Varespladib: targeting the inflammatory face of atherosclerosis

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This editorial refers to 'Randomized trial of an inhibitor of secretory phospholipase A₂ on atherogenic lipoprotein subclasses in statin-treated patients with coronary heart disease†', by R.S. Rosenson et al., on page 999

Atherosclerosis is a complex disease and in its pathogenesis depends on the interaction between lipoproteins and inflammatory mediators. This interaction orchestrates the progression of atherosclerosis from its earliest stage when oxidized lipoproteins and leucocytes penetrate dysfunctional endothelium and enter the subendothelial space, right until the end of the process when the plaque becomes unstable and ruptures, leading to a clinical event. Whereas our pharmacological armamentarium that targets the lipid component of the risk factor spectrum has been tremendously successful with the clinical introduction of statins in the middle of the 1990s, drugs that target the inflammatory face of atherosclerosis have thus far been scarce.

Among the wide range of chemokines, adhesion molecules, and pro-oxidative substances that affect macrophage recruitment into the arterial wall, members of the phospholipase A₂ (PLA₂) family have received considerable attention since their purification from human plasma lipoproteins in 1987. PLA₂s are small and relatively stable ubiquitous enzymes that hydrolyse the sn-2-acyl bond of phospholipids in cell membranes as well as in lipoproteins. This enzymatic activity yields non-esterified fatty acids and lysophospholipids in cell membranes as well as in lipoproteins. This wide association studies for plasma lipids identified a single nucleotide polymorphism in PLA2G6, the gene encoding PLA₂-VI, as a significant predictor of plasma triglyceride levels (P = 4 × 10⁻⁶). So, in summary, PLA₂s may both affect lipid metabolism and act at the interface between lipoproteins and macrophages promoting plaque progression and instability.

Out of the large family of PLA₂s, two have been in the spotlight of cardiovascular research: sPLA₂-IIa and, in particular, Lp-PLA₂. Results emerging from prospective studies consistently show that high levels of Lp-PLA₂ as well as high activity are associated with coronary heart disease (CHD) risk, as summarized by a large-scale meta-analysis published earlier this year. Given the strong and consistent association between this biomarker and CHD risk, the obvious next question is that of causality. One approach to address this is by Mendelian randomization; if a biomarker is causally associated with CHD risk, then a genetic variant that affects its plasma concentration or activity should itself be putatively associated with CHD risk. A recent Mendelian randomization study failed to show consistent associations between PLA₂G7 genetic variants, Lp-PLA₂ activity, and CHD risk, which some consider an argument against causality. It should be acknowledged, however, that this might have been caused by lack of statistical power. Some have raised questions about the validity of Mendelian randomization studies to rule out causality per se. Another approach to assess causality is the use of targeted inhibition of Lp-PLA₂ activity. Darapladib is a specific inhibitor of Lp-PLA₂ activity that was recently tested in the Integrated Biomarkers and Imaging Study (IBIS)-2, which used intracoronary ultrasound to assess plaque characteristics. Darapladib had no effect on the co-primary endpoints of plaque deformability and plasma C-reactive protein levels, but the investigators of the trial were encouraged by the finding that darapladib prevented expansion of the necrotic core of atherosclerotic plaque. Supporters of Lp-PLA₂ inhibition may also question the rationale for including changes in C-reactive protein as co-primary endpoint given the lack of biological evidence linking Lp-PLA₂ with this acute phase protein. The slight increase in blood pressure as well as other
undesirable odour- and taste-related side effects associated with darapladib may, however, limit the ascension of this compound. Despite the somewhat disappointing intravascular ultrasound results, two large phase III trials were initiated, recruiting patients with stable coronary artery disease (STABILITY) and patients with an acute coronary syndrome (SOLID-TIMI 52). Both studies are fully enrolled and the results are expected in 2012 and 2014, respectively.

A phospholipase family member that has received less attention in cardiovascular research is sPLA2-IIa. Extracellular depositions of sPLA2-IIa are higher in atherosclerotic plaques of patients who suffered a myocardial infarction than in patients with stable or unstable angina. In a small Japanese cross-sectional study, plasma concentrations of sPLA2-IIa were higher among CHD patients than in controls. In addition, among patients with CHD, elevated concentrations were associated with a higher risk of recurrent events. In a large prospective case–control study in the EPIC-Norfolk cohort, elevated concentrations of sPLA2-IIa were confirmed to be associated with an increased risk of CHD. Interestingly, in the same study, measurement of sPLA2-IIa activity was an even better predictor of CHD risk. Plasma sPLA2-IIa levels can be reduced with conventional pharmacotherapy since treatment with irbesartan and pravastatin has been shown to reduce sPLA2-IIa concentration and activity.

Varespladib is a novel selective sPLA2 inhibitor with specificity towards several isoforms of the PLA2 family including sPLA2-IIa, sPLA2-V, and sPLA2-X (Figure 1B). In animal studies, varespladib had protective effects on experimental atherosclerosis. In humans, the Phospholipase Levels And Serological Markers of Atherosclerosis-1 (PLASMA I) study showed that varespladib...
treatment (50–500 mg twice daily) reduced the sPLA2-IIa concentration in a dose-dependent manner in patients with stable CHD followed for 8 weeks. In addition, in this study population in which 66% used statin therapy, varespladib reduced LDL cholesterol by an additional 8%, non-HDL cholesterol by an additional 5.9%, and nuclear magnetic resonance spectroscopy-measured small LDL particle concentration by an additional 7.3%.

The main objective of this trial was to determine the efficacy of varespladib when used once daily in a population on statin therapy since varespladib is of course envisaged for use in combination with statins. In PLASMA II, reductions in sPLA2 levels (the primary endpoint of the study) reached 73 and 84%, in the 250 and 500 mg dosage groups, respectively. In addition, people in the varespladib arms experienced promising additional reductions in atherogenic lipid subfractions over and above that achieved by statins alone. Compared with placebo, varespladib 500 mg reduced LDL-cholesterol by 15%, non-HDL cholesterol by 15%, and apolipoprotein B by 11%. Varespladib also lowered HDL particle concentration, which may be considered as undesirable, but it should be kept in mind that only the small HDL subfraction was significantly reduced, a subfraction that may have fewer anti-atherogenic properties than larger HDL particles.

The PLASMA I and PLASMA II trials have set the scene for larger scale trials. Among them, the FRANCIS-ACS trial assessed the effect of varespladib on biomarkers when added to atorvastatin in 625 patients with an acute coronary syndrome. Results of this study which have very recently been published further highlight the potential of varespladib in reducing LDL cholesterol and other biomarkers. The VISTA-16 trial has recently started recruiting patients. It will test the efficacy and safety of varespladib compared with placebo in reducing cardiovascular outcomes among 6500 patients with an acute coronary syndrome who are on background atorvastatin therapy.

Although it is not certain, as yet, that LDL cholesterol reduction beyond what can be achieved by statin therapy alone does promote plaque regression, the reduction of cholesterol levels in the small LDL subclass achieved with varespladib makes it an appealing agent. In a previous issue of this journal, we have shown that cholesterol levels in larger LDL subfractions showed no association whatsoever with coronary risk.20 However, although the preliminary data on varespladib are encouraging, it should be kept in mind that other anti-inflammatory agents have appeared promising in animal and human biomarker studies but showed rather disappointing clinical results.21 The final step for PLA2s, but also for the inflammatory concept per se, to be considered as a risk factor for cardiovascular disease awaits confirmation that targeting these specific components will indeed prevent cardiovascular events. The large phase III trials testing the efficacy of darapladib and varespladib in reducing cardiovascular event rates will be important proof of the inflammatory hypothesis.

Conflict of interest: none declared.

References

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Corrigendum to the ‘Guidelines for the diagnosis and treatment of pulmonary hypertension’ [European Heart Journal (2009) 30, 2493–2537]. The Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). Authors/Task Force Members: Nazzareno Galiè (Chairperson) (Italy); Marius M. Hoepera (Germany); Marc Humbert (France); Adam Torbicki (Poland); Jean-Luc Vachiery (France); Joan Albert Barbera (Spain); Maurice Bøggetti (Switzerland); Paul Corris (UK); Sean Gaine (Ireland); J Simon Gibbs (UK); Miguel Angel Gomez-Sanchez (Spain); Guillaume Jondeau (France); Walter Klepetko (Austria) Christian Opitz (Germany); Andrew Peacock (UK); Lewis Rubin (USA); Michael Zellweger (Switzerland); Gerald Simonneau (France).

Withdrawal of sitaxentan in the treatment of pulmonary arterial hypertension

The 2009 ESC Practice Clinical Guidelines for the diagnosis and treatment of pulmonary hypertension included the endothelin receptor antagonist sitaxentan in sitaxentan at a grade of evidence-based treatment for pulmonary arterial hypertension. Sitaxentan was recommended with a Class I/Level A grade of evidence in WHO functional class III patients and Class Ila/Level C grade of evidence in WHO functional class II and IV. Sitaxentan was initially authorized by the European regulatory agency as Thelin in 2006 but in December 2010, after the manufacturer withdrew Thelin from the worldwide market following new information on two cases of fatal liver injury, marketing authorization was also withdrawn by the EMA.

In the light of the withdrawal and the EMA’s advice to patients taking Thelin (not to stop medication but review treatment at the next scheduled appointment), the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the ESC and the European Respiratory Society (ERS) has issued its own recommendations for treating physicians. This has been published in the European Heart Journal in February as a CardioPulse article (European Heart Journal 2011; 32:386–387).

The Task Force recommends:

(1) For the time being, no PAH patient should start de novo therapy with Thelin

(2) For patients already on treatment with Thelin, transition to another endothelin receptor antagonist such as bosentan (Tracleer) or ambrisentan (Volibris) should be considered.

(3) In cases where a PAH patient was treated with Thelin because of previous adverse reactions with Tracleer and Volibris, the transition to another class of PAH-approved drugs should be considered (prostanoids or PDE-5 inhibitors)

The Task Force is monitoring the status of sitaxentan, along with all other clinical developments relevant to pulmonary hypertension. This information will be incorporated in the next update of the ESC Practice Clinical Guidelines.

The online version of the Guidelines has been updated with a note added to the title page bringing attention to the fact that the drug has been withdrawn. The occurrences of ‘sitaxentan’ have also been highlighted where they occur throughout the text.

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