Beyond JUPITER: where next for inflammatory biomarkers?

While it is recognised that atherosclerosis is a chronic inflammatory condition evolving over several decades, conventional anti-inflammatory treatments have been largely unsuccessful or have even aggravated atherosclerosis. This has created confusion about the potential role of inflammatory biomarkers. Can the use of inflammatory biomarkers improve cardiovascular risk prediction? This was the leading question posed by Professor Peter Libby, Chief of Cardiovascular Medicine at Brigham and Women’s Hospital, and Mallinckrodt Professor of Medicine, Harvard Medical School, Boston, USA.

Given that it is present in atherosclerotic plaque, C-reactive protein (CRP) is the main biomarker under consideration in this context. CRP offers a number of advantages, both pharmacodynamic (long half-life and lack of diurnal variation) and practical (robust, reproducible, accessible and inexpensive assay). Comprehensive analysis by the Emerging Risk Factors Collaboration has shown that CRP levels were linearly associated with an increased risk of cardiovascular events although more modestly than previously believed. However, it is unlikely that CRP is causal as genes associated with elevations in CRP were not associated with increased risk of CHD, therefore implying that CRP is a marker of risk rather than a target for treatment. This suggests that the use of CRP may add predictive value to traditional risk factors. Based on this, accumulating evidence-based, global risk algorithms, such as the Reynolds Risk Score, which include inflammatory biomarker data and family history have been incorporated into routine clinical practice.

Furthermore, JUPITER has validated the concept that a biomarker of inflammation could guide statin therapy in a more effective manner. Indeed, recent meta-analysis supports the value of CRP in this setting, in both men and women. On this basis, screening guidelines in North America have endorsed the use of hsCRP among intermediate-risk patients as a proven method to target lipid-lowering therapy.

Does CRP have a future beyond JUPITER?

Two randomized, placebo-controlled trials are testing the hypothesis that anti-inflammatory agents normally used in other indications may be relevant as cardiovascular therapeutic agents in the secondary prevention setting. One of these trials, the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS), is evaluating canakinumab, an antibody that inhibits the endogenous pro-inflammatory protein interleukin-1-beta in patients with stable coronary artery disease. IL-1beta promotes atherothrombosis and also plays a role in the autoimmune process that causes insulin
resistance. The primary endpoint is major cardiovascular events, defined as recurrent MI, stroke and cardiovascular-associated death. The second trial, the Cardiovascular Inflammation Reduction Trial (CIRT) is evaluating the use of low-dose methotrexate on top of the current standard of care (including high-dose statin therapy) in stable post-MI patients.

Results from these trials may help in supporting the utility of inflammatory biomarkers, both in guiding statin treatment and help to personalize management strategies.

*Medical writing for ISA2012 reportage was funded by an unrestricted educational grant from AstraZeneca.*