ICU
MANAGEMENT & PRACTICE

COVID-19: Therapies Targeting Interleukin-6-Mediated Cytokine Release Syndrome

The current pandemic will be remembered for a long time for the huge loss of lives and disruption it caused to the way of life as we know it. In the absence of a viable vaccine, physical distancing and symptomatic management are the only interventions health care providers have at hand.

Studies have demonstrated the association of interleukin-6 (IL-6)-mediated cytokine release syndrome and mortality. This review examines the effects of blocking pro-inflammatory cytokines such as IL-6, nonselective inhibition of Janus kinase, and selective suppression of Janus Kinase 2.

Cytokine release syndrome (CRS) refers to the massive increase in the levels of cytokines caused by the release of interleukin-6 (IL-6), causing symptoms such as high fever and hypoxic pneumonitis that often requires patients to be assisted with ventilators. Clinicians have tried to manage cytokine release syndrome and subsequent inflammation by blocking IL-6 with the help of a human monoclonal antibody called tocilizumab.

Data from both China and the United States have shown that the use of tocilizumab early has the potential to reverse pneumonitis without causing any side effects. The reversed pneumonitis can be observed on x-rays as early as three weeks. Tocilizumab is approved for use in the US and China. Research is underway to see if siltuximab with glucocorticoids can be used to treat COVID-19-associated pneumonia.

Another way to block interleukin-6 is by inhibiting receptor signal transduction through Janus Kinases (JAK 1/2). Ruxolitinib can greatly reduce IL-6 activity, but it has deleterious effects on cytokines such as IL-2, IL-7, and IL-15. It also interferes with the host's antiviral immunity mediators such as natural killer cells, dendritic cells, and beneficial cytotoxic T lymphocytes. Due to this, the use of ruxolitinib is associated with infections such as hepatitis B, TB, and cryptococcal pneumonia.

A much better candidate for JAK inhibition to counter IL-6-associated pathology is baricitinib. Baricitinib inhibits JAK signal transduction, and also neutralises a protein called AAK1, which can facilitate entry of SARS-CoV-2.

Other Janus kinase two inhibitors in use are fedratinib and pacritinib that act on JAK2 with next to no effect on JAK 1 at therapeutic doses. There have been no serious adverse events noted with the two but have the additional advantage of suppressing Th1 T cells that mediate cytokine release syndrome. These should be preferred over ruxolitinib.

Fedratinib decreases the maturation of dendritic cells and reduces the action of natural killer cells with no effect on T cells. It can have gastrointestinal side effects and anaemia. It has no advantage over ruxolitinib in terms of action against AAK1.

Pacritinib is better than ruxolitinib in that it only inhibits natural killer cell activity but allows nonalloreactive T cells and beneficial Tregs to function. The most common side effects include diarrhoea and thrombocytopaenia.

Given the dramatic increase in morbidity and mortality, it is hard not to get excited by the appeal of novel therapies. However, caution should be exercised in using new drugs and repurposing existing ones.

Source: Critical Care Explorations
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