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EDITORIAL

Targeting inflammation to improve long-term outcome in ST-segment elevation myocardial infarction survivors

Borja Ibanez [1,2,3]*

[1]Clinical Research Department, Centro Nacional de Investigaciones Cardiovasculares (CNIC), c/Melchor Fernandez Almagro, 3. 28029. Madrid, Spain; [2]Cardiology Department, IIS-Fundación Jiménez Díaz University Hospital, Madrid, Spain; and [3]CIBER de Enfermedades Cardiovasculares, Spain

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This editorial refers to 'Association of plasma interleukin-6 with infarct size, reperfusion injury, and adverse remodelling after ST-elevation myocardial infarction' by C. Tiller *et al.*, pp. 113–123.

ST-segment elevation myocardial infarction (STEMI) is still a leading cause of mortality and morbidity worldwide. The widespread use of reperfusion, mainly primary percutaneous coronary intervention (pPCI) has been associated with a dramatic reduction of STEMI-associated mortality. Reperfusion for STEMI represents one of the greatest achievements in medical history, exemplified by the massive reduction of in-hospital mortality: 25% in early 1980s, to less than 5% in 2010s. However, STEMI survivors are a vulnerable population at high risk for developing recurrent events, such as heart failure, malignant arrhythmias, and all-cause death.[1] It is known for a long time that the major determinants of adverse events in STEMI survivors are the extent of myocardial loss (i.e. infarct size) and left ventricular (LV) systolic function.[2] In recent years, it became apparent that microvascular injury [microvascular obstruction (MVO) and intramyocardial haemorrhage] is also an independent predictor of long-term adverse events. The accurate identification of these processes theoretically allows a better stratification of long-term risk in STEMI survivors. From all diagnostic modalities, there is only one that is able to identify and quantify all these processes: cardiac magnetic resonance (CMR). Cardiac magnetic resonance is the gold standard for cardiac anatomy and function evaluation. Cardiac magnetic resonance is also the best diagnostic modality for myocardial tissue characterization. Therefore, there is big hope in the role of CMR examination to tailor management of STEMI survivors. CMR is increasingly used in randomized clinical trials (RCTs) to test the benefits of new therapies. A recent consensus document recommends the selection of infarct size,[3] Left ventricular ejection fraction (LVEF) and MVO as the ideal CMR endpoints.

Despite reperfusion is the mainstay treatment for STEMI, and a pre-requisite for myocardial salvage, it can exacerbate injury to the myocardium (a process known as reperfusion injury[2]). Therefore, final damage to the myocardium is the result of ischaemia/reperfusion (I/R) injury. I/R injury involves several cardiac compartments, such as cardiomyocytes, microcirculation, and even circulating cells. Inflammation plays a prominent role in reperfusion-related injury.[2] Neutrophils become activated during I/R and interact with other cell types (e.g. platelets) to form plugins that obstruct the microcirculation, contributing to MVO early after reperfusion. Beyond getting impacted in the microcirculation, neutrophils infiltrate the post-I/R myocardium and release deleterious substances, such as myeloperoxidase, NETs, and others, contributing to final damage of the myocardium. The post-I/R inflammatory process occurs several days (sometimes weeks) after STEMI. In fact, the inflammation-related myocardial oedema formation is maximal around 1 week after STEMI but can be perpetuated for several weeks.[4] Beyond neutrophils, circulating pro-inflammatory inflammatory mediators [such as interleukins (IL)] also contribute to the injury to the myocardium during the days/weeks following STEMI. Among them, IL-6, which is generated by different cardiovascular cell types, is a prominent cytokine upregulated after large STEMIs. IL-6 is produced from the myocardium during I/R in humans, and can be derived from hypoxic cardiomyocytes, playing a role in neutrophil-mediated reperfusion injury in the myocardium.[5] Previous studies have shown that high levels of circulating IL-6 receptors early after STEMI are associated with future adverse cardiac events.[6]

A recent study undertaken in more than 350 STEMI patients showed that the levels of IL-6 one day after reperfusion were associated with larger infarctions and lower LVEF as evaluated 4 months later by CMR.[7] Since that study only performed imaging at one time point in the chronic phase, it did not address the potential role of IL-6 on cardiac remodelling, a dynamic process. To address this open question, in the present issue of the journal, Tiller *et al.*[8] evaluated STEMI patients with two CMR studies (early and late after reperfusion) and studied the associations between CMR parameters and IL-6 levels. In summary, 170 consecutive STEMI patients treated by

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* Corresponding author. Email: bibanez@cnic.es

pPCI who were enrolled in the ongoing MARINA-STEMI observational cohort study were included in this report. All patients underwent IL-6 sampling at 2 days, and two CMR studies, at 4 days and at 4 months after STEMI. Infarct size, MVO, intramyocardial haemorrhage, LV volumes, and LVEF were the main variables quantified on CMR studies. Left ventricular remodelling was identified as ≥10% increase in LV end-diastolic volumes between CMR scans. Population was divided into two groups according to IL-6 levels above or below the median. Baseline characteristics were significantly different between the two groups. Subjects in the 'high IL-6' group were older, had worse cardiovascular risk profile, presented more frequently with anterior STEMI, and had poorer PCI results (final Thrombolysis in Myocardial Infarction flow 3). On early CMR exam, patients in the 'high IL-6' group had larger LV volumes, poorer LVEF, a larger extent of infarctions, and more prevalent (and larger) microvascular injury. In multivariate analyses, IL-6 levels were associated with all these parameters. Seventeen percent of the population met the criteria of LV adverse remodelling (change in LV volumes between CMR scans), with IL-6 identified as an independent predictor of this. Authors conclude that circulating IL-6 levels early after STEMI can serve as a biomarker of poor prognosis. They further speculate that IL-6 appears as a promising therapeutic target.

Authors are to be congratulated for the execution of a comprehensive longitudinal observation CMR study in a cohort of STEMI patients. This and other similar cohorts are important as hypothesis generators. The present study complements previous studies identifying IL-6 as a biomarker associated with more severe infarctions and thus of poor prognosis. Despite IL-6 is proposed as a better discriminator than other inflammatory markers (such as C-reactive protein) in the present study, it is very difficult to separate them since they are part of a general inflammatory response to the infarction process. The study adds to the growing evidence showing that inflammation after STEMI contributes to the final degree of myocardial injury.

What are the clinical implications of these findings? From the predictive perspective, with the exception of LVEF, currently, there is not a single marker that has a role for the management of STEMI patients. All STEMI patients are managed equally and the long-term therapies are only affected by LVEF (e.g. to guide the implant of an implantable cardioverter defibrillator or to guide the addition of secondary prevention pharmacological interventions[1]). There is a strong need to perform RCTs under the principles of precision medicine (e.g. perform a large trial where the post-MI therapy is based on any of the markers discussed in this document). Until those trials are performed, all the evidence generated is welcome but will unlikely change practice.

One of the main results of the study is the association between baseline IL-6 levels and adverse LV remodelling. The clinical implications of LV adverse remodelling today are less clear than several decades ago. In fact, in a recent CMR study undertaken in >350 patients undergoing two CMR studies (1 week and 6 months after STEMI), the evaluation of LV volumes and LVEF at the two timepoints did not add further prognostic value to the sole evaluation at baseline.[9] That study concluded that a single early CMR is enough to estimate risk for cardiovascular events without the need for a late CMR. In fact, it has been proposed that LV remodelling is no longer a relevant outcome after MI.[10]

The second conclusion of the authors about the potential role of IL-6 axis as a promising therapeutic target deserves some comments. Despite authors did not evaluate the value of IL-6 axis as a therapeutic target, this has been done by others. In a rodent study, the injection of an antibody against IL-6 receptor attenuated post-MI LV remodelling.[11] This strategy has been tested in a small trial of 117 non-STEMI patients, who were randomized to a single dose of tocilizumab (a humanized IL-6 receptor antagonist) or placebo before PCI.[12] PCI-related cardiac injury was significantly less in patients randomized to tocilizumab. This proof of concept trial is being followed-up by the ongoing ASSAIL-MI-trial, which is testing the effect of tocilizumab on myocardial salvage in 200 STEMI patients.[13] Other trials testing inflammation as a therapeutic target have been performed with disparate results. The METOCARD-CNIC trial demonstrated that the early injection of the β1-adrenergic receptor blocker metoprolol was associated with smaller infarctions, improved LVEF and less heart failure admissions in 270 STEMI patients.[14] Metoprolol is a unique β-blocker that has been demonstrated to target neutrophil dynamics to reduce reperfusion-related injury.[15] The demonstration of its benefits during acute inflammatory processes came from a recent publication of its benefits is coronavirus disease 2019 patients with acute respiratory distress syndrome, where metoprolol injection was associated with a significant reduction in lung inflammation and this translated into less days on mechanical ventilation.[16] Colchicine is another anti-inflammatory therapy that has been tested in STEMI patients albeit with disparate results. An early trial suggested that colchicine administration during ongoing STEMI was associated with smaller MI size as assessed by biomarkers and by CMR,[17] but in a more recent trial, high-dose colchicine injected at the time of reperfusion did not reduce CMR-based MI size.[18] After an encouraging pilot study,[19] rituximab (a monoclonal anti-CD20 antibody targeted against human B cells) is being tested in the European Commission-funded RITA-MI2 study. Other drugs targeting different inflammation mediators such as pexelizumab, inclacumab, or losmapimod have been tested in different STEMI studies with inconclusive results.

In summary, the present study adds to growing evidence linking inflammation with poor outcomes in patients presenting with STEMI. While the evidence so far is not conclusive, targeting inflammation still appears as a valid approach to further improve the prognosis of STEMI survivors.

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