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Reducing residual cardiovascular risk: opportunities beyond antibodies?

- Potential for nanotechnology in the age of precision medicine

Atherosclerosis is a lipid-driven chronic inflammatory disease that underlies the development of angina, heart attack and stroke. New understanding of the disease process implies its 'nanoscale' nature, and suggests potential for the application of nanotechnologies in clinical practice.

According to **Professor Erik Stroes (Academic Medical Center, Amsterdam, the Netherlands)**, one of the researchers in this field: *'Current approaches to treating cardiovascular disease by simply prescribing a statin for everyone will change dramatically within the next decade. Molecular imaging techniques and innovative novel therapeutic modalities - including local delivery strategies and selective anti-inflammatory interventions - highlight the need for personalized medicine in patients with cardiovascular disease. This is an exciting era with lots of challenges!'*

Undoubtedly low-density lipoprotein cholesterol (LDL-C) has a pivotal role in atherogenesis, from the formation of early fatty streaks to the development of the lipid-rich core in the plaque.[1] Yet even after intensive LDL-C lowering therapy with statin plus ezetimibe, a significant residual risk of recurrent heart attacks and strokes persists in high risk patients. Whether further LDL-C lowering with monoclonal antibody therapy targeting proprotein convertase subtilisin/kexin type 9 (PCSK9) translates to significant reduction in cardiovascular events, as suggested by recent post hoc analyses,[2,3] awaits definitive evidence from ongoing cardiovascular outcomes studies.[4-7]

Even though there is a close interaction between inflammation and LDL-C, however, it is highly likely that LDL-C lowering alone will not fully neutralize inflammation within the atherosclerotic lesions, commented Professor Stroes. Therefore, other trials are focusing on the role of anti-inflammatory treatment. These include the CANTOS study (using canakinumab, an inhibitor of interleukin-1beta) and the CIRT trial (using methotrexate), in patients at high risk of heart attacks and strokes.[8,9]

While anti-inflammatory treatments are a promising approach, there is also the risk of immunosuppression due to long-term systemic use. The use of highly selective and targeted therapies may help to overcome this limitation. Nanotechnology, which involves packaging of nanoparticles of therapeutic compounds, avoids the first pass clearance of a drug by the liver, and thus allows the compound to be delivered locally to non-hepatic tissues, including the atherosclerotic plaque. When conjugated with targeting ligands, nanoparticles can be directed to specific cells associated with plaque composition and the development and progression of atherosclerosis, such as macrophages.

The advantage of this approach over pharmacotherapy or monoclonal antibody therapy is that it allows high concentrations of the agent to be achieved locally in the plaque with low systemic concentrations, thereby improving therapeutic efficacy with less risk of side effects. Nanomedicine is already established in oncology and emerging research shows promise in the early diagnosis of buildup of plaque in arteries, as well as in monitoring its progression or disappearance (regression) following treatment.[10,11]

Yet, as inflammation associated with atherosclerosis is multifactorial in nature, there is also the possibility of detrimental effects. This may help to explain why a recent study[12] showed that a nanomedicine approach using liposomal nanoparticles loaded with the anti-inflammatory agent prednisolone led paradoxically to accelerated atherosclerosis, by promoting toxicity of the lipid-loaded macrophages. Further research is needed to close the gap between understanding atherosclerosis to the translation of targeted molecular tools.

Nanotechnology, in addition to potent anti-inflammatory, antibody and antisense therapeutics, may offer new hope in the next decade, for addressing the substantial residual burden of heart attacks and strokes that persists in high risk patients despite best evidence-based therapy.

Professor Stroes will be presenting the plenary lecture 'The use of novel therapies in atherosclerosis: from antibodies to nanotechnology' on Wednesday 1st June, K. Landsteiner Hall, 09:30-10:00.

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