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Editorial

Targeting interleukin-6 after cardiac arrest—Let us not forget the brain

The role of inflammation in mediating secondary injury after cardiac arrest was suggested twenty years ago by Adrie et al.,[1] in the description of post-resuscitation disease as a sepsis-like syndrome. Although inflammation was mentioned by Vladimir Negovsky et al.,[2] in his treatise on post-resuscitation disease in 1983, it was not highlighted. Similarly, early attempts to understand and/or modulate post-resuscitation disease in canine cardiac arrest models developed by Peter Safar revealed that sepsis-like sequelae such as disseminated intravascular coagulation and positive blood cultures were common, but outcomes were not improved with available interventions targeting those mechanisms such as hemabsorbtion using a charcoal filter.[3,4] In this issue of *Resuscitation*, Meyer et al.,[5] report on blood levels of cytokines and other inflammatory markers in EDTA biobank samples and their correlations to organ injury in a secondary analysis of the Interleukin-6 (IL-6) receptor antibodies to modulate the systemic inflammatory response after out-of-hospital cardiac arrest (IMICA) trial. Recall that in that trial in adults with out-of-hospital cardiac arrest of a presumed cardiac cause, treatment with tocilizumab (8 mg/kg over 1 h vs placebo initiated by 240 min) significantly reduced systemic inflammation including decreasing circulating C-reactive protein (CRP) and leukocyte levels vs placebo, and tocilizumab decreased myocardial injury including reductions in serum levels of CPK MB, troponin T, and N-terminal pro B-type natriuretic peptide.[6] However, no differences in survival, neurological outcome, or circulating neuron specific enolase (NSE) levels were observed—arguing against a benefit on the brain.

Tocilizumab is a humanized IL-6 receptor monoclonal antibody developed as an anti-rheumatic drug that is also used to treat COVID-19 and other autoimmune conditions. In this secondary analysis of the IMICA trial, we now see that treatment with tocilizumab early after cardiac arrest in adults, as anticipated, markedly increased IL-6 levels at 24, 48, and 72 h vs placebo, given that it blocks both soluble and cell surface IL-6 receptors.[7] The IL-6 increases with treatment were marked reaching a mean level of 708.9 pg/mL at 24 h vs 106.4 pg/mL with placebo treatment. IL-5 levels were also increased vs placebo at 24 and 48 h, a marker often associated with allergic immunity and eosinophilic facilitation of IL-6 production.[8] Also, IL-17 levels were decreased vs placebo at 72 h, a reduction in key autoimmune associated inflammatory signaling of the JAK/STAT pathway and STAT3 transcription.[9] Neutrophil and monocyte levels were also reduced by treatment vs placebo at 24 and 48 h. Effects on these facets of systemic inflammation also appear to have been linked to the cardioprotection seen in patients treated with tocilizumab. Beyond what was previously reported, treatment significantly reduced the vasoactive inotrope score (by ~50%) vs placebo further supporting a cardioprotective effect. Prior reports from the ASSAIL-MI trial suggested that tocilizumab improves myocardial salvage in ST-elevation myocardial infarction,[10] although modestly, and an effect on neutrophils was recently indicated to mediate that benefit.[11] Detrimental effects of neutrophils in myocardial ischemia–reperfusion injury have been posited since the preclinical work in the laboratory of Benedict Lucchesi in the 1980s,[12] although other effects of tocilizumab on IL-6 signaling may be involved.

The IMICA trial, including the work of Meyer et al.,[5] published in this issue of *Resuscitation* represents a valuable advance in the field and begins to modulate the potential role of the inflammatory response to cardiac arrest using a targeted anti-inflammatory tool. Reducing myocardial damage and improving hemodynamics are of course highly desirable. Several other facets of this work, however, merit discussion.

In this study, treatment with tocilizumab did not affect elevated blood levels of the contemporary brain injury biomarker neurofilament light chain over 72 h. This mirrors the findings previously reported in this same sample with the classical biomarker NSE and is consistent with the lack of effect of tocilizumab on neurological outcome in the trial. IMICA was a phase 2 trial with blood levels of CRP the primary outcome, and thus, was not powered to assess neurological outcome or blood-based biomarkers of brain injury. Nevertheless, tocilizumab has a molecular weight of 145 kDa, and blood brain barrier (BBB) disruption, particularly to large molecules, is extremely variable both in magnitude and temporal course after cardiac arrest in humans.[13,14] Thus, delivery of tocilizumab to brain was probably low with IV administration. Consistent with that premise, in rhesus macaques treated with the human equivalent of 8 mg/kg IV, cerebrospinal fluid (CSF) levels of tocilizumab do not increase until ~24 h later and are low, reaching values of only ~0.1 μg/mL-well below the reported ~4 μg/mL required to effectively inhibit the IL-6 receptor.[15] Additional insight on brain penetration of tocilizumab stems from its use to treat cytokine release syndrome (CRS) that can be encountered in the treatment of refractory B-cell malignancies. In CRS, IL-6 is a central mediator.[16] Most CRS symptoms respond rapidly after treatment with tocilizumab except for the neurotoxicities. It has also been suggested that sometimes, these neurotoxicities worsen with treatment related to the rise in serum IL-6 linked to receptor blockade[15]—an effect seen here after treatment of patients with cardiac arrest.[5] Fortunately, detrimental effects on acute readouts of brain injury in patients treated after cardiac arrest

were not observed. However, longer-term outcome assessments will be important in follow-up and in future trials.

Existing data suggest that IL-6 is a potential target to mitigate secondary brain injury after cardiac arrest. IL-6 levels have been long known to be markedly increased in various forms of acute brain injury[17] with CSF levels in patients with traumatic brain injury (TBI) like those seen in the serum of patients with sepsis.[18,19] In cardiac arrest, Oda et al.,[20] reported that CSF levels of IL-6 were elevated >2000-fold vs control (median of 2040 vs 1 pg/mL, respectively) in resuscitated adults and a level of 2708 pg/mL was associated with unfavorable outcome. Similar to TBI,[19] CSF levels were even higher than serum levels in cardiac arrest patients post resuscitation. Thus, there is a robust IL-6 response in brain after cardiac arrest, but it remains unclear if IL-6 mediates key secondary injury mechanisms such as neuronal death, cerebral edema, or BBB injury. Recently, IV administration of tocilizumab reduced CRP levels in CSF in patients with amyotrophic lateral sclerosis, but three treatments were given, and CSF was assessed at 8 weeks—reflecting delayed effects of IV administration.[21] In pre-clinical studies, administration of tocilizumab into CSF could achieve therapeutic levels, but the intranasal route could not.[16] Pre-clinical studies of early IV plus CSF administration of tocilizumab are thus warranted in models of cardiac arrest.

The IMICA trial included almost exclusively adults with a shockable rhythm[1] and thus patients that experienced arrests of a cardiac rather than asphyxial etiology. Given the cardiac rather than neurological protection afforded by toclilzumab, and an increase in circulating IL-6 levels, it is unclear that it would produce benefit or raise concerns for risks in adults who experience arrests of asphyxial phenotype, such as with opioid overdose, where brain injury predominates.[22] A similar concern might be raised in children suffering out-of-hospital cardiac arrest, given that they generally result from a respiratory event, and post-arrest myocardial dysfunction is less of a therapeutic target.[23]

Despite the promise of these new tocilizumab studies in cardiac arrest, there may be more effective ways to target IL-6 signaling. Trans IL-6 signaling mediates pro-inflammatory effects such as leukocyte recruitment, while classical signaling has anti-inflammatory effects.[24] Unlike tocilizumab, which blocks both pathways, newer agents such as recombinant sgp130, which selectively block trans-signaling, may be more effective, with less risk for immunocompromise. George et al.,[25] in a pre-clinical model of myocardial ischemia–reperfusion, reported enhanced efficacy of recombinant sgp130Fc vs an anti-IL-6 antibody in attenuating neutrophil infiltration, infarct size, and myocardial dysfunction. Trans IL-6 signaling is also believed to represent the dominant mechanism for pathogenic actions of IL-6 in brain.[26] Acute and post-acute IL-6 signaling is associated with poor outcomes clinically after TBI[19] and has been linked to both autoimmune and neurodegenerative diseases involving the CNS,[27–29] although some beneficial effects of trans signaling have recently been suggested on microglial repopulation that supports neurogenesis.[30] Thus, pre-clinical studies evaluating sgp130 are warranted in models of cardiac arrest. However, systemic administration of sgp130 which is also a large molecule, may likely require modification to enhance BBB delivery to achieve sufficient brain levels to block trans IL-6 signaling. Again, CSF delivery might be required. Given the robust IL-6 target after cardiac arrest, BBB permeable selective small molecule IL-6 inhibitors should also be developed and tested. They would have the additional potential benefit over monoclonal antibodies of a shorter half-life and a more titratable effect.

Less selective approaches have been recently shown in pre-clinical studies to reduce circulating IL-6 after cardiac arrest, including novel lipase and protease inhibitors and hemofiltration, among other therapies.[31–33] Given the findings here, selective approaches targeting IL-6 may represent a favored approach. Surprisingly, targeted temperature management (TTM) at 32 vs 36 °C did not impact circulating IL-6 levels in patients post arrest[34]—consistent with CSF findings of the effect of hypothermia on IL-6 in randomized controlled trials of patients with TBI.[35] How therapies selectively targeting IL-6, and their interaction with TTM at various levels, also merits exploration.

The IMICA trial, and this valuable secondary analysis, have begun to reveal the potential role of inflammation in secondary injury after cardiac arrest. Even without direct effects on brain, targeting IL-6 with tocilizumab might confer benefit in some patients. However, if there is potential to produce breakthrough effects in the treatment of cardiac arrest, it is highly likely that therapies targeting IL-6, or other aspects of inflammation, will also require brain targeting in order to yield measurable improvement in neurological outcomes.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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