

Interleukin-1 Blockade in Acute Myocardial Infarction and Heart Failure: Ready for Clinical Translation?

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Abstract

The synthesis and release of Interleukin-1 (IL-1) are finely regulated processes necessary for the initiation of an inflammatory response to injury. Release of IL-1 α from injured cells and of mature IL-1 β from circulating monocytes initiates the local and systemic inflammatory response, respectively. An intense IL-1-dependent response occurs during Acute Myocardial Infarction (AMI) and promotes Heart Failure (HF). In advanced HF, a chronic IL-1 β -dependent process alters cardiovascular function leading to impaired performance, poor quality of life and increased morbidity and mortality. Here in reviewing the evidence in preclinical studies; we discuss potential strategies to disrupt IL-1 signaling in AMI and HF, and review the results of the initial pilot clinical trials.

Keywords: Inflammation; Interleukin-1; Atherosclerosis; Myocardial infarction; Ischemia; Heart failure

Cardiovascular disease is the leading cause of death worldwide [1]. Acute Myocardial Infarction (AMI) and Heart Failure (HF) remain among the leading causes of death and hospitalization. The improvements in the acute care of patients with AMI have led to a gradual reduction in mortality over time, but also consequently to an increased number of survivors, who remain at significantly higher risk of HF.

A link between inflammation and heart disease has been identified long ago. Several observational studies have shown that patients with acute coronary events have increased inflammatory markers (leukocytosis, neutrophilia, increased erythrocyte sedimentation rate, fibrinogen, C Reactive Protein (CRP), and others [2,3].

Inflammation, broadly defined as a coordinated cellular-humoral response to injury, is highly preserved across species and fundamentally essential for repair, healing and survival. Injured cells release 'alarm signals' (such as ATP) in the extracellular space and trigger a local inflammatory response [4,5]. Resident cells (i.e. endothelial cells) actively participate in the inflammatory response by initiating chemotaxis and recruitment of leukocytes. Leukocytes migrate to sites of tissue injury to provide defense from potential infections and facilitate tissue repair. Although an inflammatory response is necessary, this response occasionally becomes a mechanism for progressive injury, impaired healing and disease.

Interleukin-1 (IL-1) is an apical pro-inflammatory mediator inducing the synthesis and expression of several hundreds of secondary inflammatory mediators [6]. Two related genes code for two different proteins IL-1 and IL-1 β , and both binds the same IL-1 receptor (type I). IL-1 β is the main form of circulating IL-1. IL-1 β is synthesized as a precursor (proIL-1 β) and activated (by cleavage) by caspase-1 in the setting of a finely regulated macromolecular structure (inflammasome) [6,7]. Caspase-1 also participates in the secretion of active IL-1 β which then binds the membrane IL-1 receptor in the same cell (autocrine) or neighboring cells (paracrine), or enters the circulation targeting distant cells (endocrine) [6]. IL-1 α , on the other hand, is mostly expressed as membrane-bound or released from the cytoplasm during cell death, and is important in the initiation of the local inflammatory response during tissue injury while it participates less in the systemic inflammatory response [6]. Of note, IL-1 α is already active as a precursor and does not require cleavage by caspase-1 in the inflammasome for activation or release. The production and release of active IL-1 β depend, on the

other hand, on the activation of caspase-1 within the inflammasome [7]. The inflammasome is composed of a structural scaffolding protein, apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC), a sensor, cryopyrin/NLRP3 or other NLRs, and an effector enzyme, caspase-1 [8]. The release of active IL-1 β is also dependent upon the formation of membrane channels through a P₂X₇ receptor mediated process [4,9,10]. The P₂X₇ receptor is an ATP-sensing receptor involved in both the triggering of cryopyrin activation, mediating K⁺ efflux, and secretion of active IL-1 β [4,9,10].

Atherosclerosis and atherothrombosis are the underlying mechanisms for the great majority of first and recurrent AMI. Atherosclerosis refers to the buildup of a 'plaque' in the intima of the artery constituted by an aggregate of cellular and extracellular components and leading to plaque growth (plaque progression) and rupture (plaque complication). Formation of a platelet-rich thrombus on a ruptured (or eroded) atherosclerotic plaque is referred to as atherothrombosis. Inflammation and IL-1 are involved in plaque formation by determining the degree of endothelial dysfunction and leukocyte activation and thus promoting increased permeability and cholesterol deposition [11]. These very same processes promote plaque progression and ultimately plaque complication by inducing plaque rupture due to a tissue destructive process within the plaque characterized by endothelial cell and leukocyte death, metalloproteinases activation, and activation of the platelets and of the coagulation cascade [11]. Human atherosclerotic plaques indeed express IL-1 α and IL-1 β , and the expression appears to correlate with the progression of atherosclerotic plaques [12]. Experimental studies in mice who were genetically predisposed to develop atherosclerosis have shown that the inhibition of IL-1 signaling reduces the formation and progression of atherosclerotic plaques; whereas increased IL-1

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Received October 29, 2012; **Accepted** October 31, 2012; **Published** November 02, 2012

Citation: Toldo S, Mezzaroma E, Abbate A (2013) Interleukin-1 Blockade in Acute Myocardial Infarction and Heart Failure: Ready for Clinical Translation? *Transl Med* 3: e114. doi:10.4172/2161-1025.1000e114

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activity favors progression of atherosclerosis [13-16]. IL-1 has also a prothrombotic effect [17] further contributing to the promotion of atherothrombosis.

Acute myocardial infarction represents a classic example of sterile inflammatory response in which the intensity of the response both reflects the degree of injury but also determines the progression of the disease [18,19]. Injury to the tissue induces release of cell debris that functions as 'danger signals' including ATP, pro-IL-1 α , HMGB1 α etc. [20]. Through a coordinated sequence of events, leukocytes infiltrate the injured tissue and remove the debris and promote healing [18]. The heart is one of those organs in which a *restitutio ad integrum* does not occur and dead tissue is replaced by a non-functional scar [21]. Furthermore, the healing of the infarct is a highly dynamic process that starts within hours and is likely not complete for several weeks [21]. Cell death is initially necrotic in the core by an abrupt decrease in cellular ATP levels, but progresses in the border-zone and also non-ischemic myocardium to be more of a programmed cell death that is generally referred to as apoptotic, due to the characteristics DNA fragmentation and caspase-3 activation [22,23].

As in all forms of sterile inflammation, IL-1 is largely involved in the recruitment of the leukocytes and coordination of the response. IL-1 α is contained in the cytoplasm of cardiac resident cells (endothelial cells, cardiomyocytes, fibroblasts) and is released during cell death in its pro-form which is already active [6,24]. Dead cells may also release pro-IL-1 β in the tissue, which is cleaved to active IL-1 β by extracellular enzymes such as neutrophil elastase [6]. Injured but not dead resident cells also release active IL-1 β following activation of the inflammasome [6]. Once leukocytes are recruited to the infarct, then the major source of IL-1 β is likely the activated leukocyte.

Inhibition of the formation of the inflammasome in mouse models of AMI using genetic mutants [25,26], silencing [19] or pharmacologic inhibitors [19] has shown a reduction in the degree of myocardial injury and an improvement in the healing and remodeling processes.

Silencing or pharmacologic inhibition of the purinergic ATP/ADP receptor P₂X₇ prevented caspase-1 activation during AMI, suggesting that extracellular ATP is an important trigger for the formation of the inflammasome [19]. Nevertheless, it cannot be excluded that other triggers may be also important and/or that P₂X₇ is important for other mechanisms such as release of mature IL-1 β . Recent data suggest that other purinergic receptors such the adenosine A₂B receptor may be also involved in the formation of the inflammasome in response to myocardial injury [27].

Genetic deletion of the IL-1 signaling receptor (IL-1R1) was protective in a mouse model of AMI due to ischemia/reperfusion [28] as well as in a model of severe nonreperused AMI [29], as shown by smaller infarct size, reduced left ventricular enlargement and dysfunction. On contrary, the mouse lacking the naturally occurring IL-1 receptor antagonist developed a severe form of cardiomyopathy characterized by increased cardiomyocyte apoptosis after AMI [29]. Administration of the recombinant form of the IL-1 receptor antagonist, Anakinra (Kineret™, Biovitrum, Stockholm, Sweden) immediately after the onset of ischemia or 24 hours later lead to a significant reduction in cardiomyocyte apoptosis, left ventricular enlargement and dilatation at 7 days after permanent coronary artery ligation [30]. These effects were largely independent of changes in infarct size, suggesting that the benefits were not due to infarct sparing, although a high dose of anakinra did produce a mild reduction in infarct size in this model of nonreperused myocardial infarction [30,31]. When administered prior to reperfusion, in a model of myocardial ischemia-

reperfusion, anakinra lead to a significant reduction in infarct size [32,33]. However, these effects were not seen when treatment was administered after reperfusion (personal communication). The finding of minimal to no effects on infarct size with administration of anakinra after the onset of ischemia or after reperfusion is in contrast with the infarct sparing effects seen with anakinra pretreatment or in genetic models of IL-1 signaling deletion, whereas the effects on remodeling are consistent. This suggests that IL-1 signaling may be involved in healing after myocardial infarction by multiple mechanisms. An initial surge of IL-1 activity early during acute myocardial infarction may be related to the release of intracellular IL-1 α during cell necrosis [6,24], and a second increase in IL-1 activity occurs later in the course as a result of recruitment of leukocytes to the injured site and activation of the inflammasome and release of active IL-1 β .

Several different IL-1 blockers have been developed in the past few years [34]. The use of a recombinant chimeric protein composed of the IL-1 receptor, the IL-1 receptor associated protein and the Fc fragment of an immunoglobulin constitutes the "IL-1 trap" designed by Regeneron (Tarrytown, NY, USA). The beneficial effects on cardiac remodeling seen with the use of the murine IL-1 trap in the mouse provided the initial evidence that IL-1 blockade in cardiac remodeling is a class effect [35]. The IL-1 trap also blocks the effects of endogenous IL-1 receptor antagonist yet this is not associated with evident adverse effects suggesting that the effects of exogenous IL-1 receptor antagonist are exerted, as expected, by competing with IL-1 and IL-1 α at a membrane receptor level. In none of these experiments there was evidence of impaired healing or increased risk of cardiac rupture suggesting that IL-1 signaling is involved but not necessary for cardiac healing after acute myocardial infarction.

The evidence supporting the role of IL-1 β vs IL-1 α in cardiac remodeling after acute myocardial infarction is less straightforward. An initial report had suggested that blockade of IL-1 β impaired healing in the heart and favored cardiac rupture in a model of severe nonreperused myocardial infarction in the mouse [36]. The investigators used a commercial hamster anti-mouse IL-1 β antibody developed for immunohistochemistry by Genzyme to block IL-1 β . The characteristics of the antibody like the IgG class, the presence or absence of stimulatory properties, the ability to activate the complement or antibody mediated cell death were not reported [36]. The deleterious effects of IL-1 β blockade in this study were evident in a reduction of collagen deposition, and increased incidence of cardiac rupture 5-7 days after surgery. This pattern of impaired healing and increased rupture was not seen in the studies using genetic models of IL-1 receptor deletion nor in the studies using anakinra or IL-1 trap [28-33,35]. However, in these entire studies, IL-1 blockade was obtained by non-selectively blocking IL-1 β and IL-1 α and thus raising the issue of whether IL-1 β blockade alone was responsible for the adverse effects. More recent studies using two different IL-1 β antibodies specifically developed as therapeutics have shown a protective role of IL-1 β blockade [37,38]. Both of these antibodies had shown to have powerful inhibitory effects on IL-1 β signaling without cell toxicity. The discrepancy between these recent studies compared with the earlier study is difficult to reconcile, but likely relates to differences in the characteristics of the antibody used [39,40]. The data obtained with the IL-1 β blockade are in line with the data deriving from the studies in which inhibition of caspase-1 or the inflammasome is used since the caspase-1/inflammasome is the main source for active IL-1 β . In auto-inflammatory diseases the IL-1 β released induces the synthesis, processing and release of more IL-1 β [6,41]. When tested in the myocardial infarction model, IL-1 β blockade with the 1400.24.17 IL-1 β antibody ameliorated the cardiac remodeling process but did not affect the intensity of the local or systemic inflammatory response [38],

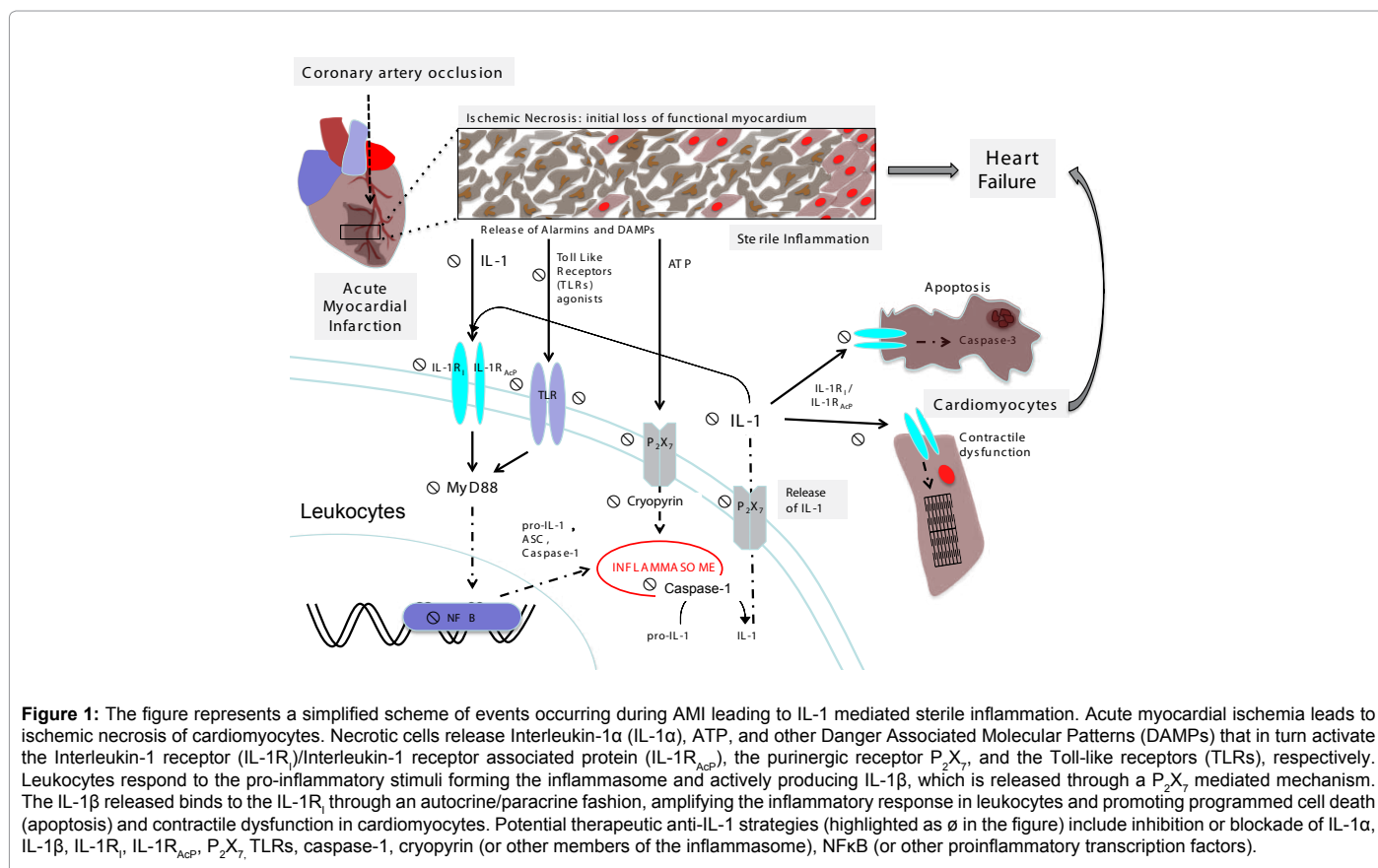
suggesting that in AMI in the mouse IL-1 β is not essential for the initial inflammatory response and the related inflammation does not follow an auto-inflammatory pattern, and other triggers (i.e. IL-1 α , ATP or other cell debris) are equally or more important in determining the intensity of the sterile inflammatory response.

There are very few, and small, clinical trials of IL-1 blockade in patients. The MRC-ILA-HEART study [42] randomized 186 patients with non-ST segment elevation acute myocardial infarction within 48 hours of symptom onset in 3 centers in UK to either anakinra 100 mg daily for 14 days or placebo. The results are however not available yet. The VCU-ART pilot study [43] enrolled 10 patients with ST-segment elevation acute myocardial infarction randomized 1:1 to anakinra 100 mg daily for 14 days (as in the MRC-ILA-HEART study) or placebo. The VCU-ART study was designed as a safety and feasibility study but had a pre-specified primary efficacy endpoint on remodeling measured at 3 months with cardiac magnetic resonance [43]. Anakinra had no effects on infarct size measured with cardiac magnetic resonance. At 3-month follow up, 2 patients had new onset heart failure at 3 months in the placebo group and none in the anakinra group. The VCU-ART2 study [44] was designed as a follow up study including 30 additional patients with STEMI. Treatment with anakinra was safe, it lead to a trend toward more favorable effects on LV ejection fraction, which did not reach statistical significance, and to numerically lower incidence of new onset heart failure at 3 months (1 patient vs. 4 patients in placebo).

Heart failure is a clinical syndrome of inappropriate cardiac contractility or inappropriate cardiac filling. IL-1 β was identified as one of the 'soluble myocardial depressant factors' in the plasma of patients with sepsis and septic shock [45]. *In vitro* studies identified effects of IL-1 β on calcium currents and β -adrenergic responsiveness

by affecting adenylyl cyclase activity without changes in β -adrenergic receptor density [46] and/or activity of calcium L-type channels [47]. IL-1 β also mediates the systolic dysfunction induced by ischemia [48]. A recent study in patients with systolic heart failure showed that the increased IL-1 activity in the plasma was sufficient to induce a reversible cardiomyopathy in the mouse [49]. Pretreatment with anakinra before the plasma of patients with heart failure prevented the reduction in systolic function and the desensitization of the β -adrenergic receptors [49]. In this pilot study, 7 patients with stable symptomatic systolic heart failure and elevated CRP levels (>2 mg/L) were enrolled and treated them open-label with anakinra 100 mg daily for 14 days. Anakinra treatment was associated with a significant increase in exercise capacity (peak VO₂) and improved ventilator efficiency (V_E/VCO₂), paired with a significant reduction in CRP levels [49]. After 14 days of anakinra, CRP and Interleukin-6 levels had dropped by nearly 90%, suggesting that IL-1 activity regulates the systemic inflammatory response in heart failure. Furthermore, the reduction of IL-1 β plasma concentration by nearly 90% in the presence of IL-1 β blockade is indicative of an underlying auto-inflammatory process in HF. A follow up study on patients with heart failure and preserved ejection fraction is ongoing in the same center.

The identification of IL-1 as a therapeutic target and the availability of many clinically approved IL-1 blockers is a formidable opportunity to translate these findings from the bench to the bedside (Figure 1). The figure presents a simplified scheme for IL-1 activation in AMI and HF and highlights several potential targets for intervention. As for all new therapeutic areas, many issues will need to be addressed and discussed including selection of the patients, the agents used, the dose, the duration, and then the efficacy, safety and cost-effectiveness [34].



Acknowledgements and Disclosures

Dr. Abbate is supported by an American Heart Association Scientist Development Grant. Dr. Mezzaroma is also supported by an American Heart Association Post-Doctoral Grant. During the last 36 months, Dr. Abbate has received research grants from XOMA, Novartis and Gilead, and has lectured for XOMA and Novartis, and has consulted for Gilead, Janssen, Omni Biopharma, and XOMA.

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