Lipid Hypothesis for Cardiovascular Disease is Challenged, Exposing Weakness

By Chuck Dinerstein, MD, MBA — August 28, 2017

The reigning theory underlying cardiovascular disease, the lipid hypothesis, suffered a defeat this week at the hands of the inflammatory hypothesis when canakinumab, a human monoclonal antibody that targets interleukin-1β [1] was shown [2] to reduce cardiovascular events in the absence of lipid lowering. These were the results of a study published in the New England Journal of Medicine. 17,482 patients met the inclusion criteria of a history of myocardial infarction and an elevated C-reactive protein, a marker of inflammation, which remained high despite “aggressive secondary prevention strategies.” The study tested placebo against three varying doses of canakinumab. The study made the following statistically significant findings:

- "At 48 months, the median reduction from baseline in the high-sensitivity C-reactive protein level was 26 percentage points greater in the group that received the 50-mg dose of canakinumab, 37 percentage points greater in the 150-mg group, and 41 percentage points greater in the 300-mg group than in the placebo group … By contrast, canakinumab use resulted in no significant reduction from baseline in the LDL cholesterol or HDL cholesterol level and in a 4 to 5% median increase in the triglyceride level."
- "At a median follow-up of 3.7 years, the incidence rate for the primary end point (nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death) was 4.50 events per 100 person-years in the placebo group, 4.11 events per 100 person-years in the group that received the 50-mg dose of canakinumab, 3.86 events per 100 person-years in the 150-mg group, and 3.90 events per 100 person-years in the 300-mg group."
And because no therapy comes without risk

- "Neutropenia was more common among patients who were assigned to receive canakinumab than among those in the placebo group, and significantly more deaths were attributed to infection or sepsis in the pooled canakinumab groups than in the placebo group (incidence rate, 0.31 vs. 0.18 events per 100 person-years) …The patients who died from infection tended to be older and more likely to have diabetes than those who did not die from infection. …Thrombocytopenia [a reduction in the number of platelets, cells involved in forming clots] was more common among patients who were assigned to receive canakinumab than among those in the placebo group, but no significant difference in the incidence of hemorrhage was observed."

The authors were quick to narrow their findings to those patients already receiving lipid therapy that have “residual inflammatory risk as assessed by means of a high-sensitivity C-reactive protein level of 2 mg or more per liter;” and to assert that this may represent two different populations that “require personalized approaches to treatment.” They also point out that interleukin-1? is only one of many anti-inflammatory pathways that “might serve as targets for atheroprotection.”

The bottom line is that coronary artery disease is multifactorial, it isn’t just lipids or inflammation. These two factors are engaged in a dance of sorts, along with other ‘dancers’ we may not yet have identified that result in atherosclerosis. There is no monolithic cause of atherosclerosis; it is a result of interactions of many factors. The study helps to balance the belief that lipids are the cause of atherosclerosis with the idea that inflammation also plays a role. In my view, the study provides us with an opportunity to reduce the effects of atherosclerosis further. But more importantly it punctures the myth of a monolithic cause for disease, we should heed this message.

[1] Interleukin-1? is a molecule called a cytokine that is produced by a number of cells and is a blood-borne signal in our body’s inflammatory response. Canakinumab has anti-inflammatory effects first acknowledged in approval for “use in rheumatologic disorders.”

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