



## Correspondence

### Recent developments in COVID-19 therapeutics & current evidence for COVID-19-associated multisystem inflammatory syndrome

Sir,

We read with interest the article by Varghese *et al*<sup>1</sup> and would like to commend the authors for providing valuable information on the clinical manifestations and management of COVID-19. Based on the current evidence, we would like to offer our additional insights on the recent developments in COVID-19 therapeutics and the newly recognized multisystem inflammatory syndrome (MIS) in children.

The COVID-19 pandemic caused by the SARS-CoV-2 has been an unprecedented global health challenge. There have been 24,193,010 confirmed cases of COVID-19 globally affecting 216 countries and 826,141 deaths, as of August 27, 2020<sup>2</sup>. In India, there have been 3,310,234 cases with 60,472 deaths<sup>3</sup>. Given the unprecedented magnitude of the pandemic's impact on health and economy, therapies for COVID-19 are being actively investigated, and there are more than 1000 treatment and over 173 vaccine trials taking place worldwide, including 31 candidate vaccines in clinical evaluation and 142 in pre-clinical evaluation<sup>4,5</sup>.

Recently, the antiviral agents remdesivir and favipiravir, which act by inhibiting viral replication, have been approved for COVID-19 treatment in severely ill patients by the Government of India<sup>6,7</sup>. Remdesivir has been shown to be effective in critically ill adults and recommended by the National Institutes of Health guidelines for hospitalized patients with severe COVID-19 (those with SpO<sub>2</sub> ≤94% on ambient air or requiring supplemental oxygen or those on mechanical ventilation or extracorporeal membrane oxygenation)<sup>8</sup>. The recommended duration of therapy is five days in non-intubated patients that may be extended to 10 days in ventilated patients. However, there is insufficient

evidence to support for/against the use of remdesivir in patients with mild or moderate manifestations. Favipiravir, an oral medication, is mainly used for mild/moderate COVID-19 disease.

In June 27, 2020, low-dose dexamethasone has also been approved for use in severe COVID-19 disease in India<sup>6</sup>. A study from a series of randomized controlled trials known as the RECOVERY programme showed dexamethasone to be effective in patients who were critically ill with COVID-19<sup>9</sup>. For patients on ventilators, the treatment was shown to reduce mortality by 35 per cent, and for patients requiring only oxygen, mortality was reduced by 20 per cent. The benefit was only seen in patients with severe manifestations, and was not observed in patients with mild disease.

Given the cytokine release syndrome, tocilizumab, an interleukin-6 (IL-6) inhibitor, has recently shown to be effective in improving survival in critically ill ventilated patients to 75 per cent and reducing duration of mechanical ventilation requirement to five days<sup>10</sup>. As noted by the authors, convalescent plasma has also been found to be of benefit in severely ill patients with COVID-19, and a phase II, open-label, randomized controlled trial to assess the safety and efficacy of convalescent Plasma to Limit COVID-19-Associated Complications in Moderate Disease (PLACID Trial) initiated by the Indian Council of Medical Research (ICMR) is in progress<sup>11</sup>.

Among international trials, the World Health Organization (WHO) SOLIDARITY trial<sup>12</sup> aims to help find an effective treatment for COVID-19 among adult patients. This was originally set to compare four treatment options against standard of care, to assess their relative effectiveness against COVID-19 including

remdesivir; lopinavir/ritonavir; lopinavir/ritonavir with interferon beta-1a and hydroxychloroquine (HCQ). So far, more than 3,500 patients have been recruited in 35 countries, in over 400 hospitals. On June 17, 2020, the HCQ arm of the trial was stopped based on recent evidence including the preliminary SOLIDARITY trial data and RECOVERY trial<sup>13</sup> results showing that HCQ did not result in the reduction of mortality of hospitalized COVID-19 patients. Several other medications such as colchicine, 5-fluorouracil, ribavirin and non-anti-infectives such as famotidine are also under study. However, paediatric experience with therapeutic agents for COVID-19 such as remdesivir and others shown to be effective in adults, is limited.

Although previously thought to affect children less severely, COVID-19 has recently been associated with a novel spectrum of severe paediatric illness with features resembling Kawasaki disease (KD), macrophage activation syndrome, Kawasaki shock syndrome and toxic shock syndrome, with markedly elevated inflammatory markers and multisystem involvement labelled as MIS by the WHO<sup>14</sup>.

The pathogenesis of MIS is not fully understood, and it is thought to be a post-infectious immune-mediated phenomenon. A recent report emphasized that this entity is different from KD, affecting older children, with higher inflammatory markers, fibrinogen, higher rates of shock and coronary artery involvement than KD. Coronary abnormalities were seen in 61 per cent of patients with COVID-19-associated KD like symptoms compared with about 10 per cent risk of coronary abnormalities with classic KD<sup>15</sup>.

Majority of the patients with MIS have been reported to be critically ill needing advanced respiratory support and aggressive treatment of circulatory shock with inotropes. Treatment of MIS with immunomodulatory agents such as intravenous immunoglobulin and corticosteroids has been described, and some patients have been treated with IL-6 inhibitors such as tocilizumab, IL-1 inhibitors such as anakinra and tumour necrosis factor-alpha inhibitors such as infliximab<sup>15,16</sup>. Most of these patients have also required anticoagulation with enoxaparin and/or aspirin as a key component of management<sup>16</sup>. The WHO advises that management of MIS should involve multidisciplinary care with paediatric cardiology, infectious disease, intensive care and rheumatology specialists, and the initial laboratory evaluation of a child with suspected

MIS should include troponin, B-type natriuretic peptide, a 12-lead electrocardiogram and ECHO in addition to inflammatory markers, coagulation profile and ferritin levels. Supportive care for myocardial dysfunction to maintain adequate systemic perfusion and continuous cardiac monitoring as well as follow up with paediatric cardiology for cardiac dysfunction or coronary abnormalities is advised. It is hoped that treatment strategies for COVID-19 and this novel paediatric syndrome will likely evolve in the light of new evidence, as more scientific data become available.

**Conflicts of Interest:** None.

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