COVID-19 and myocardial injury: is there a role for interleukin-1 inhibition?
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Coronavirus pneumonia 2019 (COVID-19) pandemic was declared on 11 March 2020 by the WHO, with more than 400 000 people infected and more than 18 000 died as of 26 March.

Myocardial injury is common in COVID-19 patients, particularly in the ICU. Shi et al. recently reported myocardial injury in 20% patients with COVID-19 associated with a death rate of 51 vs. 4.5% (P<0.001).

Macrophage activation syndrome (MAS) is a frequently undiagnosed severe and fulminant form of cytokine storm syndrome, mostly observed during viral sepsis and caused by overwhelming release of pro-inflammatory cytokines. Indeed, increased plasmatic concentrations of cytokines resembling MAS phenotype were found in ICU patients with COVID-19, along with higher levels of troponin I; NT-proBNP stands for N-terminal pro-Brain Natriuretic Peptide and C-reactive protein. In MAS, T-cells and antigen-presenting cells are
hyperactivated through Toll-like receptors with repeated stimulation causing a massive autocrine loop of interleukin (IL)-1 and a subsequent, uncontrolled release of pro-inflammatory cytokines, including IL-6, IL-18, interferon (IFN)-γ, tumour necrosis factor alpha (TNFα) and ferritin, further precipitating clinical conditions, leading to endothelial dysfunction, multiple organ dysfunction and death (Fig. 1).

IL-1 blockade gave encouraging results in similar clinical settings. Indeed, a posthoc analysis of a phase III randomized trial on the IL-1 receptor antagonist anakinra in septic patients showed improved 28-day survival (35 vs. 65%, \( P < 0.001 \)) in patients with MAS phenotype. Furthermore, IL-1 blockade with anakinra in septic patients is currently being assessed in PROVIDE (Personalized RandOmized trial of Validation and restoration of Immune Dysfunction in sEvere infections and sepsis; ClinicalTrials.gov NCT03332225). CANTOS (Canakinumab Antiinflammatory Thrombosis Outcome Study) showed that IL-1 inhibition in patients with a previous myocardial infarction and increased C-reactive protein effectively reduced recurrent cardiovascular events. In the setting of COVID-19 infection, the additive effect of overwhelming IL-1 production associated with cardiovascular comorbidities, MAS and incessant adrenergic stimulation may synergize in a deadly vicious circle. In specific settings, such as pericarditis, nonselective inhibition of IL-1, either alfa and beta is superior to the selective inhibition of IL-1 beta because of the blocking of IL-1 alfa that can be secreted by mesothelial cells.

Considering the potential key role of IL-1 in COVID-19 infection, its inhibition may be proposed as a potential therapeutic option. Randomized trials are needed to clarify the potential usefulness of IL-1 blocking agents.

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**Conflicts of interest**

There are no conflicts of interest.

**References**