IN THE LITERATURE

Is regression of coronary atherosclerosis possible by infusing recombinant apolipoprotein A-I?

Nissen SE, Tsunoda T, Tuzcu EM, Schoenhagen P, Cooper CJ, Yasin M, et al. Effect of recombinant ApoA-I Milano on coronary atherosclerosis in patients with acute coronary syndromes: a randomized controlled trial. *JAMA* 2003;290(17):2292-300.

Background: Observational studies have implicated plasma concentrations of high-density lipoprotein (HDL) cholesterol and its main protein apolipoprotein (apo) A-I as protective factors against coronary artery disease (CAD).[1] A naturally occurring human mutation of apo A-I (apo A-I Milano) has been associated with protection against CAD.[2] Infusions of apo A-I Milano have been shown to reduce atherosclerosis in animal models.[3]

Design: This double-blind, randomized controlled pilot trial recruited patients who required coronary angiography for recent acute coronary syndromes. Following angiography and intravascular ultrasonography to measure atherosclerotic plaque volume, patients were randomly assigned to receive weekly infusions of one of the following for 5 weeks: placebo, low-dose (15 mg/kg) therapy with apo A-I Milano/phospholipid complexes (ETC-216) or high-dose (45 mg/kg) therapy with ETC-216. Intravascular ultrasonography was repeated 6 weeks later. The primary outcome was change in percent atheroma volume.

Results: A total of 47 patients completed the study. Those in the combined ETC-216 cohort had a significant reduction in the mean percent atheroma volume and the total volume of atherosclerotic plaque burden compared with baseline values (Table 1).

Commentary: The rapid regression of atherosclerosis observed in the ETC-216 cohort is astonishing. This degree of change in plaque volume is comparable to that previously observed with intensive LDL reduction therapy using statins over 18–24 months.

Atherosclerosis evolves over decades. The small but significant change in plaque size achieved using this novel compound derived from a recombinant mutant human protein suggests that the disease course can be altered rapidly. However, there are important caveats. First, the significant differences were derived from comparisons against baseline values in the combined treatment group: formal paired comparison of the ETC-216 and placebo groups showed no statistical difference, although the study was admittedly not powered for a direct comparison. Second, because the placebo was saline rather than the phospholipid alone without the apo A-I Milano, it is unknown whether the regression was mediated in whole or in part by the phospholipid component of ETC-216. Third, there was no evidence of a dose response. Fourth, despite the promise of newer measurements of atherosclerosis (e.g., intravascular ultrasonography) as markers of efficacy, all new therapies must ultimately be proven to reduce the incidence of clinical events. More experience is required for both ETC-216 as a therapeutic agent in atherosclerosis and intravascular ultrasonography as a diagnostic and prognostic tool. Nonetheless, this study provides preliminary evidence of the effects of apo A-I Milano.

Practice implications: The results clearly require confirmation in larger trials using hard end points of morbidity and mortality. This study suggests the possibility of a new treatment paradigm for atherosclerosis, namely medical therapies to rapidly mobilize cholesterol from existing atherosclerotic plaques and thereby reduce plaque burden. In practice, this type of acute therapy might complement subsequent long-term maintenance therapies (e.g., with ASA, statins and ACE inhibitors) in addition to newer modalities that will stabilize and prevent the regrowth of atherosclerotic lesions, with improvements in cardiovascular outcomes.

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Table 1: Change in coronary atherosclerotic plaque volume, as measured by intravascular ultrasonography*

Study group	Change in % atheroma volume from baseline, median (and 95% CI)	*p* value	Change in total atheroma volume from baseline, mm^3, median (and 95% CI)	*p* value
Placebo	0.03 (–1.11 to 1.43)	0.97	–0.2 (–8.6 to 8.2)	0.97
ETC-216				
15 mg/kg	–1.14 (–2.24 to –0.56)	0.03	–15.0 (–29.6 to –4.9)	0.02
45 mg/kg	–0.34 (–1.21 to 0.43)	0.45	–12.0 (–20.6 to –2.9)	0.007
Combined	–0.81 (–1.53 to –0.34)	0.02	–13.3 (–20.7 to –7.2)	< 0.001

Note: CI = confidence interval.
*Adapted from Nissen SE, Tsunoda T, Tuzcu EM, Schoenhagen P, Cooper CJ, Yasin M, et al. Effect of recombinant apoA-I Milano on coronary atherosclerosis in patients with acute coronary syndromes. *JAMA* 2003;290:2292-300.

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