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EDITORIAL

Anti-inflammatory therapies in acute coronary syndromes: is IL-1 blockade a solution?

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This editorial refers to 'The effect of interleukin-1 receptor antagonist therapy on markers of inflammation in non-ST elevation acute coronary syndromes: the MRC-ILA Heart Study'†, by A.C. Morton *et al.*, on page 377

Elevation of circulating levels of C-reactive protein (CRP) at the time of hospital admission predicts a poor outcome in patients with an acute coronary syndrome (ACS) and is thought to reflect an important inflammatory component in the pathogenesis of this condition.[1,2]

C-reactive protein is also the preferred systemic inflammatory biomarker for risk stratification in heart disease.[3] The link between inflammation and ACS is complex. Atherosclerosis, the primary cause of ACS, is a chronic inflammatory disease of coronary arteries,[4] but exacerbations of the inflammatory process within the atherosclerotic plaque may lead to plaque rupture with thrombosis and subsequent myocardial ischaemia.[5] Myocardial injury following an ischaemic event is an additional source for a local and systemic inflammatory response; importantly, the intensity of the systemic response is also a predictor of adverse events.[6] There are therefore at least three potential sources of inflammation in ACS: (i) the baseline chronic inflammation seen in patients at risk and related to hypercholesterolaemia, diabetes, obesity, and others; (ii) the inflammatory events within the atherosclerotic plaques; and (iii) the systemic inflammatory response to ischaemic myocardial injury (*Figure 1*). As such it is not surprising that inflammatory biomarkers predict adverse outcomes.

Which are the key mediators in the acute systemic inflammatory response in acute coronary syndrome?

Observational data and experimental studies reveal several candidate mediators; the role of each in patients with ACS is, however, unknown. The great majority of clinical studies are limited to associations between biomarker levels and outcomes, without any possibility of determining causality. The results of the MRC-ILA Heart Study are therefore most welcome, as they present the first available data of a targeted anti-inflammatory therapy in ACS.[7] Morton and colleagues are to be congratulated for their interventional study. The same group of investigators had shown that interleukin-1 (IL-1), a central mediator in the local and systemic inflammatory response,[8] plays a central role in vascular biology.[9] In the MRC-ILA Heart Study, 182 patients with non-ST segment elevation myocardial infarction (NSTEMI) were randomly assigned to anakinra, a recombinant IL-1 receptor antagonist, the most widely used IL-1 blocker, or placebo in an attempt to determine whether IL-1 blockade would be sufficient to blunt the acute inflammatory response seen in ACS. The primary endpoint of the study, the area under the curve for CRP within the first 7 days, was significantly reduced by anakinra treatment. These data indisputably establish that IL-1 is a key mediator in the systemic inflammatory response in NSTEMI. Similar data confirmed the observations in two small pilot studies of patients with more severe disease, i.e. ST segment elevation myocardial infarction (STEMI).[10,11]

Is interleukin-1 blockade in acute coronary syndrome beneficial?

Whereas it is clear that elevated CRP levels predicts poor outcomes in patients with ACS, it is not clear whether reducing CRP levels reduces subsequent events. Treatment with high dose statins has been shown to reduce CRP levels and prevent recurrent events, but whether the two effects are mechanistically connected is not known. One may speculate that CRP participates in the pathogenesis of the disease, but the large bulk of evidence suggests CRP as being a marker rather than a mediator. CRP is primarily produced by the liver in response to IL-6, which in turn is a known secondary cytokine produced in response to apical cytokines such as IL-1.[8] The large reduction in CRP levels following IL-1 blockade in the MRC-ILA Heart Study suggests therefore that enhanced IL-1 activity is present in ACS, and proposes that CRP in ACS is a surrogate for IL-1 activity.

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Although pre-clinical studies of IL-1 blockade in ACS models show beneficial effects,[12] suggesting therefore that a strategy of IL-1 blockade leading to reduce CRP levels would be associated with improved outcomes, can one conclude the same in humans? Although the data from the MRC-ILA Heart Study do not support the hypothesis of a beneficial effect of IL-1 blockade in ACS,[7] one must consider the obvious limitations of a small sample size with a small number of events. Moreover, lacking the details of clinical outcomes for secondary endpoints, the interpretation of the MRC-ILA Heart Study remains uncertain.

Is there is a dissociation between C-reactive protein levels and outcomes?

C-reactive protein levels at admission or at discharge clearly predict worse outcome in patients with ACS; however, by 30 days, in the majority of the patients CRP levels have 'normalized', and only those who have persistently elevated levels remain at increased risk.[13] The MRC-ILA Heart Study shows that 14 days of 100 mg daily anakinra significantly reduced CRP levels at 7 and 14 days but not at 30 days. These findings probably are the result of two concurrent mechanisms: the spontaneous reduction in the placebo group and a loss of inhibition in the anakinra group after cessation, with a regression to the mean phenomenon. These data indicate that whether the source of inflammation as the stimulus for CRP in ACS is the ruptured plaque or the ischaemic myocardium, inflammation is 'resolved' within 1 month, and as such a treatment strategy of 14 days of anakinra may appear appropriate.

However, the MRC-ILA Heart study presents data on the late occurrence of excess events in the anakinra-treated arm up to 12 months. Whether this finding is biologically relevant or is due to a misdistribution of a randomization error because of the small number of events is unknown. It is difficult to interpret how 14 days of anakinra treatment would lead to excess events so late. Given the short half-life of anakinra (4–6 h each day for only 14 days), could events 12 months later be related biologically? The healing of the plaque (or the stented segment) might be affected during the 14 days but it is unclear whether these effects would affect outcomes months later. Since the clinical events are few and not well characterized as to the type of MI (spontaneous, procedural,

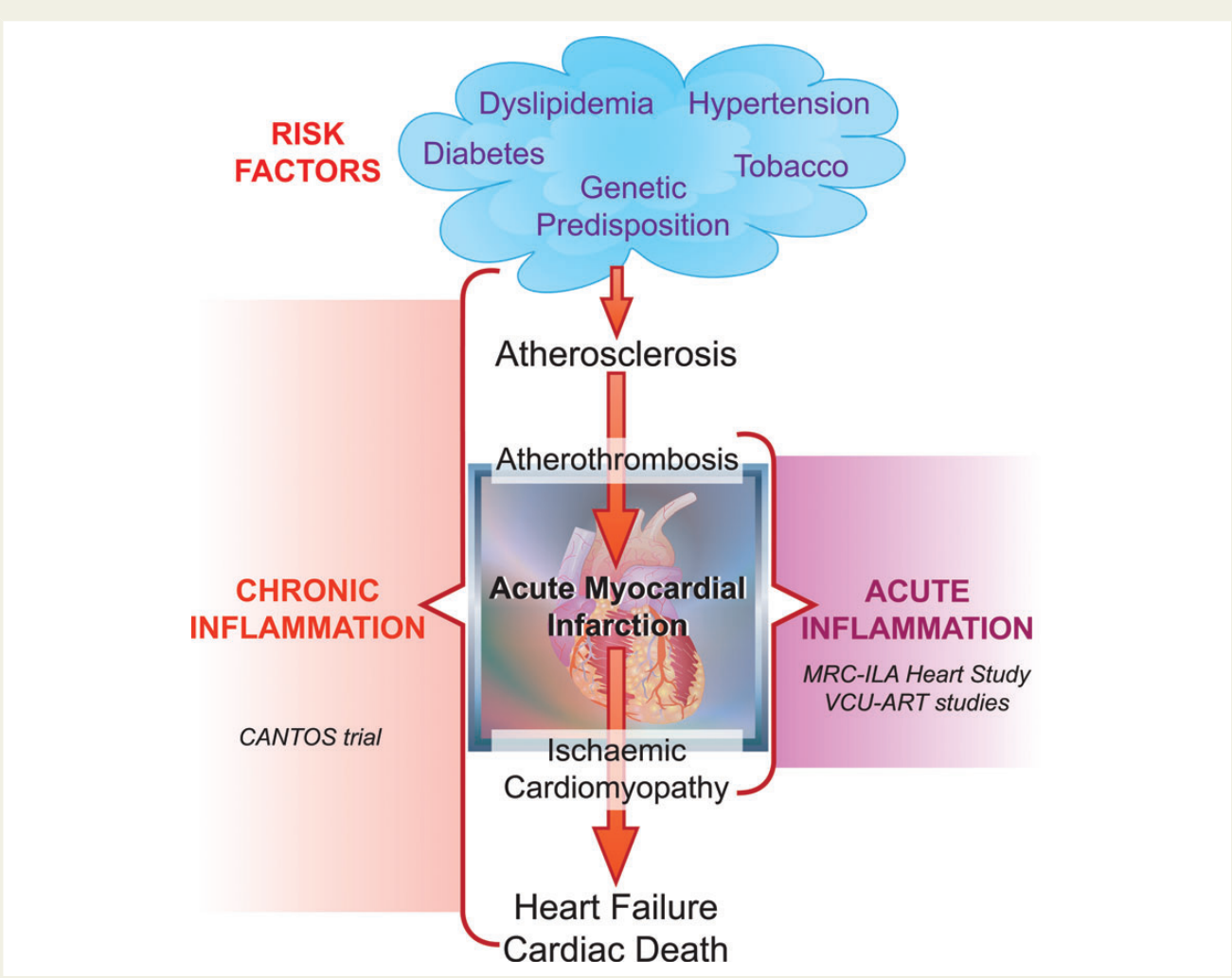

Figure 1 Schematic representation of acute and chronic inflammation in heart disease.

other?), linking the late events to 14 days of anakinra treatment would require large numbers of patients. Although there are no large clinical studies of IL-1 blockade in ACS, two small studies in STEMI showed a trend toward more favourable outcomes with anakinra in terms of incident heart failure, but the number of events was small.[10,11] A large trial of IL-1β blockade with canakinumab (CANTOS trial[14]) is ongoing, now having enrolled 10 000 patients. The CANTOS trial design assesses prolonged treatment efficacy and not the short-term effects in ACS. Nevertheless, data from the CANTOS trial and its substudies will be complementary to those which are currently available. As of now, it is unknown whether a reduction in the systemic inflammatory response (i.e. CRP levels) with IL-1β neutralization will reduce recurrent clinical events.

What's next in 'inflammation and acute coronary syndrome'?

The MRC-ILA Heart study is the first study to show that the acute inflammatory response in ACS is IL-1 dependent, and that it is modifiable by anakinra. While waiting for the results of the CANTOS trial, which will look at delayed treatment (>30 days), new and larger studies should examine an optimal intensity or duration of IL-1 blockade in ACS. To draw a parallelism, the initial studies with statins had shown that statins reduced cholesterol levels, studies on the effects on clinical outcomes have followed, and the optimal intensity of cholesterol lowering is still being explored.

One fundamental question generated from the MRC-ILA Heart is whether a 14-day treatment is sufficient. Since by day 30, regardless of group allocation, most patients had reduced levels of CRP, one may argue that prolonged treatment is not needed, or not in those with low CRP levels. In contrast, given the underlying chronic vessel inflammatory process, prolonged treatment may be needed.

An additional question to be addressed is whether or not all patients with ACS will require additional treatment. Larger infarcts (i.e. STEMI) are associated with a more intense acute inflammatory response, with CRP levels continuing to rise for 48–72 h[10,11] and may therefore benefit more from an anti-inflammatory strategy aimed at blocking the deleterious effects of uncontrolled inflammation.

Professor Attilio Maseri, a major pioneer in the field,[15] once commented that treatment of all patients with ACS in the same way is like treating all patients with anaemia the same way; thus a haematologist would ridicule such an approach. Cardiologists need a better phenotypic characterization of ACS patients before determining the best treatment.[16]

In conclusion, the MRC-ILA Heart Study investigators have contributed greatly to the understanding of whether the acute inflammatory response in NSTEMI is IL-1 mediated, and the answer is a clear yes. More studies are now needed to address whether inhibition of the acute inflammatory response with IL-1 blockers will reduce morbidity and mortality.

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