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TREATMENT MODALITIES OF CYTOKINE STORM IN COVID-19

Internal Medicine

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ABSTRACT

This publication delves into the management of the cytokine storm linked to COVID-19, which is an uncontrolled release of cytokines. Although the pathophysiology is complicated, it involves loss of both local and systemic regulatory control over the production of proinflammatory cytokines, leading to morbidity and mortality of COVID-19 cases. In this study, we summarize previous findings and analyze data from other studies to provide a comprehensive understanding of the treatment roles, while also highlighting the efficacy and mechanisms of action of glucocorticoids, Anakinra and Tocilizumab.

KEYWORDS

COVID-19; cytokine storm; hyperinflammation; immunomodulators

INTRODUCTION:

A "cytokine storm" is a complex immunological response characterized by the body releasing an overwhelming quantity of cytokines, leading to acute inflammation and tissue damage. This disorder arises from an imbalance between pro-inflammatory and anti-inflammatory cytokines, which leads to an overly pro-inflammatory immunological response. It's a hyper-inflammatory disease where an excess of cytokines can lead to major complications and, in severe cases, even death.[1,2] There are several important pro-inflammatory cytokines that have a major impact on the etiology and severity of COVID-19. GM-CSF, interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), interferon-gamma (IFN-γ), interleukin-10 (IL-10), and monocyte chemo-attractant protein-1 (MCP-1) are significant cytokines among them.[3,4] An excess of chemical release could lead to a cytokine storm, or systemic inflammatory reaction, which could affect the brain and liver among other organs.[5]

Cytokine Storm:

Cytokine storms vary in length depending on the underlying cause and the therapy administered. Despite the possibility of multiple underlying causes, the late-stage clinical manifestations of cytokine storm typically converge and overlap.[6] Fever is present in most cytokine storm patients, and in more serious situations, it may be high grade. In addition, patients may experience arthralgia, headache, rash, diarrhea, exhaustion, anorexia, and mental disorders. These symptoms may be directly related to immune cell-mediated responses, acute-phase physiological changes, or cytokine-induced tissue damage. Rapid case advancement may lead to vasodilatory shock, hemostatic imbalance, dyspnea, hypoxemia, hypotension, disseminated intravascular coagulation, and death from either vascular occlusion or catastrophic hemorrhages.[7] Many people have cough and dyspnea, which can develop into acute respiratory distress syndrome (ARDS), marked by hypoxemia potentially requiring mechanical ventilation. Patients with cytokine storm have low platelet counts, coagulopathy, and hyper-inflammatory conditions, which make them especially vulnerable to spontaneous bleeding.[8,9] Elevated proinflammatory cytokine levels during a cytokine storm lead to dysregulation of endothelial cell function and compromise the integrity of cell barriers, resulting in tissue damage and increased vascular permeability.[10] The cytokine storm mechanism is mediated not just by pro-inflammatory cytokine production but also by HMGB1 and eicosanoids.[11] It is commonly acknowledged and believed that the human body's first line of defense against a viral infection is the innate immune system's rapid and well-coordinated reaction.[12] The cytokine storm process is a key factor in the induction of neuroinflammation and clotting in the cerebral vasculature in severe COVID-19 patients. Furthermore, the blood-brain barrier may change as a result of the cytokine storm, enabling viral entrance into the brain via the hematogenous pathway. These cytokine storm processes demonstrate how it can lead to extensive tissue damage, malfunctioning organs, and serious side effects in a variety of medical diseases.[13,14] Naturally occurring microbial infections like those caused by Staphylococcus aureus and Streptococcus species can also cause cytokine storm. These bacteria produce superantigens that cross-link T-cell receptors and the major histocompatibility complex, causing polyclonal activation of T cells, cytokine production, and toxic shock syndrome. The most potent T-cell mitogens are called superantigens, and even at concentrations of less than 0.1 pg per milliliter, bacteria can excite T cells uncontrollably, leading to fever, shock, and even death.[15,16] The overall treatment plan for cytokine storm involves managing the underlying illness and removing factors that can trigger aberrant immune system activation, administering supportive care to preserve vital organ function, and limiting the collateral damage caused by the activated immune system. The cornerstone of treatment for cytokine storm linked to bacteria is antibiotics. Since there are fewer antiviral medications available for viral infections than for bacterial infections, targeted treatment is more difficult for these patients.[17]

Cytokine Storm Treatment:

The general treatment strategy involves supportive care, elimination of triggers, and targeted immunomodulation control of the underlying disease. The aim of the study is focused on immunomodulatory treatments, including Glucocorticoids, Anakinra, and Tocilizumab.

Glucocorticoids:

Glucocorticoids are known for their anti-inflammatory properties and have been used as a standard treatment in severe cases of COVID-19 to palliate the cytokine storm. Glucocorticoids such as dexamethasone have the capacity to inhibit the gene transcription of many pro-inflammatory cytokines, chemokines, and adhesion molecules, giving them anti-inflammatory potential.[18,19] As a broad-spectrum immunosuppressant, dexamethasone can also lower the protective role of T cells, inhibit the synthesis of antibodies by B cells, and stop macrophages from clearing dead cells. This lead to an elevation in the plasma viral load and a heightened likelihood of secondary infections.[18] Corticosteroid therapy's beneficial effects in viral respiratory infections vary depending on the patient type, dosage, and timing of treatment. Corticosteroid dosages too high could have the opposite effect. Because of this, the benefits of dexamethasone therapy are restricted to the very sick and cannot be disseminated. Individuals with COVID-19 who have reached to a point where they require respiratory support.[20,21]

Anakinra:

Anakinra, a recombinant IL-1 receptor antagonist, suppresses the proinflammatory effects of IL-1 by blocking the binding of both IL-1α and IL-1β to IL-1R. It has been successfully utilized to treat auto-inflammatory illnesses such as Rheumatoid arthritis and cytokine storms.[22] A Retrospective cohort research including patients with COVID-19 and ARDS demonstrated the safe use of high-dose anakinra and its ability to enhance respiratory function.[23] Anakinra was shown to decrease mortality and the need for mechanical ventilation in another cohort study of individuals with severe COVID-19 pneumonia without causing significant side effects.[24]

Tocilizumab:

Tocilizumab, an IL.6 receptor antagonist, can prevent cytokine storms by impeding the IL-6 signal transduction pathway.[25] The FDA has cleared it for use in the treatment of CRS following CAR T-cell therapy. High levels of IL-6 and d-dimer were shown to reflect systemic inflammation and thrombotic state, and they were also found to predict COVID-19 in-hospital mortality in a prospective cohort analysis.[26] Other studies with pneumonia and COVID-19 revealed that tocilizumab markedly lowered the probability of death or mechanical ventilation.[27,28] However, serious infections, thrombocytopenia, neutropenia, and liver damage are among potential risks resulting from Tocilizumab.[29]

DISCUSSION:

Cytokine storm in COVID-19 may be caused by a dysregulated acquired immune system and hyper-inflammatory innate immune responses. Here, we addressed putative processes underlying the COVID-19-induced CRS before providing an overview of potential treatment strategies. In fact, the CRS is highly associated with catastrophic outcomes such as multiple organ malfunction resulting in physiological decline and mortality among critically sick COVID-19 patients. Treatment success and patient mortality rates for COVID-19 are largely dependent on timely management of the cytokine storm in its early stages using tools like immunomodulators and cytokine antagonists, as well as a reduction in lung inflammatory cell infiltration. However certain drugs, such as corticosteroids, have the potential to cause serious adverse effects, like elevated blood pressure and gastrointestinal ulcers.

The creation and widespread distribution of vaccines that successfully fend off SARS-CoV-2 infection offer hope that the epidemic may eventually be under control. But at the moment, a large portion of the population, particularly in developing nations, lacks access to vaccines; this, along with the rapid rate of mutation (and the subsequent emergence of viral variations), makes vaccines less effective. Moreover, underlying health issues that COVID-19 patients may have include diabetes, cancer, heart disease, and autoimmune disorders could make the treatment less successful.

CONCLUSION:

In conclusion, the inflammatory network is so intricate, focusing on a single inflammatory signaling pathway may trigger compensatory immune responses later on. Thus, it is important to weigh the benefits and risks of anti-inflammatory medications. The analyzed research indicate that glucocorticoids can significantly reduce mortality in cases of severe COVID-19. Anakinra and Tocilizumab have demonstrated comparable outcomes, particularly in terms of reducing the requirement for mechanical breathing and increasing patient survival rates. In light of the data presented here and the authors' perspective, antibodies that target inflammatory cytokines remain a desired therapeutic target; hence, inflammatory inhibitors and other COVID-19 strategies may be more effective when used in conjunction with one another than when used in isolation. To clarify the significance of anti-inflammatory therapies in reducing hyperinflammation, more research is required.

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