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Pharmacological immunomodulation in COVID-19 with vascular dysfunction

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ABSTRACT

Coronaviruses are so named because of the halo of spike (S) proteins that decorate their surfaces and infect cells through interactions between its S protein with specific cellular receptors to bind host cells leading to hyperresponsiveness of immune system as 'cytokine storm' which contributes to toxic-metabolic encephalopathy in severe cases. As a result, systemic proinflammatory cytokines and biomarkers are elevated and immune modulators have the potential to inhibit cytokines and to treat the cytokine storm.

KEYWORDS

COVID 19; Immune system; Cytokine storm; Immune modulators; Vascular dysfunction

ARTICLE HISTORY

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Introduction

The cytokine dysregulation developed a hyperinflammatory syndrome (also termed cytokine release syndrome), a dysfunction in autonomic tone to the cytokine release. Inflammatory cytokines can spread through the bloodstream and it is likely an indirect effect of the virus and has been associated with rapid clinical deterioration leading to acute respiratory distress syndrome (ARDS), multiorgan failure and death.

Methods

Upregulation of inflammasomes, dysregulation of T cells with unfettered production of cytokines/chemokines, including IL6, TNFα, and CCL2, the virus alters the microenvironment of the immune system pertains to macrophages. Highly inflammatory FCN1+ macrophages predominate over fatty acid–binding protein 4 (FABP4+) macrophages in severe COVID-19, the macrophage activation syndrome (MAS) and endothelial damage leads to micro- and macro thrombotic episodes. In milder cases, the expansion of clonal CD8+ T cells in the lung microenvironment causing an adaptive immune response to the control of COVID-19 [1].

Results

Immunomodulator drugs either stimulate or suppress the immune system, modulate the immune response of both adaptive and innate immunity and significantly reduce hyperinflammation. Specific Immune Modulators such as anti-cytokines, the Interleukin (IL)-1 Receptor antagonists which inhibit the proinflammatory cytokines IL-1α and IL-1β is effective in treating MAS [2]. IL-6 Receptor Antagonists, Tocilizumab is a recombinant monoclonal antibody bind the membrane-bound IL-6 receptor (mIL6R) and soluble IL-6 receptor (sIL6R) and by inhibiting signal transduction, interrupt the inflammatory storm in severely ill COVID-19 patients who have extensive lung lesions and high IL-6 levels [3]. Ruxolitinib, a potent and selective oral inhibitor of both JAK1 and JAK2 protein kinases, interrupts signaling downstream of multiple proinflammatory cytokines, which constitute the cytokine storm and increased activation of the JAK-STAT pathway. Nebulized sargramostim 125 µg twice daily for 5 days is an effective strategy for pneumonia-associated ARDS. High-dose IVIG at a dose of 0.3–0.5 g/kg/day for 5 days normalize body temperature within 1–2 days but thromboembolic complications were reported in some cases. Low-dose dexamethasone (6 mg once daily, orally or intravenously) for 10 days reduced deaths by one-third in patients on mechanical ventilation in RECOVERY trial. Triple antiviral therapy of lopinavir/ritonavir, ribavirin, and nebulized IFNβ-1b could shorten the duration of viral shedding. Statins inhibit MyD88 pathway and tend to preserve MyD88 levels during hypoxia and stress confer a protective effect in COVID-19 patients. Recombinant human ACE (rhACE2) is a novel therapy for acute lung injury. Macrolides, azithromycin and clarithromycin, are antibiotics with immunomodulatory and anti-inflammatory effects, downregulate proinflammatory cytokines and known to prolong the QT interval and potentially increase the risk of sudden cardiac death in combination with other QT-prolonging therapies such as chloroquine.

Patients with elevated CRP and lymphopenia are most benefit from hydroxychloroquine. By increasing endosomal pH and disturbing the glycosylation of cell surface receptors, these medications provide an important defense against viral entry and replication. It may bind to gangliosides with high affinity and preventing SARS-CoV-2 from binding with the ACE-2 receptor, but RECOVERY trial & ORCHID study showed a lack of evidence of efficacy. Targeting PGD2/DP2 signaling as Ramatroban is a potent, reversible, and selective antagonist of PGD2/DP2 receptors which shown to inhibit PGD2-stimulated IL-13 secretion, used orally as an immunotherapeutic approach for immune dysfunction and lymphopenia in COVID-19. Convalescent plasma shown to be beneficial for COVID-19 patients with a better outcome within 14 days of onset of symptoms with severe infection by stabilizing the immune system, but randomized controlled trial failed to show any benefit within 28 days. Complement C5a inhibition with

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vilobelimab showed a mortality benefit and JAK inhibitors, baricitinib, is the most thoroughly studied with a survival benefit effect and low risk of serious adverse events [4].

Discussion

The crucial step is the process of viral entry into the host cells, the surface spike glycoprotein, which binds to ACE2 receptor in brain vascular endothelium and smooth muscle cells and enter the cells by endocytosis. After priming by TMPRSS2 (transmembrane protease serine 2), it is activated and then internalized. The endocytic pathway including endosomes and lysosomes and the autophagy process in viral entry has attracted. The Spike protein dependent pathway is thought to be more important for cell entry and BBB (blood brain barrier) crossing and it is the potential therapeutic strategy for specific antibodies or vaccine production. The presence of the virus in the brain stem affects chemo sensing neural cells related to respiration as well as respiratory center neurons and damage the lung ventilatory function. Brain and lung crosstalk as SAR-CoV-2 through ACE2 as the receptor for viral cell entry and induce lung injury by increasing the immune system cytokines and downregulate the central ACE2 protein expression and inhibit ACE2 activity. It reduces the sensitivity of the baroreceptor reflex control of the heart rate and increases sympathetic tone which eventually results in high blood pressure and cardiac dysfunction.

Viral infection results in an imbalance in homeostatic procoagulant and anticoagulant pathways and overactivation of NADPH oxidase-2 (Nox2), resulting in increased reactive oxidant species and platelet activation. Virus directly infecting stromal cells by interaction with CD13 or CD66a adhesion molecules and induce platelet aggregation via PAC-1 binding and these persisting changes of blood cell physical phenotypes contribute to long-term microcirculatory dysfunction. Cytokines induce cytoskeletal changes in myeloid cells and erythrocytes and reduce oxygen delivery. In severe COVID-19, low-density phenotype that is prone to neutrophil extracellular trap formation (NET), with elevated size and deformability causing vascular occlusion [5]. The coagulopathy characterized by an increase in procoagulant factors such as fibrinogen with an increase of plasma D-dimers have been associated with higher mortality. The incidence of cerebral infarction in COVID-19 is 4.5% [6]. Thromboprophylaxis with LMWHs is recommended in hospitalized patients with high levels of D-dimer indicating hypercoagulative state [7,8]. Intravenous recombinant tissue plasminogen activator (rt-PA) for selected patients. Immunomodulatory MSCs (mesenchymal stem cell) therapy could help to cure the inflammation and coagulopathy by a vascular effect. Mesenchymal stem cell transplantation improves pulmonary function within 2 days, having anti-inflammatory and anti-fibrotic effects with regenerative potential in vascular dysfunction of Covid-19. These cells are ACE2 and TMPRSS2 negative, making them a good cell target not influenced by SARS-CoV-2 infection and used to treat covid-19 intubated-ventilated patients presenting with acute respiratory distress syndrome of less than 96 h. Very small embryonic like stem cells (VSELs) have endothelial angiogenic potential and counteract lymphopenia. Exogenous ACE2 with human recombinant soluble ACE2 is a novel treatment for stroke and reverse endothelial dysfunction [9-11].

Conclusions

Viral cytopathic effects in peripheral smear and the peculiar morphological findings would suspect a diagnosis of Covid 19 in the absence of a negative RT-PCR or antibody results. The recent COVID-19 pandemic underscores the coagulation defects and healthcare professionals must carefully identify the underlying coagulation disorders to guide appropriate treatment strategies and to improve the patient outcomes.

Disclosure Statement

No potential conflict of interest was reported by the authors.

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