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Cytokine Storm In COVID-19: New Implications

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Abstract

SARS-CoV-2, the virus responsible for COVID-19, poses a significant global health threat. As of May 25th, 2020, it has claimed over 347,000 lives worldwide. Research indicates that severe COVID-19 cases exhibit elevated pro-inflammatory cytokine levels, particularly interleukin-6 (IL-6), compared to milder cases. This cytokine surge correlates with poor patient prognosis. Moreover, postmortem lung tissue analysis reveals significant infiltration of pro-inflammatory cells (T-helper 17 cells and macrophages) in those who succumbed to the virus. Collectively, this evidence strongly implicates the cytokine storm in COVID-19 mortality. This review provides a concise analysis of the pathologic and clinical manifestations of the COVID-19 cytokine storm. SARS-CoV-2 infection appears to trigger a distinct elevation in IL-6 and induces lymphocyte fatigue. The IL-6 inhibitor tocilizumab demonstrates initial promise in mitigating this response, with evidence suggesting relative safety and efficacy.

Keywords: *Immuno-regulation, cytokine-storm, and COVID-19.*

Introduction

Wuhan, China, saw an outbreak of a new coronavirus disease in December 2019. The World Health Organization (WHO) off[1]icially identified the sickness as coronavirus disease 2019 (COVID-19) on February 11, 2020, and the causative agent as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 had spread to over 212 nations by May 25, 2020 , with 5,529,195 confirmed cases and 347,192 deaths worldwide as a result. [1].

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The potential cytokine storm's function in COVID-19 mortality is under intense scrutiny, but defining and diagnosing it accurately poses challenges [2]. The absence of specific criteria in the International Classification of Diseases (ICD) further hinders progress. Scholars like Cron and Behrens (2020) describe cytokine storm as an uncontrolled cascade of cytokine production triggered by various stimuli, including infections and autoimmune disorders. This response causes increased immune cell activation and the release of pro-inflammatory cytokines. [3]. However, differentiating this phenomenon from related terms like "cytokine release syndrome" (CRS) requires further investigation. While CRS shares some characteristics with cytokine storm, its characterization by distinct feature: multi-organ dysfunction (MOD) [3]. Furthermore, the diagnostic criteria for cytokine storm syndrome (CSS) outlined in specific literature (e.g., may not be directly applicable to COVID-19 [4]. These criteria primarily focus on hemophagocytic lymphohistiocytosis (HLH) and secondary HLH, which are conditions linked to specific genetic and autoimmune disorders, unlike the contagious nature of COVID-19 [5].

An increasing amount of research suggests a close connection between severe COVID-19 and higher concentrations of pro-inflammatory cytokines , particularly interleukin (IL) , compared to individuals with moderate illness [6]. Analysis of bronchoalveolar lavage fluid (BALF) cells using transcriptome sequencing in COVID-19 patients reveals excessive release of chemokines , such as CXCL10 and CCL2, triggered by SARS-CoV-2 infection [7]. Additionally, high cytokine levels are associated with poorer patient outcomes [8]. When COVID-19-related deaths were investigated postmortem, the lungs of the people who died showed signs of T-cell overactivation and ARDS [8]. An elevations in T-helper (Th) cells and increased CD8+ T cell cytotoxicity are the characteristics of this phenomena [9]. It is thought that SARS-CoV-2 infection triggers and activate both adaptive and/or innate immune responses which results in uncontrollably high inflammation responses that ultimately culminate in the cytokine storm [10]. This event has the potential to cause endothelial and epithelial cells to undergo apoptosis, which could result in vascular leakage and ultimately cause ARDS, and other syndromes(might be severe), or even death [11].

To address the high death ratio associated with cytokine storm , this review examines its pathological and clinical features in COVID-19. We analyze the potential and safety of various treatments and their underlying mechanisms while acknowledging the limited evidence supporting the direct benefit of regulating cytokine expression on COVID-19 mortality.

Insights into Coronavirus Infections, What Can We Learn?

Many studies highlighted the similarities and differences between the clinical features and pathogenesis of MERS, SARS, and COVID-19. All three share initial influenza-like symptoms: a high fever, throat irritation, painful cough, muscle pain, and dyspnea. Progression to pneumonia is typical in all three diseases [12-14]. Analysis of fatal SARS cases reveals levels elevations of IL-6, IL-1β, IFN, and CXCL10, indicating the crucial role of innate immunity, primarily driven by dendritic cells and macrophages. Histopathological studies demonstrate diffuse alveolar damage, focal bleeding, and effusions of the pleura, pulmonary consolidation, and edema in SARS patients – features that closely resemble those seen in COVID-19 . Both SARS and COVID-19 show a lower numbers of CD8+ and CD4+ T cells in blood, with this depletion associated with mortality in SARS cases [15]. Interestingly, a distinctive characteristic of pathology of COVID-19 is the higher concentrations of the pro-inflammatory CCR4+ CCR6+ Th17 cells, suggesting potential differences in underlying disease mechanisms [15].

This review analyzes the comparative immune-pathogenesis of MERS-CoV and SARS-CoV. MERS-CoV infects human epithelial cells, inducing a delayed but pronounced response involving interferon (IFN), chemokines (e.g., IL-8), and pro-inflammatory cytokines (e.g., IL-1β, IL-6) [15, 16]. In contrast, SARS-CoV targets the epithelial airway cells, leading to a deleytion of the release of specific chemokines like CCL2, CCL3, CCL5, and CXCL10 [17]. Notably, MERS-CoV uniquely infects monocytes, macrophages, and DCs, unlike SARS-CoV [18]. This infection triggers delayed but elevated levels of the pro-inflammatory chemokines and cytokines in these cells, while SARS-CoV, although unable to replicate in these cell types, still stimulates increased cytokine and chemokine production [19]. Interestingly, both viruses utilize angiotensin-converting enzyme-2 (ACE2), to enter cells, suggesting potential overlap in their target cell populations. This notion is further supported by studies using murine models. In BALB/c mice infected with SARS-CoV, an increase in pathogenic inflammatory monocyte-macrophages (IMMs) is observed [7]. These IMMs, stimulated by IFN-α/β receptors, release chemokines (CCL2, CCL7, CCL12) and pro-inflammatory cytokines (TNF, IL-6, IL-1β), further amplifying their own accumulation [20]. Therefore, one possible tactic to prevent lethal SARS-CoV" infection could be to target the IFN pathway, IMMs, or cytokine, including (Neutrophils, monocytes, and T lymphocytes) which are drawn into the lungs by the chemokines that active monocytes and macrophages to release [19]. Activation of the effector T cells enter to the lungs and destroy the pneumocytes that are infected with viruses [21]. However, this immune response can also cause collateral damage [22].

New approaches cytokine storm in COVID-19

IL-6 Inhibition

Tocilizumab (TCZ), a humanize antibody targeting the IL-6 receptor, is being explored for severe COVID-19 treatment. It hinders IL-6 binding, potentially mitigating immunosuppression. Case reports document successful application of TCZ in critically ill patients, resulting in improved clinical status and reduced CRP levels [23]. However, limitations were identified, with three critically ill patients succumbing despite receiving TCZ and methylprednisolone, suggesting a potential need for repeated dosing [24]. In contrast, another study reported successful symptom control and recovery in all patients, with minimal adverse events [25]. A prospective study further supports TCZ's potential, demonstrating improved respiratory parameters and increased survival rates [26]. However, a case report highlights the need for caution: two patients with CRS treated with TCZ developed severe HLH, raising concerns about potential unforeseen adverse effects [26]. Initial evidence suggests TCZ holds potential, but further research is crucial to optimize its use, identify suitable patient groups, and minimize potential risks [27].

PD-1 Checkpoint-Inhibitor

Lymphocyte exhaustion characterizes COVID-19. PD-1 checkpoint inhibitors, which can reverse lymphocyte anergy, could offer a novel therapeutic approach. While no studies have examined their use in COVID-19 as of May 4th, 2020, these therapies have proven beneficial in cancer and sepsis treatment [28] . The PD-1/PD-L signaling pathway is crucial for peripheral tolerance but also plays a role in inflammatory conditions like sepsis [28]. However, checkpoint inhibitors have shown a survival benefit in sepsis without causing a cytokine storm [29]. The hyper activation of CD4+ and CD8+ T cells and their high cytotoxic granule levels in COVID-19 are similar to fatal H7N9 disease [30]. This exhaustion phenotype in both diseases suggests a potential for therapeutic reversal with checkpoint inhibitors.

Corticosteroids

Glucocorticoids, with their anti-inflammatory and immunosuppressive properties, are considered potential treatment for severely sick patients with COVID-19. They suppress pro-inflammatory cytokines and diminish T cell and macrophage activity [25]. However, their use in COVID-19 is debated. Concerns surround increased mortality and delayed viral clearance based on data from SARS and MERS, with studies suggesting potential harm in non-severe cases [31]. While one study observed benefits of corticosteroids in SARS-CoV severe infections, another indicated potential benefits for critical COVID-19 patients without impacting mortality [32]. Additionally, the limited cytokine storm in COVID-19 and the potential for corticosteroids to worsen lymphocytopenia raise concerns about their widespread use [33]. Therefore, administering corticosteroids in COVID-19 demands cautious consideration of dose, duration, and timing to navigate the potential benefits and drawbacks.

Intravenous Immunoglobulin (IVIG)

IVIG offers potential benefits in severe infections due to its immunomodulatory, anti-inflammatory, and passive immunity-inducing properties. IgG molecules bind to specific target antigens, triggering both humoral and cellular immune responses [34]. Clinical evidence is mixed. One case report details recovery with IVIG and prednisolone in severe glandular fever, demonstrated by decreased Th1 cytokine levels and viral load [35]. Similarly, a study found reduced cytokine levels, viral load, and mortality with IVIG in severe H1N1 influenza A [35]. A wider analysis suggests potential mortality benefits for specific Ig molecules in severe sepsis or septic shock, while another analysis showed no such benefit for polyclonal IVIG in adult mortality based on high-quality trials [35]. Therefore, although IVIG holds promise, further research is crucial to define its optimal use and identify patient subgroups who may benefit most, acknowledging its limitations.

Cytokine-Adsorption Device

Cytokine adsorption therapies aim to remove harmful substances from the bloodstream using methods like ECMO or dialysis. Devices like Cytosorb® specifically capture inflammatory mediators. Both case reports and ongoing trials show potential promise [36]. A study observed decreased IL-6 and IL-8, improved hemodynamics, and respiratory function in a severe ARDS case using combined venous arterial-ECMO and hemoadsorption [37]. Dialysis, which can remove water-soluble mediators and potentially utilize adsorptive filters, offers another approach [38]. While initial evidence is encouraging, further research is crucial to establish the long-term safety and efficacy of cytokine adsorption in managing cytokine storms.

Hydroxychloroquine (HCQ)

Despite limited evidence, the US approved hydroxychloroquine (HCQ) for emergency use in COVID-19 on March 28th, 2020 [8]. A review of studies conducted before this date not found any clinical benefit of using HCQ in patients with COVID-19 [39]. However, a later study involving critically ill patients reported a depletion in the mortality rate (15%) in the low-dose HCQ group compared to the expected 50% mortality rate [40]. While this suggests a potential benefit for low-dose HCQ in critically ill patients, the same study raises concerns about the safety of high-dose HCQ in this population. Therefore, many future trils is essential to determine the effectiveness and safety of HCQ for COVID-19 treatment, considering both dosage and patient selection.

New Implications

This paper highlights the crucial role of the cytokine storm in COVID-19 mortality, while acknowledging the limitations in current treatment options. While various approaches are being

explored, further research is necessary to establish optimal treatment strategies. In addition, it is emphasizes the potential of TCZ, a drug targeting the IL-6 receptor, in managing the cytokine storm. However, it stresses the need for further studies to optimize its use, identify suitable patients, and minimize potential risks.

The review also explores the potential of PD-1 checkpoint inhibitors, which can reverse lymphocyte energy, as a novel therapeutic approach. While no studies were conducted at the time of writing, the paper suggests investigating this avenue due to the success of these therapies in treating cancer and sepsis. Furthermore, the review acknowledges the anti-inflammatory properties of corticosteroids but emphasizes the need for cautious consideration due to potential drawbacks like increased mortality and delayed viral clearance. It highlights the importance of carefully evaluating dose, duration, and timing of administration. Similarly, the review acknowledges the potential benefits of Intravenous Immunoglobulin (IVIG) but emphasize the need for further research" to define its optimal use and identify specific patient subgroups who may benefit most.

Furthermore, the review highlights the promising initial evidence from case reports and ongoing trials regarding the use of cytokine adsorption devices like Cytosorb® in managing cytokine storm. However, it stresses the need for further research to establish their long-term safety and efficacy. Finally, the paper concludes that the approve supporting the efficacy of HCQ in treating COVID-19 is limited, despite its initial approval for emergency use **(Table 1)**.

Conclusion

In conclusion, while the cytokine storm plays a significant role in COVID-19 mortality, there is a critical need for further research to develop safe and effective treatment strategies for managing this complication. The paper explores various potential approaches, highlighting both promising avenues and the need for further investigation to ensure optimal patient care.

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List of Tables

Table 1: New approaches regarding treatment of COVID-19

Treatment	Description	Evidence
Tocilizumab (TCZ)	Targets the IL-6 receptor, potentially mitigating immunosuppression.	Initial evidence suggests potential, but further research is crucial to optimize its use, identify suitable patient groups, and minimize potential risks.
PD-1 Checkpoint-Inhibitor	Reverses lymphocyte anergy, offering a novel therapeutic approach.	No studies conducted yet, but promising due to success in treating cancer and sepsis.
Corticosteroids	Anti-inflammatory and immunosuppressive properties.	Debated due to concerns about increased mortality and delayed viral clearance. Requires cautious consideration of dose, duration, and timing.
Intravenous Immunoglobulin (IVIG)	Immunomodulatory, anti-inflammatory, and passive immunity-inducing properties.	Mixed clinical evidence. Further research needed to define optimal use and identify suitable patients.
Cytokine-Adsorption Device	Removes harmful substances from the bloodstream using methods like ECMO or dialysis.	Encouraging initial evidence from case reports and ongoing trials. Further research needed to establish long-term safety and efficacy.