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Titel des Beitrags:
Cardiometabolic effects of genetic upregulation of the interleukin 1 receptor antagonist: a Mendelian randomisation analysis.

Abstract:
To investigate potential cardiovascular and other effects of long-term pharmacological interleukin 1 (IL-1) inhibition, we studied genetic variants that produce inhibition of IL-1, a master regulator of inflammation. We created a genetic score combining the effects of alleles of two common variants (rs6743376 and rs1542176) that are located upstream of IL1RN, the gene encoding the IL-1 receptor antagonist (IL-1Ra; an endogenous inhibitor of both IL-1? and IL-1?); both alleles increase soluble IL-1Ra protein concentration. We compared effects on inflammation biomarkers of this genetic score with those of anakinra, the recombinant form of IL-1Ra, which has previously been studied in randomised trials of rheumatoid arthritis and other inflammatory disorders. In primary analyses, we investigated the score in relation to rheumatoid arthritis and four cardiometabolic diseases (type 2 diabetes, coronary heart disease, ischaemic stroke, and abdominal aortic aneurysm; 453,411 total participants). In exploratory analyses, we studied the relation of the score to many disease traits and to 24 other disorders of proposed relevance to IL-1 signalling (746,171 total participants). For each IL1RN minor allele inherited, serum concentrations of IL-1Ra increased by 0.22 SD (95% CI 0.18-0.25; 12.5%; p = 9.3 × 10(-33)), concentrations of interleukin 6 decreased by 0.02 SD (-0.04 to -0.01; -1.7%; p = 3.5 × 10(-3)), and concentrations of C-reactive protein decreased by 0.03 SD (-0.04 to -0.02; -3.4%; p = 7.7 × 10(-14)). We noted the effects of the genetic score on these inflammation biomarkers to be directionally concordant with those of anakinra. The allele count of the genetic score had roughly log-linear, dose-dependent associations with both IL-1Ra concentration and risk of coronary heart disease. For people who carried four IL-1Ra-raising alleles, the odds ratio for coronary heart disease was 1.15 (1.08-1.22; p = 1.8 × 10(-6)) compared with people who carried no IL-1Ra-raising alleles; the per-allele odds ratio for coronary heart disease was 1.03 (1.02-1.04; p = 3.9 × 10(-10)). Per-allele odds ratios were 0.97 (0.95-0.99; p = 9.9 × 10(-4)) for rheumatoid arthritis, 0.99 (0.97-1.01; p = 0.47) for type 2 diabetes, 1.00 (0.98-1.02; p = 0.92) for ischaemic stroke, and 1.08 (1.04-1.12; p = 1.8 × 10(-5)) for abdominal aortic aneurysm. In exploratory analyses, we observed per-allele increases in concentrations of proatherogenic lipids, including LDL-cholesterol, but no clear evidence of association for blood pressure, glycaemic traits, or any of the 24 other disorders studied. Modelling suggested that the observed increase in LDL-cholesterol could account for about a third of the association observed between the genetic score and increased coronary risk. Human genetic data suggest that long-term dual IL-1?/? inhibition could increase cardiovascular risk and, conversely, reduce the risk of development of rheumatoid arthritis. The cardiovascular risk might, in part, be mediated through an increase in proatherogenic lipid concentrations.

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