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# Immunosuppression for COVID-19: repurposing medicines in a pandemic

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It might seem paradoxical to suggest immunosuppression could play a role in managing COVID-19. The seemingly logical therapeutic option for this disease would be an antiviral. Unfortunately, repurposing antiviral therapies has proven disappointing so far, and evidence to support their routine use in COVID-19 is currently lacking.<sup>1-4</sup>

While the current standard of care for most people with COVID-19 is supportive, a subset of patients become severely unwell with a potentially life-threatening hyperinflammatory state called cytokine release syndrome.<sup>5</sup> This clinical state is difficult to predict in advance. When it occurs it is characterised by rapidly worsening multiorgan dysfunction including respiratory failure and a clinically distinctive coagulopathy involving immunothrombosis of the pulmonary vasculature.<sup>6</sup> Antigens presented by infected cells activate both the innate and adaptive immune systems. The uncontrolled upregulation of immune cells leads to a surge of proinflammatory cytokines including interleukin-6 and interleukin-1. This in turn increases vascular permeability and inflammatory cell recruitment into lung parenchyma causing acute lung injury and subsequent respiratory failure. As a myriad of proinflammatory molecules and inflammatory markers are involved in both the typical immune response to infection and this hyperinflammatory and hypercoagulable state, the key drivers of inflammation and mortality in severe COVID-19 are contentious. As such, the benefit of treating this hyperinflammatory state has not yet been completely established in COVID-19.

In patients with severe COVID-19, there is significant mortality in the second week of disease,<sup>7,8</sup> despite many studies describing a progressive fall in viral count.<sup>9,10</sup> This may partially explain the lack of success with antivirals. In this situation, immune-driven damage, such as cytokine release syndrome, may be what is driving mortality. Therefore early recognition and prompt initiation of immunosuppression may benefit these patients.

Cytokine release syndrome is a known phenomenon, and pathophysiologically similar syndromes exist in autoimmune diseases such as systemic juvenile idiopathic arthritis and adult onset Still's disease. It is also encountered as a complication of chimeric antigen receptor T-cell (CAR T-cell) therapy used for haematological malignancies.

Interleukin-6 and interleukin-1 driven pathways have a central role in cytokine release syndrome associated with COVID-19 and in other previously recognised cytokine release syndromes. Therapies targeting these pathways include tocilizumab (an interleukin-6 receptor antagonist) and anakinra (an interleukin-1 receptor antagonist). These are both registered by the Therapeutic Goods Administration (TGA) for cytokine release syndrome-like autoimmune conditions such as systemic juvenile idiopathic arthritis. Anakinra has previously been used in the treatment of macrophage activation syndrome, a cytokine release syndrome associated with autoimmune conditions.<sup>11</sup> Tocilizumab is registered for the management of cytokine release syndrome secondary to CAR T-cell therapy. The possibility of adopting these immunosuppressive therapies in COVID-19 is supported by early evidence from observational studies.<sup>12</sup> However, these drugs need the same caution as any off-label and experimental prescribing in COVID-19 until they are validated in clinical trials.<sup>13-15</sup>

Not all immunosuppressive drugs hold the same promise. While systemic corticosteroids are effective immunosuppressants, previous and current outbreaks suggest that their broader physiological effects lead to uncertain benefit and potential harm.<sup>16-18</sup> Accordingly, they are avoided in routine care unless for a recognised indication. Colchicine has also generated interest due to its effect on the inflammasome-mediated interleukin-1 beta pathway which is part of the innate immune response. However, its use in COVID-19 remains unproven.<sup>19</sup> Baricitinib, a Janus kinase inhibitor used for rheumatoid arthritis, was identified through a machine-learning exercise as potentially reducing viral entry into cells in COVID-19, but currently has no established use in cytokine release syndrome.<sup>20</sup>

Some important distinctions exist between the rational repurposing of immunosuppression in COVID-19 and other widely discussed experimental therapies.<sup>21</sup> Tocilizumab is already part of the evidence-based management of CAR T-cell-induced cytokine release syndrome,<sup>6,22</sup> a condition that shares pathological similarities. In contrast, proposed antiviral strategies that include chloroquine, hydroxychloroquine, and ivermectin are reliant on novel mechanisms of action and low-quality evidence, while raising significant safety concerns.<sup>23,24</sup>

COVID-19 poses a multifaceted threat requiring a multimodal and stratified treatment approach, possibly transitioning from virus-targeted approaches in the early state of disease to immunomodulation in late-onset immune-mediated disease. The example of interleukin-6 and interleukin-1 inhibition demonstrates that a cohesive and considered approach towards off-label prescribing in COVID-19 is needed. This should be used in consultation with relevant subspecialties and

drug and therapeutic committees.<sup>21</sup> Decision making should also include patients and their families.<sup>25</sup> As it is not yet standard of care, reporting safety and efficacy outcomes as part of clinical trials is highly desirable. With such measures, repurposed medicines can be appropriately recruited into the pandemic fight without defying sensible prescribing.<sup>21,25</sup> ◀

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