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Editorial

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A Novel Application for a Rheumatologic Medication

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Rheumatology has enjoyed significant advances in pharmacotherapy over the past two decades. Now, with our arsenals buffered, we ask, "Can these novel anti-rheumatic drugs escape the niche of rheumatology? Is their utility beyond the joints and autoimmunological processes? Say perhaps, myocardial infarctions?"

Enter tocilizumab (Actemra®). Tocilizumab is a novel humanized monoclonal antibody approved by the US Food and Drug Administration in 2010 for the treatment of rheumatoid arthritis and (later) juvenile idiopathic arthritis. The drug is administered as either a monthly intravenous infusion or as a weekly (or every other week) subcutaneous injection. The dose of the monthly infusion can vary between 4 mg/kg and 8 mg/kg but the once a week or every other week injection is 162 mg subcutaneously. In patients with rheumatoid arthritis, interleukin 6 (IL-6) is overproduced in the body, causing fatigue, anemia, inflammation and damage to bones, cartilage and tissue. Acting as an antagonist of IL-6 receptors, tocilizumab interferes with the pro-inflammatory effects of the IL-6–IL-6 receptor interaction. This response can be objectively gauged with serum C-Reactive Protein (CRP), offering a clinically practical and quantitative measure of inflammation.

Elevations in IL-6 are seen in a variety of other inflammatory events, and myocardial infarction is certainly not an exception. Acute Myocardial Infarction (MI) occurs when myocardial ischemia, a diminished blood supply to the heart muscle, exceeds a critical threshold and overwhelms myocardial cellular repair mechanisms designed to maintain normal function. Ischemia at this critical threshold level for an extended period results in irreversible myocardial cell damage or death. This cellular destruction causes release of not only cardiac enzymes, such as Troponin which is often measured to assess the presence and severity of myocardial injury, but also triggers the release of cytokines. In one study, plasma IL-6 levels were increased at all sampling points from admission to discharge in patients with acute MI as compared to IL-6 levels in controls.[1] Another study demonstrated a peak IL-6 level 1-2 days following acute MI with gradual return toward baseline over 12 weeks.[2]

The elevation in serum IL-6 levels has demonstrated worse outcomes in the setting of acute MI. In one study, elevated IL-6 levels were independent predictors of adverse events.[3] In another, univariate analysis, IL-6 was related to mortality.[4] IL-6 elevations also correlated with impaired left ventricular systolic and diastolic dysfunction following acute MI up to 6 months.[5] Knowledge of IL-6 elevation directly correlating with negative outcomes following MI with no current pharmacologic interventions for MI directly antagonizing IL-6 led our team to hypothesize that the administration of a single dose of tocilizumab 162 mg subcutaneously within 24 hours of admission for acute MI will be beneficial in lowering 30 day major adverse cardiac events (MACE). Hence the genesis of "Short Term Administration of Tocilizumab following Myocardial Infarction", or STAT-MI (ClinicalTrials.gov Identifier: NCT02419937). An extension of this trial, the STAT-MI-extended, looks at 90 and 180 day MACE.

Subjects eligible for enrollment must be over the age of 18 and have clinical, physical examination, serologic, and electrocardiographic evidence of acute myocardial infarction. A detectable elevation in serum cardiac troponin I is a critical serologic finding required. We are

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also focusing on Type I MI, those due to an acute thrombotic event. Exclusion criteria focus mainly on the potential immunosuppressive nature of tocilizumab, with those having active or chronic infections at the time of their MI not eligible for enrollment.

To date 19 subjects have been enrolled utilizing a randomized, placebo controlled, double blind approach. Our primary outcome is difference in 30 day occurrence of MACE between groups. Secondary outcomes include length of hospitalization, readmission rate, and CRP levels at 0, 24, and 48 hours. Safety analysis will be conducted at the midpoint of enrollment. Overall we aim to enroll up to 108 subjects to achieve statistical significance of our primary outcome.

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I affirm that this manuscript has neither been submitted nor is simultaneously being submitted elsewhere.

The views expressed in this material are those of the authors, and do not reflect the official policy or position of the US government, the Department of Defense, or the Department of the Air Force.

The voluntary, fully informed consent of the subjects used in this research was obtained as required by 32 CFR 219 and AFI 40-402, Protection of Human Subjects in Biomedical and Behavioral Research.

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This trial was registered with www.clinicaltrials.gov (NCT02419937)

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