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EDITORIAL

Targeting inflammation in traumatic injury: entering a new era

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Trauma is often referred to as the "Silent Pandemic", and in recent history has been the most common cause of death and chronic morbidity in children and adult men until mid-life [1]. As humans age, non-communicable diseases are predominant but trauma remains a significant cause of death. Following a traumatic event, otherwise typically healthy people abruptly enter a state of acute critical illness. Early mortality is most often due to traumatic brain injury and/or bleeding causing haemorrhagic shock. In patients who survive, the effects of trauma and bleeding and trauma-induced coagulopathy (TIC) [2], can lead to a systemic inflammatory response syndrome (SIRS). Human transcriptomics show that circulating leukocytes manifest a "genomic storm" and plasma multiomics reveal a massive release of cellular constituents into the circulation early after injury [3–5]. This release includes damage-associated molecular patterns (DAMP) molecules that initiate inflammation by interacting with pattern recognition receptors on immune and other cells [6]. The ensuing production of pro-inflammatory mediators and activation of complement and coagulation cascades, when excessive, can lead to early multiple organ dysfunction (MODS), which peaks on average about 2–3 days after the traumatic event [7].

The potential benefit of targeting the early inflammatory response to reduce MODS, and hence its downstream consequences, has been an area of intense research and debate for over 2 decades. This concept has been supported by pre-clinical research showing that targeting pro-inflammatory mediators (e.g., interleukin (IL) 6 and 8) or post-receptor signaling (e.g., Burton's tyrosine kinase, 9) after haemorrhagic shock in rodents dramatically reduces early organ injury. However, based on the many failed trials targeting the immune response in sepsis, another common cause of acute SIRS leading to MODS [10], many intensivists would likely caution against relying on data from rodent models to guide trials in humans. Conversely, those working in basic trauma research frequently point to the unique characteristics of trauma, such as the precise knowledge of the time of onset and the unique nature of the non-infectious inflammatory response after trauma and shock as a reason to consider anti-inflammatory agents in trauma. Based on an article in this issue of Intensive Care Medicine [11], the debate on whether and how to target the inflammatory response following trauma is likely to substantially shift. Shepherd and co-workers report the results of the TOP-ART trial that tested the safety and effectiveness of the anti-malarial, artesunate, to reduce MODS at 48 h in severely injured trauma patients. Artesunate was reasoned to be a good agent for the trial because of its impressive safety record in patients with severe malaria, its known anti-inflammatory properties, and because artesunate significantly reduced early organ damage in a well-calibrated model of hemorrhagic shock in rats [12].

The investigators are to be applauded for the well-planned and executed trial design that included, enrollment criteria targeting a high MODS cohort (adult massive hemorrhage protocol patients), informed consent, drug administration within 4 h of injury using a parallel group two-stage dosing regimen, and frequent post-dosing sampling to confirm adequate drug levels. Importantly, serious adverse events were monitored after every 15 patients by a Drug Monitoring Committee. The trial was ended early after 90 patients had been randomized to artesunate or placebo instead of the planned 105 patients due to a higher incidence of venous thromboembolic events in the artesunate group (3% vs. 17%, placebo vs. artesunate) that was not statistically significant but a safety signal. In addition, an analysis of the

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per protocol patients (48 artesunate and 27 placebo) showed no reduction in the primary outcome of Sequential Organ Failure Assessment (SOFA) scores at 48 h in the artesunate group despite achieving adequate drug levels. There were also no differences between the artesunate and placebo groups for secondary endpoints including MODS at later timepoints, time to recovery parameters or single organ dysfunction. It is notable that the degree of haemorrhagic shock in the artesunate cohort was more severe, and that the randomization numbers did not reach the target due to the early termination of the study.

Therefore, what have we learned from TOP-ART? First, using a rigorous trial design it is feasible to carry-out trials targeting the inflammatory response in trauma that includes informed consent prior to drug administration. Second, because inflammation and coagulation are inextricably linked [2], it would be wise to include biomarkers of coagulation activation in the design of trials targeting the immune response. Thirdly, the inclusion of biomarker measurements, in this case markers of the inflammatory response such pro-inflammatory cytokines, would provide evidence whether the drug had impacted its intended biologic target. Due to the complexity of the response to trauma, biomarkers might also be useful to stratify patients into treatment responsive and non-responsive sub-groups as has been described in a secondary analysis of the PAMPer trial [5, 13]. In one proposed scheme, biomarkers could also be used to stratify patients prior to the intervention [14]. Finally, we need to rethink the pre-clinical models used to validate therapeutic targets for trauma clinical trials. Small animal models of haemorrhagic shock alone (without significant tissue trauma) and without a critical care component may not be adequate to represent the dynamic and heterogenous nature of the human response to severe injury. We should also not ignore the fact that artesunate, although profoundly beneficial in the treatment of severe malaria, is not selective for a specific biologic target. As the number of approved drugs targeting specific molecules and pathways of the inflammatory response for other diseases expands, we should remain open to the possibility that one or more will be effective and safe in subsets of trauma patients.

The era of precision medicine with its multiomic strategies has begun to provide greater clarity on the impact of patient and injury characteristics on the heterogeneity of the human response to injury. This effort will bring us closer to defining patient subgroups based on the biology of the injury response and this will, in turn, permit us to link this biology with targeted treatment approaches.

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Declarations

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TRB has no conflicts of interests.

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