Cytokine storm in covid-19

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Abstract

Cytokines are a collection of proteins, peptides, or glycoproteins synthesized by immunity system cells. They are often act as signaling molecules and have a function of immunity, inflammation, and haematopoiesis initiation and regulation. In general, the cytokines are subdivided into two subgroups pro-inflammatory and anti-inflammatory cytokine.

The Pathogenicity of The novel coronavirus illness 2019 (COVID-19), which has now expanded worldwide and became a public health crises, is mainly linked to the cytokine storm according to the latest researches and clinical studies.

In the present article, the major lines of the cytokines and the effects of its storm in the covid-19 sickness and lethality will be discussed in addition to the main strategies that may involve in the storm management and control because as the pandemic spreads, discovering a specific therapy for COVID-19 becomes more important in order to improve patient outcomes and saving the lives.

الخلاصه

السيتوكينات عبارة عن مجموعة من البروتينات أو الببتيدات أو البروتينات السكرية التي يتم تصنيعها بواسطة خلايا جهاز المناعة. غالبًا ما تعمل كجزيئات إشارات ولها وظيفة المناعة والالتهاب وبدء تكوين الدم وتنظيمه. بشكل عام ، تنقسم السيتوكينات إلى مجموعتين فرعيتين للسيتوكين المؤيد للالتهابات والمضاد للالتهابات.

ترتبط إمراضية مرض فيروس كورونا الجديد 2019، الذي انتشر الآن في جميع أنحاء العالم واصبح ازمة صحية بشكل أساسي بعاصفة السيتوكين وفقًا لأحدث الأبحاث والدراسات السريرية.

في هذا المقال ، ستتم مناقشة الخطوط الرئيسية للسيتوكينات وتأثيرات العاصفة في مرض كوفيد -19 وفتكه بالإضافة أكثر أهمية من أجل COVID-19 إلى الاستراتيجيات الرئيسية التي قد تنطوي على إدارة العاصفة ومكافحتها من تحسين نتائج المرضى وإنقاذ الأرواح

1- Introduction

A- Cytokine

Cytokines are a series of signaling molecules mainly have a structure of protein, peptide, or glycoprotein and produced in general by the immune cells .the key function of the cytokines is the immunity responce, inflammation reaction, and haematopoiesis process initiation and regulation [1]. The individual cytokine specifying name is based on the precise molecule function, site of synthesis or its site and target of action, For example, the lymphokines are cytokines created and secreted throughout the body by the lymphocytes [2]. In addition, the name (interleukins (ILs) is derived from the function of these specific cytokines in the leukocytes cellular responses regulation and they are also secreted by these cells. [3] [4]. Even apicomolar amounts of the cytokines can facilitate a biological response because the cytokines have a strong affinity for their receptors. [5] The cytokine superfamily includes interleukins, chemokines (have a chemotactic properties), colony-stimulating factors (CSF), interferons, the transforming growth factor (TGF) and tumor necrosis factor (TNF) families, the cytokines major groups having structural similarities but diverse cytokine activities and produced by different cells of the body. In their reciprocal receptor systems, cytokine families sharing sequence similarity, and show homology, and some versatility, although they don't share similar functionality. [6] Cytokines are synthesized in the Golgi apparatus and released as soluble structures by the endoplasmic reticulum. [7], other cytokines might be converted into cytosolic forms that can migrate intracellularly, or they may remain membrane bound, or return to the nucleus to serve as transcriptional regulators [8].

The factors that enhance cytokine expression in vivo include: Cell-cell contact, local complement activation, microbial species and their soluble products, immune complexes / autoantibodies trauma, ischemia, sheer stress, radiation, ultraviolet light, reactive oxygen and nitrogen intermediates, extracellular matrix components, and DNA (mammalian or microbial), heat shock proteins, and cytokines themselves in autocrine loops [9, 10]. Autocrine activity occurs when a cytokine binds to a receptor on the membrane of the same cell that produced it. Paracrine activity occurs when cytokines bind a target cell receptor near the producer cell Endocrine activity occurs when cytokines travel via the bloodstream and act on target cells in distant parts of the body [11] and as explained in table (1).

Table (1): Cytokine biological function (7).

Cytokine	Biological function
Pro-inflammatory cytokines	
IL-1β, IL-1α, IL-6, TNFα, IL-12, IL-18, IFNγ	Activation of B- and T-lymphocytes, leukocytes, epithelial and endothelial cells. Strengthening of inflammatory reactions.
Anti-inflammatory cytokines	
IL-4, IL-10, IL-19, IL-20, IL-22, IL-24, IL-26, TGFβ	Inhibition of the production of pro-inflammatory cytokines. Anti-proliferative.
Interferons	
IFNα, IFNβ, IFNγ	Antiviral compounds. Immunomodulation and inhibition of cell growth.
Th1-cytokines	
IL-2, IL-12, IL-15, IL-18, IL-21, IL-23, IFNα, IFNγ	Strengthening cell-mediated immunity. Th1-cell differentiation. Activation of natural killer cells and macrophages. Increasing IFNγ.
Th2-cytokines	
IL-4, IL-5, IL-10, IL-13	Strengthening antibody-mediated responses. Differentiation and growth of B- and Th2-cells. Stimulation of eosinophils. Inhibition of Th1-cells.
Chemokines	
see section 2.3.4.2	Induction of chemotaxis of different cells.
Growth factors	
Erythropoietin, M-CSF, G-CSF, GM-CSF	Maturation of erythroid cells. Differentiation and proliferation of neutrophils and monocytes. Activation of mature monocytes and macrophages.

Pro-inflammatory cytokines are a mutual term for immune_regulatory cytokines responsible for inducing and progressing the inflammation reaction. The equilibrium of pro-inflammatory and anti-inflammatory cytokines determines the overall outcome of an inflammatory response. [12] The source of the proinflammatory cytokines is the active macrophagocytes and mainly have the functions of inflammatory reactions up-regulation. Interleukin-1 (IL-1) and tumor necrosis factor (TNF) are the main members of the Proinflammatory cytokines and frequently play a role in the mediation of fever, tissue damage, and, in some cases, shock and even death during the inflammation process. Endothelial adhesion molecules like IL-1 and TNF are essential for leukocyte attachment to endothelial cell surfaces prior to tissue emigration. Proinflammatory cytokines cause inflammation by activating a cascade of gene products that are rarely generated in healthy people [13].

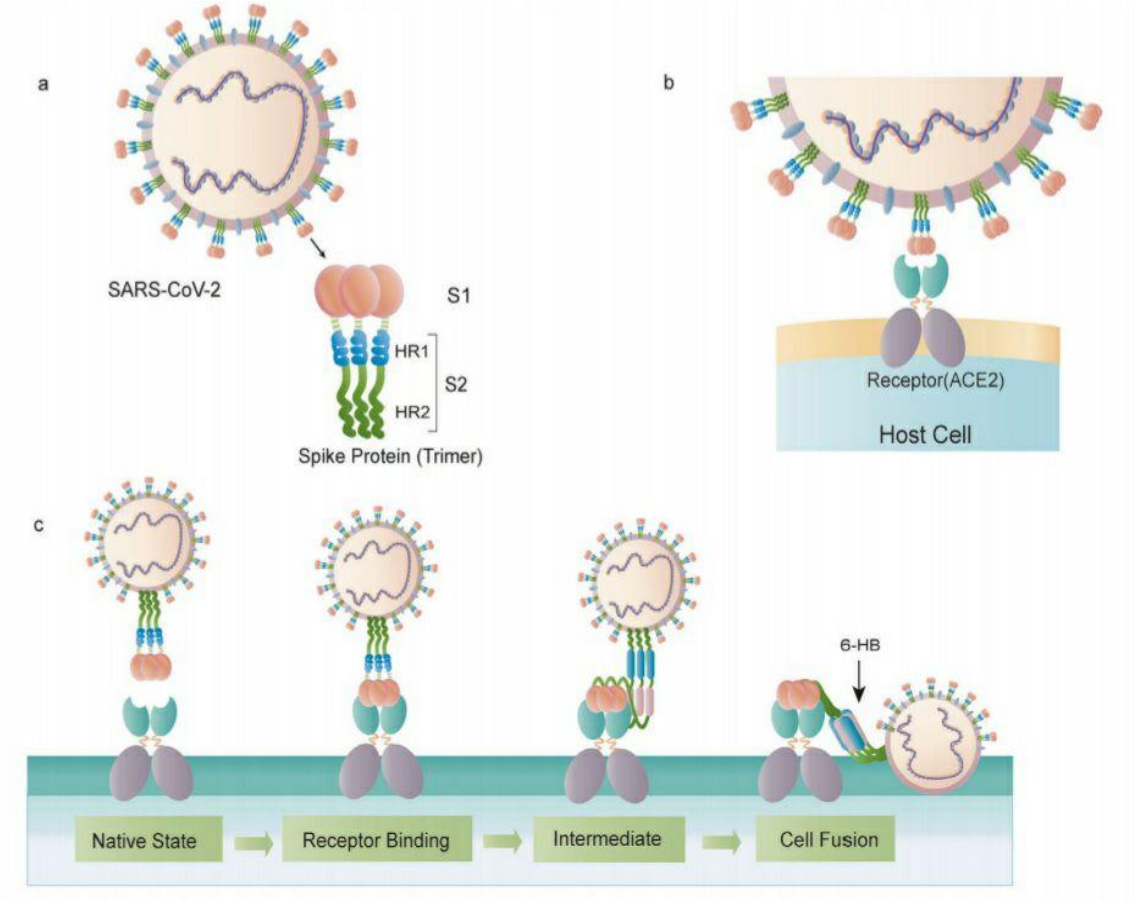
Although endotoxins and other inflammatory products can cause it, the proinflammatory cytokines IL- 1, TNF and occasionally, IFN- are mostly powerful in inducing gene expression. Furthermore, in this mechanism, IL-1 and TNF work together in a synergistic manner. When infections, shock, ischemia, active T cells, or contaminants trigger these two molecules, they target the endothelium and start a cascade of inflammatory mediators. IL1, alpha, IL1, beta, IL6, and TNF-alpha are the primary proinflammatory cytokines responsible for early reactions [14]. IL1, IL6, TNF-alpha act as endogenous pyrogens, activating the macrophages and mesenchymal cells (fibroblasts, epithelial, and endothelial cells) to produce secondary mediators and proinflammatory cytokines genes, increasing the secretion of acute phase proteins, or attracting inflammatory cells [15].

B- COVID-19…

In 31 -December 2019, WHO was informed of several cases of unknown cause pneumonia in China, A novel coronavirus was identified later in 2020 as the cause and the infectious disease was named as COVID-19 [16]. The COVID-19 epidemic was spread largely around the world and became a public health crises [16].

SARS-CoV-2 virus outer surface is rich in the glycosylated S proteins. The S protein has an external N-terminus, a transmembrane (TM) domain anchored in the viral membrane, with a short-t intra-cellular C-terminal area about 180–200 kDa in size .When the virus contacts with the host cell, the S protein undergoes significant structural change in order to merge the virus with the cellular membrane.

The spikes are covered with polysaccharide particles to avoid finding by the host immune cells upon entry. The angiotensin transforming enzyme 2 (ACE2) is known to be the major site of the SARS-CoV-2 binding with the infected cells. the S protein are activated by the host cell membrane TM protease serine 2 (TMPRSS2), upon the activation, the S protein attaches to the receptor, and initiate the process of viral entry to the host cells and mediate the infection process. [19] Immediately after the viral entry to the cells, the viral RNA is release and transformed to poly-proteins structures, later, the protein cleavage and the replicase–transcriptase complex formation aid in the viral genomic RNA replication and transcription. Viral nucleic acid is replicated in the host cell, and structural proteins are synthesized, folded, and packaged in preparation for viral particles creation [20] as shown in (Figure2).



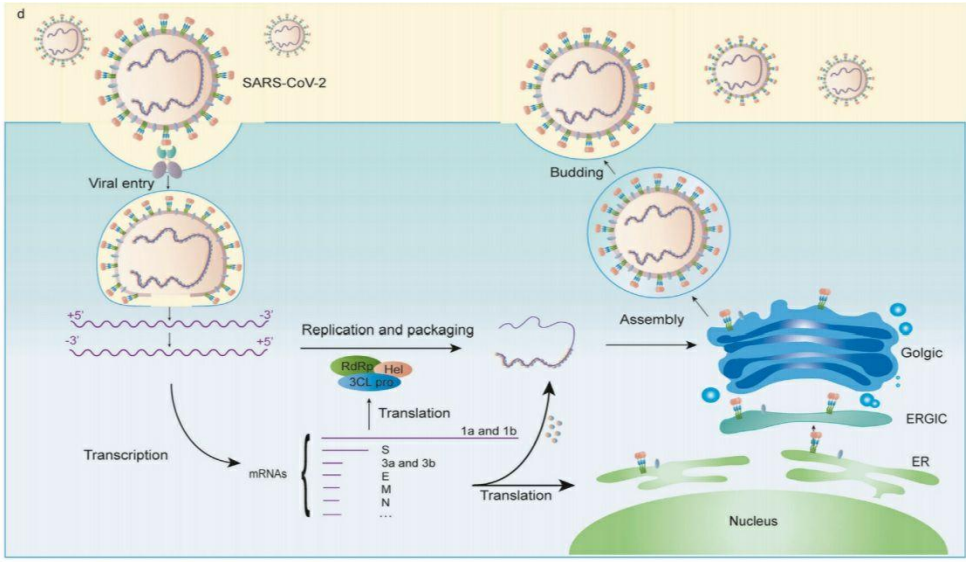


Figure (2) Diagram of COVID-19 S protein. a S protein configuration . b the attachment between the S protein with ACE2 receptor. c The viral entry to the host cell enabled by S protein. d The reproductive process of the covid-19[18].

The SARS-CoV-2 S – protein is evolutionarily conserved across all human coronaviruses because it is crucial in receptor recognition, viral adhesion, and host cell invasion. Additionally its one of the most vital targets for COV -19 vaccines and healing researches [19]. The fundamental unit via which the S protein interacts with the receptor is the trimer of S protein on the surface of the viral envelope [23]. The RBD is situated in the S1 domain and is primarily responsible for virus binding to the receptor, whereas the HR domain, which comprises HR1 and HR2, is found in the S2 domain and is mainly associated with virus fusion. [24].

2. Cytokine storm

A- Definition and Pathogenesis….

The cytokine storm," that may also be known as hypercytokinemia is an abrupt hyper-inflammatory reaction caused by uncontrollable inflammatory response by the immune cells whereas a high rate of inflammatory cytokines production is accrue exceeding that of normal state. The high levels cytokines in return resulted in positive feedback on the immune system to activate and recruited to the site of damage with an overall outcome of organ injury.

A cytokine storm can result in serious illness in a variety of situations, like infection, malignant diseases, and organs damage. Patients with severe COVID-19 infection have a cytokine storm and thought to have a high mortality rate [28].

A number of COVID-19 manifestations in SARS-CoV-2 infected patients seem to be influenced by cytokine storm: like the respiratory distress syndromes, thromboembolism disease like the acute ischemic strokes caused by occlusion of a large vessel and myocardial infarction, encephalitis, acute kidney injury, and vasculitis (Kawasaki-like syndrome in children and renal vasculitis in adult) [25] In severe COVID-19 cases, the high levels of the cytokines within the lung produces alveoli damage, hyalines membranes formation, and thrombi creation. Proteinuria and haematuria are found in 40% of COVID-19 patients, indicating infection and damage to the kidneys. [29].

The kidney pathogenesis in covid-19 is related to that the proximal tubules brush border is rich in the ACE2 receptors cells so infection correlated renal injury happens but yet the impact of the role of the cytokines storm in the kidney injury is indefinite . Both the cardiac muscles and the GIT cells having ACE2 receptors, and that may clarify the cardio toxicity and the GIT symptoms in the COVID-19 patients [30]. Individual with cardiac and vascular illness, high blood pressure, high body weight, diabetes mellitus and dyslipidemia are usually involved with strong COVID-19 cases according to latest data , whereas other data suggest that SARS-CoV-2 infects the heart, resulting in myocardial inflammation and infarction. Cytokine storm and poor outcomes are more common in patients with underlying cardiovascular disease [31].

B- Diagnosis….

Several biochemical abnormalities are a characteristic identifications for covid19 cytokine storm such as the high ranks of IL-2, IL-7, granulocyte colony stimulating factors, , monocyte chemo-attractant proteins 1, macrophages protein 1, tumor necrosis factors and interferons, [32] .

Excessive ferritin (mean 12976 ng/ml in the fetal cases with 6140 ng/ml in mild and moderate cases; p 0.0001) and IL-6 (p 0.0001) are predictive markers of fatality and severe disease, according to a retrospective, multi-center research in Wuhan, China, including 150 confirmed cases of COVID 19 [33].

C- Immuno-senescence and cytokine storm:

The old individuals, particularly men with comorbid conditions, are more susceptible a bleak outcome and have a higher chance of serious illness or death. Immune function also deteriorates with age, a process termed as "immunosenescence" [34].

a decrease in CD3+ T cell development, a The loss of CD8+ T cells led to an increase in regulatory T cells (Treg) and a decline in B lymphocytes, as well as an reversal of the CD4 to CD8 [CD4/ CD8] T cell ratio [35] (steadily increasing CD4/CD8 ratio). Covid-19 provoked cytokine storm is thought to play a role in immunosenescence-related poor outcomes in older adults. The virus has the ability to infect T cells. It would still be unsure whether lymphocyte strengthens or diminishes the cytokine storm after infection. In a recent study, Intravenous Mesenchymal stem cell transplant employing an immunomodulatory therapy method was found to be effective as a cohort study showed seven ill patients with pneumonic COVID-19 [36]. Immunomodulatory therapy aimed at calming the cytokine storm has been found to be effective . In elderly individuals, immunomodulatory therapy targeting cytokines storm has the potential to enhance outcomes and minimize COVID-19-related death [37].

D- Significance….

Hypercytokinemia is an uncontrolled hyperinflammation reaction resulting in a widespread responding to a site - specific inflammatory process due to either viral or wide ranges of bacterial infection.This may cause tissue damage, vascular injury, and targeting multiple impairment, which harms the organ systems [38]. TNF and IL-1 and chemotactic cytokines IL-8 & MCP-1] levels primarily elevated in hyper-cytokine condition, allowing for a sustaining release of Interlukin6. By acting on gp130, The membrane attached receptor [mIL 6R] or soluble receptor [sIL 6R] ;both are the receptors that Interlukin6 binds to via the Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway, modulates levels of IL-6, MCP-1, and GM-CSF, and hence contributes to the continuation of inflammatory process by Initiating response caused by acute phase action. Ferritin measured in serum, complement levels, C-RP, & anti coagulation indicators may all amplified by IL 6 as well as other immune-modulatory cytokines, and can all be measured with widely viable laboratory testing [39]. The acute phase activity of the cytokine storm is boosted. Low T cell level results in poor clearance of virus when elevated cytokines concentration is negatively correlated with total counting of lymphocyte. Controlling upstream events of cytokine responses, like JAK-STAT triggering in the macrophages causing decrease in IL1 and IL6 synthesis, could be an approach for treating the cytokines storming [40]. Approaches targeted cells based on investigated informations as well, but somehow the time taken by anti B lymphocyte guided such a drug like rituximab to provide a therapeutic efficacy might be too extensive for medical use. As a result, concentrating on upstream occurrences can be more advantageous [41].

When infection occurs, the macrophages & dendritic cell launch a rapid autoimmune reaction that includes leukocytosis and the production of cytokines. Lympopenia develops as a result, particularly in critically ill patients requiring intensive care admission . Healthy cells in the lungs, kidneys, heart, blood vessels, and brain are all harmed as cytokines production becomes speedily uncontrolled. When the endothelial barriers in lung is breached, the cytokines storming injury begins [42].

We believe that the immune system's cytokine network connects with the cytokine network of central nervous system, particularly when compromised with blood-brain barrier. Generation of reactive oxygen species, the phagocytosis as well as apoptosis, and the cytokines expression all increased. In the CNS as a result of microglia and IL-1 activation [43], Neuro-inflammation, induced the oxidative stress and the synaptic pruning malfunction result in neural tissue damage. Activation and phagocytosis of macrophages initiate this process. Proliferation of T cell, neutrophil chemotactic action, and mast cell agranulocytes are all examples of Tcell induction. Inflammatory cytokines circulate in bloodstream, potentially exacerbating the cytokines storm [44].

E- Clinical Aspects for Diverse Medical Conditions: Cytokines Storm & Highly Risk Patients

Middle East respiratory syndrome with prevalence of [17–29 percent], acute myocardial damage (myocarditis, infarction, as well as cardiogenic shock), septicemia, systemic organ failure, stroke, pulmonary emboli & secondary infection are among the serious complications linked to COVID-19 [45]. As a result, patients with cardiovascular diseases, high BMI, cancer, and primary IGs deficiencies, auto-immune disorders, and those on immunosuppressive medications who are at high risk of serious COVID-19 morbid condition and cytokines storming must be managed according to special caution. The optimization of treatment methods may be aided by assessing and immune response at various time points [46].

F- Coagulopathy Influenced by COVID-19 and its consequences

Patients infected by coronavirus, especially those who are younger, enhanced the coagulation opportunity, which increases the risk of arterial and venous thromboembolism Tissue-related variables play a vital function in activation of coagulopathy in case of infection scenario. The cytokines have been demonstrated to activate the coagulation system in vitro [47].

Vascular ischemic stroke was described in young COVID-19 persons who were asymptomatic or mildly symptomatic in a case study . In critically unwell individuals, acute venous thromboembolism (VTE) appears to be prevalent. VTE [mostly deep vein thrombosis (DVT)] occurred in 22.2 percent of 54 needed to be treated with enoxaparin once they admitted [48].

In a study of 81 serious COVID-19 ill patients did admit to the intensive care, 25 percent of those who did not receive VTE preventive treatments established lower limb deep vein thrombosis, 40 percent of these patients passed away through spectacular accuracy and precision of D-dimer level greater than 1.5g/mL indicated VTE. [49]. In a study included 191 people found that people with D-dimer levels greater than 1.0 g/mL had a significantly higher mortality rate than people with levels less than 1.0 g/mL[50]. Deepest venous thrombosis, pulmonary emboli, MI, and systemic vascular embolism are all examples of acute stroke. All contributed to a 31 percent overall thrombosis rate, with pulmonary embolism accounting for 81 percent of all complications. A prolonged partial thromboplastin clotting time >5 sec. and a prothrombin time >3.0 s have both been shown to predict the coagulation issues individually [51].

Unless the hazard of bleeding exceed the danger of blood clots, American Society of Haematology did recommend prophylaxis with enoxaparin or fondaparinux which is an option to heparin with low molecular weight to limit risk in hospitalized COVID-19 patients [52]. The level of fibrinogen must be checked in late disease stages after 10 to 14 days, with values greater than 2.0 g/L indicating disseminated intravascular coagulation. LMWH should be required in all hospitalized patients for COVID-19, unless it is contraindicated [53].

There is a need for more investigation into the link between high coagulation indicators and D dimer, cytokines storming & the severity of other symptoms. Anticoagulation treatments that are most effective in treating or avoiding blood coagulation should be researched as soon as possible [54].

G- Therapeutic Approaches to Cytokine Storms

For therapeutic purposes, many different phases of the cytokine storm cascade can be addressed as shown in table 2 &figure 3 respectively The initial factor represented by viral infection, in addition to amplifying negative effects that keeping the hyper-inflammation cycle going [55].

Immune responces can improve the progression of infection even when the antiviral medications are not used. According to case condition, pharmacological interactions with medications used, like antiviral, antimalarial (such as chloroquine and hydroxychloroquine), or immunosupressives as tocilizumab, should be assessed [56].

1) NSAIDs and corticosteroids

Corticosteroids and nonsteroidal anti-inflammatory medicines (NSAIDs) can effectively reduce inflammatory reactions; but, if the virus is not cleared quickly enough, it might cause additional issues elevating the transmission risk. In spite of using corticosteroids to modulate cytokines storming at the short term, their usage in respiratory virus infections is linked to higher mortality, a higher chance of secondary infection, a longer stay in the ICU. COVID-19-related fever may potentially be masked by corticosteroids [57].

2) Interleukin-6 (IL-6) blocker

Is an important cytokine in cytokine storms . Inhibiting IL 6 is thus considered as an effective strategy for therapeutic management as shown in figure (4) [58] Tocilizumab is an antibodies bound to receptors of interlukin6 which are both membrane bounded and soluble that inhibit the interlukin 6 signal transduction after binding to the membrane protein gp130. [58]. Clinical symptoms improved after treatment with tocilizumab, according to a trial of 21 COVID-19 patients [59].

An Italian Regulatory Drugs Agency is testing tocilizumab in COVID-19 patients . The trans-signaling pathway mediated by sIL-6R is responsible for IL-6's pro-inflammatory actions. The anti-inflammatory as well as regeneration events of Interlukin 6 are mediated by cis-signaling cascade through mIL-6 receptor, which is located upon phagocyte, neutrophil cells, a few T-lymphocytes, & liver cells [60]. Tocilizumab also isn't specific for such sIL-6receptor, while it blocks the mIL-6receptor, resulting in unwanted adverse effects like bronchitis. Tocilizumab may be replaced with recombinant soluble gp130 protein (sgp130), which reduces the pro-inflammatorion consequences whenever it bonded to Interlukin6 receptor due to its binding to sIL-6receptor. [61]. COVID-19 cytokines storming could be treated with IL-1 inhibitors. Anakinra's phase III clinical trial showed that it improved survival without causing any extra worse reactions . Interlukins respectively can be used for COVID-19 as pharmacologic alternatives since they reduce the pro-inflammation progress of Interlukin-1 [62].

3) Janus Kinase Inhibitors

Middle east respiration syndrome penetrates the host cell lines through endocytic receptors, that is controlled by kinases associated numb such as adaptor for complex protein2 (AP2) with kinase associated protein (AAK1) and G-associated kinase (GAK1) [63]. Drug that has high affinity to block AAK1 such as Ruxolitinib is being researched more and more for COVID-19 treatment (ChiCTR2000029580).

AAK1 blockers in toxic doses are required to inhibit NAK, on the other hand, Baricitinib has an advantage in inhibiting both the AAK1 & GAK proteins (2–4 mg daily dose), as well as inhibiting the signalling pathways of JAK 1 and 2, causing reduction of inflammatory reaction of interlukin6. Also, it has the ability to be prescribed with another antivirals & anti-inflammatory because of its low plasma protein binding and limited interaction with cytochrome P450 (CYP) enzymes with a benefit for COVID-19 patients [64].

H- Decisions influenced by Cytokines Storms

Its recommend that cytokine storm diagnosis should depend on cytokines storms and care method for patients assured or suspected to be infected with COVID-19 due to the correlation between the severity of infection squelae and the cytokine storming syndrome (Table 1). The current comprehensive evidence-based guidelines for diagnosing and treating macrophages activation associated with cytokines storming syndrome [65] are foundation of our approach. The COVID-19 committee of Surviving Sepsis Campaign did recommend an accepted dose of steroids for endotracheal intubation ARDS cases (dexamethasone 10 mg/day or methyl-presolone 60 mg daily) . Cytokine storm management is clinically complex and problematic because to the lack of the recognized treatment. Although our proposed methodology [66] could be used as a viable method, clinical judgments have been made depending on the profile of individual patient & sickness severity. The immune-suppressive drugs like corticosteroids and immune modulating agents like monoclonal antibody which act as anti interlukin6 (tocilizumab), both are expensive and not available, Even within the developed countries, supplies of COVID-19 may be in limited supply during the pandemic . Additional research is needed into the relationship between neuro-invasion and cytokine storm [67]. Patients either with or without the cytokines storming in COVID-19 should be studied for a long time to determine the immune aspect of pathogenesis and diagnostic markers for the severity of disease. The immune memory of infection with SARS- CoV2 is predicted to linger after the cytokine storm has passed [68]. Increasing the risk of recurrence of infection in patients who had previously tested positive for covid_19 but had cured the infection. Limiting the damage should be the focus of research in the future [69]. Assessing the key involved in pathogenesis processes associated with cytokines storming might develop diagnosis criteria & therapeutic solutions for critically ill COVID-19 patients [70].

Conclusion

The emergent COVID-19 virus have become a challenges to the medical health staffs worldwide. The severity and Mortality of covid-19 is mainly due to the cytokine storm which is a destructive inflammatory reaction accompanied by a secretion of a enormous levels of the pro-inflammatory cytokines induced by the virus . Medications that are Targeting and lowering the cytokines levels during COVID-19 patients managing should be initialized within the primary lines of treatment in order to improve the survival and lowering the mortality rates.

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