the risk of death was 6.1%, cardiac arrest was 0.8%, MI was 9.9%, and need for revascularization was 16% at 5 years in the treated group [5]. Another example is seen in the Reduction of Atherothrombosis for Continued Health (REACH) registry, which documented the incidence of cardiovascular death, MI, and stroke and/or hospitalization over a 1-year follow-up in more than 68,000 patients worldwide [6]. The majority of patients received contemporary preventive pharmacologic therapy, yet the incidence of cardiovascular death and/or MI was only 5.3% when multiple risk factors were present. However, the incidence increased to 12% when symptomatic coronary, cerebrovascular, or peripheral vascular disease was present in one anatomic location, to 21% when present in two locations, and to 26% when present in all three locations. Hence, the role of inflammation in atherosclerosis has become an intriguing and promising novel therapeutic target.

The high risk of recurrent cardiovascular events despite standard-of-care therapies has prompted research efforts directed at reducing atherosclerotic burden and improving stability of vulnerable plaques in hope of further reducing the risk of cardiovascular events. Lipoprotein-associated phospholipase A₂ (Lp-PLA₂) is a calcium-independent phospholipase whose products, lysophosphatidylcholine (lyso-LPC) and oxidized nonesterified fatty acids (oxNEFAs), have potent proinflammatory properties [7]. Evidence continues to support a causative role for Lp-PLA₂ in the development of atherosclerosis and the idea that selective inhibition of Lp-PLA₂ retards progression of plaque instability, namely necrotic core development and smooth muscle cell and fibrous tissue destruction.

Lp-PLA₂ Pathogenic Mechanisms and Their Role in Atherosclerosis

Pathogenic Mechanisms

Lp-PLA₂, also known as platelet-activating factor (PAF) acetylhydrolase or type VIIA PLA₂, belongs to the phospholipase A₂ superfamily. Lp-PLA₂ is produced by inflammatory cells involved in atherogenesis (macrophages and monocytes) and accumulates in human atherosclerotic lesions. It is now known that approximately 70% to 80% of Lp-PLA₂ circulates bound to LDL and that the remainder is bound to high-density lipoprotein (HDL), lipoprotein (a), and some very low-density lipoproteins [8]. Lp-PLA₂ is a phospholipase A₂ calcium-independent enzyme that acts on water-soluble polar moieties of phospholipids with short sn-2 ester bonds [8]. In particular, Lp-PLA₂ rapidly degrades polar phospholipids present in oxidized LDL. This action results in the production of lyso-LPC and oxNEFAs [9,10], which exhibit a wide range of proinflammatory and proapoptotic effects [7,11,12].

Lp-PLA₂ and Atherosclerosis

Initially, the biological role of Lp-PLA₂ in atherosclerotic lesion development was controversial. A few studies pointed toward Lp-PLA₂ as an atheroprotective enzyme. This idea was generated from in vitro studies demonstrating that PAF, a substance with known inflammatory properties, was hydrolyzed by Lp-PLA₂ [13]. However, subsequent investigations have refuted Lp-PLA₂ as the major enzyme responsible for hydrolysis of PAF in vivo [14,15], and more recent evidence suggests that Lp-PLA₂ actually has an active role in atherosclerotic development and progression [7,11,16]. Increased circulating Lp-PLA₂ activity has been shown to predict increased cardiovascular risk [17]. Its proatherogenic role is thought to be derived from Lp-PLA₂'s ability to generate the previously mentioned key proinflammatory mediators lyso-LPC and oxNEFAs. There is evidence proposing a regulatory

role of these proinflammatory lipids in promoting atherosclerotic plaque development, which can lead to formation of a necrotic core. This process involves recruitment and activation of leukocytes [7,18], induction of apoptosis [7,19,20], and impaired removal of dead cells [21, 22]. Lp-PLA₂ products (lyso-LPC and oxNEFAs) have been postulated to be crucial in determining plaque instability. The demonstration of Lp-PLA₂ being highly upregulated in macrophages undergoing apoptosis within the necrotic core and fibrous cap of vulnerable and ruptured plaques, but not in stable lesions, supports this notion [23]. These observations suggest a causative role for Lp-PLA₂ in the development of atherosclerosis, and that inhibition of Lp-PLA₂ could decrease the phenotypic hallmarks of plaque instability, specifically necrotic core progression and smooth muscle cell and fibrous tissue destruction.

Lp-PLA₂ Inhibitors

Direct/Selective Inhibitors

Darapladib (SB-480848) is a selective Lp-PLA₂ inhibitor that has been shown to reduce Lp-PLA₂ in the circulation and within atherosclerotic lesions. With the current evidence supporting Lp-PLA₂ as an independent marker of cardiovascular risk and events [24•], researchers have begun investigating darapladib as a novel therapeutic agent targeting the inflammatory mechanism of atherosclerosis. Recently, there have been three important studies published investigating darapladib: one preclinical study using a porcine model and two phase 2 human studies.

The study by Wilensky et al. [25••] evaluated the effects of darapladib on atherosclerotic lesion area, composition, and gene expression in diabetic/hypercholesterolemic (DM-HC) swine. The DM-HC porcine model was used because pigs have a plasma lipoprotein profile similar to humans, whereas Lp-PLA₂ associates with different lipoprotein fractions in mice (mainly HDL), rendering the mouse model inadequate for studying the effects of Lp-PLA₂ inhibition. Diabetes mellitus was induced in male Yorkshire domestic farm pigs with a single intravenous injection of streptozotocin. Three days after diabetes induction, a hyper-lipidemic diet was instituted with serum cholesterol levels ranging between 400 and 800 mg/dL throughout the study period. One month after DM-HC induction, the pigs were randomly assigned into either a control group or treatment group receiving oral darapladib. Specimens were harvested 28 weeks after induction (ie, 24 weeks after initiation of treatment). There were 17 pigs in the control group and 20 in the treatment group, with three pigs that did not undergo DM-HC induction acting as age-matched controls. Significantly larger atherosclerotic lesions were observed in the control group compared with the treatment group, and controls were also more likely to demonstrate high-risk features. Seven of the 17 coronary lesions (41%) in the control group demonstrated a fibroatheroma or thin fibrous cap atheroma compared with two of 20 (10%) in the treatment group. The mean necrotic core area was significantly smaller in the darapladib-treatment group compared with the control group ($P<0.015$). These phenotypic changes were associated with significantly decreased lesion macrophage content assessed by cathepsin S immunohistochemistry ($P<0.036$). The results showed that selective inhibition of Lp-PLA₂ activity decoupled the primary effect of hypercholesterolemia from the resulting inflammatory immune effect, resulting in more stable and less vulnerable atherosclerotic lesions.

A study by Mohler et al. [26••] evaluated the ability of darapladib to produce sustained inhibition of plasma Lp-PLA₂ activity in patients with stable coronary heart disease (CHD) or CHD-risk equivalents while receiving concomitant atorvastatin therapy. Specifically, 959 patients were randomized to either 20 or 80 mg of atorvastatin and concomitant administration of 40, 80, or 160 mg of darapladib or placebo. Of note, after 4 weeks from baseline, plasma LDL levels were checked and only patients with levels lower than 115 mg/dL were randomized to receive darapladib or placebo. Compared with placebo, Lp-PLA₂ activity decreased by 43%,

55%, and 66%, respectively, in response to increasing doses of darapladib. Sustained dose-dependent inhibition was achieved regardless of atorvastatin dose or LDL levels above or below 70 mg/dL. There was a significant reduction in high-sensitivity C-reactive protein (hsCRP) ($P<0.015$) and interleukin-6 ($P<0.028$); known biomarkers of CV risk, at week 12 from baseline compared with placebo, but this was only observed in the group receiving the highest dose of darapladib (160 mg). The concern that inhibition of Lp-PLA₂ may adversely affect platelet activity was not supported in this study. No effects on platelet biomarkers associated with increased platelet aggregation (P-selectin, CD40 ligand, and urinary 11-dehydrothromboxane B₂) were observed. Also, no clinically important effects on vital signs, electrocardiograms, or laboratory data were observed in the darapladib group compared with placebo.

A phase 2 human study by Serruys et al. [27••] involved 330 patients with angiographically documented coronary artery disease who were treated with either 160 mg daily of darapladib or placebo for 12 months. In the study, 175 patients received darapladib and 155 received placebo. Eighty-six percent ($n=130$) of individuals in the placebo group completed treatment compared with 88% ($n=152$) in the darapladib group. Patients were followed to determine the effects of darapladib on coronary plaque deformability via intravascular ultrasound (IVUS). Secondary end points included several biomarkers (hsCRP, LDL, Lp-PLA₂ activity, and several markers of platelet activation) and clinical safety parameters. Plasma Lp-PLA₂ activity decreased by 59% in the darapladib group ($P<0.001$ vs placebo), whereas there was no significant difference in plasma LDL levels between placebo and treatment groups at 12 months. Although there was no significant difference in the primary end point of coronary plaque deformability ($P=0.22$) or a significant difference in hsCRP between the two groups ($P=0.35$), a significant decrease in the progression of necrotic core size (a secondary end point) was observed. In the placebo group, core size, which was determined by IVUS-based radio frequency analysis, increased significantly from baseline ($4.5 \pm 17.9 \text{ mm}^3$; $P<0.009$), whereas core size in the darapladib group did not ($-0.5 \pm 13.9 \text{ mm}^3$; $P=0.71$). Although the trial failed to demonstrate an effect on the primary outcome, the results demonstrated that darapladib prevented necrotic core expansion, indicating a potential therapeutic result. Necrotic core size is a primary component of vulnerable plaques. Such vulnerable plaques have increased risk of sudden luminal thrombosis formation, often in non-flow-limiting lesions [28]. Clinically, this results in unstable coronary syndromes and ischemic sudden death. Other important findings include a favorable safety profile and lack of effects on biomarkers of platelet activation.

The Stabilization of Atherosclerotic Plaque by Inhibition of Darapladib Therapy Trial (STABILITY) is a phase 3 randomized, double-blind, parallel-assignment, safety/efficacy study sponsored by GlaxoSmithKline that is currently recruiting participants. The primary outcome is time to first occurrence of any major adverse cardiovascular event, including cardiovascular death, nonfatal MI, or nonfatal stroke. Patients will be randomized on a one-to-one basis to receive either darapladib or placebo in addition to standard therapy for CHD. There are 638 study locations worldwide and the estimated enrollment is 15,500 patients. The study began in December 2008 and is expected to be completed in October 2012. This is the first and currently the only study evaluating the effects of selective inhibition of Lp-PLA₂ with darapladib on cardiovascular event outcomes.

Indirect Inhibitors

Indirect inhibitors of Lp-PLA₂ are essentially comprised of lipid-lowering agents. Most of the investigative work on nonselective Lp-PLA₂ inhibitors involves fibrate therapy, which has been shown to decrease Lp-PLA₂ mass and activity in plasma. In a randomized trial of patients with obesity and metabolic syndrome, participants were given 200 mg daily of fenofibrate, 120 mg of orlistat three times daily, or combined therapy for 6 months. Lp-PLA₂ activity was

reduced by 22% in the fenofibrate group, 14% in the orlistat group, and 35% in the combination-therapy group. In the fenofibrate group, the reduction in Lp-PLA₂ activity correlated with changes in LDL cholesterol ($P<0.01$) [29]. In another study done to evaluate gemfibrozil therapy on Lp-PLA₂ activity and cardiovascular events, gemfibrozil reduced Lp-PLA₂ activity by an average 6.6% compared with placebo ($P<0.0001$). They also found that the reduction in cardiovascular events with gemfibrozil versus placebo was larger for patients with the highest Lp-PLA₂ activity [30]. In a study by Kuvin et al. [31], 1 g daily of extended-release niacin was shown to reduce Lp-PLA₂ levels by 20% in patients with stable CHD [31]. Statins have also been shown to lower Lp-PLA₂ levels. In the Diabetes and Combined Lipid Therapy Regimen (DIACOR) study, simvastatin decreased Lp-PLA₂ levels by 34.5% and LDL cholesterol by 34.1% versus baseline [32].

Although lipid-lowering agents decrease circulating levels of Lp-PLA₂, this likely does not correlate with significant reductions in cardiovascular events. As the “critical pool” of Lp-PLA₂ is found within atherosclerotic plaque lesions, more direct targeting by pharmacologic agents may be necessary.

Conclusions

The persistent residual risk of recurrent adverse cardiovascular events despite patients receiving evidence-based standard-of-care therapies has prompted intense research into novel approaches aimed at reducing atherosclerotic burden, particularly vulnerable atherosclerotic plaques, in hopes of further reducing the risk of cardiovascular events. These efforts have unquestionably demonstrated the key role inflammation has in atherosclerosis. Lp-PLA₂ has emerged as a new independent marker of increased risk of cardiovascular events. Clinical evaluation of the efficacy of direct inhibitors of Lp-PLA₂, such as darapladib, will help elucidate Lp-PLA₂'s role in atherosclerotic development, and more importantly the role of darapladib in reducing progression to high-risk lesions, which are the pathologic substrate of ischemic death, MI, acute coronary syndromes, and ischemic stroke.

The previously mentioned studies have demonstrated some key findings, making it reasonable and exciting to proceed with investigations such as the STABILITY trial. One of the more contentious issues has been whether selective inhibition of Lp-PLA₂ would result in increased platelet activity, which was not substantiated in any of these studies. It now seems that darapladib's effect is independent of cholesterol abundance, demonstrating an independent role for vascular inflammation in development of atherosclerotic disease, with Lp-PLA₂ as the link between lipid metabolism and inflammation. Ultimately, clinical trials are now needed to determine if selective inhibition of Lp-PLA₂ does in fact reduce adverse cardiovascular events and death.

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