Immunomodulatory therapy in dengue: need for clinical trials and evidence base

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Dengue infection is a major public health problem especially in the Southeast Asian region (SEAR). The incidence of dengue is estimated at 390 million infections with a prevalence of 3.9 billion worldwide. Notably, the mortality due to severe dengue is 15.9 times higher in children under 14 years of age.1 Infections such as dengue, tuberculosis and malaria remain a bigger challenge for children in low- and middle-income countries (LMICs) but unlike infection with SARS-CoV-2 have not attracted global attention and continue to be neglected. More children died of dengue in the last 2 years than from COVID-19.1 Vaccines and antiviral drugs for dengue have not taken off despite initial enthusiasm. Unlike the vaccine trials, well-designed randomised controlled trials for therapeutic strategies for dengue in both children and adults are currently lacking and hence treatment options beyond supportive care are minimal.

The recent COVID-19 pandemic has helped illustrate the importance of interplay between host and viral factors in determining disease severity. A subset of patients with COVID-19 have a stormy course due to an exaggerated immune response rather than the viraemia itself. Targeting host pathways that are exploited by viruses has emerged as the focus of newer therapies. This has resulted in a paradigm shift in the management of viral infections from supportive care and antivirals to immunomodulatory drugs. Corticosteroids, interleukin (IL)-6 receptor blockers and baricitinib are now strongly recommended by the WHO in management of severe and critical COVID-19.2

Dengue infection predominantly causes an asymptomatic or mild illness. However, −25% of those infected can develop an illness with a febrile or viraemic phase, a critical phase that coincides with the peak of disease, and finally the recovery phase. Severe dengue can develop in −3%. Previous infection with dengue increases the risk of developing severe disease, due to mechanisms such as antibody-dependent enhancement that promote viral replication.

POSSIBLE ROLE FOR IMMUNOMODULATION IN DENGUE

Numerous factors suggest that the immune system plays a key role in the pathogenesis of dengue.1 The answer to successful immunomodulation in dengue probably lies in careful patient selection with an aim to restore immune homeostasis. Suppressing the immune system during the viraemic phase could potentially be counterproductive. Whereas opportunities for immunomodulation might exist in the critical phase to either prevent onset/halt progression of disease severity, or to mitigate end-organ dysfunction in critically ill patients (figure 1). Immunomodulation early in the critical phase is of particular interest since it might help alleviate the huge burden placed on healthcare systems during outbreaks of dengue by reducing the need for hospitalisation. Once the critical phase is established, the disease may run a mild, moderate or severe course. Severe dengue can manifest with increased vascular permeability, coagulopathy or end-organ involvement.1 Although judicious fluid therapy may suffice in the vast majority, immunomodulation may help reduce the intensity of vascular leakage reflected by the need for excessive fluids to maintain effective circulating volumes. Also, a proportion of these patients develop severe hyperferritinaemia and progressive hepatic dysfunction that portends a poor prognosis.

Ferritin levels >10 000 ng/mL, elevated lactate dehydrogenase, elevated aspartate transaminase and alanine transaminase levels are characteristics of this subset.3 Recognition of patients at the onset of progressive end-organ damage would therefore provide an opportune interval for immunomodulation to prevent patients from becoming critically ill (figure 1).

RESEARCH PRIORITIES FOR IMMUNOMODULATION IN DENGUE

Corticosteroids

A Cochrane review which included eight trials concluded that the evidence to evaluate the effects of corticosteroids in the treatment of early stages of dengue fever and dengue-related shock was insufficient.5 Most of these studies were either

Figure 1  Clinical course of dengue infection with potential time frames for immunomodulation.
Anakinra

Anakinra competitively binds to the IL-1 receptor and thereby prevents amplification of the inflammatory cascade caused by elevated IL-1 levels. It was shown to improve survival in adults with sepsis-associated hyperinflammation, coagulopathy, and hepatobiliary dysfunction. Anakinra could potentially be studied in severe dengue with hyperferritinemic sepsis where similar features are encountered. The short half-life also favours use in conditions where secondary infections are a cause for concern. However, the cost and availability of anakinra in LMICs are major limiting factors at present.

Baricitinib

Baricitinib (Janus kinase and Numb kinase inhibitor) has recently been proposed for use in patients with the hyperinflammatory phenotype of dengue. JAK inhibitors target AAK1 (AP2-associated protein kinase 1) and GAK (cyclin G-associated kinase) which are pivotal in regulation of clathrin-mediated endocytosis. In dengue mouse models, inhibition of AAK1 and GAK pathways was associated with reduced viral load and thus mortality. Also, targeting the JAK pathway alters the intracellular signalling of cytokines. The potential of baricitinib as a dual antiviral and anti-inflammatory agent in dengue needs to be further evaluated with clinical trials. The short half-life and oral route of administration make it more favourable and convenient for use in children. Also, the low cost would be an added advantage in LMIC settings.

Intravenous immunoglobulin

IVIG has been considered in hyperferritinemic sepsis to help neutralise infections which have no specific therapy. In dengue, IVIG may perhaps be helpful in the presence of concomitant infections which in turn can exacerbate the degree of organ dysfunction. However, the availability and cost of IVIG can vary widely depending on the product.

Significant developments have been made in the management of hyperinflammation secondary to infections such as influenza and COVID-19 due to the collective work of researchers and clinicians across the globe. Unfortunately, in the absence of robust data, there continues to be a huge void in research into the optimal management of dengue and its associated mortality. Lack of robust clinical and laboratory parameters to guide immunomodulation is a major challenge at present. We speculate that drugs such as anakinra, baricitinib, corticosteroids and IVIG may find a role in the treatment of severe dengue in children. There is a dire need for well-designed trials evaluating multiple drugs like the RECOVERY and Solidarity trials in COVID-19. Coherent and coordinated efforts at an international level by entities such as the WHO are required to conduct trials across multiple countries in SEAR that are affected by this infection with high morbidity and mortality.

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weak in methodology or were underpowered. The role of corticosteroids needs to be further explored through well-designed trials before being dismissed as a therapeutic option especially in LMIC settings. Studies that have trialled corticosteroids during different phases of the disease showed a mortality benefit early in the critical phase when effective and sustained drug doses were maintained. We suggest there may be scope for evaluating the role of corticosteroids at lower doses (methylprednisolone 1–2 mg/kg/day or an equivalent steroid) in this phase (figure 1). Corticosteroids might also be trialled during the critical phase in those with severe dengue-associated hyperferritinemia. The basis for such use can be extrapolated from hyperferritinemic sepsis where promising results were noted with the use of methylprednisolone along with plasma exchange and intravenous immunoglobulin (IVIG). However, caution needs to be exercised since bacterial infections commonly coexist at presentation in this phenotype.