Targeting hyperinflammation in infection: can we harness the COVID-19 therapeutics momentum to end the dengue drugs drought?

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The COVID-19 pandemic has accelerated potential therapeutics into clinical trials at a remarkable pace. It has also brought global attention to the concept of a biphasic illness with an initial viraemic phase, followed by a life-threatening inappropriate and excessive host hyperinflammatory phase in some patients, which might respond to immunomodulation. In this subgroup, a self-amplifying cytokine storm is thought to lead to monocyte and macrophage activation, with subsequent tissue damage, clinically manifesting as fever, organ dysfunction, elevated ferritin, cytopenias, and hypercytokinaemia. Dexamethasone and tocilizumab are now standard of care in treatment of severe COVID-19, following demonstration of efficacy in both the REMAP-CAP and RECOVERY trials.[1,2] Several trials investigating other immunomodulatory agents in COVID-19 are ongoing.

Virus-driven hyperinflammation is not unique to COVID-19; several epidemic viral infections, including dengue,[1] Ebola, and influenza, have been identified as triggers for hyperinflammatory syndromes. We suggest two immunomodulatory agents undergoing evaluation for treatment of hyperinflammation in COVID-19 that might have broader applicability to dengue due to similar pathophysiology, ample safety data, and short half-lives: an interleukin-1 receptor (IL-1R) antagonist (anakinra) and a Janus kinase (JAK) and Numb-associated kinase (NAK) inhibitor (baricitinib).

Dengue causes approximately 96 million symptomatic infections, 24 million hospital admissions, and half a million intensive care unit admissions every year worldwide.[2] Despite the huge burden of morbidity, there are no direct-acting or host-directed antiviral agents licensed to treat dengue. Similar to COVID-19, the severe manifestations of dengue (shock, coagulopathy, and multi-organ impairment) occur late in the disease course when viraemia is in rapid decline, and are likely to be driven by an excessive host immune response.[3] High IL-1, ferritin, and C-reactive protein are all associated with severe disease.[1,4] Dengue-associated hyperinflammation is an increasingly recognised, but still under-diagnosed, phenomenon; among patients with severe dengue, mortality is higher in those with hyperinflammation (39%) than in those without (22%).[1] Attempts to evaluate targeted immunomodulation in the hyperinflammatory phenotype of dengue have stalled due to industry and academic disinterest in this neglected disease area.

Anakinra targets the IL-1β hyperinflammatory loop, which mediates hyperferritinaemia, coagulopathy, and fever. Anakinra improved survival in a subgroup of patients with sepsis-associated hyperinflammation (ferritin >2000 ng/mL, coagulopathy, and liver enzyme elevations)[5] and is under evaluation for management of hyperinflammation in influenza and COVID-19. Anakinra can be given intravenously, which circumvents contraindications to subcutaneous delivery in patients with poor peripheral absorption, thrombocytopenia, and coagulopathy, all of which are common manifestations in severe dengue. We believe that anakinra's safety profile and wide therapeutic margin, and the central role of IL-1 in the cytokine storm, warrants its assessment in dengue-associated hyperinflammation.

Baricitinib targets cellular viral entry and replication, and modulates the pro-inflammatory cytokine response to viral infection. Baricitinib has been proposed independently by both artificial intelligence[6] and the GenOMICC consortium[7] as a high-priority drug for COVID-19 and has recently been added to the RECOVERY trial. The ACTT-2 trial evaluating baricitinib as adjunctive treatment of COVID-19 has shown promising results, with shorter time to recovery and fewer serious adverse events in the baricitinib group than in patients treated with remdesivir plus placebo.[8]

Further rationale for the extension of baricitinib to dengue comes from in-vitro studies using a combination of the NAK inhibitors erlotinib and sunitinib, which prevented uptake of multiple viruses (hepatitis C virus, dengue virus, and Ebola virus) by inhibition of adaptor protein-2 associated protein kinase 1 (AAK1) and cyclin G-associated kinase (GAK; pivotal regulators of clathrin-mediated endocytosis and intracellular

assembly of viral particles).[9] A combination of sunitinib and erlotinib was protective in a dengue mouse model, with decreased viral load, increased survival, and altered cytokine profile. The combination also had a dose-dependent effect on preventing dengue infection of human primary monocyte-derived dendritic cells.[10] However, to exert both antiviral and immunomodulatory effects in humans, sunitinib and erlotinib might need to be administered at higher-than-tolerable doses.

By contrast, baricitinib is expected to exert JAK1, JAK2, AAK1, and GAK inhibition at therapeutic levels in humans without toxicity.[6] It has convenient once daily, oral administration. Children and adolescents are the populations at greatest risk of severe dengue in hyperendemic regions, and clinical trials investigating baricitinib for other indications suggest that it can be safely used in this patient group. Baricitinib is already available across much of the Asian continent, where the burden of dengue is greatest. Thus, we believe that a clinical trial of baricitinib treatment in carefully selected patients with dengue who have a hyperinflammatory phenotype and high risk of progression to severe disease is needed.

The momentum generated during the COVID-19 pandemic to investigate immunomodulation as host-directed therapy for infection-associated hyper-inflammation should not be limited to newly emerging viral infections. Exploring therapeutic targets of host pathways exploited by viruses could help to populate the barren therapeutic pipelines of other neglected and clinically important tropical infections that cause considerable global morbidity and mortality, such as dengue.

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