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Treating Acute Myocardial Infarctions With Anti-Inflammatory Agents

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There is an unmet need to further reduce the size of acute myocardial infarctions above and beyond the current standard of care of early reperfusion therapy with primary percutaneous coronary intervention (angioplasty/stenting) and anti-platelet agents to keep the infarct related artery patent. Even a 5% reduction in myocardial infarct size may be clinically meaningful.[1] It is known that the inflammatory process occurs early after coronary artery occlusion/reperfusion with very early influx of neutrophils.[2] There has been concern that if the inflammatory response is too severe it could contribute to additional myocardial cells dying and lead to infarct extension with a larger infarct size. On the other hand, the early inflammatory response is the first step in the healing phase of myocardial infarction. Experimental studies from the 1980s suggested that certain anti-inflammatory medicines, such as steroids and non-steroidal anti-inflammatory agents, such as ibuprofen, administered early during infarction would reduce the size of myocardial infarction.[3] There was considerable excitement about this possibility and clinical studies were planned and some were carried out. However, there was underlying concern that inhibiting the inflammatory cascade early after occlusion might then inhibit the healing phase of acute myocardial infarction.

In a series of studies from the early 1980s our research group assessed the effects of methylprednisolone, ibuprofen, and indomethacin on the healing phase of myocardial infarctions. Methylprednisolone was shown to enhance "mummification" of the myocardium whereby large sheets of necrotic, but architecturally preserved muscle fibers remained in the center of the myocardial infarction during the healing phase.[4] Steroids clearly suppressed the process whereby necrotic debris is removed from the infarct and delayed the shrinkage of the scar. Short term administration of methylprednisolone resulted in thinner scars and reduced left ventricular function.[5] Non-steroidal anti-inflammatory drugs including ibuprofen and indomethacin when administered early and acutely after myocardial infarction contributed to an increase in myocardial infarct expansion, that phenomenon whereby necrotic myocytes thin, stretch, slip by each other resulting in a thin and elongated infarct, thinned scar, regional ventricular dilatation and then global dilatation.[6-9] This phenomenon of adverse left ventricular remodeling is known to occur in patients, especially those with large infarcts and can contribute to heart failure, myocardial rupture and death. There were a few clinical studies that examined the effect of steroids on myocardial infarct size in which the results were negative; although one meta-analysis suggested corticosteroids did no harm and perhaps improved survival.[10-12] Clinical trials that tried to impede the function of neutrophils, including their ability to adhere to the walls of blood vessels and trials of anticomplement strategies were negative.[13] Thus, after pre-clinical studies showing concern about inhibiting the healing phase of infarction coupled with negative clinical trials, the enthusiasm for treating myocardial infarctions with anti-inflammatory drugs faded . . . . . until recently.

Work by investigators including Ridker and Libby and others clearly showed that inflammation played a crucial aspect of the pathogenesis of atherosclerosis and its sequelae.[14] Studies in patients with chronic coronary artery disease showed that colchicine[15] and some very specific anti-inflammatory agents such as interleukin-1 (IL-1) receptor antagonist canakinumab,[16] were capable of reducing major adverse cardiovascular events. Recent studies are now exploring a more focused approach on inhibiting the interleukin 1 or 6 pathway for reducing inflammation in the setting of acute myocardial infarction with some early promising results. Abbate et al[17] reported on the effects of an interleukin-1 blocker, anakinra, given once daily or twice daily over 2 weeks in patients with acute ST segment elevation myocardial infarction. Anakinra did not reduce enzymatic estimates of myocardial infarction, but it did decrease the high-sensitivity C Reactive Protein (high sensitivity-CRP) area under the curve, verifying an anti-inflammatory action. Over the course of 1 year, anakinra reduced the composite endpoint of all-cause death and new-onset of worsening heart failure. The change in LV volumes and ejection fraction

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Table 1. Recent Clinical Studies Showing a Benefit of Anti-Inflammatory Agents for Acute Myocardial Infarction.

Author	Reference	Drug studied	Primary outcome
Abbate et al	[21]	Anakinra (recombinant IL-1 receptor antagonist)	No difference in the primary endpoint (death, recurrent AMI, unstable angina, stroke); but reduced death or heart failure (HR = 0.16)
Abbate et al	[17]	Anakinra	Reduced high sensitivity C-reactive protein area under the curve; reduced death or new onset heart failure
Broch et al	[20]	Tocilizumab	Myocardial salvage index greater in tocilizumab group vs. placebo group. Less microvascular obstruction (no-reflow) with tocilizumab
Kleveland et al	[19]	Tocilizumab	In non-ST elevation MI study, tocilizumab reduced C-reactive protein and high sensitivity Troponin T
Tardif et al	[22]	Colchicine	Composite of death from cardiovascular cause, resuscitated cardiac arrest, MI, stroke, urgent hospitalization for angina leading to revascularization, occurred in 5.5% of colchicine patients versus 7.1% of placebo patients; $P = 0.02$

did not differ between anakinra and placebo over the course of 12 months, but anakinra did improve stroke volume and stroke work, compared to placebo.

It is known that there is an increase in levels of IL-6 measured in patients with myocardial infarction and that increased levels are associated with poorer clinical outcome.[18] Kleveland et al[19] reported in 2016 a clinical trial in which the effect of a single dose of the interleukin-6 receptor antagonist, tocilizumab, was given to patients with non-ST-elevation myocardial infarction to assess its effect on hs-CRP (a marker of inflammation) as well as high sensitivity Troponin T (hs-TnT a marker of infarct size). Tocilizumab is the same agent being used to treat cytokine storm and severe pneumonias in cases of COVID-19. In the Kleveland study, tocilizumab reduced the hs-CRP area under the curve over days 1-3 post myocardial infarction compared to a placebo-controlled group. It also reduced the median area under the curve for the hs-TnT (159 ng/L/hr) versus the placebo group (234 ng/L/hr; $P = 0.007$). At 6 months follow-up, no safety issues were observed in the treated group.

Broch et al[20] recently published a randomized prospective clinical trial of the interleukin-6 receptor inhibitor, tocilizumab, given acutely to patients with acute ST-segment elevation myocardial infarction. They carried out a randomized, double-blind, placebo-controlled trial of 195 patients who were admitted with acute ST-segment elevation myocardial infarction within 6 hours of symptom onset. Magnetic resonance imaging with gadolinium contrast injection was performed at day 3-7 to assess ischemic risk zone and infarct size in order to determine the salvage index; microvascular obstruction was also determined. Final infarct mass was also assessed at 6 months by magnetic resonance imaging, as was left ventricular end-diastolic volumes. Tocilizumab resulted in a larger myocardial salvage index (69% vs 64% in the placebo group), with an adjusted between group difference of 5.6% [95% confidence interval of 0.2-11.3; $P = 0.04$). Microvascular obstruction was reduced in the tocilizumab group as was the area under the curve for CRP during hospitalization. However, at 6 months there was only a non-significant trend toward less infarct mass in the treated group versus placebo group (7.2% vs 9.1%; $P = 0.08$). Very importantly, there was no between-group differences in baseline adjusted left ventricular (LV) volumes at 6 months. The mean LV end-diastolic volumes were 157 in the tocilizumab group and 160 in the placebo group. There were no myocardial ruptures, cardiac deaths or development of heart failure at 6-month follow up. This suggests that this anti-inflammatory agent indeed reduced early inflammation, salvaged myocardium but did not adversely affect LV remodeling or induce LV rupture. In addition, there were only a few infections in each of the 2 groups. Table 1 summarizes some of the recent clinical studies that show a benefit of anti-inflammatory agents (especially targeted anti-inflammatory drugs on acute myocardial infarction). Note that while one study by Tardif et al[22] showed a beneficial effect of colchicine when given within 30 days of acute myocardial infarction, not all studies with this agent have been positive. Tong et al[23] did not observe a significant benefit on cardiovascular events in patients treated with colchicine for 11 months following an acute coronary syndrome; and in-fact observed an increase in total death rate with colchicine, mainly from non-cardiac causes.

Whereas the exact mechanism or mechanisms by which certain anti-inflammatory agents have benefit in some studies remains to be determined, some of the possible mechanisms are listed in Table 2.

In conclusion, while earlier studies raised concerns regarding the use of anti-inflammatory agents in the setting of acute myocardial infarction for fear of inhibiting the healing phase and contributing to myocardial infarct expansion and even rupture, and in most cases failed to show benefit in clinical trials, newer studies that administer a short term dose of anti-inflammatory agents targeting the interleukin pathways show promise in improving myocardial salvage without adversely affecting the healing phase of infarction or worsening adverse LV remodeling. Why was there a difference in older studies with anti-inflammatory agents versus newer, more positive clinical studies? Many of the earlier studies in acute myocardial infarction were done in the pre-primary percutaneous coronary intervention for reperfusion era and before powerful antiplatelet agents were used for routine therapy to keep the infarct-related vessel patent. Thus, it is likely that currently reperfused infarcts are smaller in size with less overall inflammation. They are less likely to be transmural with less LV remodeling and rupture, which may have given the newer agents an advantage.

Table 2. Potential Mechanisms for the Positive Effects of Anti-Inflammatory Agents on Myocardial Infarction.

1. Reduction of ischemia/reperfusion injury improving myocardial salvage
2. Less microvascular obstruction (no-reflow) which may improve healing and/or reduce adverse LV remodeling
3. Reduction of inflammation stabilizes atherosclerotic plaque thus reducing myocardial infarct extension
4. Reduction in neutrophils may contribute to less microvascular obstruction and less plaque instability
5. Suppression of interlukin-1's negative effect on contractility of surviving myocardium

In addition, the newer therapies are more focused on the interleukin pathways, which may result in less early inflammation without affecting the later healing phase of infarction. The use of more targeted and receptor-specific agents may help explain the differences in outcomes in more recent positive clinical studies versus older negative trials. Larger clinical trials are now needed to determine the long-term effects of inhibiting the interleukin 1 and 6 pathways on clinical outcomes following acute myocardial infarction. It is crucial that when an anti-inflammatory agent is discovered that reduces infarct size in the early phase that the effect of the drug on the late or healing phase of the infarct scar is also investigated, to be certain that the drug does not promote infarct expansion and adverse LV remodeling, or cause LV rupture.

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