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REVIEW ARTICLE

DARAPLADIB AND ATHEROSCLEROSIS

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SUMMARY

This review will focus specifically on lipoprotein-associated phospholipase A_2 (Lp-PLA_2) and its inhibitor darapladib. Lp-PLA_2 is bound predominantly to apolipoprotein B (apoB)-containing lipoproteins and highly expressed in the necrotic core of atherosclerotic lesions. It rapidly degrades oxidatively modified phospholipids in modified LDL, for example, leading to formation of proinflammatory and cytotoxic products (i.e., lysophosphatidylcholine and oxidized nonesterified fatty acids). In a study conducted in diabetic and hypercholesterolemic swines, selective Lp-PLA_2 inhibitors (i.e., darapladib) reduced the development of advanced coronary atherosclerosis. Specifically, darapladib treatment considerably decreased the area of plaques and the necrotic cores, and reduced medial destruction, resulting in fewer lesions with an unstable phenotype. In the IBIS 2 study conducted in humans, darapladib significantly halted the increase of the necrotic core volume (−0.5 ± 13.9 mm^3; P = 0.71) that was observed in the cohort receiving placebo (4.5 ± 17.9 mm^3; P = 0.009), resulting in a significant treatment difference of −5.2 mm^3 (P = 0.012). In conclusion, despite standard-of-care treatment, patients with coronary artery disease continue to have recurrent cardiovascular events. PLA_2 inhibition may represent a new approach for the treatment of atherosclerosis if the benefit of this intervention is confirmed by the results of ongoing event-driven outcome trials.

INTRODUCTION

Atherosclerosis is the main cause of coronary heart disease, currently the leading cause of death worldwide and predicted to stay the main cause in 2030 (1). In the formation of atherosclerotic coronary lesions, a critical primary step is the accumulation and oxidation of LDL particles. Oxidized LDL favors leukocyte recruitment, activation and cell death, leading to the generation of complex atherosclerotic plaques (2). These plaques have a high content of necrotic core, a thin inflamed fibrous cap (intense accumulation of macrophages) and scarce presence of smooth muscle cells. In the necrotic core underlying the thin fibrous cap, hemorrhage, calcification and intraplaque vasa vasorum are commonly found (3, 4). These lesions have been identified as vulnerable plaques, referring to their association with cardiovascular clinical events.

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LIPOPROTEIN-ASSOCIATED PHOSPHOLIPASE A_2

The phospholipase A_2 (PLA_2) superfamily currently comprises 15 groups, a number of subgroups and 5 types of enzymes: the secreted PLA_2s (sPLA_2s), the cytosolic PLA_2s (cPLA_2s), the Ca^{2+}-independent PLA_2s (iPLA_2s), the platelet-activating factor acetylhydrolases (PAF-AHs) and the lysosomal PLA_2s (5). Of these five, the sPLA_2s and the PAF-AHs have been associated with atherogenesis and its complications. A comprehensive review has previously addressed sPLA_2 and its inhibitors in more detail (6).

This review will focus specifically on lipoprotein-associated phospholipase A_2 (Lp-PLA_2), which is produced and secreted by inflammatory cells involved in atherogenesis (7-10). It is also bound predominantly to apolipoprotein B (apoB)-containing lipoproteins and is highly expressed in the necrotic core of atherosclerotic lesions (11-13). Although this enzyme was first described as platelet-activating factor acetylhydrolase (or group-VIIA PLA_2), it has a much broader substrate specificity (14). Lp-PLA_2 rapidly degrades oxidatively modified phospholipids in, for example, modified LDL, leading to the formation of proinflammatory and cytotoxic products (i.e., lysophosphatidylcholine [LPC] and oxidized nonesterified fatty acids) (7, 15, 16). LPC promotes recruitment and activation of leukocytes, initiation of apoptosis and impaired clearance of apoptotic bodies (11). A pathology study showed that Lp-PLA_2 staining in plaques with pathological intimal thickening was nearly absent, while in complex lesions, such as thin-cap fibroatheromas and ruptured plaques, intense Lp-PLA_2 expression was shown within necrotic cores and surrounding macrophages, including those in the fibrous cap. The degree of macrophage apoptosis was greater in thin-cap fibroatheroma and ruptured plaques than in pathological intimal thickening plaques (12). This may imply that cytotoxic compounds derived from Lp-PLA_2 play an important role in plaque vulnerability. These observations therefore suggest that Lp-PLA_2 inhibition may favorably affect rupture-prone lesions.

In epidemiological studies, increased concentrations of Lp-PLA_2 predict future cardiovascular events. The level of Lp-PLA_2 was associated with almost a doubling of the risk of cardiovascular events in the highest quintile as compared with the lowest quintile in a study comparing 580 men who had had a coronary event to 1,160 control subjects who had not experienced such an event (17). Another trial studied the prognostic value of Lp-PLA_2 in 466 patients with stable coronary heart disease (18). The participants were followed up for a median of 4.0 years. Higher Lp-PLA_2 levels were associated with a greater risk of events; the hazard ratio per standard deviation was 1.28 (P = 0.009) after adjusting for clinical and lipid variables and C-reactive protein (CRP). Koening et al. (10) reported on a study of the prognostic value of plasma concentrations and activity of Lp-PLA_2 in 1,051 patients with coronary heart disease. In multivariable analyses, Lp-PLA_2 mass and activity were strongly associated with cardiovascular events after controlling for traditional risk factors, severity of coronary heart disease (CHD), statin treatment, cystatin C and *N*-terminal pro-brain natriuretic peptide (proBNP). In a community-based cohort of 5,531 older adults (The Cardiovascular Health Study) involved in a population-based cohort study of men and women aged 65 years and older, the mean Lp-PLA_2 level was higher in participants with ECG-detected abnormalities associated with advanced cardiac disease. By multivariable adjustment, there was a significant 27% greater risk of prevalent cardiac heart failure per standard deviation increment of the Lp-PLA_2 level and a modest but significant 12% greater risk of prevalent myocardial infarction (19).

In the past, there was considerable discussion on whether the role of Lp-PLA_2 in atherogenesis was primarily proinflammatory (generation of lysophosphatidylcholine) or anti-inflammatory (degradation of platelet-activating factor [PAF] or PAF-like lipids). As previously mentioned, the enzyme was first described as PAF acetylhydrolase, although it has much broader substrate specificity (20, 21). It rapidly degrades oxidatively modified phospholipids in LDL cholesterol (LDL-C), leading to the formation of proinflammatory and cytotoxic products, as mentioned above (7, 15, 16). Because enhanced cell death and impaired clearance of apoptotic bodies are thought to be key mechanisms for necrotic core expansion (22), Lp-PLA_2 inhibition may have a favorable effect on rupture-prone lesions. Its precise role in atherosclerosis, however, has remained controversial, with diverging opinions regarding its anti- or proatherogenic effects (23).

DARAPLADIB

With the advent of a selective and extremely potent and substrate-competitive inhibitor of this enzyme, it became clearer that Lp-PLA_2 had a predominantly proinflammatory role in atherogenesis (7). An Lp-PLA_2 inhibitor being tested as a potential therapeutic option is darapladib. Darapladib has demonstrated selectivity for Lp-PLA_2 over other sPLA_2 enzymes thought to play a role in atherogenesis, namely sPLA_2 types IIA, V and X. Whereas the IC_{50} value of darapladib for Lp-PLA_2 is 0.27 nM, darapladib demonstrated < 10% inhibition of the other sPLA_2s at 1 μM (13), a concentration 10-fold higher than the maximum concentration achieved following clinical dosing. The weak activity of darapladib against these three sPLA_2s is expected because they have a very different catalytic mechanism compared to Lp-PLA_2.

Lp-PLA_2 inhibition, with the subsequent reduction of its product, LPC, has attenuated the inflammatory cascade and cell death in in vitro studies (11, 15, 16). Furthermore, darapladib decreased intraplaque LPC content, decreased the expression of a panel of inflammatory genes and reduced necrotic core in coronary lesions in a porcine model of coronary atherosclerosis (24). In humans, treatment with darapladib not only inhibited Lp-PLA_2 activity within carotid plaques, but it also reduced activity of the intracellular proteases (caspase-3 and caspase-8) that are responsible for apoptotic cell death (25).

In animal studies, selective Lp-PLA_2 inhibitors (i.e., darapladib) have shown reduced development of advanced coronary atherosclerosis in diabetic and hypercholesterolemic swine (13). Specifically, darapladib treatment resulted in a considerable decrease in the areas of the plaques and necrotic cores and reduced medial destruction, resulting in fewer lesions with an unstable phenotype. The mean plaque area (± SEM) in the left anterior descending coronary artery was 0.178 ± 0.046 mm^2 in the treated group versus 0.636 ± 0.212 mm^2 in the control group. The mean necrotic core area (± SEM) from the arterial section with the greatest plaque area was significantly reduced from 0.87 ± 0.33 mm^2 to 0.03 ± 0.003 mm^2 (P = 0.015) with treatment. Overall, the mean medial destruction score for control coronary vessels was 2.4 ± 0.027, whereas in the treatment cohort the score was reduced (1.2 ± 0.24; P = 0.003). More advanced coronary lesions (i.e., thin fibrous cap atheroma) were found in the control group than in the treated cohort (41% vs. 10%; P = 0.05). The mean ratio of macrophages to total intimal and medial area was 1.78 ± 0.44% in the control group and 0.71 ± 0.18% in the treated cohort (P = 0.036).

In a multicenter, randomized, double-blind, placebo-controlled study in 959 patients with CHD or CHD risk equivalent receiving atorvastatin 20 or 80 mg, the effects of 12-week darapladib treatment (40, 80 and 160 mg p.o.) on Lp-PLA_2 activity, biomarkers and oxidized lipids were evaluated (ClinicalTrials.gov Identifier NCT00269048) (26). Darapladib 40, 80 and 160 mg dose-dependently inhibited Lp-PLA_2 activity by approximately 43%, 55% and 66%, respectively, compared with placebo (P < 0.001 at week 12). Sustained dose-dependent inhibition in Lp-PLA_2 was noted overall in both atorvastatin groups and at different baseline LDL-C (≥ 70 mg/dL vs. < 70 mg/dL, respectively) and HDL-C (< 40 mg/dL vs. ≥ 40 mg/dL, respectively). Interestingly, at week 12, there was no significant interaction between atorvastatin or darapladib and the change in Lp-PLA_2 activity (P = 0.60). Likewise, there was no interaction between baseline LDL-C (< 70 mg/dL vs. ≥ 70 mg/dL) or HDL-C (< 40 mg/dL vs. ≥ 40 mg/dL) and the change in Lp-PLA_2 activity at 12 weeks at any of the darapladib doses (P = 0.12 and 0.13, respectively). Although high-sensitivity CRP (hs-CRP) at baseline was low due to intensive background atorvastatin therapy, treatment with darapladib 160 mg (n = 161) produced a 20.2% reduction (P = 0.003; within-group comparison) versus a reduction of 13.0% with placebo (P = 0.15; between-group comparison). Patients treated with darapladib 160 mg (n = 150) had a 21.5% reduction in interleukin-6 (P < 0.001; within-group comparison), which was also statistically significant compared with placebo (P = 0.028).

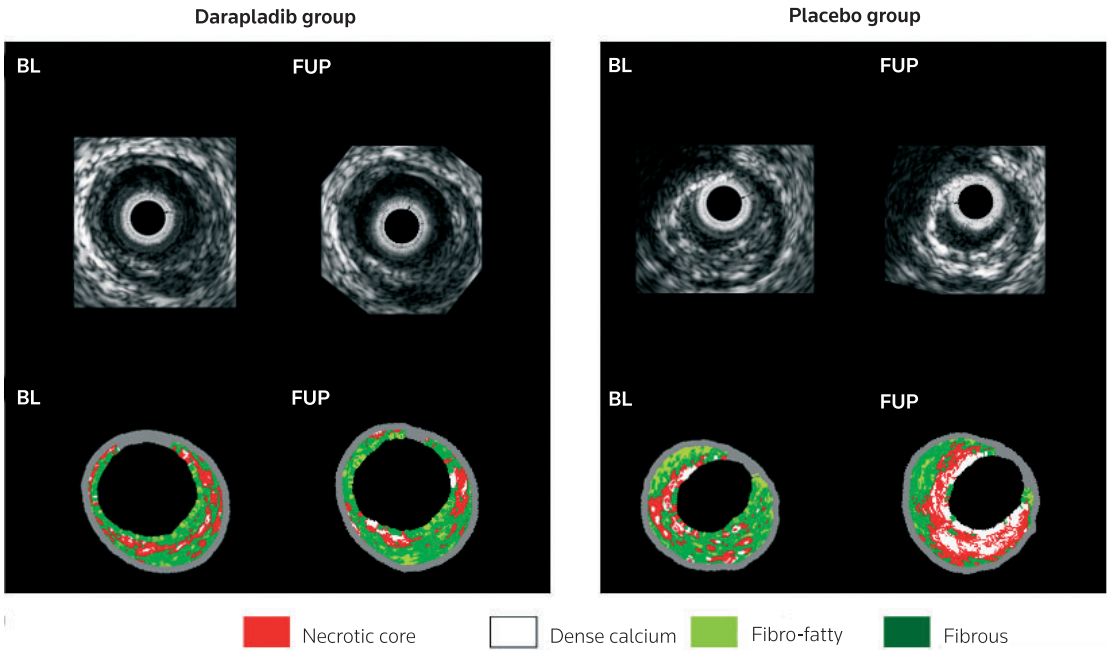

Figure 1. Temporal changes in the necrotic core in a patient receiving either darapladib or placebo in the IBIS 2 study. In contrast to placebo, two cross sections from the darapladib-treated patient demonstrate reduction in necrotic core area depicted in red. Of note, concomitant increase in fibrous tissue (in green) is consistent with a plaque stabilization effect. BL, baseline; FUP, follow-up.

The international, multicenter, randomized, double-blind, placebo-controlled Integrated Biomarkers and Imaging Study-2 was conducted in 330 patients with angiographically confirmed coronary heart disease (ClinicalTrials.gov Identifier NCT00268996) (27). At 12 months, darapladib produced no difference in LDL-C (84 ± 31 mg/dL with 160 mg darapladib versus 88 ± 34 mg/dL with placebo; P = 0.37). The primary endpoint was coronary atheroma deformability (intravascular ultrasound [IVUS] palpography) and plasma hs-CRP. Secondary endpoints included changes in necrotic core size (IVUS radiofrequency), atheroma size (IVUS greyscale) and blood biomarkers. The Lp-PLA_2 activity was inhibited by 59% with darapladib (P < 0.001 versus placebo). After 12 months, there were no significant differences between groups in plaque deformability (P = 0.22) or plasma hs-CRP (P = 0.35). In those participants receiving placebo (n = 140), the hs-CRP level was 1.0 mg/L (95% confidence interval [CI]: 0.8-1.2 mg/L) compared with 0.9 mg/L (95% CI: 0.8-1.1 mg/L) in the darapladib group (n = 162). However, a significantly higher percentage of patients achieved very low levels of hs-CRP (< 1 mg/L) on darapladib (62%) than on placebo (45%) (P < 0.008). In the placebo-treated group, however, necrotic core volume increased significantly (4.5 ± 17.9 mm^3; P = 0.009), whereas darapladib halted this increase (−0.5 ± 13.9 mm^3; P = 0.71), resulting in a significant treatment difference of −5.2 mm^3 (P = 0.012) (Fig. 1). These intraplaque compositional changes occurred without a significant treatment difference in total atheroma volume (P = 0.95).

There are three ongoing clinical trials in which the effect of darapladib is being assessed: STABILITY (ClinicalTrials.gov Identifier NCT00799903), SOLID-TIMI 52 (ClinicalTrials.gov Identifier NCT01000727) and Lp-PLA2, Progenitor Cells and Coronary Atherosclerosis in Humans AIM III (Table I). In brief, the STABILITY (STABilization of atherosclerotic plaque by Initiation of darapLadIb TherapY) trial is a clinical outcome study of darapladib versus placebo in patients with CHD to compare the incidence of major adverse cardiovascular events (MACE) (i.e., death due to a cardiovascular cause, nonfatal myocardial infarction and nonfatal stroke). The patients will remain in the trial until a specified number of MACE have occurred. It is anticipated that the participants (N = 15,500) will be in the study about 3 years. This trial has completed recruiting participants. The second largest study, SOLID-TIMI 52 (Stabilization Of pLaques usIng Darapladib-Thrombolysis In Myocardial Infarction 52), is a clinical outcome study of darapladib versus placebo in patients within 30 days after an acute coronary syndrome to compare the incidence of MACE. This study is currently enrolling and is expected to include 11,500 participants.

CONCLUSIONS

Despite standard-of-care treatment, patients with coronary artery disease continue to have recurrent cardiovascular events. Lp-PLA_2 inhibition may represent a new approach for the treatment of atherosclerosis if the benefit of this intervention is confirmed by the results of ongoing event-driven outcome trials.

Table I. *Ongoing darapladib studies.*

Trial name	STAbilization of atherosclerotic plaque By Initiation of darapLadIb TherapY (STABILITY)	Stabilization Of pLaques usIng Darapladib Thrombolysis In Myocardial Infarction 52 (SOLID-TIMI 52)	Lp-PLA2, Progenitor Cells and Coronary Atherosclerosis in Humans AIM III
Brief summary	This study will test whether darapladib can safely lower the chances of having a cardiovascular event (e.g., cardiovascular death, heart attack or stroke) in people with coronary heart disease	This trial will test whether darapladib can safely lower the chances of having a cardiovascular event (e.g., cardiovascular death, heart attack or stroke) when treatment is started within 30 days after an acute coronary syndrome	A prospective, randomized, double-blind, placebo-controlled trial to assess and quantify the effect of long-term administration of darapladib 160 mg on coronary endothelial function, progression of coronary atherosclerosis as determined by intravascular ultrasound (IVUS) and atherosclerosis in patients with early atherosclerosis
Detailed description	Subjects will be randomized 1:1 to either darapladib or placebo administered in addition to standard therapy. Following the baseline visit, subjects will be followed at 1 month, 3 months and every 6 months until the end of the study. Average time in the trial for an individual subject is expected to be approximately 3 years	Patients will be randomized 1:1 to either darapladib or placebo administered in addition to standard therapy. Following the baseline visit, subjects will be followed at 1, 3 and 6 months and every 6 months until the end of the study	Participants will be randomized 1:1 to either darapladib or placebo administered in addition to standard therapy. Patients with evidence of coronary endothelial dysfunction, as determined by intracoronary administration of acetylcholine during angiography and IVUS, will be followed for 6 months during once-daily dosing of darapladib. Coronary endothelial function is determined by the changes in coronary artery diameter and coronary blood flow response to the intracoronary administration of acetylcholine and adenosine. The patients will be followed in the clinic at 3 and 6 months. They will have follow-up angiography, assessment of endothelial function and IVUS with virtual histology during the 6-month visit
Intervention	Darapladib 160 mg or placebo In addition to standard therapy	Darapladib 160 mg or placebo In addition to standard therapy	Darapladib 160 mg or placebo In addition to standard therapy

DISCLOSURES

Colin H. MacPhee and Elizabeth Tarka are employees of GlaxoSmithKline.

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