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Translational overview of cytokine inhibition in acute myocardial infarction and chronic heart failure

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ABSTRACT

Many cytokines are currently under investigation as potential target to improve cardiac function and outcome in the setting of acute myocardial infarction (MI) or chronic heart failure (HF). Here we aim to provide a translational overview of cytokine inhibiting therapies tested in experimental models and clinical studies. In various experimental studies, inhibition of interleukin-1 (IL-1), -6 (IL-6), -8 (IL-8), monocyte chemoattractant protein-1 (MCP-1), CC- and CXC chemokines, and tumor necrosis factor-α (TNF-α) had beneficial effects on cardiac function and outcome. On the other hand, neutral or even detrimental results have been reported for some (IL-1, IL-6, IL-8, and MCP-1). Ambivalence of cytokine function, differences in study designs, treatment regimens and chosen endpoints hamper the translation of experimental research into clinical practice. Human studies are currently limited to IL-1β inhibition, IL-1 receptor antagonists (IL-1RA), IL-6 receptor antagonists (IL-6RA) or TNF inhibition. Despite favorable effects on cardiovascular events observed in retrospective cohort studies of rheumatoid arthritis patients treated with TNF inhibition or IL-1RA, most prospective studies reported disappointing and inconsistent results. Smaller studies ($n < 100$) generally reported favorable results of anticytokine therapy on cardiac function, but only one of the larger studies ($n > 100$) evaluating IL-1β inhibition presented positive results on outcome. In conclusion, of the 10 anticytokine therapies tested in animals models beneficial effects have been reported in at least one setting. In larger clinical studies, findings were unsatisfactory in all but one. Many anticytokine therapies with promising animal experimental data continue to require further evaluation in humans.

Key words: Cytokines, Inflammation, Immune modulation/therapy, Myocardial infarction, Heart failure.

Introduction

Acute myocardial infarction (MI) and chronic heart failure (HF) are associated with decreased quality of life and unfavorable long-term outcome [1–3] and novel therapeutic strategies are still needed to improve clinical outcome. After successful introduction of antiplatelet inhibitors, beta-blockers, statins, and renin-angiotensin-aldosterone inhibitors, more recently there is increasing interest to target inflammation more specifically by immunomodulation or specific anticytokine treatment.

Cardiac remodeling is one of the major contributors to progression of MI to HF and considered to be importantly mediated by inflammation [4]. Epidemiological studies

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suggest that circulating concentrations of inflammatory markers, such as C-reactive protein (CRP), are associated with subsequent risk of atherosclerosis formation, coronary heart disease (CHD) and cardiac remodeling [5]. In the setting of acute MI, elevated CRP levels are associated with impaired myocardial reperfusion [6]. In principle, the inflammatory response is a protective mechanism short-term but may lead to chronic overcompensatory failure. It is a complex conjunction between innate (quick and non-specific) and adaptive (slow and specific) immune systems [4,7]. Upon tissue damage or endothelial cell stress, cardiomyocytes, leukocytes and platelets can release various inflammatory cytokines attracting antigen presenting cells. Antigen presenting cells such as dendritic cells, monocytes and macrophages from the innate immune system will recognize released self-antigens or danger signals and start to interact with B and T cells from the adaptive immune system [8,9]. This interaction may be caused by the formation of receptor complexes and via cytokine production further activates and amplifies the instigated inflammatory response. Cytokines, such as interleukin-1 (IL-1), monocyte chemoattractant protein-1 (MCP-1), tumor necrosis factor-α (TNF-α) were previously found to be elevated in MI and HF [10,11]. They are known to promote cell death of cardiomyocytes and cell hypertrophy by induction of intracellular signaling cascades such as NF-κB, JAK/STAT and PI3K pathways in leukocytes. Some cytokines may even function as biomarker(s) while the extent of elevation has been associated with outcome and degree of cardiac injury [12,13]. Anticytokine therapy targeting inflammation is widely used and successful in rheumatoid arthritis [14] and is currently an active field of investigation for treatment of MI and HF. Since their fluctuations during the process of cardiovascular remodeling and observed associations with clinical outcome, cytokines have attracted attention as potential therapeutic targets. The aim of this review is to provide a contemporary and translational overview of potential effects of cytokine inhibition on cardiac function and outcome in the setting of acute MI and chronic HF.

Outline of this review

For the selection of clinical studies, a total of 923 articles were screened (Supplements Methods). Irrelevant articles based on article type, study design, patient population, and drug therapy were excluded. In total, 25 articles including 14 randomized clinical trials (RCTs) were reviewed thoroughly. For selection of animal experimental studies, we included search results and references of the clinical search and initially reviewed 56 articles of which 50 articles were considered relevant and are discussed. Since there are many pro-inflammatory cytokines being studied in the experimental field, we mainly focused on those that are currently under investigation in the clinical setting. An introductory overview of cytokine levels and their mechanisms in cardiovascular disease has been given in the Supplements.

Anticytokine therapy in experimental MI models

IL-1 inhibition in small animals

A variety of experimental MI models evaluated the effect of IL-1 inhibition. Pre-treatment with IL-1 receptor antagonist (IL-1RA) showed positive effects on left ventricular ejection fraction (LVEF) and infarct size in a murine ischemia reperfusion model (Fig. 1) [15]. IL-1 receptor 1 knockout mice (IL-1R1, one of the receptors of the IL-1R superfamily) undergoing permanent coronary artery ligation, had larger infarct size compared to controls [16]. This aligns well with the observation that genetically engineered rat overexpressing IL-1RA in an ischemia reperfusion model had reduced infarct size and apoptosis [17]. IL-1RA overexpression in mice undergoing permanent coronary artery ligation had an equivalent effect on cardiac function and in the infarct-remote zone collagen expression was reduced, suggesting involvement of IL-1 in cardiac fibrosis [18]. Both pre- and post-treatment with IL-1RA have been reported to exert beneficial effects on cardiac function, dimensions and infarct size after permanent coronary artery ligation and ischemia reperfusion in mice and rats. Anakinra (recombinant human IL-1RA inhibitor) treatment initiated in the first weeks after permanent coronary artery ligation also resulted in improved left ventricular (LV) dimensions and fractional shortening (FS) [19]. These findings have been replicated in a comparable study with immediate and delayed treatment of anakinra causing a reduction in infarct size [20]. IL-1 inhibition with IL-1 trap, also known as rilonacept, a long-acting IL-1 inhibiting agent, was likewise successful in a chronic MI model. Using different dosages, less apoptosis and smaller infarct size was observed and LV dimensions and FS were attenuated [21]. Moreover, specific IL-1β inhibition after permanent coronary artery ligation led to less LV dilatation and increased FS [22]. Interestingly, in a larger chronic MI study, detrimental effects have been reported with mice having larger infarct size, lower collagen gene expression and more ventricular ruptures after treatment with a similar dose of IL-1β antibody [23]. Taken together, there appears to be evidence for both beneficial as well as detrimental effects of IL-1 inhibition on cardiac function and infarct size in experimental MI.

IL-6 inhibition in mice and rats

Few studies investigated the effect of activation and inhibition of interleukin-6 (IL-6) and its receptor. One study evaluated IL-6 receptor antagonist (MR16-1) or placebo treatment after permanent coronary artery ligation in mice [24]. FS increased, left ventricular end-diastolic diameter (LVEDD) was smaller and the survival rate was higher than controls. In an opposed model using gp130 knockout mice, the IL-6 binding common receptor, increased IL-6 and STAT3 expression, LV dilatation, LV rupture and mortality was seen compared to the wild-type [25]. The effect was attenuated with an additional genetic reduction of STAT3, suggesting the