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Immunomodulation in COVID-19

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The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), continues to spread globally despite unprecedented social isolation and restrictions resulting in widespread economic decline. More than 3·2 million people have been infected and more than 230 000 of them have died. To date, no treatments have been definitively shown to be effective; however, a multipronged approach to mitigate transmission, morbidity, and mortality is ongoing.[1] While upstream prevention strategies such as vaccination are ideal, these strategies are unlikely to be available in time to address current clinical need. Instead, fast-tracking of drug development and repurposing of approved drugs[2] has facilitated and expedited clinical trials that might hasten effective therapeutics. Many of these drugs act, at least in part, to directly limit viral replication. By contrast, the use of interleukin-6 (IL-6) inhibition might have benefits by controlling the pathological immune response to the virus. Here, we expand on the theoretical basis of IL-6 inhibition and propose potential benefits from other immunomodulators that could, in theory, prove more efficacious.

For the latter phase of convalescence, hospitalised patients with COVID-19 can develop a syndrome of dysregulated and systemic immune overactivation described as a cytokine storm or hyperinflammatory syndrome that worsens acute respiratory distress syndrome and can lead to multisystem organ failure.[3–5] The scarce systematic data available have shown an association between ferritin, lactate dehydrogenase, IL-6, IL-1, d-dimer, and C-reactive protein and severe disease.[6–8] If this group can be identified before decompensation, early and aggressive immunomodulatory treatment might prevent need for intubation and extracorporeal membrane oxygenation. To date, observational studies[9] suggest a possible benefit but results of placebo-controlled randomised clinical trials are not yet available. Given the methodological limitations of existing studies, more evidence is needed. With the rapidly expanding number of critically ill patients, there is an urgent need to identify multiple putative biological targets. While IL-6 inhibition attenuates key aspects of the cytokine cascade, we posit other immune targets of inhibition to be considered and their potential to be more efficacious in the setting of COVID-19, specifically IL-1 inhibitors and Janus kinase (JAK) inhibitors.

Observational data show overlapping clinical features in severe COVID-19 with macrophage activating syndrome (MAS) and secondary haemophagocytic lymphohistiocytosis (HLH).[7] Hyperinflammatory states, specifically in fatal cases, highlight why consideration of HLH and MAS therapies are warranted. Furthermore, the pathogenesis underlying SARS-CoV-2 involves several key pathways that can be manipulated, and use of these therapies can mitigate the propagation of an overdriven inflammatory response (figure).[10] Although few patients with severe COVID-19 would meet criteria for MAS, it is proposed that they are on the spectrum and that MAS or secondary HLH therapies might be of benefit. IL-1 inhibitors are key therapeutics in the treatment of

MAS or secondary HLH, but also boast an impressive safety profile with risk for infection and demonstrated safety when used in pregnant women and children.[11] By inhibiting IL-1 signalling, they reduce a prominent drive on NF-κB-mediated upregulation of multiple cytokines, including IL-6. Additionally, a post-hoc analysis of a randomised controlled trial in sepsis indicated that patients with sepsis who had features of transaminitis and coagulopathy, a phenotype emerging within the COVID-19 population, might uniquely benefit from IL-1 inhibition.[12] Ongoing clinical trials using IL-1, IL-6, or JAK inhibitors in COVID-19 are listed in the appendix.

JAK inhibitors can treat a cytokine storm by inhibiting multiple inflammatory cytokines. Most JAK inhibitors are particularly effective at JAK 1 and JAK 2 inhibition—less so JAK 3 and TYK 2—and therefore are particularly effective at inhibition of IL-6 and interferon (IFN)-γ, but also inhibit IL-2 and the IFN-α/β signalling cascade. Most JAK inhibitors have been associated with increased risk for thrombosis, viral reactivation,[13] and myelosuppression. However, these adverse effects (except myelosuppression) are likely to be dependent on duration and dose. As with IL-1 inhibitors, JAK inhibitors generally have short half-lives and can have efficacy within days. These characteristics are favourable given that duration of use in patients with COVID-19 should be short term. Ruxolitinib, a JAK 1/2 inhibitor, received US Food and Drug Administration approval for steroid-refractory graft-versus-host disease, a frequently fatal complication of allogeneic haematopoietic cell transplantation characterised by unconstrained inflammation and tissue damage.[14] Off label, it has also effectively managed inflammatory complications in patients with genetic disorders that result in overactivity of the STAT1 pathway and in resistant MAS or secondary HLH of multiple causes, including viral.[15] Further understanding of the complex crosstalk that occurs, involving both viral and host survival strategies, might identify the need to target multiple different mechanisms to safely balance viral destruction while promoting host survival.[16] Clinical trials will be key in determining these effects across a potential heterogeneous population, while simultaneously monitoring the side-effect profile of these drugs to ensure any potential benefits are not outweighed by harms.

In conclusion, as insight is gained into the clinical phenotypes associated with COVID-19, we propose JAK and IL-1 inhibitors as therapeutic targets warranting rapid investigation. Multidisciplinary collaboration with experts in haematology, inflammation, tissue damage, and repair and resolution is paramount.

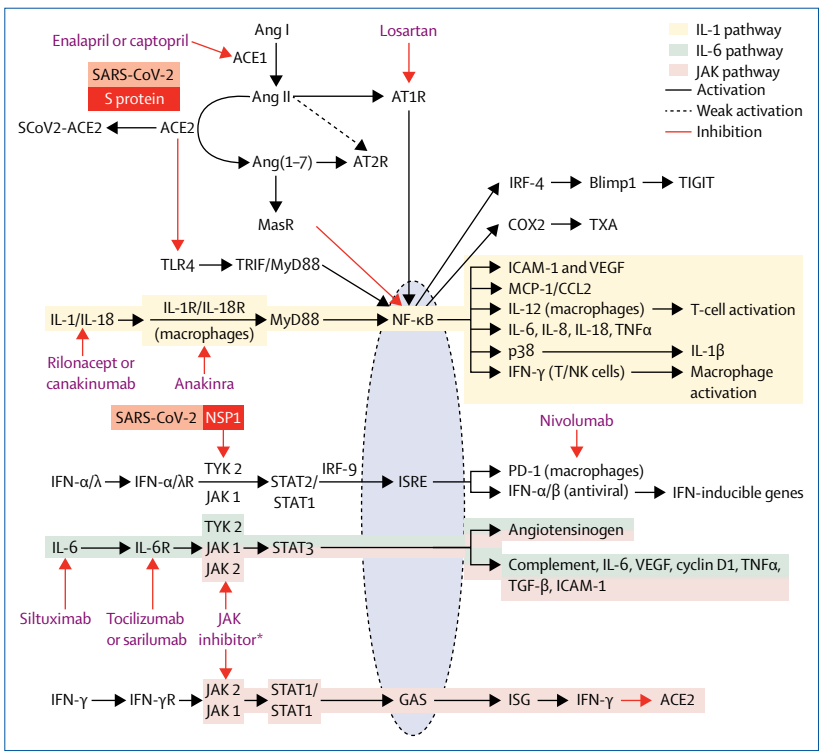

Figure: **SARS-CoV-2 interaction with the inflammatory system and therapy targets within the system**
TLR4, AT1R, IL-6, IL-1, IL-18, type 1 IFNs, and IFN-γ receptor binding activates specific signalling cascades and translocation of nuclear transcription factors into the nucleus (blue ellipse), where they interact with their respective chaperones (NF-κB) or their targeting sequences on DNA (ISRE, GAS) to activate the production of multiple proteins including additional cytokines, chemokines, cell surface molecules, and more. SARS-CoV-2 also directly interacts with ACE2 (via S protein) causing uninhibited Ang II activation of AT1R while also decreasing TLR4 inhibition; in addition, SARS-CoV-2 inhibits TYK 2 (vis NSP1), further driving inflammation by causing downstream effects that overlap with the immunomodulatory pathway. Anticytokine, JAK inhibitors, and antihypertensives can limit hyperinflammation by interacting and inhibiting these signalling cascades. ACE=angiotensin converting enzyme. Ang=angiotensin. ATR1=type 1 angiotensin II receptor. AT2R=type 2 angiotensin II receptor. COX=cyclooxygenase. GAS=IFN-γ activation site. ICAM=intercellular adhesion molecule. IL=interleukin. IFN=interferon. IRF=IFN regulatory factor. ISG=IFN-stimulated gene. ISRE=IFN-stimulated response element. JAK=Janus kinase. MCP=monocyte chemoattractant protein. NSP=non-structural protein. PD-1=programmed cell death 1. R=receptor. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. TGF=transforming growth factor. TLR=toll-like receptor. TNF=tumour necrosis factor. TRIF=TIR-domain-containing adapter-inducing interferon-β. TXA=thromboxane. TYK=tyrosine kinase. VEGF=vascular endothelial growth factor. *JAK inhibitors: ruxolitinib, tofacitinib, baricitinib, peficitinib, fedratinib, and upadacitinib.

See **Online** for appendix

CJT is a principal investigator for two randomised controlled trials investigating angiotensin II receptor blockers in the treatment of COVID-19 among inpatient and outpatients. NEI is also a co-investigator on these grants. SGH has served as a consultant for Incyte, Bristol-Meyers Squibb, and Generon, outside of the submitted work. NEI and SL-E contributed equally. All remaining authors declare no competing interests.

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