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It's Time to Reassess the High-Density Lipoprotein (HDL) Hypothesis: CSL112, a Novel Promising Reconstituted HDL Formulation

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Clinical intervention studies have provided clear evidence that low-density lipoproteins are causally involved in the development of atherosclerosis. In contrast, data for high-density lipoproteins (HDLs) are still inconclusive. A number of antiatherogenic properties have been ascribed to HDL, but the hypothesis that HDL is causally related to cardiovascular disease has been challenged seriously by recent data. Genetic analysis failed to show a causal association between genetically raised plasma HDL-cholesterol (HDL-C) levels and risk of myocardial infarction,[1] and recent large-scale clinical trials have failed to demonstrate a clinical benefit of HDL-C–raising therapies when added to standard therapy.[2,3] Consequently, one may assume that HDL-C–raising therapies do not result in cardiovascular risk reduction. Nonetheless, this simple conclusion cannot be drawn, given that these HDL-C trials tested drugs that delayed HDL catabolism to increase HDL-C, thereby generating large cholesteryl ester–enriched particles. Large HDL particles, in contrast to small dense human HDL_3 particles, do not interact efficiently with the ATP binding cassette transporter A1 (ABCA1).[4] This appears to be of critical importance, given that ABCA1 is the major mediator of cholesterol efflux to HDL from macrophages. Recent studies provided strong evidence that HDL-C efflux capacity is inversely associated with incident coronary heart events, independent of established cardiovascular risk factors.[5,6] Consequently, HDL-targeted interventional studies should focus on increasing the range of particles capable of promoting cholesterol efflux via ABCA1. A promising approach to elevate the functional activity of plasma HDL is the direct infusion of small reconstituted HDL particles designed to favor interaction with the ABCA1 transporter. Previous small clinical studies have suggested protective effects of reconstituted HDL infusions on coronary plaque burden compared with baseline.[7] More recently, a well-powered prospective randomized multicenter trial on infusion of the HDL-mimetic agent CER-001 in coronary atherosclerosis patients was conducted.[8] Intravascular ultrasonography and quantitative coronary angiography were performed at baseline and at 2 to 5 weeks after the last infusion of the HDL-mimetic agent. Disappointingly, compared with placebo, infusions of CER-001 did not result in a significant reduction in coronary atherosclerosis. The failure of the study to achieve its primary efficacy parameter is likely to be multifactorial. The dosage could have been too low and/or not frequent enough, and the duration of the study could have been too short, and thus potentially favorable effects of infusion of CER-001 in the long term could have been overlooked. Moreover, it is known that inflammation alters HDL composition and function. Post-translational modifications, phospholipid depletion, and enrichment with proinflammatory proteins like serum amyloid A and apolipoprotein C-III are thought to transform atheroprotective HDL into dysfunctional or even proatherogenic forms of HDL.[9,10] Furthermore, the phosphatidylcholine moiety of administered reconstituted HDL is rapidly hydrolyzed in plasma,[11] generating lysophospholipids that might alter the functionality of HDL.[12]

Despite this disappointing result, the development of new reconstituted HDL formulations continues. CSL112 is a promising novel reconstituted HDL infusion therapy. CSL112 particles consist of 2 molecules of apolipoprotein A-I and ≈110 molecules of phosphatidylcholine.[13] CSL112 was shown to be significantly more potent than native HDL at enhancing cholesterol efflux from macrophages via the ABCA1 transporter, indicating active remodeling in plasma.[14] Tricoci et al now present safety and pharmacokinetics/pharmacodynamics results of CSL112 from a phase IIa randomized clinical trial among patients with stable atherosclerotic disease.[15] CSL112 promoted a rapid and marked increase in the capacity of serum to efflux

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cholesterol. Study drug–related adverse effects were reported to be mild and attributable to vessel puncture or infusion-site bruising. These results show early promise and strongly support the continued assessment of reconstituted HDL infusions like CSL112 as a new therapy for patients with high-risk coronary artery disease. Further randomized clinical trials are eagerly awaited and will reassess the HDL hypothesis.

Disclosures

None.

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