How to stabilize unstable plaque

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Online publish-ahead-of-print 23 May 2011

This editorial refers to 'Inhibition of rupture of established atherosclerotic plaques by treatment with apolipoprotein A-I' by G.J. Reimers et al., pp. 37–44, this issue.

Association studies and epidemiological observations have shown that high plasma levels of high-density lipoprotein-cholesterol (HDL-C) provide cardiovascular protection. The anti-atherosclerosis activity of HDL is multifaceted and may include anti-thrombotic, anti-oxidative, and anti-inflammatory mechanisms. However, reverse cholesterol transport through which cholesterol is removed from tissues and plaques and shuttled to the liver for excretion with bile is thought to be the major action of HDL in its atheroma-preventing effort.

These observations and experimental findings gave rise to studies in experimental animals and phase I and II trials of short-term infusions of reconstituted HDL with the aim of accelerating reverse cholesterol transport. In the ERASE clinical trial reconstituted HDL (made of human apolipoprotein A-1, Apo A-1, and soybean phosphatidylcholine) that was administered beginning shortly after an acute coronary syndrome tended to reduce coronary plaque volume as measured with intravascular ultrasound.

Acute coronary syndromes are mainly caused by injury to plaques, especially rupture, with the consequences of platelet activation and acute thrombus formation at the plaque site. Thus, in addition to reducing plaque burden, improvement of plaque quality (stability) is an important therapeutic goal. Reimers et al. describe experimental studies to specifically examine the integrity of pre-existing plaques and changes in plaque composition in atherosclerosis-prone mice receiving low-dose human Apo A-1. Lesions were induced in Apo E knock-out mice by feeding high-fat, high-cholesterol chow. In this model, there is a high incidence of vulnerable and ruptured plaque in brachio-cephalic arteries. Reimers et al. treated their animals after 9 weeks on the high-fat chow with phosphate-buffered saline or human Apo A-1 at a low dose (8 mg/kg) given only four times (twice weekly for 2 weeks). Results are quite astonishing and

Figure 1 Cartoon summarizing actions of Apo A-1 that contribute to stabilizing plaques or maintaining plaque stability as described by Reimers et al. In addition, reconstituted HDL and Apo A-1 have several other beneficial effects including anti-inflammatory, anti-thrombotic, and anti-oxidative activity in addition to their promotion of reverse cholesterol transport.

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include reductions in plaque disruption and plaque haemorrhage and an almost 3-fold increase in the number of smooth muscle cells (SMCs) within the plaque. These Apo A-1 effects indicate an improved plaque stability. This is further corroborated by an analysis of the fibrous cap. In Apo A-1-treated mice, the fibrous cap contained about twice as many SMCs compared with control atherosclerotic mice. In addition, smooth muscle cells in the cap of Apo A-1-treated mice less commonly expressed S100A4 and less matrix metalloprotease-13 (MMP13) (Figure 1). These latter two proteins mark ‘synthetic phenotype’ SMCs with less contractile but increased migration capacity, traits that are thought to destabilize the fibrous cap (Figure 1). In totality, these findings by Reimers et al. are remarkable for the low dose of Apo A-1 and the short period of treatment that induced a phenotype transition of plaques from vulnerable or rupturing to stable. Of course, conclusions that may be drawn from these findings are limited as no ‘hard outcomes’ such as survival were assessed. Moreover, ‘humans are a poor model for diseases in rodents’, and it remains to be determined whether these benefits of low-dose Apo A-1 can also be realized in patients with coronary artery disease. It is also unknown whether these changes in plaque stability are a result of anti-inflammatory actions of Apo A-1 and its effects on reverse cholesterol transport or whether the Reimers paper describes a new mechanism of action of Apo A-1.

There are also other promising Apo A-1-based anti-atherosclerotic treatments that have been or are currently being explored. These include Apo A-1-Milan, which has a point mutation introducing an additional cysteine into the molecule. Preliminary studies in humans suggest reductions in coronary artery plaque burden by treatment with this mutated Apo A-1. The activation of the reverse cholesterol transport ATP-binding cassette transporter A1 (ABCA1) pathway by Apo A-1 is thought to depend on certain domains within the molecule that mediate its affinity to ABCA1. Several investigators have developed small peptides that retain this particular affinity and, thus, activate reverse cholesterol transport and reduce plaque in arteriosclerosis-prone mouse models. As shown by Reimers et al., attention should not only be paid to the reduction in plaque burden when evaluating treatments with Apo A-1 or Apo A-1 mimetics but also to their efficacy in changing plaque phenotype and raising plaque stability.

Conflict of interest: none declared.

References