Abstract:

A systematic review and meta-analysis of anti-cytokine therapies targeting IL-1 and TNF-α in myocardial infarction and heart failure.

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Background: Acute and chronic inflammation influence cardiac healing and remodelling following a myocardial infarction (MI), which may result in heart failure (HF). Numerous pre-clinical studies have reported increased morphological and functional recovery following immune-modulatory interventions. Some clinical trials have been conducted but outcomes have been inconsistent.
Aims: To assess the benefits of targeting inflammatory cytokines in post-MI patients with heart failure or at high risk of developing HF using a systematic review and meta-analysis of clinical trials.
Methods: Clinical trials using cytokine modulation were identified searching PUBMED and clinicaltrials.gov. The search terms: cytokines, interleukin, 'myocardial infarction', 'ventricular remodelling', 'ischemia reperfusion' and 'heart failure' were combined with string terms for each intervention using simple Boolean connectors. Inclusion criteria were randomised placebo controlled clinical trials with comparable outcomes, written in English and published in the last 50 years to target immunological factors in patients with, or at risk of developing HF. The selected trials targeted interleukin-1 (IL-1) using Anakinra or Canakinumab, and tumour necrosis factor-alpha (TNF-α) with Etanercept. Trial characteristics were extracted, and assessed for risk of bias. Data of major adverse clinical event (MACE) including MI and mortality rates were pooled using MedCalc to calculate heterogeneity. Following heterogeneity assessment, a random effects model was implemented. Pooled random effects, p-values and 95% confidence intervals were calculated using the Dersimonian Laird method. The risk ratio (RR) and confidence intervals (CI) for mortality and MACE were calculated.
Results: Of 12,919 patients with MI, 2,125 were classified as HF and 10,794 at high risk of HF. The RR and CI for mortality and MACE when using IL-1 inhibitors and TNF-α inhibitors were 1.10 (0.57 - 2.12) and 1.07 (0.92 - 1.25) respectively.
Conclusions: Although individual studies had very promising outcomes, our meta-analysis demonstrates that sufficient evidence is still lacking to support anti-IL-1 and TNF-α therapy post-MI to significantly reduce adverse outcomes. However, due to significant heterogeneity in trial design and outcome measures, only limited conclusions can be drawn from the present meta-analysis. Future studies need to consider biochemical as well as physiological measures over an extended follow up period to determine the true benefits of immune-modulation both immediately after acute MI and in preventing HF.