Medical Xpress

Million man study examines long-term effects of blocking inflammation

February 25 2015

Inflammation - the body's response to damaging stimuli - may have a protective effect against cardiovascular disease, according to a study published today in the journal *Lancet Diabetes and Endocrinology*.

The finding is one of the outcomes of research using a powerful new genetic tool that mimics the behaviour of certain anti-inflammatory drugs. The technique allows researchers to study the effects of inhibiting interleukin-1, a master regulator of inflammation, on a range of different outcomes not yet investigated in clinical trials.

Interleukin-1 plays a central role in regulating the body's inflammatory response, setting off a cascade of signals within the body against infection and other damage. Certain drugs, such as anakinra, reduce inflammation by blocking interleukin-1. This action also occurs naturally in individuals who carry particular genetic variants.

Although inflammation is meant to be protective, a disproportionate response can be damaging to the body - for example, causing potentially life-threatening symptoms seen in severe cases of influenza infection. It also plays a crucial role in a number of autoimmune diseases such as rheumatoid arthritis. Although scientists suspected that it would also be likely to increase risk of cardiovascular disease, until now little evidence existed to confirm or disprove this suggestion.

To examine the long-term implications of blocking this pathway, researchers from the Interleukin-1 Genetics Consortium developed a

'genetic score' to combine the effects of two of these natural genetic variants. They looked at the effect of this score on key biological indicators of inflammation, comparing it to the effect of anakinra. They investigated this score in relation to several medical conditions including rheumatoid arthritis and coronary heart disease by analysing data from over a million individuals.

The researchers found that individuals who carried the genetic variants - in other words, had naturally-occurring interleukin-1 inhibition - showed a decreased risk of developing rheumatoid arthritis. This was as anticipated: anakinra is one of the drugs used to treat the condition. The variants had no impact on the risks of developing type 2 diabetes or ischaemic stroke.

Surprisingly, however, blocking interleukin-1 increased an individual's risk of developing coronary heart disease: the risk of a heart attack was 15% higher in people who inherited a greater tendency to block interleukin-1. The researchers also observed raised levels of LDL-cholesterol - so-called 'bad cholesterol' - in these individuals, which may explain some of this increased risk.

Blocking interleukin-1 also increased an individual's risk of developing abdominal aortic aneurysm, a swelling of the main blood vessel that leads away from the heart, down through the abdomen to the rest of the body; one in 50 deaths amongst men over 65 years of age is due to such an aneurysm rupturing.

Although anakinra has been tested in clinical trials and shown to be effective in treating symptoms of rheumatoid arthritis, there has been little research into its effect on coronary heart disease. This is, in part, because of the complexity of studying heart disease and the number of individuals and length of study required in order for an effect to become apparent. By studying naturally-occurring interleukin-1 inhibition, the

researchers have been able to infer that the drug could potentially elevate the risk of coronary heart disease and abdominal aortic aneurysms.

Professor John Danesh from the Department of Public Health and Primary Care at the University of Cambridge, [who leads the consortium], says: "Drugs such as anakinra are licensed for the treatment of inflammatory conditions including rheumatoid arthritis, but we know little about the long-term health consequences of blocking interleukin-1.

"Our approach was to use 'nature's randomised trial' to get answers currently beyond the resolution of drug trials. Our genetic analysis suggests, surprisingly, that blocking interleukin-1 over the long-term could increase the risk of cardiovascular diseases."

Dr Daniel Freitag, lead author of the study, also at the University of Cambridge, adds: "The common view is that inflammation promotes the development of heart disease - we've shown that the truth is clearly more complicated. We need to be careful that drugs like anakinra that aim to tackle rheumatoid arthritis by inhibiting interleukin-1 do not have unintended consequences on an individual's risk of heart disease."

Professor Peter Weissberg, Medical Director at the British Heart Foundation, which helped fund the study, said: "It is important to remember that this is not a study of an anti-arthritis drug but a gene that can mimic its effects. The effects of a gene are lifelong, whereas a drug only affects a person while it is being taken.

"Nevertheless the study suggests that patients who are prescribed anakinra should have their cardiovascular risk factors carefully managed by their doctor."

Provided by University of Cambridge