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The role of IL-6 and other mediators in the cytokine storm associated with SARS-CoV-2 infection

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Learning objectives: “The role of IL-6 and other mediators in the cytokine storm associated with SARS-CoV-2 infection”

1. To define the immunopathogenesis of the cytokine storm associated with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).
2. To explore the role of the IL-6 in the SARS-CoV-2 inflammatory and viral responses.
3. To describe the role of biological immunotherapies targeting the hyperinflammatory immune response in SARS-CoV-2.
4. To outline the therapeutic strategy targeting upstream and downstream immunologic pathways in SARS-CoV-2.

CME items:

**Question 1.** Multiple studies have been published on the immunopathogenesis of the cytokine storm related to SARS-CoV-2. Among the recent findings, choose the option that best describes this inflammatory response:

A. When compared to healthy controls, there is no evidence that CD14+ IL-1β monocytes are increased in the PMBCs of COVID-19 patients.
B. Postmortem pathological findings in 1 patient infected with SARS-CoV-2 indicated an increase of CD4 and CD8 cell counts.
C. In vitro studies show that IFN responses are impaired in patients with severe SARS-CoV-2 disease.
D. Activating the intracellular kinase, Bruton’s tyrosine kinase (BTK) could be a promising strategy for reducing COVID-19-related complications.

**Question 2.** Regarding our current understanding of the clinical and epidemiological features of COVID-19, which of the following statements is true?

A. Cytokine storm (CS), hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS) are clearly distinct diseases with no overlapping immunopathology.
B. With clinical features similar to Kawasaki disease, the pediatric multisystem inflammatory syndrome (multi-system inflammatory syndrome in children, or MIS-C) has now been associated with SARS-CoV-2 infection.
C. Children are thought to be a significant source of spread of SARS-CoV-2 in the community.
D. Both the number of cases worldwide and the case fatality associated with both SARS-CoV and Middle East respiratory syndrome (MERS)-CoV are higher than that of SARS-CoV-2.

**Question 3.** Which of the following is true regarding IL-6 in acute SARS-CoV-2 infection?

A. After an anti-IL-6 receptor treatment, the acute phase reactant C-reactive protein (CRP) should not be used as a marker for disease progression.
B. IL-6 is not a useful marker for disease progression as there seems to be no difference between the IL-6 values in survivors compared with nonsurvivors.
C. An IL-6 cut-off based on prospective clinical data has been determined for COVID-19.
D. An increase of IL-6 has been associated with a severe response to SARS-CoV-2 (defined as the development of sepsis, acute respiratory distress syndrome [ARDS], requirement for mechanical ventilation, and death).

**Question 4.** Regarding the use of anti-IL-6R, tocilizumab, which of the following statements is true:

A. Tocilizumab is an FDA-approved treatment for critically severe COVID-19 patients.
B. The administration of a single dose of tocilizumab has been associated with an increase in serious infections.
C. Data is currently insufficient to recommend the use of IL-6R inhibitors for the treatment of SARS-CoV-2 infection.
D. Clinical studies have universally shown an increase in survival rates for the patients treated with tocilizumab and other IL-6R inhibitors.

**Question 5.** Which of the following immunologic targets has been shown in clinical trials to provide clinical improvement in severe COVID-19 patients? Choose the best option for target and clinical improvement:

A. IL-17 receptor antagonists have been clinically shown to decrease the lung neutrophil recruitment and to reduce progression to ARDS.
B. The use of an adenosine analogue with antiviral activity against a broad range of RNA virus families, remdesivir, has revealed a decrease in recovery time and is currently FDA approved for use in children and adults with severe COVID-19.
C. By decreasing acute systemic inflammation, anti-TNF biologics have been shown to decrease mortality in severe COVID-19 patients.
D. The use of the nonglycosylated human decoy IL-1 receptor antagonist (IL-1Ra) in severe SARS-CoV-2 patients has shown significant improvement in survival in patients with features of MAS.