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Review Article

A REVIEW: TOCILIZUMAB, A RAY OF HOPE IN COVID-19 PNEUMONIA

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ABSTRACT

With the increased number of cases of coronavirus disease 2019 (COVID-19) all over the world which was discovered in December 2019 in Wuhan city of China, there are more positive rates and deaths encountered during the second wave due to this dreadful infection mainly focusing on youngsters diagnosed with COVID-pneumonia. Amidst this devastating situation, there is ray of hope by the emerging clinical trials on Tocilizumab, a potent interleukin-6 (Il-6) inhibitor which likely reduces the mortality of those patients having severe COVID-19 pneumonia as a result of Cytokine Release Syndrome. This syndrome is triggered by burst of inflammatory markers secondary to COVID-19 which is characterized by decrease in T-cells and Natural Killer cells, an increase in IL-6, fever, organ and tissue dysfunction, and an abnormal coagulation function eventually leading to death.

Keywords: COVID-19, Cytokine release syndrome, Coronavirus disease 2019 pneumonia, Tocilizumab.

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INTRODUCTION

In December 2019, a new strain of coronavirus, severe acute respiratory syndrome–coronavirus 2 (SARS-CoV-2), was perceived to arise in Wuhan, China. Along with SARS-CoV and Middle-East respiratory syndrome–coronavirus, SARS-CoV-2 is the third coronavirus to cause extreme respiratory illness in humans, called coronavirus disease 2019 (COVID-19). This was declared as a pandemic by the World Health Organization in March 2020 and has had considerable economic and health impacts all over the world [1].

With its mutating strains, COVID-19 has caused more anguish in the second wave than the first. This time, many young people, including children, are also being infected, data from several resources have shown. However, there is expansion in death rates not only in geriatric, comorbid patients yet additionally in healthy youths due to multi-organ failure as a result of cytokine release syndrome (CRS) in COVID-19 pneumonia.

WHAT IS CRS?

CRS is a form of systemic inflammatory response syndrome which is triggered by different mechanisms related to certain drugs and infections. It was previously stated as influenza like syndrome which occurred after systemic infection such as sepsis and immunotherapies such as Coley's toxins [2]. It occurs when large numbers of white blood cells are activated and release inflammatory cytokines, which induce more white blood cells production. CRS is also an adverse effect of some monoclonal antibody medications and also adoptive T-cell therapies. This can produce some detrimental effects on various body functions [3].

CAUSES OF CRS

CRS occurs when excess amounts of white blood cells, including B-cells, T-cells, natural killer cells, macrophages, dendritic cells, and monocytes are activated and release inflammatory cytokines, which further activate more white blood cells in a positive feedback loop of pathogenic conditions [3]. This can occur when the immune system is battling pathogens, as cytokines produced by immune cells increases more effector immune cells such as T-cells and inflammatory monocytes (which differentiate into macrophages) to the site of inflammation or infection. Likewise, activation and stimulation of further cytokine production are the result of pro-inflammatory cytokines binding their associated receptor on immune cells. This process, when dysregulated, can be dangerous due to systemic hyperinflammation, hypotensive shock, and multi-organ failure [4].

Severe CRS or cytokine reactions not only occurs in adoptive T-cell therapies but also in a number of infectious and non-infectious diseases including graft-versus-host disease, COVID-19, acute respiratory distress syndrome (ARDS), sepsis, Ebola, avian influenza, smallpox, and systemic inflammatory response syndrome [5].

Although SARS-CoV-2 is adequately cleared by the early acute phase against viral response in most individuals, some advancement to a hyperinflammatory condition can be life-threatening due to pulmonary involvement. Thus, systemic hyperinflammation leads to inflammatory lymphocytic and monocytic infiltration of the lung and the heart, causing ARDS and cardiac failure [6].

Patients with severe COVID-19 and ARDS have traditional serum biomarkers of CRS including elevated C-reactive protein (CRP), lactate dehydrogenase, interleukin (IL)-6, and ferritin [7].

SYMPTOMS OF CRS

Clinical manifestations include fever, fatigue, loss of appetite, muscle and joint pain, nausea, vomiting, diarrhea, rashes, fast breathing, rapid heartbeat, low blood pressure, seizures, headache, confusion, delirium, hallucinations, tremor, and loss of coordination. Laboratory tests and clinical monitoring show low blood oxygen, widened pulse pressure, increased cardiac output (early), potentially diminished cardiac output in later stage, high levels of nitrogen substances in the blood, elevated D-dimer and transaminases, factor I deficiency and excessive bleeding, and elevated level of bilirubin [3].

PATHOPHYSIOLOGY OF CRS

CRS and sepsis share several symptoms in common, and patients with CRS are at increased risk of infections, not only for the immunosuppressive treatments but likely also for the CRS-related immune dysregulation and tissue damages, specifically at mucosal barrier. However, infections principally involve the respiratory tract in patients having CRS.

The exacerbated reaction as a result of infections or biological therapy is brought about by the quick recruitment of macrophages and

neutrophils, which produce pro-inflammatory cytokines and adjust the delicate balance between a controlled immune response and a host-damaging reaction. Damaged tissues release molecules that are normally absent outside the cells, including high-mobility group box 1, ATP, uric acid, and DNA, further intensifying the inflammatory responses. All these molecules are part of the presumed damage-associated molecular patterns (DAMPs). It is significant that pathogen-associated molecular patterns and DAMPs are perceived by the same group of innate immunity receptors, such as pathogen recognition receptors (PRRs), which include toll-like receptors (TLRs), sufficiently expressed in neutrophils and macrophages. Association of TLRs and other PRRs results in further activation of NF-κB (nuclear factor kappa-light-chain-enhancer of activated B-cells) and the release of cytokines (IL-6, TNFα, IL-1, etc.) and other inflammatory mediators [8].

Ferritin can be also regarded as a pro-inflammatory signaling molecule, and hyperferritinemia has been noticed in different CRS-related conditions such as macrophage activation syndrome and septic shock [9]. It could exert a pathogenic role in these diseases instead of being only the consequence of hyperinflammation. In fact, ferritin synthesis is intervened, not only by iron availability but also by IL-1, IL-6, and TNF, which are highly expressed during CRS. However, on the other hand, it can initiate the expression of pro-inflammatory cytokines, thus turning out to be essential for a horrendous loop [10].

When COVID-19 progresses from severe to terminally ill, patients may develop extreme cytokine storm, secondary ARDS, followed by shock, tissue perfusion disorders, and even multi-organ collapse [11]. In SARS-CoV-2 patients with a poor prognosis, IL-6, IL-10, and TNF-α rapidly rise and reach high levels. Contrarily, in patients with milder symptoms, these cytokines reach lower levels, with their impression increasing and declining during the illness and recovery phase, respectively [12].

These recent findings play a key role of the host immune response, especially of CRS, as a recognizing cofactor in the extreme life-threatening forms of COVID-19. Why few patients develop a successful immune response, which is safe and not pathogenic, and why few others have a non-protective life-threatening immune response is a major inquiry. It is likely that genetic history, which is additionally involved in inflammatory responses, immune-mediated diseases (including autoimmunity), and comorbidities, may not only debilitate the host, but also may share traditional pathways in inflammatory damaging reactions.

TREATMENT OF CRS RELATED COVID-19 PNEUMONIA

Cytokine storm is considered as a crucial factor in the rapid progression of COVID-19. Hence, the treatment of cytokine storm adds as rescue to those patients who are hit by severity. At present, there is no particular drug for SARS-CoV-2 and cytokine storm induced by COVID-19. The IL-6 receptor antagonist Tocilizumab (TCZ) which is approved by the US FDA is used in the treatment of CRS. Since IL-6 is one of the key cytokines engaged in infection-induced cytokine storm, the treatment of cytokine storm actuated by COVID-19 with TCZ has expansive possibilities [13]. However, the clinical experience and data related to TCZ in the treatment of COVID-19 are restricted. IL-6 is assumed to play a critical part in the pathogenesis of CRS, although its contribution has not yet been fully explained.

TCZ, a biological drug that binds to the IL-6 receptor and prevents IL-6 from signaling, is utilized effectively in the management of autoimmune diseases. It has also been endorsed for the treatment of severe or life-threatening CRS related with chimeric antigen receptor T-cell immunotherapy in patients with malignancy, rheumatoid arthritis, giant cell arteritis, systemic juvenile idiopathic arthritis, and also polyarticular juvenile idiopathic arthritis [14].

TCZ is a key cytokine resulting in an inflammatory storm which may result in increased alveolar-capillary blood-gas exchange dysfunction, especially impaired oxygen diffusion, and in due course lead to pulmonary fibrosis and organ failure. In light of certain reports, TCZ can be appropriate and viable drug for COVID-19 patients [15].

"Diagnosis and Treatment Plan of Novel Coronavirus Pneumonia (seventh trial edition)" in China suggests TCZ as an immunotherapy drug for critically ill patients [16]. In a single-center study from Wuhan, China, which included 15 patients with COVID-19 pneumonia at risk for cytokine storm, the treatment with TCZ showed to have a clinical benefit, although doses ranged from 80 mg to 600 mg [17].

In addition, a retrospective study consisting of small sample size concluded that the treatment with this drug has proven to reduce the intensive care unit (ICU) admissions and/or mortality in patients with severe SARS-CoV-2 pneumonia [18]. Moreover, risk of in-hospital mortality was lowered in patients treated with TCZ in the first 2 days of ICU admission compared with patients whose treatment did not include early use of TCZ [19].

The Randomized, Embedded, and Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia study published in 2021 was, until now, the largest trial (n=803) to examine TCZ in COVID-19, and showed a survival benefit [20]. Moreover, TCZ group was also more likely to be discharged from the hospital within 28 days than patients in the usual care group according to the Randomized Evaluation of COVID-19 Therapy (RECOVERY) Collaborative Group [21].

A prospective, multicenter randomized controlled clinical study by the university of science and technology of China included 188 patients with common type (including critical risk factors) and severe COVID-19, in which TCZ combined with traditional therapy not only showed reduced body temperature but also obvious improvement of pulmonary lesions. Therefore, for patients with severe COVID-19 caused by cytokine storm, TCZ is a notable drug in clinical research [22]. A research group from the University of Science and Technology of China conducted a small clinical trial after uncovering the mechanism of cytokine storm in patients with severe or critical COVID-19, was treated with TCZ along with their traditional therapy and found out that their fever and all other symptoms improved noticeably within few days, decreased their oxygen intake, and lung lesion opacities were clear, percentage of lymphocytes in peripheral blood returned to normal on 5th day of the intervention, elevated CRP had significantly decreased [23].

A pilot, prospective, open, and single-arm multicenter study where D-dimer was considered as mortality predictor involved 63 severe COVID adult patients and showed remarkable improvement in CRP, D-dimer, ferritin levels, and respiratory parameters after receiving TCZ for 6 days [24]. Similarly, a prospective study consisting of 100 patients diagnosed with COVID-19 pneumonia and ARDS requiring ventilation showed rapid, sustained, and significant clinical improvement with TCZ at a dose of 8 mg/kg by two consecutive intravenous infusions 12 h apart [25].

TCZ when administered, irrespective of the routes can reduce the risk of invasive mechanical ventilation or morbidity in patients with severe COVID-19 which was proven by a retrospective observational cohort study which included severe COVID-19 pneumonia who were treated with this drug given either intravenously at 8 mg/kg bodyweight (up to a maximum of 800 mg) in two infusions, 12 h apart, or subcutaneously at 162 mg administered in two simultaneous doses, one in each thigh [26]. A randomized, double-blind, and placebo-controlled trial showed less significant infection than placebo in COVID-19 patients who were hospitalized, although did not show efficacy of IL-6 receptor blockade [27].

Although subsequent randomized clinical trials determining TCZ efficacy in COVID-19 reported conflicting results, these trials varied considerably in size, study design, and illness severity of the patients enrolled. For example, few initial trials [27,28] failed to conclude mortality benefit for TCZ; however, these trials selected <300 patients

each and were consequently underpowered to identify differences in mortality between study groups. Additional limitations of early trials were exclusion of critically ill patients [27,28] and imbalances in the utilization of steroids between TCZ-treated and TCZ-untreated patients [29].

CONCLUSION

TCZ may have a positive impact on improving CRS-associated immune damaging, lung functional injuries, and arterial oxygen saturation. It may bring about promising result and may prove to be an effective treatment to improve inflammation in the lungs in those patients with COVID-19 pneumonia. However, further clinical trial studies are needed to demonstrate its efficacy in patients with specific characteristics such as age, concentration of IL-6, and various clinical manifestations.

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CONFLICTS OF INTEREST

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